

**STUDYING THE WILLINGNESS TO PARTICIPATE  
IN ACUTE STROKE RESEARCH TRIALS**

By

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## ABSTRACT

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Achieving representative, timely recruitment to acute stroke trials is challenging, yet little research has explored the factors determining whether or not stroke patients agree to participate in clinical research. This prospective study collected survey data from 200 acute stroke patients (or their consultees) from two NHS Trusts in the West Midlands to determine the influence of sociodemographic, clinical or attitudinal factors on decision-making about trial participation. Respondents were offered either a real or hypothetical trial.

128 respondents (64%) agreed to trial participation. Few measurable factors were associated with decision-making, although patients able to consent for themselves were more likely to agree participation than consultees deciding on their behalf. Participation decisions may be strongly influenced by attitudes and perceptions about trial research rather than sociodemographic factors. Participants who perceived their stroke severity to be moderate or severe were significantly more likely to agree to trial participation. Respondents offered a real trial were almost six times more likely to participate than those offered a hypothetical trial. Disparities were found between self-rated stroke severity and clinician assessed NIHSS scoring.

Acute stroke trial recruitment would benefit from recruitment strategy planning and training if trials are to produce timely findings based on representative patient samples.

This work is dedicated to my Family.....

Mummy has finished writing her book!

“For us who nurse, our nursing is a thing which, unless we are making progress every year, every month, every week, take my word for it, we are going back....”

Florence Nightingale



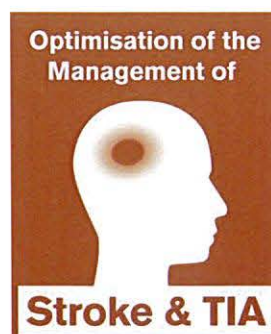
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## ABBREVIATIONS

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### **BHH**

Birmingham Heartlands Hospital

### **CI**

Confidence Interval

### **CLOTS**

Clots in Legs Or sTockings after Stroke

### **Consort**

CONsolidated Standards Of Reporting Trials

### **CRN**

Comprehensive Research Network

### **CT**

Computerised Tomography

### **CTIMP**

Clinical Trial of an Investigational Medicinal Product

### **DH**

Department of Health

### **DIAS4**

Desmoteplase In Acute ischaemic Stroke 4

### **ECCASS**

European cooperative acute stroke study

### **ED**

Emergency Department

**FAST**

Face, Arm, Speech Test

**GCS**

Glasgow coma scale

**GPs**

General Practitioners

**HBM**

Health Belief Model

**HBP**

High Blood Pressure

**ICH GCP**

International conference on harmonisation Good Clinical Practice

**IMD**

Index of Multiple Deprivation

**IRB**

Institutional review boards (US)

**IST-3**

International Stroke Trial-3

**LOS**

Length of stay

**MCA**

Mental Capacity Act

**NIHR**

National Institute of Health Research

**NIHSS**

National Institutes of Health Stroke Scale

**NHS**

National Health Service

**NRES**

National Research Ethics Service

**OR**

Odds Ratio

**PI**

Principal Investigator

**PIS**

Participant Information Sheet

**PPI**

Patient and Public Involvement

**QE**

Queen Elizabeth (Hospital)

**R&D**

Research and development

**RCP**

Royal College of Physicians

**RCT**

Randomised Controlled Trial

**ROSIER**

Recognition Of Stroke In the Emergency Room.

**SAH**

SubArachnoid Haemorrhage



**SES**

SocioEconomic Status

**SPSS**

Statistical Package for the Social Sciences

**SRN**

Stroke Research Network

**SSNAP**

Sentinel Stroke National Audit Programme

**SSS**

Scandinavian Stroke scale

**TIA**

Transient Ischaemic Attack

**TOAST**

Trial of ORG 10172 in Acute Stroke Treatment (classification)

**TpA**

Tissue plasminogen Activator

**TPB**

Theory of Planned Behaviour

**UK**

United Kingdom

**US**

United States (of America)

**USA**

United States of America

**vs**

Versus

# CHAPTER 1

## INTRODUCTION

---

### Overview

The focus of this thesis is to determine the willingness of stroke patients to participate in acute stroke research trials within the National Health Service (NHS) and to ascertain whether any identifiable patient or clinical characteristics influence the decision to participate. This chapter reviews the background to this study and research within the context of stroke medicine. A review of the pertinent literature is explored in chapter two and following this the research methodology is described. In the fourth and fifth chapters the results of this study are reported and discussed. A final chapter provides a conclusion to this study.

In this introductory chapter, the first section provides an introduction to research within the NHS and recruitment to clinical trials. Section 1.2 details the challenges associated with recruitment to acute stroke trials in patients with acute stroke. This leads on to section 1.3 where an American study relevant to this project is discussed (Kasner et al 2009). Finally in section 1.4 the research objectives are outlined taking into consideration the gaps identified in the recruitment literature.

### **1.1 Research in the NHS**

Research is important to patients, the Government and the Department of Health (DH) (NIHR CRN 2014a). The NHS constitution describes clinical research as 'core business' for the NHS and comes with a political duty and commitment. The Health and Social Care Act 2012 and recent government policies reinforce this commitment

to the promotion and delivery of health research as a core NHS role (DH 2010, DH 2012a, DH 2012b, DH 2012c) since much of the care delivered within it is based on experience or uncertainties and lacks evidence but research provides this evidence.

The National Institute for Health Research (NIHR) is the research arm of the NHS in England (NIHR CRN 2015). It was created to implement the government's health research strategy: to embed research focused upon improving care and patient treatment into everyday clinical practice (DH 2006). The NIHR Clinical Research Network (CRN) and similar networks in Scotland, Wales and Northern Ireland provide the infrastructure to support the practical delivery of research in the NHS (DH 2011, UK Clinical Research Collaboration 2009).

#### 1.1.1 Clinical Trials

Improvements in clinical care depend on implementation of an evidence base of research relating to the safety and effectiveness of treatments, devices and medical approaches. Clinical trials, and more specifically, Randomised Controlled Trials (RCTs) are considered the gold standard for research (Chalmers et al 1981; Stolberg et al 2004 and McDonald et al 2011) and attempt to address genuine uncertainty where clinical equipoise exists.

RCTs are mostly quantitative, comparative, controlled experiments, with treatment effect less open to bias than observational studies (Stolberg et al 2004). The process of randomisation enables a fair comparison as the treatment a patient receives as part of a trial is randomly selected, based on chance (most commonly done by a computer programme but essentially, like tossing a coin) to decide treatment

allocation. Randomisation is considered to be a powerful experimental design since, if all other variables are equally accounted for (including unknown confounders), any difference in outcome can be attributed to the intervention (McGovern 2001).

In order for the results of clinical trials to be generalisable and applicable to the wider population, a representative sample of patients needs to participate, reflecting the demographics and characteristics of the wider population on the basis of factors such as age, gender and ethnicity (Sheikh et al 2004). An under representation affects the generalisability of research findings (Hussain-Gambles et al 2004; Mason et al 2003) and may lead to inequalities in access to healthcare. Under recruitment to RCTs is problematic and well documented (Campbell et al 2007).

Despite the importance of diversity of trial participants, Murthy et al (2004) noted (in the case of cancer research) that little information was available about factors that affect the representation of groups in clinical trials, namely race, ethnicity, age and sex.

Involving participants from ethnic minority groups demands special consideration. For example, availability of Patient Information sheets (PIS) in a native language or presence of an interpreter, when necessary. Few trials have information leaflets translated to other languages, unless the trial is exclusively aimed at a particular ethnic group and trial sites may not have access to interpreters at the time of need. Furthermore, neurological deficits (including stroke), maybe more difficult to detect in ethnic minorities e.g. language impairment and slurred speech, if the patient is not

able to communicate in English, further hampering inclusion (Hussain-Gambles et al 2004).

Cultural barriers to randomisation may exist in a belief that illness is 'God's will' and if it is God's will, the patient will get better. Gaining an understanding of how patients decide whether or not to participate in a trial, and their attitudes towards research trials may enable the recruitment process to be more transparent, inform recommendations for improving the consenting process and lead to increased trial enrolment (Halpern, 2002).

Wider ethical considerations regarding consent are extensively documented in the ethical literature. These include the more recent advances in law to address the difficulty of consent in emergency research and the alternatives to patient consent utilising a personal legal representative or a professional legal representative (statutory instrument, became UK law in 2004). Whilst this recognises the need for emergency research, for urgency of starting treatment, it does not support a waiver of consent for urgency of starting research, for example blood sample biomarker studies (low risk studies) requiring samples immediately on admission. These low risk studies are time sensitive in the Emergency Department (ED) with difficulty in delivery without a waiver of consent and yet the legislation does not currently reflect the urgency of starting research (Lemaire 2014).

## **1.2 Stroke disease**

Whilst acute stroke trials have the potential to improve the evidence base for stroke care, the success and wider utility of stroke trials are often hampered by poor trial

recruitment. Overall, the numbers of stroke patients enrolled into trials are small and relatively little research relates to the actual recruitment of patients into acute clinical trials (Kasner et al 2009).

Recruiting to clinical trials has its own challenges and recruitment is complicated yet further by an added time pressure in patients with an acute neurological event such as stroke, where therapies, such as thrombolysis, need to be administered rapidly for maximum effect (Rose and Kasner 2011).

### 1.2.1 Definition of stroke

The current definition of stroke supported by World Health Organisation dates back to 1976 as a descriptive term for rapidly developing clinical symptoms lasting more than 24 hours and comprising of a focal loss of cerebral function with a presumed vascular origin (Hatano 1976). Where symptoms last for less than 24 hours, a diagnosis of Transient Ischaemic Attack (TIA), a warning sign, may be applied. Classically there are no warning signs of a stroke and the majority of strokes are not preceded by a TIA (Hankey 1996).

The pathological background for stroke may either be ischaemic or haemorrhagic and is the interruption of the blood supply to the brain, affecting the supply of oxygen and nutrients and thus causing damage to the brain (Stroke association 2015). Ischaemic stroke (infarction) is the more common type of stroke (85%) and is the blockage of a blood vessel resulting from an array of risk factors (Feigin et al 2014). Haemorrhagic stroke is where a blood vessel bursts (accounting for approximately 15% of all strokes) and is often the result of high blood pressure (hypertension).

Subarachnoid haemorrhage (SAH) occurs mainly as a result of rupture of an aneurysm at the inferior surface of the brain. Although patients with SAH may develop symptoms in accordance with the current definition of stroke, it may not cause direct damage to the brain. Therefore they are often excluded from the majority of stroke studies (Truelsen et al 2000).

Attempts at a 21<sup>st</sup> century definition of stroke with advances in science and technology have not gained full backing from the World and European stroke organisations primarily due to the inclusion of silent cerebral infarction and silent cerebral haemorrhage within a universal stroke definition (Sacco et al 2013). A new definition incorporating tissue criteria as well as clinical criteria can have significant effects on disease surveillance and prognosis (Sormani 2009). This would be critical for clinical research that reports outcome measures according to the accepted definition of stroke.

### 1.2.2 Epidemiology

There are approximately 152,000 strokes annually in the United Kingdom (UK) (Townsend et al 2012) with significant financial impact on the NHS, annual direct care costs in excess of £2.8billion and additional costs of lost productivity, disability and informal care costs estimated to raise this to £9billion a year (Saka et al 2009). Stroke continues to be the main cause of complex, adult disability worldwide and is the second most common cause of death globally (Lopez et al 2006). Fifty per cent of all stroke survivors are left with a disability (Adamson 2004; RCP 2014b).



With manifestations of coexisting conditions (such as ischaemic heart disease, peripheral vascular disease, diabetes and hyperlipidaemia for example) and of atherosclerotic disease, age remains the single most important risk factor for stroke (Seshadri et al 2006). In younger patients, stroke may be due to more unusual causes i.e. arterial dissection, migraine or blood disorders affecting people, of working age.

South Asian, black African and black Caribbean people in the UK are at an increased risk of stroke compared to the rest of the UK population, with more exposure to risk factors notably diabetes, smoking and high blood pressure (Wang et al 2013). Black and south Asian people have strokes at a younger age compared to their white counterparts and black people are twice as likely to have a stroke compared to white people.

### 1.2.3 Manifestation

The symptoms of stroke are varied, often reducing patients' physical and/or mental capabilities. Patients may present with any number or combination of symptoms. Physical impairments caused by stroke include those highlighted in the Act FAST campaign (Facial weakness, Arm weakness, Speech problems, and Time to get help if one or more of these signs are seen, DH 2013b), as well as individual or a combination of other symptoms such as co-ordination problems (ataxia), eye problems (hemianopia), decreased level of consciousness and cognitive impairments - which can present as: disorientation, poor memory and an inability to sequence a task. Each of these symptoms in isolation can complicate the consent process but in combination can prove a significant challenge to researchers.

Acute stroke may alter a patient's level of consciousness, cause inattention / neglect and an inability to follow commands (RCP 2013). A deficit in this area may affect a patient's ability to give valid consent for research (Demarquay et al 2005). However transient the current mental state may be, a consultee (usually a family member or a legal representative) may need to be approached to determine what the proposed participant's wishes would be in relation to being involved in research.

Speech problems such as expressive (expressed) or receptive (received) speech or aphasia (no speech) can result from a stroke. Verbal cues, guessing and suggestion are commonplace in the context of such deficits, especially in the early phases of stroke recovery. Patients can also suffer from excessive fatigue due to stroke (wakeful moments may be brief). This creates a challenge to determine if information about a research study has been understood and retained. Other forms of communication such as writing may equally be affected.

Hemiplegia (weakness affecting one side of the body) is a commonly experienced symptom of stroke (Lawrence et al 2001). This may result in a dominant arm and hand being affected, so that the patient cannot hold a pen to sign his or her name on a consent form. Cerebellar strokes can present with a lack of co-ordination and result in difficulty writing. Some patients may be able to make a mark or use a non-dominant hand to indicate their agreement; in this case it would be considered best practice for this to be witnessed by a member of the clinical team. Another option may include witnessed verbal consent where clinical staff are present throughout the whole information giving and consent process to verify its conduct, protocol allowing.

The consent process is complex in stroke as, unlike many other conditions, understanding, retaining information, reading and writing may all be affected. Communication problems cannot in themselves be taken to indicate reduced mental capacity or inability to provide valid consent, however, they may raise concerns. Researchers use strategies such as pacing information, checking understanding and testing recall to highlight any issues within the support of the Mental Capacity Act (2005), DH (2005). Should mental capacity be affected by the stroke, a personal or professional legal representative can be consulted for research should they be available and the research protocol permits this. A personal representative or consultee often is a close family member.

Consultee decision-making must always be based on the presumed will of the patient. In a limited review, Flaherty et al (2008) found only 30% of patients who experienced stroke provided their own consent whilst Kasner et al (2009) found 47%. In acute stroke studies, it is often necessary to involve family members in decision-making. This has been identified as a source of stress and a perceived burden of responsibility with urgent decision-making on behalf of a family member by consultees. Similar stress was not reported by self-consenting patients (Demarquay et al 2005).

Supporting patients and their families at this stressful time is fundamental to ensuring patient choice and its availability for as long as possible. Lecouturier et al (2010) suggested that improvements in study participation could be achieved through

increasing the time spent with patients and families talking about research, but acknowledge that this may not always be possible in emergency research.

In some emergency research scenarios, it is possible to go for deferred consent with a legal representative and verbal consent at the outset. Participants can then effectively 'consent to continue' post-recovery in a study where initial consent by the individual was not possible. Increasingly, studies have included documentation to enable this for example Roffe et al (2014), approved by National Research Ethics Service (NRES 2011b). This reflects one of the cornerstones of informed consent in that it is an on-going process (Berg et al 2001).

#### 1.2.4 Diagnosis

Stroke remains a clinical diagnosis, and needs to be distinguished from stroke-mimics such as hemiplegic migraine, global amnesia or seizures (Rose and Kasner 2011). This is often in the context of acute neurological deficits, with an incomplete medical history, limited physical examination and imperfect neuroimaging. Previously fit people can suddenly become vulnerable patients unable to convey their wishes, communicate with medical staff and family or comprehend the seriousness of their situation.

Initial nursing assessments undertaken as part of standard clinical care using tools such as the Glasgow Coma Scale (GCS), Face Arm Speech Time (FAST) Test, Recognition Of Stroke In the Emergency Room (ROSIER) and the National Institute of Health Stroke Scale (NIHSS) are often used to assess stroke patients (DH 2013b; Nor et al 2005; Brott et al 1989). They also serve as useful indicators of challenges

that researchers may encounter when screening a patient for trial eligibility, discussing participation and obtaining informed consent.

### 1.2.5 Management

Computerised Tomography (CT) scanning, although more readily available and quick to perform in the emergency department, may not be sensitive enough to pick up early, subtle changes in brain matter, making radiological diagnosis difficult at an early stage (Yew and Cheng 2009). Recruitment to trials may be time sensitive and therefore it is not always possible to wait for neuroimaging confirmation of a stroke prior to recruitment. As a result, some patients may no longer be eligible for a trial following confirmation of diagnosis (several days later in some cases).

The acute phase of a stroke is generally considered to last 24-72 hours post stroke (Summers et al 2009). During this time a research approach can be unexpected and few people would have thought about the concept of research when feeling 'well' and now must consider it whilst 'unwell' and experiencing acute neurological symptoms.

The acute phase of an illness is a difficult time within which to carry out research since symptoms can fluctuate, a diagnosis may not be fully apparent, the range of symptoms that can be experienced are extensive and their range of intensity can fluctuate. The priority of the patient and relatives is often not research as they attempt to rationalise what has occurred and are concentrating on "best treatment" following such a sudden event. This adds further difficulty to the recruitment process.

Clinical research undertaken in the early acute phase of a stroke is dependent upon effective collaboration between researchers and clinical nursing staff to safely implement protocols, given the inherent challenges of research in this context (Campbell et al 2015).

Catastrophic changes are common in the brains of people with stroke and therapies need to be administered rapidly for maximum effect whether part of standard care or a research intervention (Rose and Kasner 2011). As a result, acute stroke studies often have a limited recruitment window within which participants can be included in the study, ranging from a few hours to 48 hours from stroke onset (UKCRN 2015).

During this period, patients and their relatives may be seeking general stroke information and trying to understand the emergency situation they have found themselves in, and are not ready to consider research study-specific information. The acute neurological deficits resulting from a stroke can be transient, fluctuate and make recruitment to studies (specifically receiving consent) particularly challenging (Dani et al 2008).

The opportunity for recruitment may be affected if the patient has delayed seeking medical attention for example, choosing to stay at home in the hope symptoms would resolve or being unable to call for help (Shah et al 2007), there is no clear onset time of symptoms, or if the patient is unable to convey this and presents alone.

This is in contrast to some other disease areas where time may not a restricting factor for recruitment, mental capacity unaffected and a diagnosis may be well established,

for example in areas such as hypertension or diabetes. As a result, people can consent themselves, conditions maybe more chronic, long standing or allow for a later more relaxed introduction to research, not time pressured.

Timely identification of potential research participants and anticipating and overcoming intrinsic impairments associated with stroke are therefore fundamental to successful recruitment to acute stroke studies.

#### 1.2.6 Research opportunities

Information on ethnic minority participation rates across all disease specialities is documented in the literature (Mason et al 2003; Hussain-Gambles et al 2004). The importance of representation of individuals with different demographics has been a focus of many studies, as this will ensure that findings are generalisable to the wider society (Durant et al 2011). Under-representation of racial and ethnic minorities, gender and age have been reported extensively, in numerous specialities (Murthy et al 2004, Heiat et al 2002, Bartlett et al 2003).

Historically, there were limited opportunities for patients to participate in stroke research, which was underfunded in comparison to other disease areas (such as cancer and heart disease) and had a limited public profile (Rothwell 2001). The NIHR has raised the public profile of stroke research and provided new opportunities to offer research to patients who have experienced stroke. Between 2006 and 2014, stroke research benefited from a dedicated NIHR Stroke Research Network (SRN), which led to a six-fold increase in the number of patients who had experienced stroke participating in clinical research (NIHR CRN 2012a); and now forms part of a

cardiovascular research theme (of which six themes exist covering all disease specialties) across the whole of England.

There are now more stroke studies than ever before included on the NIHR CRN Portfolio. Studies range from randomised clinical drug trials to observational studies and cover stroke prevention, diagnosis, acute treatment, rehabilitation and on-going care. While it may take several years to see the results of such research studies translated into clinical practice, the clear aim is to ensure that patients who have experienced stroke receive evidence-based care.

Disparities in disease and medical setting mean that results from other disease areas are not necessarily applicable to a stroke population for a number of reasons: namely that stroke has a rapid onset and results in a loss of function (positive neurology) as opposed to causing pain. Some patients may not survive the initial event, whereas others may have reduced mental capacity and cognitive dysfunction that can affect their ability to provide valid informed consent.

To participate in a research trial, potential patients must have the mental capacity to weigh up the benefits and risks of a clinical trial (NRES 2011b). A fundamental principle of UK law is the right of every adult to make their own decisions; unless there is proof that they lack the capacity to make a particular decision at the time it needs to be made. The Mental Capacity Act (MCA) 2005 (DH 2005) and the Adults with Incapacity (Scotland) Act 2000 provide guidance for determining a person's capacity to make a decision. It specifies that it is important to help people take part as



much as possible in the decision process, and recognises that some participants may require help to make or communicate their decisions (vulnerable adults).

To be valid, consent must be informed, competent and voluntary (ICH GCP 1996). Stroke, by virtue of the deficits that result from the condition and recent breakthroughs in treatment interventions (with time restrictions) adds complexity to this process (Liebeskind 2007). It is vital that cognitive impairments, visual disturbances, communication or physical deficits do not preclude patients from participating in acute stroke studies. Such deficits must be recognised and overcome to enable these patients to participate and ensure that research findings are applicable to the whole stroke population (McCormack and Reay 2013).

In a Cochrane review by Treweek et al (2011), many studies are reported as having looked at recruitment to mock trials. A mock or hypothetical trial differs from a real trial in that no treatment results from giving consent but researchers must be mindful to ensure no confusion or deception occurs. Treweek et al conclude that it is difficult to know how findings from mock trials would apply to real trials. Other research has suggested that willingness to participate in a hypothetical trial to be a valid predictor of actual participation in a range of disease areas, such as infectious disease, arthritis and schizophrenia (Halpern et al 2001; Taylor et al 2007b; Jeste et al 2009) - although such a design cannot inform potential retention rates of participants.

The use of hypothetical trials exposes the results to criticism that hypothetical choices may not reflect actual decisions for trial participation. However, as Durant et al (2011) point out, these approaches are widely used in survey research based on the theory

of 'reasoned action' that is, the behaviour is determined by someone's intention to perform the behaviour (Ajzen and Fishbein, 1980).

### **1.3 Previous Research**

Identifying and recognising factors associated with trial participation could aid research design, be cost and time saving and enable efficient targeting of additional support to groups. There is, however, little research on the actual recruitment process itself. One particular study in recent years, from a single, urban university hospital in Philadelphia, US has investigated participation in acute stroke trials (Kasner et al 2009). Kasner et al (2009) used a survey tool to study who would take part in acute stroke research. The study consisted of a survey which included recruitment to a real trial (if patients met the criteria for trial entry) or a mock version (if the patients did not satisfy the inclusion criteria). Over a period of 15 months, 200 respondents completed the survey. Fifty-seven per cent stated they would participate in the proposed acute trial. Kasner et al found no differences in willingness to participate with respect to age, sex, race, educational level, 'self-assessed' stroke severity or stroke type, vascular risk factors or co-morbidities. Demographic factors, clinical factors and prior knowledge about research were found to have little impact on the decision to participate in acute stroke trials, but pre-existing negative attitudes and external influences about research strongly inhibited participation.

Influences on the recruitment process have been highlighted by research and literature to date under the umbrellas of organisational factors, clinical disease factors and population specifics. Clinical and population factors pertinent to stroke have already been discussed. Organisational factors include researcher availability,

confidence of clinician, relevance of the research question and a scientific, rigorous design which fits with clinical practice (Fletcher et al 2007).

Other potential organisational factors include delays due to legislative approval, the rate of active participation and commitment of recruiting sites, and the application of appropriate analysis and reporting procedures (McDonald et al 2011). However, it has been suggested that a feeling of hope is associated with research involvement (Weiss Roberts et al 2002) and video clips are used in *healthtalkonline* ([www.healthtalkonline.org](http://www.healthtalkonline.org)) promoting clinical trials from the participant perspective by those who have taken part in trials before. McDonald et al also propose that constraints on clinicians' time and lack of available staff can largely be overcome with a team approach to research but still does not answer the question why some trials recruit well and others less well.

The National Institute of Health Research (NIHR) identified that many trials up until 2011 were not recruiting to target without extending their timescales. Recruitment was found to be most successful in centres that recruited their first patient within 30 days of approval. The NIHR has attempted to address this and incorporates it specifically in 'time to target' higher-level objectives (NIHR CRN 2014b).

Elkins et al (2006), suggest that characterizing predictors of recruitment may help optimize future trial design. This has cost implications in terms of trial set-up, investment of working time for all parties involved in the research process and the need for timely research to keep pace with clinical advances, therefore relevance to the population.

The need for research to be embedded within standard care has been raised recently by Reynolds (2011) who found new technology and social media not to have increased participation. Reynolds highlighted that unhealthy people (possibly the more socioeconomically disadvantaged) and the elderly are less likely to be recruited and yet are more likely to need the benefits of new drugs developed as a result of clinical trial research.

Kasner et al (2009) noted that in the context of an acute event, potentially influencing factors in decision-making were not clear. Gaining an understanding of how patients decide whether or not to participate in a trial, and their attitudes towards acute stroke research trials may enable the recruitment process to be more transparent, inform recommendations for improving the consenting process and lead to increased trial entry (Halpern 2002). Characterising the predictors of recruitment may help to identify barriers to recruitment, aiding trials in making more realistic estimates of the rate of enrolment (Elkins et al 2006).

#### **1.4 Gaps in the literature**

Although a variety of data and information are recorded regarding stroke admissions, for research purposes, a prospective research study to identify possible factors associated with trial participation has not been done in the UK for stroke disease. Information regarding the acceptability of research, and willingness of stroke patients to participate during the acute phase of their illness is important and it is not clear whether cultural differences or systematic healthcare differences would mean that results from the US would apply to the UK. Currently a knowledge gap exists in our

understanding of influences on the decision to participate in acute stroke trials in the UK.

By utilising a similar approach to Kasner, embedding survey research alongside recruitment to a real trial or hypothetical example, decision-making in relation to participation and the rationale behind it could be explored, compared and contrasted with the available literature and aim to fill the current gaps from a UK perspective.

#### 1.4.1 Study objectives

- To determine whether demographic factors, level of education, prior research experience and issues related to the stroke experience itself have any impact on the decision to participate in acute stroke trials.
- To assess general attitudes towards clinical trials, external influences and opinions regarding the participation decision.
- To explore differences in trial participation decision-making between patients and their representatives, in conjunction with the reasons stated for the participation decision.

## **CHAPTER 2**

### **LITERATURE REVIEW**

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#### Overview

This chapter provides a review of the literature on recruitment to clinical trials. The literature will be reflected on critically with regard to its influence on the design and conduct of this study and the associated gaps in the evidence base identified in relation to acute stroke trial recruitment.

The first section highlights research literature and the drivers associated with recruitment to clinical trials. Section 2.2 explores recruitment and includes theories of behaviour and decision-making regarding participation in a clinical trial. This is followed by section 2.3 that describes the components of a recruitment process and valid, informed consent. Section 2.4 considers clinical trial participants and non-participants. The final section summarises the literature, noting the research methodologies used in previous studies and reflects on its implications for this study.

#### **2.1 Research literature**

Research is important to patients, the government and the DH. A consensus wide consumer poll of 3000 people (NIHR CRN 2014a), found that 95% felt it was important that the NHS carries out clinical research and 89% reported they would be willing to participate in a study if diagnosed with a medical condition or disease. The NIHR is the research arm of the NHS and is an opportunity to embed research within

front-line activity and deliver the best possible treatments for patients based on the evidence of what works.

For any type of clinical research study, patients must first be identified and assessed to determine whether they are eligible to participate (ICH GCP 1996). They must be given information about the research and time to consider whether they wish to participate. They must provide their written consent before receiving care in accordance with the research protocol, with relevant data collected and monitoring throughout to ensure patients' safety and wellbeing.

Clinical trials are used to guide advances in care and inform statutory bodies such as the National Institute for Health and Care Excellence (NICE) to secure the most consistent, high quality, evidence based care for NHS patients (Nice guidelines 2014). Arguably, these guidelines are only as good as the evidence on which they are based, for example licences for treatments maybe for age specific or restrictive use due to the age range used in the trials, on which the granted licence was based.

A recent example is the restricted licence for a thrombolytic drug (Tissue plasminogen Activator –TpA) which was granted in 2003 for use within a 3 hour window of stroke onset and in those under 80 year olds until the completion of further research which included older patients in the sample (IST Collaborative Group 2012) and a longer time window. Considering that the average age of stroke patients is close to the original maximum licence for use, a significant proportion of the stroke population was not able to access this treatment for several years.

The research process can be lengthy but many randomised controlled trials (RCTs) either fail to recruit sufficient participants or need to extend trial periods in order to meet target recruitment (Sully et al 2013). Extending trial length is not only costly but also risks minimising impact as clinical care advances over time (the research question is no longer valid or becomes irrelevant). Subsequent delays to clinical advances result in the continuation of weak evidence based practice in the absence of more robust research findings, and can ultimately result in diverting research resources away from future studies (McDonald et al 2011).

### 2.1.1 Representative Sample

Recruiting a representative sample is important in clinical trials so that results can be generalised to the wider population. Murthy et al. (2004) found enrolment in cancer trials for all patient groups to be low. In cooperative group cancer trials (breast, colorectal, lung and prostate cancer clinical trials), racial and ethnic minorities, women and the elderly were less likely to enrol than white males, and younger patients. Under-representation of certain demographic groups has also been reported by Heiat et al (2002) in heart failure clinical trials and by Bartlett et al. (2003) in a cholesterol trial. Of the studies published on enrolment to trials, the majority use retrospective data. Kumar (2003) argues for the need for prospective studies to determine the extent of lower inclusion rates for some patient groups i.e. those identified for trials but not included for randomisation.

Disease stigma, anxieties related to understanding the implications of participation, worries about trial medication, as well as cost and time concerns were found to be common amongst ethnic minority groups (Rooney et al 2011). MacNeill et al (2013) in



an asthma paediatric study, found Bangladeshi parents to have a greater respect for medical opinion, limited grasp of spoken or written English and yet, increased participation (at the expense of limited understanding).

Suggested improvements in the general literature for minority group inclusion note the use of multilingual trial documentation, employment of personal approaches (MacNeill et al 2013) and addressing researcher reluctance to include participants from all cultural and linguistic spectrums. Sheikh et al (2009) and Carman et al (2014) point towards a mixed methods approach to inform strategies on minority group inclusion.

Despite a high incidence of acute stroke in the UK and significant cost implications for the NHS, the evidence base for treatments across the stroke care pathway is weak (National Clinical Guidelines for Stroke, 2008). Dani et al (2008) suggest this may be due to an inability of people with stroke to take part in the decision and informed consent process due to impairment, particularly where recruitment takes place soon after the stroke event.

## **2.2 Recruitment to Clinical Trials**

The process of decision-making with regard to an acute clinical trial usually follows a set approach with the clinical team determining the suitability of a patient to be approached and their eligibility for enrolment (ICH GCP 1996). Information about the trial, the risks and potential benefits, and the requirements that participants will have to fulfil if they participate, is provided both in a verbal and written form and 'sufficient time' as deemed necessary, should be given. This is considered by ethics boards

prior to approval for research in the NHS and in line with trial design allows for the maximum available time to consider a research trial (Hardicre 2013).

Various techniques used by individuals to make decisions have been documented over time and include: rational decision-making - weighing up pros and cons (advocated by the likes of Plato and Benjamin Franklin); simple prioritisation; satisficing – examining alternatives only until an acceptable one is found; maximising - where all alternatives are examined in order to determine the best one; elimination, acquiescence and superstition amongst others.

Planning is not always possible prior to decision-making and its absence can add difficulty to the process. Behrendt et al (2011) used a qualitative approach to clarify patients' needs and understanding about informed consent. Whilst a clear informed consent consultation was requested by respondents, adequate advanced notice was also specified. In contrast, over-thinking or over-analysing a situation can adversely affect decision-making so greatly that an action or decision is never taken.

### 2.2.1 Decision-making

Decision-making is largely regarded as a reasoning or emotional process resulting in the selection of a course of action from several different possibilities. A decision-making process results in a final outcome, which may or may not prompt an action and is based on the values and preferences of the decision-maker. It can be rational or irrational and based on explicit or implicit assumptions.

Human performance has been studied from popular perspectives such as the psychological, cognitive and normative. From a psychological perspective a decision is considered in the context of a set of needs, preferences and values. A cognitive perspective reflects an on-going process embedded within the interaction with the environment whilst a normative perspective is largely concerned with the logic of decision-making.

The strategy in decision making of weighing up pros and cons is a recognised taught technique for decision-making (Franklin's rule), however, without time, cognitive resources and access to relevant information (required to enable this) as a process, arguably it may not best describe how most people make decisions. Nightingale (2008) states that people simply decide without thinking too much about the decision making process.

Uncertainty is formally integrated in the likes of decision analysis and robust decision research (Jungermann 1983). Despite exposure to logical decision-making in a medical institution, the general public are in a foreign environment, affected by a sudden, unexpected, serious health event with the need to rationalise the complexities of a clinical research trial. Rational choice theory incorporates the ideology that people try to maximise benefits whilst minimising costs (Schacter et al 2011) and may play a role in decision-making.

McCann et al (2013) studied recruitment to clinical trials highlighting an increasing link between potential participants' health states and health care situations interacting with other considerations. In particular they note the nature and significance of trial

entry decisions influenced by communication and relationship to recruiter; implications of trial interventions and processes; perception of the common good (helping others) and what non/participation might reflect about them as individuals.

Recency, wishful thinking, cognitive inertia, peer pressure, anchoring (unduly influenced by initial information shaping the view of subsequent information), role fulfilment, illusion of control, are all amongst other debated biases in judgement and decision-making.

## 2.2.2 Theories of behaviour

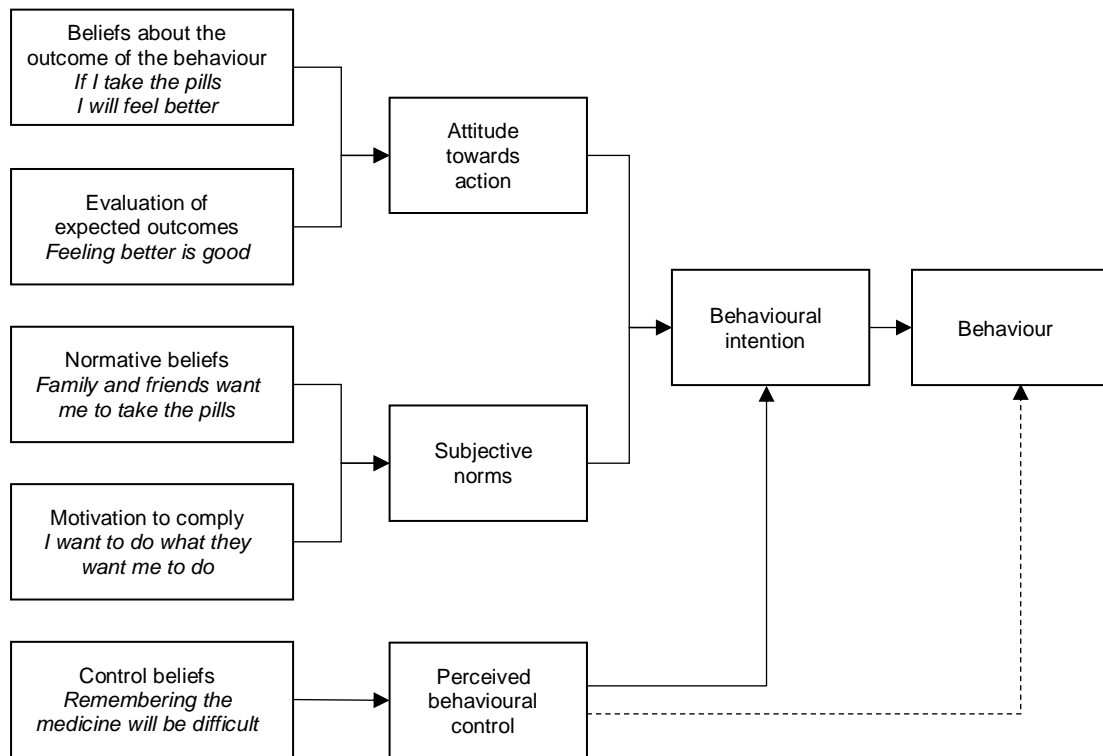
Many models and theories of human behaviour exist within the social sciences, the majority of which focus on the drivers of individual health behaviours, and have their roots within the discipline of psychology, although there are also a number of behaviour theories which focus on the behaviour itself or the relationship between behaviour, individuals and the social and physical environments within which they occur.

### *2.2.2.1 Theory of Planned Behaviour (TPB) and reasoned action*

The Theory of Planned Behaviour (TPB) is one of the most commonly cited and applied behavioural theories, adopting a cognitive approach to explaining individuals' attitudes and beliefs (Ajzen 1985, 1991; Ajzen and Madden 1986). TPB evolved from the theory of actioned reason (Fishbein and Ajzen 1975), which puts forward intention to act as the best predictor of behaviour.

Intention is proposed as an outcome from a combination of attitudes towards a behaviour, positive and negative evaluation of the behaviour, its expected outcomes and subjective norms (social pressures) from the perception of what others may think should be done and a person's inclination to follow these. Similarly, self-efficacy and perceived behavioural control may be additional components that influence behaviour. TPB has been widely used in health by the likes of Armitage and Conner (2001) and more recently by Taylor et al (2007a) and Munro et al (2007) with evidence suggesting a strong correlation between behaviour and both attitudes towards that behaviour and perceived behavioural control components (Figure 2.1).

**Figure 2.1: Theory of Planned Behaviour Model (Munro et al 2007)**



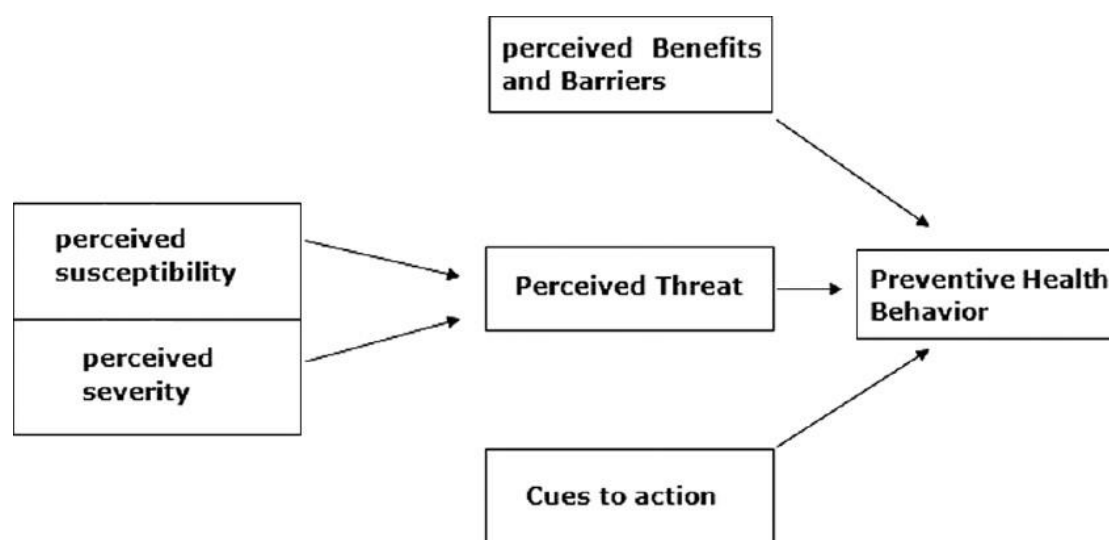
### 2.2.2.2 Health Belief Model (HBM)

An alternative popular theory of behaviour, the Health Belief Model (HBM) argues that behaviour is determined by a number of beliefs about threats to well-being, effectiveness and outcomes of actions and behaviours (Hochbaum 1958; Rosenstock 1966; Becker, 1974; Sharma and Romas, 2012). This is possibly more relevant when attempting to understand decision-making with regard to clinical trial participation, as the theory was designed and developed in the healthcare context, with perceived threat being central to the model, covering personal cognitive factors and the addition of self-efficacy (Bandura 1997) – with the recognition that stimuli may trigger adoption of behaviour (Figure 2.2).

Proponents of the theory argue that it is particularly appropriate when seeking to explain or predict patterns of behaviour, but it has also been criticised for the

exclusion of social, economic or unconscious (habitual) determinants that are generally considered at least as important as personal cognitive factors in affecting decision-making processes. The HBM, however, does not take account of institutional factors outside of an individual's control which maybe an important consideration for hospitalised patients or their next-of-kin who may be involved in a decision-making process such as that related to deciding on participation in a clinical trial.

**Figure 2.2: The Health Belief Model (Rosenstock 1974)**



With regard to predictive behaviour - whilst the mantra that has gained recognition over several decades that 'the best predictor of future behaviour is past behaviour', is noted in psychology texts (Johnston 2003), this is possibly too simplistic and past behaviour may merely be a useful marker as to what may happen in the future. Much has been written about the contribution of habit and the influence of personality typing on health beliefs and behavioural decision-making. Nevertheless, participants who have taken part in research before have an increased awareness of research. Durant et al (2011) found that those involved in research previously were more likely to sign

up for further studies when invited, provided they had not previously had a negative experience of research participation.

Additional influences on decision-making include social, cognitive and cultural considerations. For example, the desire for a particular outcome e.g. wellbeing with the assumption that medication will result in improvements, financial incentives, previous experience, level of education, nurture (cultural influences – trust or mistrust of authorities), altruism, laissez faire or religion.

### 2.2.3 Hypothetical trial behaviour

A hypothetical (or mock) research trial differs from a real trial in that no treatment results from giving consent. Care must be taken to ensure that no deception occurs and that patients being offered the hypothetical trial are fully aware that they are not being asked to consent to participate in a 'real' trial. Various articles in the research literature argue that the use of hypothetical (mock) trials is a valid predictor of actual participation in trials (Halpern et al 2001), and that using hypothetical trials as a means of understanding patient decision-making about trial participation is a valuable way to assess the barriers to, and motivators of participation in a way that can be directly transferred to 'real' trials. However, according to Treweek et al (2011), it can be difficult to assess how findings from hypothetical trials would apply to real trials. Nonetheless, researchers such as Halpern et al (2001); Taylor (2007b); Jeste et al (2009) and Tehranisa and Meurer (2014) all report positive findings in relation to a decision for trial participation using hypothetical trials, in the areas of arthritis, schizophrenia and stroke.



Jeste et al (2009) used a mock trial in schizophrenia patients to test a multi-media consent process, recognising the potential for impaired decision-making capacity in the population group being studied. This allowed for understanding, appreciation, reasoning and expression of choice in trial participation as opposed to printed, text based consent forms for informing.

Most recently, Tehranisa and Meurer (2014) used an acute stroke mock trial for patients presenting to hospital emergency departments to test the extent to which those approached to participate understood trial design (response adaptive randomisation, RAR). The authors found the trial design to be well understood by participants, although in this case, participants were without symptoms of stroke or other critical illness.

Durant et al (2011) note that approaches using mock trials were widely used in survey research based on the theory of “reasoned action”, that the behaviour is determined by someone’s intention to perform the behaviour (Ajzen and Fishbein, 1980).

Goldstein et al (2010) found independent predictors of willingness to enrol in acute stroke trials to include Catholic religion, looking at consecutive emergency department (ED) attenders and their opinion on participation in a stroke trial.

In acute stroke studies, it is often necessary to involve family members in decision-making as patients are not necessarily able to consent for themselves (DH 2005). This has been identified as a source of stress and a perceived burden of responsibility (Demarquay et al 2005). Kasner et al (2009) found surrogate decision

makers to be less inclined to agree to the participation of a patient compared to the patient who had experienced stroke themselves.

#### 2.2.4 Consultees

Consultees or proxy decision-makers are approached regarding consent (or rather assent) for clinical trial participation, as a legal representative in cases where patients are unable to consent for themselves (Hardicre 2013). In practice, this is usually a next-of-kin - the rationale behind this comes from the recognition that a consultee is able to inform from a position of knowing the patient best and thus being aware of what the patient's wishes may have been in this situation, had the patient been able to consent for themselves.

Mead et al (2013) noted that due to acute stroke, many people are not able to consent for themselves and describe proxy consent as standard. In order to facilitate information provision, easy access patient information booklets were devised – utilising short sentences, a simple grammar structure and large well-spaced text. There is currently on-going use of the easy access booklets to determine the numbers of aphasic patients enabled to independently consent as a direct result of having this available and supports the consent process in that participants should be encouraged to take part in the process as much as they are able (DH 2005).

Demarquay et al (2005) studied 56 stroke patients enrolled in urgent therapeutic trials and found (using multiple logistic regression) increasing age and baseline neurological deficit (as assessed by the Scandinavian Stroke Scale SSS) to be independent predictors of inability to give consent. The majority of patients (n=43,

77%) were consented by relatives and a proportion of these declared feeling uncomfortable with the decision citing psychological stress induced by urgent decision making. The authors of the study conclude that the responsibility of consent usually relies on relatives and questions a potential inaccuracy of decision concerning a patient's wishes or a conflict of interest.

More recently, Bryant et al (2013) found that over a third of stroke patients required surrogate consent with little being known about the level of agreement between patient and surrogate in the time sensitive decision-making process. The authors used four hypothetical acute stroke scenarios and found high surrogate-patient agreement for clinical scenarios of 87%-96% but a drop to 49%-74% with a research scenario suggesting the accuracy between surrogate-patient agreement on participation decreases with a research scenario, noting a difference in the type of decision made (clinical versus research).

Sanoff et al (2013) recorded calls to enrolling physicians. The most commonly cited reasons for non-enrolment were: unclear stroke onset time; pre-existing condition confounding outcome; mental incapacity and no legal representative; rapidly improving symptoms and no interpreter. Eleven per cent of legally authorised representatives, refused participation.

Kasner et al (2009) similarly found that patients were more likely to agree to a research study than a consultee was on their behalf adding weight to Bryant et al's (2013) call for further characterisation of the surrogate decision making in acute stroke, to be useful.

## **2.3 Components of recruitment**

Significant costs are associated with trials failing to meet recruitment targets or extending recruitment at the expense of limited resources being invested in new trials. A significant amount of current literature suggests both organisational and clinical disease factors affecting recruitment to trials. Adeoye et al (2012) suggest that improved recruitment rates could be achieved by capturing potential participants who are 'eligible but not approached' and 'treated but not enrolled'.

Prior to enrolment in a clinical trial, several important recognised steps would have needed to have occurred. Events ranging from the need to document pre-hospital activity immediately post event through to seeking medical attention and having a clinical trial 'open to recruitment and accessible' with resources (researcher) to offer a recruitment opportunity. The decision regarding trial participation rests with the competent decision-maker at this point.

### **2.3.1 Presentation and recognition**

Early treatment and secondary preventive measures can reduce the brain damage associated with a stroke and treatment of stroke is very time dependent. The multimedia campaign and associated medical personnel training (ambulance crews) with FAST Campaign has led to increased recognition of symptoms (Mellor et al 2014). However, in a UK project set in the West Midlands, Mellor et al (2014) found that delays arose from patients' lack of recognition (or denial) of the significance of their symptoms, contact with primary care as opposed to the emergency services and lack of recognition of the nature and severity of the event by initial healthcare providers.

Of 2042 presenting acute stroke patients from a multi-ethnic population in the US during an 8 year period (2005-2013), 101 patients presented one-week after acute stroke, 58% were beyond 4.5 hours (the required time for early intravenous thrombolysis treatment) with diabetic patients less likely to arrive within the prescribed time period. Patients who were men, with a history of atrial fibrillation or flutter and experiencing a transient ischaemic attack were significantly more likely to arrive within the prescribed time. Black, African-America and Hispanic patients were less likely to arrive on time (Matos-Diaz et al 2015).

Elkins et al (2006) found trials with a recruitment window of >6 hours had double the recruitment rates of those that use a recruitment window of <6 hours, suggesting a significant impact of time pressure.

Further international research by Williams et al (2009) in a retrospective audit of 331 presentations found 63% of cases presenting >12 hours after symptom onset and subsequent long in-hospital delays with only 52% being assessed by a physician within an hour of presentation with intravenous thrombolysis treatment not being routinely performed.

With access to intravenous thrombolysis treatment becoming more widely available in recent years, clinical trials in front line drugs such as IST-3, DIAS-4, ECCASS3/4, immediate CT and rapid assessment time have contributed to shorten delays post presentation but wake-up strokes, unknown time of onset and seeking help pre-hospital remain potential delays (Penaloza-Ramos et al (2014).

### 2.3.2 Site setup and resource

Barriers and facilitators to out of hospital stroke research were noted by Ankolekar et al (2014) who used semi-structured interviews to identify 13 themes associated with recruitment. Positive factors were noted to be simple stroke diagnostic tools, proxy consent and straightforward trial processes. Recruitment was reported to be easier with each new randomisation whilst barriers were reported as the emergency setting, lack of institutional support, rarity of condition and difficulty in attending training.

Ahluwalia et al (2014) noted a trend towards increased understanding and satisfaction with the informed consent process by patients where additional resources of a video link phone were used pre-hospital but warn of possible risk as a result of increasing time at the scene of the event to intervention (time) within secondary care.

Perceived clinical equipoise must exist in the research team and sufficient resources available for trial delivery when eligible patients are likely to present. Balancing resource with financial return is a significant consideration for trusts and Research and development (R&D) departments in the current financial climate.

During a trial, changes such as a relocation of services, advances in clinical care, or local changes in clinical arrangements can all affect recruitment figures. Advances in clinical care may mean the research question becomes no longer valid during the trial or needs to be adjusted to complete the trial and create the evidence base for a particular aspect of clinical care for example CLOTS collaborative (2008).

For a recruitment opportunity to occur, a clinical trial must have received a favourable ethical and local (Trust research and development) approval, be open to recruitment at the emergency care facility and have the necessary resources to be able to offer this opportunity.

Charting 300 subjects recruited for acute stroke trials, Elkins et al (2006) found that study entry criteria and organisational factors influenced recruitment rates. It is therefore necessary to not only have a trial open but also one open that patients are eligible for.

Trial-related barriers to participation include additional demands from a trial protocol on the patient such as time, discomfort, worry and travel; preference for a particular outcome may dissuade participants from trials involving a randomisation, especially if the alternative is a placebo; some patients may not wish to take medication, change their existing medication or have a fear of the unknown or adverse events (Kaur et al 2012). A complex trial design may not be in keeping with standard care treatment visits, requiring additional scheduling. Age, level of education, social circumstances, language and cultural issues (distrust of existing systems) may also have an impact. A complex trial design which outlines a schedule not in keeping with standard care treatment visits may require multiple additional clinic or hospital visits which may be difficult for those who would need to take time off work to meet trial commitments.

Clinicians may have personal concerns with reluctance to 'over-burden' a patient with research at a difficult time evidenced by less recruitment of severely ill patients.

Resources required on site to deliver a study include study team members with knowledge of the study, delegation of trial procedures and a signed delegation of duties log with personnel able to action the necessary requirements. These staff need to be available when a patient presents in order to be in the time window for recruitment. Consideration therefore needs to be given to working hours, shifts patterns and extended hours cover within a 24/7 healthcare service.

With the advent of the national research networks in 2006, the NIHR provided an infrastructure for research, funding and supplying research nurses amongst other initiatives, boosting recruitment (Darbyshire et al 2011).

Leira et al (2009) found an increased likelihood of consent to trial participation with an increased number of research contact points. Utilising pre-arrival communication between investigator and potential participants proved successful with an increased consent rate in acute stroke trials within a cohort of 100 patients (trialled in US in 2007).

Information overload is deemed to be when there is a substantial difference between the volume of information provided and the extent to which people can make use of it. This can occur due to a problem processing and tasking (a possible consequence of the clinical effects of a patient having suffered a stroke) and as a result, can influence decision-making (Kutty and Himanshu 2007). Factors affecting information overload may appear on a personal level with an individual's educational level, past experiences, the characteristics of the information in terms of quality, quantity and frequency, tasks, process, design and Information technology. Hall et al (2007)



described an illusion of knowledge, suggesting that too much knowledge can interfere with an individual's ability to make a rational decision. Raynor et al (2007) found evidence outside trials that patients had a preference for verbal information from clinicians complemented by written information.

Patient information sheets have been criticised in the literature in regard to trial recruitment. Iwanowski et al (2008) surveyed 24 investigators on informed consent for research about coronary syndromes and stroke findings. Despite there being no legal obligation to do so, investigators sought parallel consent from patients' relatives in the majority of cases - due to the patient information sheets being considered as fully read in only 15% of cases and 80% of investigators considering the amount of information being given too lengthy. Similarly Shilling et al (2011), found that both practitioners and parents in paediatric clinical trials expressed dissatisfaction with patient information leaflets; reporting them to be too long and complicated.

More recently Kirby et al (2013) tested the feasibility of electronic information provision, for an interventional study noting the amount of information accessed. From 1160 potentially eligible participants only 25% supplied an email address. Of those responding on email (106), 59% (n=63) booked to attend a recruitment clinic despite accessing no electronic information. Kirby concludes that written information may not be read, reemphasizes the importance of the consent interview and suggests new ways of presenting information are needed.

### *2.3.2.1 Informed Consent*

Clinical trials research consent differs from clinical care consent since the latter is based (at least in theory) on a body of evidence for a prescribed, recognised treatment and considered to be in the best interests of the patient. The former is carried out to create that body of evidence and may not directly benefit the participants themselves.

Valid informed consent is at the centre of ethical research practice and is essential to protect the rights and safety of patients taking part in research. Several definitions of informed consent can be found in the literature based on the International Conference on Harmonisation for Good Clinical Practice (ICH GCP 1996), which stipulates:

“A process by which a subject voluntarily confirms his or her willingness to participate in a trial, after having been informed of all aspects of the trial that are relevant to the subject’s decision to participate and by means of a written, signed and dated informed consent form.” (ICH, GCP E6 1.28)

Any new information that becomes available and which might influence a decision to carry on with trial participation, must be shared with any recruits. Continued understanding of participation must also be present which reflects the on-going nature of the consent process.

In order to participate in a clinical trial, valid informed consent to take part must be freely given and received. Care is needed due to cognitive and physical effects from a stroke so that words and details are not missed when presented with written

information. Alternative formats of documented trial details may need to be sourced to ensure that consent remains fully informed.

In emergency research, time is limited and should patients be unable to consent themselves (DH 2005), independent physician consent as well as legal representative, verbal consent or exception to consent maybe appropriate approaches given ethical approval. Legislation has incorporated EU directives with statutory instruments to allow concessions to be made in the consent process for research in the emergency setting. Flaherty et al (2008) found that only 30% of patients who experienced stroke provided their own consent.

Supporting patients and their families at this stressful time is fundamental to ensuring patient choice is available for as long as possible. Lecouturier et al (2010) suggested that improvements in rates of study participation could be achieved through increasing the time spent with patients and families talking about research, but acknowledge that this may not always be possible in emergency research. It is possible for participants to consent using conventional processes to continue in research post recovery and many studies have processes to enable this.

Alternatively, an exception to consent was researched in the emergency department using a hypothetical stroke trial by Kleindorfer et al (2011) with the majority of ischaemic stroke patients being agreeable to enrolment.

Ali et al (2006) used focus groups of individuals having had personal experience of stroke and found a preference to personal contact with researchers (face to face),

request for waiver of consent and agreement to family assent on behalf of incompetent patients. Whilst Lecouterier et al 2008 found that 50% of professionals were reluctant to agree with research without consent, a paradoxically higher percentage would personally take part in such a study.

Masuca et al (2012) found patients consented faster than legal representatives and since emerging treatments are time sensitive, called for further efforts to target this for stroke where significant numbers of patients are not able to fully consent for themselves.

Flexible consent procedures have made it possible to recruit target numbers into some stroke trials notably International Stroke Trial 3 (IST-3) using written consent, witnessed consent, assent or waiver of consent (Kane et al 2006).

Consent for research is enshrined in UK law and considered to be a planned activity. To enable emergency care research the concept of deferred consent or a 'waiver of consent' has emerged and maybe considered by the research ethics board and (under strict requirements) maybe a recognised practice in a study (NRES 2011a).

In the US, independent ethics committees, following strict requirements may approve a consent process that does not include some or all elements of informed consent or waiver the process. However, Lecouturier et al (2010) found waiver of consent not well documented in the literature and less advanced as a concept in the UK compared to the US.

Alternative consent strategies e.g. telephone consent and two-physician consent (although available) are not routinely used in clinical practice in isolation (Gilani et al 2013). Recruiting 159 patients undergoing endovascular treatment for acute stroke Gilani et al (2013) found that alternative consent strategies did not adversely affect procedural characteristics (no time delay) or patient outcomes and such consent strategies maybe more time efficient than in-person consenting.

Beauchamp and Childress (2009) advocate three elements of consent. The first is the provision of adequate information with a full and comprehensive outline of the research so that patients know exactly what is involved. According to the International Conference on Harmonisation Good Clinical Practice (ICH GCP 1996), 20 distinct elements are recommended for inclusion in patient information sheets. It is generally accepted that patients need to be given 'enough' information to make a valid informed decision, however, regulatory guidance and legislation favours maximum disclosure with researchers required to give 'full' information whether or not patients wish to receive it. Research in the literature has focused on whether this is information overload (Ferguson 2002, Fortun et al 2008) with Rose and Kasner (2011) highlighting that stroke trial patient information sheets typically range from 8 to 16 pages depending on the complexity of the trial.

A distinction between study and routine care is not always understood by participants (Lynoe et al 2004), lending support to the debate on whether informed consent is truly informed.

### 2.3.3 Clinical disease

Clinical disease symptoms can add complexity to the recruitment process and this is particularly evident in stroke disease where a sudden neurological event can have any combination of wide ranging symptoms. The need for alternative consent strategies, with a potentially unclear diagnosis during an acute event, with associated risk, despite clinical equipoise, may be an uncomfortable situation for a treating physician who may not wish to 'burden' a family with a decision for research at a difficult time.

The timing of a research approach may influence participation. Immediately post event, on seeking medical help, research options may be the only access to some treatments or may be appealing to patients. Alternatively, when patients and their family have a diagnosis and are accepting of the prognosis, research may be more favourable as an option. The time post hyperacute and pre-rehabilitation could be a difficult time within which to advocate research from a professional perspective since there may be no clarity in diagnosis or little information on prognosis. Equally it may be a difficult time to be open to the concept of a research opportunity from a patient's perspective. A strategy for enrolment is often identified at site and is disease specific in many cases.

Physicians may act as gatekeepers and maybe unwilling to participate in facilitating research trials themselves due to a lack of time, lack of resources (support staff), conflicting clinician / scientist role, lack of trials experience, lack of recognition and possibly an uninteresting research question (Rahman et al 2011). If the clinical team deemed it to be unlikely that the patient will survive the stroke event, they are often not approached for research (which may have an entry criterion related to whether or

not the patient is expected to survive for a minimum fixed period or for follow up).

There could be disagreement in terms of uncertainty or equipoise amongst professional colleagues with low referral numbers due to lack of physician engagement. Physician colleagues may agree to be part of the trial whilst disagreeing with some aspects of it.

Financial incentives may encourage investigator participation as well as protected time to carry out research duties or a research question in line with a physician's interests with clear potential to improve patient care and regular feedback (Rahman et al 2011.)

Ethnic disparities in regard to stroke disease exist in not only stroke incidence but also recurrence and mortality - which are higher particularly in South Asian and Black African-Caribbean populations (Carman et al 2014), and yet ethnic minority participation in stroke trials remains surprisingly low.

The inclusion of stroke patients across the whole (severity) scale in research trials is important so that results can be applicable to the wider stroke population. Stroke severity was noted at the outset of a research approach by Schlegel et al (2003) and evaluated using the National Institutes of Health Stroke Scale (NIHSS) – a clinical assessment tool used within stroke medicine. The scale has been widely accepted by clinical researchers and clinical care professionals due to a high level of score consistency and ease of administration with minimal training.

Kasner et al (2003) found that a modified version of the stroke severity scale could be estimated from a review of medical records. Similarly, Bushnell et al (2001) and Williams et al (2000) found that the NIHSS could be reliably estimated retrospectively from the admission neurological examination (although actual testing was preferable). Developed from work by Brott et al (1989), it has since been repeatedly validated for assessing stroke severity and found to be an excellent predictor of patient outcomes (Muir et al 1996; Frankel et al 2000).

Weimar et al (2006) analysed 1,725 consecutively admitted acute ischaemic stroke patients and found that trial design could be improved in terms of time or study size by using defined thresholds for recovery and mortality compared to a fixed inclusion criterion of an NIHSS scale. This will be discussed further in the methodology chapter.

## **2.4 Participants and Non-Participants**

Elkins et al (2006), suggest that characterising predictors of recruitment may help optimize future trial design. This has cost implications in terms of trial set-up and investment of working time for all parties. Shilling et al (2011) call for further exploration of those who decline trials and specific research on accessing 'decliners' as a group to explore reasons for declining trials at different stages of recruitment.

In other disease areas such as cancer, Jenkins and Fallowfield (2000) used a communication study (questionnaire consisting of prompts) to assess reasons for accepting or declining to take part in cancer therapy clinical trials. Of 204 cancer patients eligible for randomised clinical trials, 72% agreed to participate. The most



common reason stated for accepting entry was altruism and trust in the doctor. Of the decliners, the main reason stated was also trust in the doctor - which in the absence of detailed interview may suggest clinician influence. A preference for the doctor choosing a treatment as opposed to randomisation was also highlighted by decliners. A higher acceptance rate was noted in a trial which gave active treatment in all study arms. This is not surprising given the controversial nature of trial design with a no active treatment arm.

Lloyd-Williams (2003) used postal questionnaires with potential heart failure trial participants at the time of recruitment. No difference was found in sociodemographic characteristics between patients who agreed to participate and those who did not. The main reason stated for non-participation was age (too old), health status (too unwell) or too busy. Recommendations in light of the findings include clarity of the benefits of taking part in a study when unwell and the call for trial designs to take into account busy lives for potential participants of all ages.

Avis et al (2006) in a cohort of 208 breast cancer patients, found a 58% participation rate across phase I-III trials with phase II trials having a higher acceptance rate. From their data, reducing drawbacks, specifically travel time, and improving physician communication, were identified as areas to address to increase participation.

In other healthcare areas such as antenatal screening, Koschack (2009) found those declining deliberated more deeply on the pros and cons of research participation. Interviews were conducted with those who declined and showed personal, diverse life

experiences and philosophy in regard to specific tests (Down Syndrome), to be the main determinant.

Madsen et al (2007) explored the attitudes to clinical trials in a small group of female cancer patients using a grounded theory approach. Patients voiced positive attitudes believing trials to be necessary for medical advances. Those agreeing to participate argued participation was a moral obligation. Most expressed a discomfort with randomisation whilst decliners expressed a radical change in focus at decision time and personal choice. Patients support the suggestion that a feeling of hope is associated with research involvement (Weiss Roberts et al 2002).

Less well documented in the literature to date are the opinions and attitudes of stroke recruits and non-recruits (decliners). There appears to be a gap in the literature associated with stroke disease with unclear factors associated with declining participation in a research trial when offered. In terms of a level of willingness to participate, there may be a proportion of patients that will always decline participation, regardless of whether or not these decliners are given further details about the study. This number could be factored into trial design for numbers needing to be screened for a conversion rate to achieve target recruitment figures and factored into a recruitment strategy.

## **2.5 Reflection on the Literature**

A critical approach through this review has been adopted in order to analyse its implications for this study. In this section, the main points are summarised.

In the first section of this chapter, theories of behaviour were discussed together with debates in the literature on predictive behaviour and hypothetical situations. Decision-making was then reviewed from an individual perspective, cognitive and personal biases were noted and information overload was considered. This indicated the complexity of factors associated with the decision-making process and how this might be further compounded with disease and a need for a recruitment strategy.

Informed consent in the research process was explored and included current findings in regard to proxy decision-makers. Four identifiable components necessary for a recruitment opportunity were discussed and influences to this recruitment process were noted from the literature to broadly fall into organisational, clinical disease and population specific factors.

Disease assessment scales used within the clinical setting were outlined with regard to stroke and the most commonly used was explored further.

An absence in the literature was noted in regard to patients declining participation as little is known about that potentially very important cohort of the population and results in a gap in our knowledge of findings which are generalizable to the population and the disease area of interest, as a whole.

Previous literature in relation to low recruitment rates has cited various explanations including issues with trial design -extending the time needed to reach recruitment target; failure to approach potential participants or identify eligible participants and fewer eligible participants than anticipated (McDonald et al 2006); and barriers to

recruitment - potential participant perceptions such as perceived investment of time, perceived importance or preference for treatment (Prescott et al 1999).

Little research to date relates to the actual recruitment of stroke patients into acute clinical trials (Kasner et al 2009) with factors that may influence potential participants' decision-making about whether or not to participate remaining unclear. Although much debated, there is little clear evidence as to why many trials fail to recruit well (McDonald et al 2011).

This study arose from the lack of documented literature on the stroke trial recruitment process. There is a lack of research characterising potential participants, assessing whether particular individuals are likely to take part in or decline research and an absence of taught approach strategies for acute stroke research to maximise participation in trials.

## **CHAPTER 3**

### **METHODOLOGY**

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#### **Overview**

This study used survey methods as the primary means of data collection to explore patient recruitment into acute stroke trials. It is the intention that the findings of this study will directly inform future practice on trial recruitment. This chapter provides an overview of the research methodology (design and methods) and relates this to the research question and the purpose of the study.

The first two sections of this chapter outline the research question and the methodological considerations that underpin the study design. Section 3.3 provides a detailed description of the study design including piloting and site selection, Section 3.4 describes participant identification and sample size. This is followed by survey administration and data collection. Section 3.7 highlights statistical approaches used for data analysis.

#### **3.1 Research Question**

The overall aim of this study was to identify the motivators and barriers to trial recruitment in order to inform future trial design. This study focused solely on stroke disease and more specifically the acute phase post event and the willingness of participants to take part in an acute stroke research trial.

Trends in patient characteristics were assessed to decide whether study designs could be modified to optimise stroke patient recruitment.

The research question was therefore, what influences decision making for clinical trial participation in the context of acute stroke and are there any factors which predict participation?

### **3.2 Methodological considerations**

The research strategy employed for this study was a survey administered face-to-face, with each participant. This approach allowed quantitative information to be collected about the population of interest (stroke patients) and decision-making with regard to their participation in a clinical trial. The methodological considerations underpinning the selection of this technique are outlined in this section.

#### **3.2.1 Paradigm debates**

Social science research is subject to various debates about the epistemological issues that underpin it. At its core, these issues come from the philosophy of science, which makes basic assumptions about fundamental issues (such as the nature of truth) and what it means to know, and beliefs about the way to look at the world. These emphasise the approach and the framework which guides such research and generally falls into quantitative research versus qualitative measures - although according to the literature they are not so mutually exclusive (Niglas 1999).

This study is descriptive research aimed at examining factors associated with a situation e.g. the decision-making process associated with participation in a clinical trial, in the post stroke acute phase. Factors examined include demographics, socioeconomic, health characteristics, behaviour, attitudes, opinions, experiences

and knowledge. Descriptive studies estimate parameters in a population and describe any associations.

On an epistemological level, the study is positivist assuming objective accounts of the world can be generated and values quantitative measures (Sale et al 2002, Smith 1983). At the alternative end of the spectrum is the interpretivist perspective and requires a high validity in qualitative approach. Arguably a purely quantitative perspective, maybe insufficient to elicit the full nature of decision-making. By incorporating qualitative elements for validity, inferences maybe reportable with regard to this.

### 3.2.2 Survey research

Survey methods are commonly used in health research studies as they enable collection of data from large numbers of participants in a standardised format. Data analysis allows for statistical associations between responses to specific questions and inferences about the wider population can be deducted on the basis of these associations.

Survey limitations may include low response rates, the influence of language barriers (i.e. a sufficient command of spoken English language is assumed), or literacy issues (reading and comprehension ability). In a multicultural society, English may not be the first language or spoken at home therefore older relatives may rely on younger family members for communication outside of their own language or dialect.

Alternative research techniques would have resulted in increased difficulty for potential respondents in the cohort population being studied. Responders in the acute phase of their stroke would not necessarily have been able to interact sufficiently to perform a self-completion survey or participate in qualitative data collection methods such as a semi-structured interview on an individual or group basis. Qualitative research often takes longer to perform, for data to be collected and involves more active participation on the part of participants than a face-to-face administered survey (questionnaire).

Patients in an acute phase of illness are likely to have a reduced concentration span and be acutely unwell requiring an inpatient hospital stay, so that attending a focus group or completing an in-depth interview at the bedside would not be appropriate. Additionally, significant rehabilitation may be scheduled as part of standard care that should not be delayed for research. Repeated interactions with the same respondent over a period of time were not considered feasible in addition to clinical trial requirements and alongside clinical care.

### 3.2.3 Previous Stroke Studies

Summers et al (2009) defined the first two phases of stroke as 'hyperacute' and 'acute'. The 'hyperacute' care phase includes pre-hospital and emergency department activities, typically lasting for up to 24 hours including the stroke itself and transfer to hospital. This is followed by the 'acute' care phase that includes the admission to hospital and a stay in a critical care unit or stroke unit. Rocco et al (2007) found this acute phase to be between 1 and 7 days (commonly up to 72 hours) and this phase became the focus for this study.



Kasner et al (2009) reported the use of a survey in acute stroke with regard to trial participation (discussed in chapter 1, section 1.3). Since the survey element of Kasner's study was conducted with verbal consent, the medical records were not accessed and the severity of stroke via NIHSS scoring was not recorded.

Following direct communication with Dr Scott Kasner (Pennsylvania, US), permission was granted to adopt that questionnaire with adaptations made for this study for cross-cultural and comparative purposes, administered in the UK. The limitations of this approach are considered in section 3.6.

### **3.3 Study Design**

This study used a prospective survey tool in the context of acute stroke with two integrated components: i) A clinical trial participation decision and ii) a researcher administered questionnaire - to identify willingness to participate in acute stroke research trials and to elicit reasons why an individual may agree or decline trial participation. The study was designed to survey non-responders and decliners to acute stroke trials equally with those who chose to participate in a trial.

To minimise the risk of a low response rate and alleviate any concerns of complexity, face-to-face administration of the survey was conducted. This approach compensated for patients with the inability to read or who were illiterate or for those who had a poor command of English (English not being their first language). Additionally, an in-house interpretation service was available to help clarify understanding or expression of

English where necessary. The survey consisted of a clinical trial participation decision and a short questionnaire.

Consideration was given to the length of the questionnaire so as to avoid repeat research contacts, respondent fatigue, incomplete answers or disruption to rehabilitation and clinical care.

The administration of a face-to-face questionnaire aided the engagement of patients to take part as fully as possible under the circumstances of ill health. This approach allowed the researcher to assess and adjust the pace of questions according to any deficits or effects the patient may have experienced due to the acute event.

Inadvertent mistakes and biases made by the patient were minimised as the researcher had the ability to immediately clarify any questions that were unclear or caused confusion and equally, repeat answers for accuracy of response. It was felt that a self-completed questionnaire would have introduced the possibility of inaccuracies, incomplete answers and misunderstanding resulting in unnecessary loss of data.

Financial constraints were a consideration in the survey design with no central grant funding and an application for NIHR adoption pending. A successful adoption onto the NIHR national database would have allowed stroke research network support costs to be released and accessed for additional researchers but a rejection would result in no additional resources.

To capture a decision on clinical trial participation (from all potential participants), a mock trial was incorporated into the survey design alongside real trials, open at that site. Potential participants eligible for a real trial were offered an opportunity to consider a real trial. Patients ineligible for a real trial were offered the mock trial for consideration instead. The questionnaire accompanying this trial participation-decision consisted of a combination of closed questions using Likert scales and some open questions (to aid a response close to social reality).

This is similar to the methodology used by Kasner et al (2009) to identify those who would participate in acute stroke trials and by Goldstein et al (2010) to evaluate willingness to be enrolled in a hypothetical acute stroke trial in the Emergency Department (using exception from informed consent), although Goldstein sampled consecutive ED attendees whilst Kasner used prospective acute stroke admissions.

For the current study, a valid informed consent process was part of the study design with patient information sheets being considered for an adequate length of time (participant dependent) although the remit of an acute phase trial (typically within 72 hours from stroke onset) was stressed, where the recruitment window was short. A full consent process was planned.

All questionnaires were administered by a single researcher, which standardised the format and made sure that all questions were asked in the same way. The questionnaire was administered as soon as reasonably possible after a patient had been admitted to hospital noting the time and date of administration as a reference point (for delay in seeking help, arrival to hospital and timing of a research approach).

### 3.3.1 Patient & Public Involvement and Piloting

As the questionnaire had been devised and administered in America, it was adapted prior to use in the UK. A patient and public involvement (PPI) group for stroke disease were approached early on in study design. The study protocol and associated paperwork were reviewed by designated members of the PPI group, providing feedback that was incorporated into the final design.

The questionnaire and associated trial paperwork were piloted by 10% (n=20) of the proposed final sample size. Several stroke survivors and their families considered the documentation at various stages of stroke event (during admission, at discharge and in the community) - for appropriateness of wording and ease of understanding. Members of NHS staff also reviewed the trial documentation.

The questionnaire was devised to be short with a maximum administration time of 20 minutes. This was found to be the case and the pilot sample feedback supported the length.

At the outset of the questionnaire, all participants were asked to define what they understood by the term "clinical trial". Ambiguity was noted at piloting, surrounding respondents' understanding of this term. Any verbal response that was given was recorded verbatim to avoid any interpretation, misinterpretation, bias or guiding. At the end of the response, an accurate, official definition of a clinical trial as determined by DH, NHS Choices (2015) was given in full and understanding was checked before proceeding further with the questionnaire. This was to avert any misunderstanding or

misconceptions which may occur if respondents had not had the chance to receive clarification. The definition used can be found in Appendix 1.

As a result of the piloting phase, the scale of wellness within the questionnaire was reduced from that typically used, from 0-100 to 1-10 as several members of the healthy, non-stroke pilot sample highlighted concern that there were too many numbers in the range.

The changes as a result of the pilot and PPI feedback were incorporated into the final version of the study documents found in Appendix 2 - Survey tool and study documentation. These received a favourable ethical opinion from The Black Country NRES Committee West Midlands following a full ethics board review (05 March 2012) and two NHS Acute foundation Trusts were identified as potential recruiting sites.

### 3.3.2 Clinical Assessment Tools

A range of clinical assessment tools are used in the hospital setting for patient evaluation and monitoring. These include National Institute of Health Stroke Scale (NIHSS); Scandinavian Stroke Scale (SSS); ABCD<sup>2</sup> score (used to predict the short-term risk of a stroke following a Transient Ischaemic Attack - TIA); TOAST criteria; Bartel; Rankin and GCS, the latter three not being stroke specific but used in clinical practise in relation to patients (including stroke patients).

The NIHSS is a 15-item impairment scale used to evaluate neurologic outcomes and degree of recovery for patients with stroke (Appendix 3). The scale assesses level of consciousness, extraocular movements, visual fields, facial muscle function, extremity

strength, sensory function, coordination (ataxia), language (aphasia), speech (dysarthria), and hemi-inattention (neglect) (Lyden et al 1999; 2001). Developed from work by Brott et al (1989), it has since been repeatedly validated for assessing stroke severity and found to be an excellent predictor of patient outcomes (Muir et al 1996; Frankel et al 2000).

Each item is scored from 0 - 2, 0 - 3, or 0 - 4, and untestable items are scored as 'UN'. A score of 0 indicates normal performance. Total scores on the NIHSS range from 0 - 42, with higher values reflecting more severe cerebral infarcts. Schlegel et al (2003) classifying scores as mild (<5); moderate (between 6 and 13) and severe (>13). Muir et al (1996) highlights an upper ceiling of scoring in patients with severe strokes, as many items may not be testable.

The outcome of a clinician stroke assessment scoring was recorded as it is often used within clinical care as an indicator of patient progress, for monitoring any changes in condition, real trial eligibility or guiding treatment. This score was added to the front of the questionnaire.

An application for NIHR support via adoption onto the national portfolio database was submitted but subsequently declined, as an invitation to join NIHR as a non-commercial partner was declined at that time, by the course-fees funding body for this MPhil.

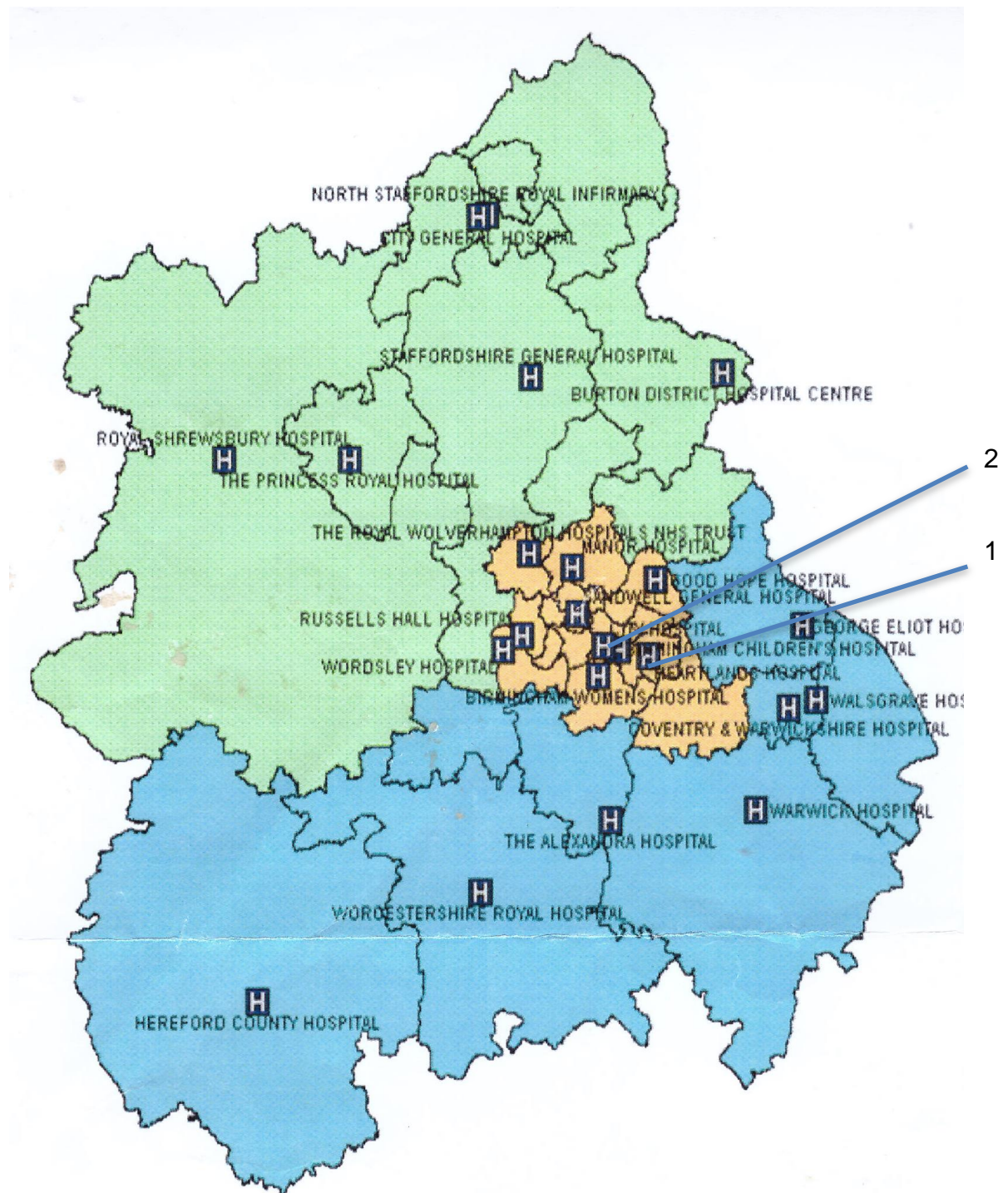
### 3.3.3 Site selection

The primary recruiting site selected was Heart of England NHS Foundation Trust - Heartlands Hospital which based on validated data, receives approximately 400 acute stroke admissions annually (Sheppard et al 2012) and whose local catchment population reflects the diversity of the city within which it is based (Birmingham, UK); has research activity from NIHR national stroke portfolio of studies (open and recruiting) and utilising research nurses integrated in clinical care team.

A second additional recruitment site was identified locally as a back-up should recruitment numbers be low or if the primary site experienced unexpected issues. This was University Hospital Birmingham – Queen Elizabeth, selected due to similarities to primary site in terms of stroke service and size. Although it was not expected that a second recruitment site would be necessary, regional reconfiguration of stroke services was planned which could have had a significant impact on the study and data collection capacity at the primary recruiting site. Figure 3.1 shows the location of the recruiting sites within the West Midlands region.

The number of researchers working on the study was capped to one due to financial constraints (funding comprising an MPhil studentship). At the primary site, the researcher was considered the principle investigator (PI). At the second site, due to substantive employment being elsewhere, a Consultant Neurologist provided oversight at the PI level for the research.

Figure 3.1 Map of West Midlands Hospital



1: Recruiting Site 1- Heartlands Hospital, Heart of England NHS Foundation Trust, B9 5SS.

2: Recruiting Site 2- Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, B15 2TH.



### **3.4 Participant Selection**

Patients were identified by the clinical care team from a prospective emergency department (ED) stroke database, TIA and minor stroke clinic referrals (from ED and GPs) and direct patient referrals to the stroke lead nurse on a daily basis (from in-hospital strokes and GPs).

#### 3.4.1 Inclusion criteria

- All new acute stroke patients who were admitted to the trust and who were deemed both approachable and likely to survive the stroke event (as identified by the clinical care team).

#### 3.4.2 Exclusion Criteria

- Patients who were considered not likely to survive the initial stroke event were excluded from the study (as deemed by the clinical care team).
- TIAs and stroke mimics

#### 3.4.3 Sample Size

Consecutive patients with a primary diagnosis of stroke were approached within a 15 month time frame (April 2012-July 2013). Patients were selected as consecutively approached as opposed to consecutive admissions, by the researcher and as opposed to patients self-selecting to complete the questionnaire, based on the (broad) inclusion and exclusion criteria. This approach aimed to result in a representative sample and provided an equal likelihood of being approached, with findings representative of wider society.

With an admission rate of approximately 400 strokes annually, consideration was made for recruitment target setting as follows: those potential respondents who may decline study consent; local 7 day mortality rates; unable to self-consent and no available consultees; too busy with investigations; too ill to approach; those not interested; missed by the clinical team and those who declined without stating a reason. A proposed recruitment target of 200 was deemed necessary (and achievable) to provide 80% power (at  $\alpha = 0.05$ ) to detect a 20% absolute difference in the likelihood of trial participation. This was in line with Kasner et al (2009).

A consolidated standard of reporting trials (Consort) diagram (Schulz et al 2010) describes predicted recruitment figures in order to elicit the final sample size for the study and how this was devised (Appendix 4). This notably included 13% of patients with a primary diagnosis of stroke (National Sentinel Stroke Audit 2008 HEFT) who died within the first 7 days of care and 18% overall who died prior to discharge.

### **3.5 Survey Tool Administration**

All eligible patients admitted with acute stroke were approached in the first instance to consider participating in a 'real trial' at the recruiting site, by the clinical care team and subsequently were offered this study. A 'real trial' was deemed to be a live, openly recruiting, acute stroke research clinical trial, with ethical and R&D approvals in place at the recruiting site. Nine real trials were available at the start of the recruitment period (although some trials were imminently due to close to recruitment).

Any stroke admissions ineligible for a 'real trial' but deemed by the clinical team as approachable (likely to survive the stroke event), were also approached about this study and simultaneously asked to consider a mock (hypothetical) trial. It was made clear both verbally and written on the patient information sheet where a mock trial was used as no deception was intended.

The mock trial was devised by selecting a Clinical Trial of an Investigational Medicinal Product (CTIMP) from the acute stroke NIHR national portfolio database. The criteria for acceptance onto the portfolio includes having been peer reviewed and deemed good quality research. A trial was chosen that was open to recruitment nationally but not registered at the primary recruitment site for this study. The trial was anonymised as a replica and cleared labelled as a hypothetical trial (a copy of which can be found in Appendix 2 – Study documentation).

A full consent process was followed allowing sufficient time for respondents to consider the information and make a valid informed choice on participation. Participation decisions in response to the trial (real or mock) were recorded, since the primary outcome of the study was the trial participation decision. If a patient's mental capacity was affected, preventing them from completing a full consent process, a consultee (representative or surrogate decision-maker), usually a relative (who knows the person best to be able to verbalise their wishes), was approached and invited to take part in this study as the 'respondent' i.e. the decision-maker for trial participation for the purposes of research. This followed the accepted current practice for stroke research with any patients unable to make a valid informed consent decision

regarding participation (at the discretion of the clinical care team) and follows the Mental Capacity Act (DH 2005) philosophy.

All stroke admissions approached and consented for this study, considered a clinical trial (real or mock) and completed the study questionnaire. No further contact as part of this study was planned (although any required commitments to a real trial remained). A flowchart of the study procedure is summarised in Appendix 5.

Recruitment at the primary site commenced in April 2012 and was analysed monthly. The target recruitment figure deviated from the actual recruited figures. This was due to changes in 'real' trial availability (studies closed or were on hold), ward closures were experienced for brief periods (due to Norovirus outbreaks) and no approachable admissions had occurred for periods in excess of two weeks at certain times. Additionally, a non-interventional trial commenced which competed for the same cohort of patients. After six months, the decision was taken to open the second (back-up) recruiting site and this happened in January 2013 with the same researcher now working across both sites. This improved recruitment and completed the study within the original time frame. Analysis across both sites was undertaken so that any differences in the characteristics of the patient cohort, disease variation and service provision between sites could be assessed.

Patients discharged from hospital prior to research contact, were considered lost to research and typically included those patients with a short length of stay, transfers out of area, transfers for neurosurgical intervention and those misdiagnosed. Those

declining this study outright due to any reason were also considered lost to research and were not contacted further.

Any patient who lacked the mental capacity to make a valid informed decision regarding participation (at the discretion of the clinical care team) and who did not have a carer or relative available, were not approached for this study and were deemed lost to research.

### **3.6 Data Collection**

An anonymised trial number was assigned to each participant for confidentiality of information recording. A centrally held file linking codes to names was stored on site in a locked filing cabinet for the duration of the recruitment period in order to determine if the same respondent completed more than one questionnaire. The questionnaires were administered by the researcher, with the respondent answering each question and responses recorded directly onto each questionnaire. Sufficient time was given for a response and where possible all measures were taken to elicit an accurate response.

Two specific, open questions allowed for a series of prompts following an initial response. These were part of a qualitative exploration and patient responses were recorded verbatim.

A National Institute of Health Stroke Scale (NIHSS) scoring was recorded for each patient on the day the patient was approached by research. Where this was retrospective (a real trial being offered when the researcher was not available), a

recorded scoring from the medical records one day either side of the research approach was used (Kasner et al 1999). Where a scoring from the medical records was not possible and this could not be obtained from any other source, these data were considered missing.

Hospital episode statistics and a local in-house stroke register were checked retrospectively for any patients discharged prior to the research exposure. This allowed for an accurate record of all research eligible stroke patients admitted during the recruitment period and to inform on recruitment overall. Data cleaning was carried out to validate stroke diagnosis and determine length of stay, which was entered retrospectively.

### **3.7 Data Analysis**

Data were recorded directly onto the questionnaires (hard copy) and uploaded by the researcher into an Excel spreadsheet prior to statistical analysis using SPSS v17.0 (Statistical Package for the Social Sciences, Chicago, IL).

Descriptive statistics (means and proportion as appropriate to data type) were calculated using standard methods. Univariate analysis using 2 sample *t* tests for continuous variables and non-parametric tests (Chi Square) were used for categorical variables, for those factors associated with trial participation (ethnicity, educational level and gender). Significance was defined as  $p < 0.05$ . Stepwise multivariable analysis explored factors independently associated with a participant's decision to take part in a trial.

Thematic analysis (Braun and Clarke 2006) was carried out on the qualitative elements of the free text within the survey tool. The data generated was coded for theme frequencies to expand the range of the study past individual experiences. This allowed for categories to emerge from the data and an interpretation of themes supported by the data (Guest 2012). As themes emerged, comparison was made with original data and cross-checked for accuracy of original meaning to ensure this had not been lost in the theme, by the researcher and a University Professor experienced in mixed methods research.

A series of set prompts was used following a verbal reason for trial decision. These were preselected from the current literature (Kasner et al 2009; NIH 2012, 2015; Healthtalk 2012, 2015).

This chapter has provided an overview of the research methodology, identifying the main methodological considerations, the study design and its associated limitations. In the next chapter the results of this study are presented.

## CHAPTER 4

### RESULTS

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#### Overview

As outlined in the methodology chapter, this study utilised survey research as the primary means of data collection. Results from a researcher-administered questionnaire and clinical trial uptake are presented together with a thematic analysis of data generated from responses given to a free text questions in which respondents described their reasons for accepting or declining participation in a research trial.

The first section describes the study participation rate followed by analysis of participant demographic and clinical characteristics. Section 4.3 presents the quantitative results of the questionnaire using univariate and multivariate analysis. The final section presents a thematic analysis together with the codes and themes that were generated from analysis of free text responses to open questions on the questionnaire.

#### **4.1 Participation Rate**

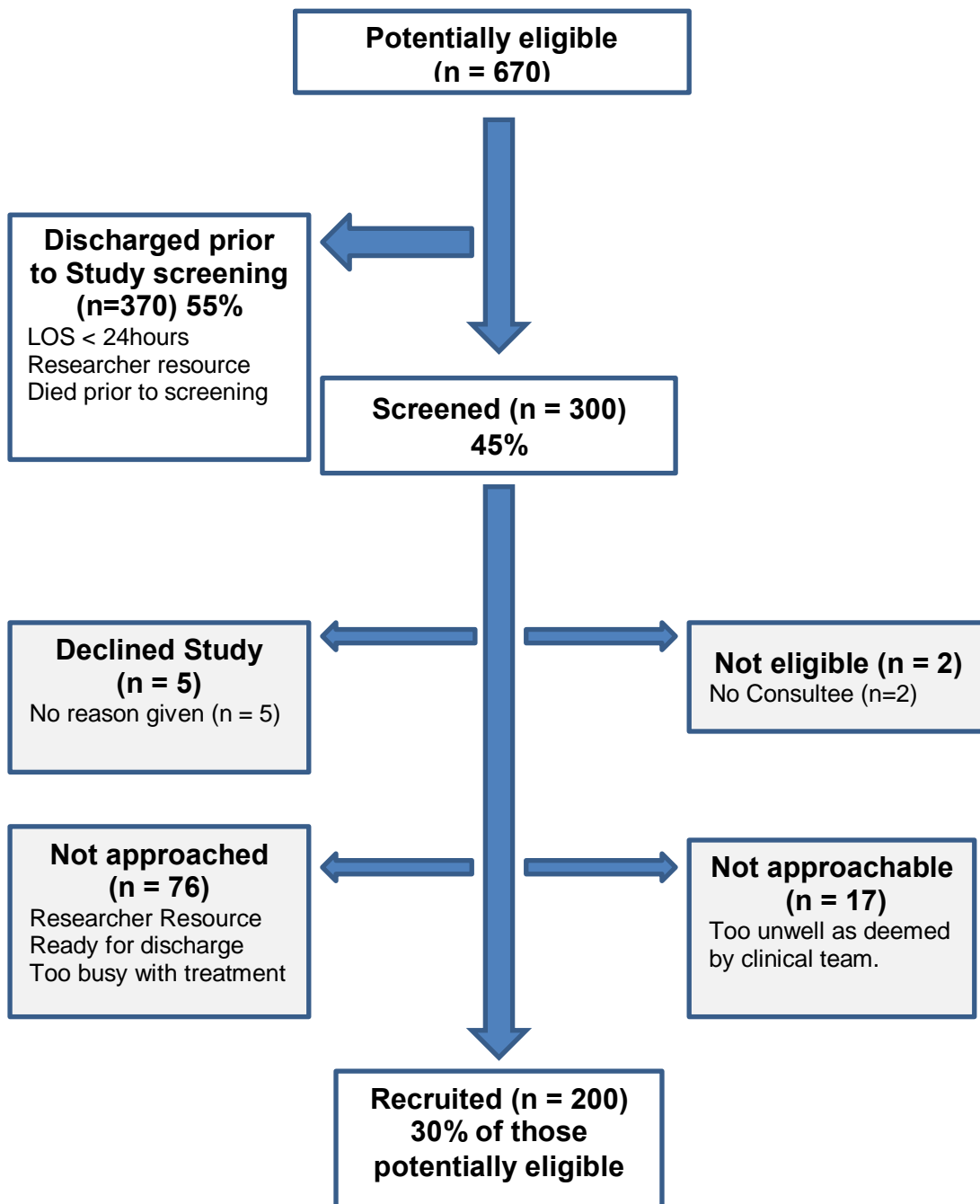
##### 4.1.1 Site Recruitment Figures

During the study recruitment period, 300 patients were screened for eligibility for the study. Of these, 100 were either not approached for study participation or declined to participate. Of the overall stroke admissions (n=670), 18% (n=120) were deemed too unwell to approach at that time, either by clinical team or having died prior to screening. 13% (n=87) of the overall stroke admissions died prior to discharge.



Of the 300 screened admissions, five direct approaches were declined by potential respondents without a reason being stated and a further two did not have a consultee available (and were not able to consent to the study themselves). The remaining 76 were either imminently being discharged, too busy with treatment or missed by a lack of researcher resource. Those with a short length of stay (LOS) of <48 hours, did not meet the criteria for an acute study and are included in those missed by the researcher. (Figure 4.1: Consort diagram of recruitment).

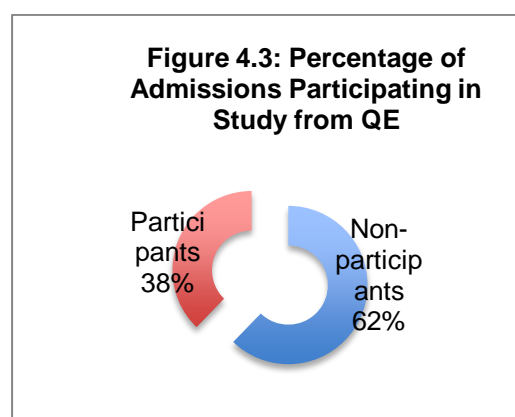
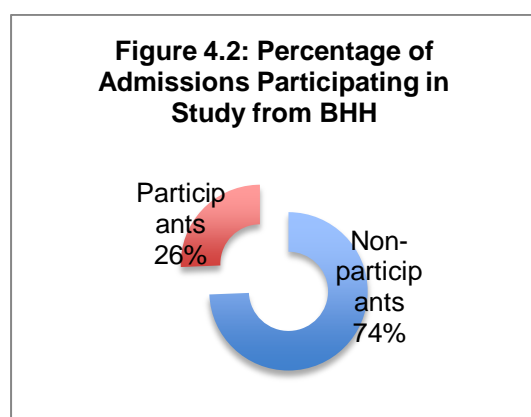
**Figure 4.1: Consort diagram of recruitment to the study**



Therefore, from 300 patients screened for inclusion, 207 (69%) were approached of whom 200 respondents (67%) from two Foundation Trust Hospitals in the West

Midlands: Birmingham Heartlands Hospital (112 participants), and the Queen Elizabeth Hospital (88 participants) completed the questionnaire. Recruitment lasted for 15 months in total with an overlap of both sites actively recruiting simultaneously in the final 7 months.

Respondents comprised 112/437 (26%) stroke admissions at the Heart of England NHS Foundation Trust - Birmingham Heartlands Hospital (BHH) (Figure 4.2) over a period of 15 months and 88/233 (38%) stroke admissions at University Hospitals Birmingham, Queen Elizabeth (QE) (Figure 4.3) over a shorter recruitment period of 7 months. The denominators comprised admissions coded using International Classification of Disease ICD codes I61, I63 and I64 (RCP 2006).



The time of stroke onset was known in 141 (70.5%) cases. For the majority of these (n=94), admission was outside of office hours (9-5) and at weekends. A third of respondents with a known onset time (n=47 of 141) had the stroke event during normal office hours.

26 out of 200 respondents (13%) woke in the morning with a stroke ('wake-up stroke'), having gone to bed the night before, (last seen) well. Of these, 19 (73%)

were able to self-consent to research whilst seven had to use a consultee. In terms of stroke severity, of the 26 'wake-up' stroke patients, four were rated on NIHSS as severe. This was increased slightly to six when 'severe' was self-rated for (perceived) stroke severity.

#### 4.1.2 Decision-maker

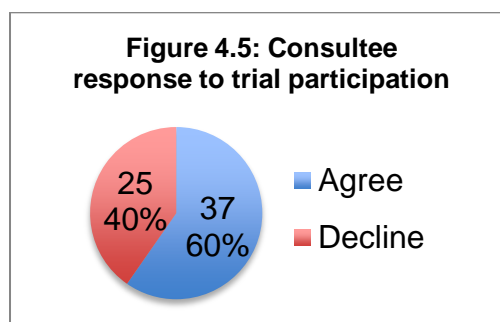
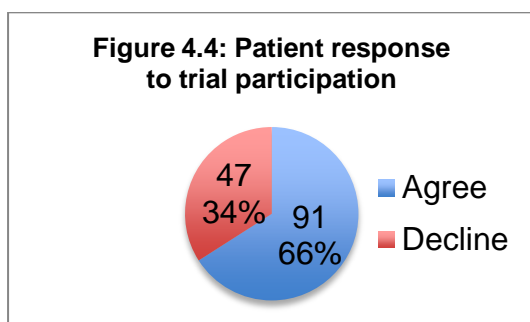
Consent for study participation was made by stroke patients themselves in 138 out of 200 cases (69%). The remaining 62 patients had a consultee as proxy decision-maker who responded to the questionnaire on their behalf (14 spouses, 40 children, 1 sibling and 7 others).

All 200 respondents considered taking part in a clinical trial (real or mock) alongside completing the questionnaire. A real clinical trial was offered to 72 respondents (36%) whilst 128 (64%) considered a mock, hypothetical trial.

Consultees were more likely to be decision-makers in more severe strokes: 84% (n=38) as rated as severe on NIHSS. However, this was not found to be the same for severe stroke as rated by self-perceived severity - where the majority of patients were able to consent themselves (53%) and consultees were the decision-makers in 47% (n=30) of cases.

128 (68%) respondents agreed to participate in a clinical trial of any sort (real or mock) with the remaining 72 (36%) declining any clinical trial. Patients who were able to consent for themselves were more likely than consultees to agree to trial

participation (as shown in Figure 4.4 and 4.5 below), although this difference was not statistically significant ( $X^2 = 0.48$ ,  $p=0.488$ ).



The time given for decision-making in an acute trial was determined by the protocol in a real trial and a comparative recruitment window for the mock. These followed the timings of the acute phase noting any delay in hospital presentation. Overall, 85.5% of respondents ( $n=171$ ) deemed that the amount of time they had been given was 'enough' and 'more than enough' time to make a decision on participation. Of these respondents, 69% ( $n=118$  of 171) agreed to trial participation. Eighteen respondents reported 'not enough time' to consider the trial but six of these respondents still agreed to participation. Five respondents reported 'barely enough time' and four of these still agreed to participation (summarised in Table 4.1).

**Table 4.1 Perception by respondent of time to consider a Clinical trial**

Time to consider ( $n= 200$ ) *		Agreed to a trial n	Declined a trial n
Not enough (18)	9%	6	12
Barely Enough (5)	2.5%	4	1
Enough (146)	73%	98	48
More than Enough (25)	12.5%	20	5

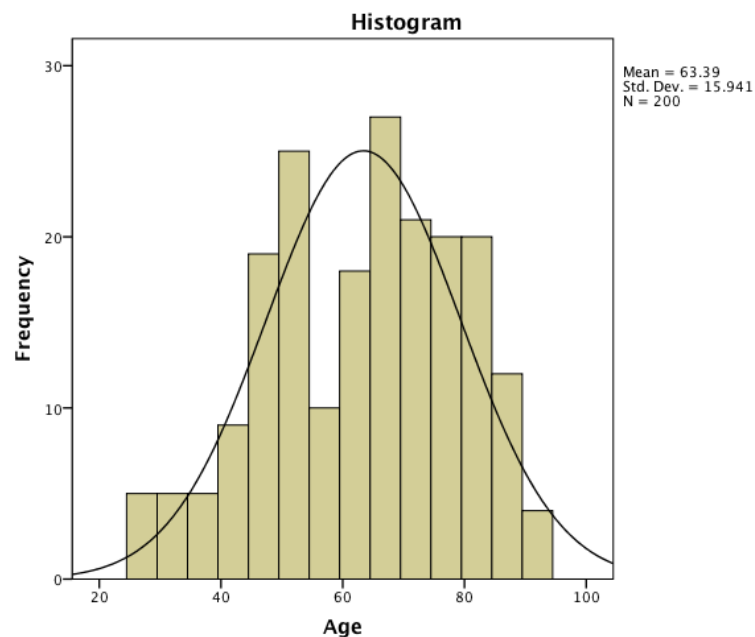
\* Percentages may not total 100 due to missing responses

## 4.2 Participant Characteristics

A summary of participant demographic and clinical characteristics is shown in Table 4.2. There was an even split in the gender of the respondents. 128 respondents agreed to participate in a clinical trial out of 200 respondents in this study. Of those, male respondents were found to be slightly more inclined to agree than their female counterparts (68 vs 60). Stroke patients were able to decide for themselves in 138 cases (69%) - with an average age of 66 years.

The age of the decision-maker was noted to follow a 'normal' distribution graph (Figure 4.6). The distribution of age range of the full 200 respondents can be viewed on the histogram below (figure 4.5). Participant ages ranged from 28 to 92 years with a mean age of 63.4 years. Decade groupings for analysis by age were used. No statistical significance was found between age and trial participation.

**Figure 4.6: Histogram of Age range distribution of respondents**



Almost half of the respondents (45% n=90) did not know the type of stroke event that had occurred (unable to recall personal knowledge) and no significant difference was found between stroke type and the likelihood that a respondent agreed or declined to participate in a trial.

No significant differences were found between any of the demographic or clinical characteristics and the likelihood that a respondent agreed or declined participation in a trial, with the exception of perceived severity of stroke. Participants in the study who perceived the severity of stroke to be either moderate or severe were significantly more likely to agree to participation in a trial than those who perceived the stroke to be mild.

**Table 4.2 Summary of Characteristics Associated with Trial Participation**

<b>Participant Characteristic (n= 200) *</b>	<b>Agreed to a trial n</b>	<b>Declined a trial n</b>	<b>p value (X<sup>2</sup> test for association)</b>
<b>Gender</b> Female (99) 49.5% Male (101) 50.5%	60 30% 68 34%	39 20% 33 17%	0.399
<b>Age group (Yrs.)</b> <50 21.5% 50-59 17.5% 60-69 22% 70-79 20.5% >/=80 18%	30 15% 24 12% 25 13% 29 15% 20 10%	13 7% 11 6% 19 10% 12 6% 16 8%	0.268
<b>Ethnicity</b> White (164) 82% Non-white (36) 18%	106 53% 22 11%	58 29% 14 7%	0.842
<b>Educational level</b> A level/GCSE and below (161) 80.5% Degree and Postgraduate (39) 19.5%	101 51% 27 14%	60 30% 12 6%	0.566
<b>Deprivation quartile</b> Quartile 1 - Most affluent (8) 4% Quartile 2 - Less affluent (34) 17.5% Quartile 3 - More deprived (45) 23% Quartile 4 - Most deprived (107) 55%	4 2% 18 9% 32 16% 71 37%	4 2% 16 8% 13 7% 36 19%	0.212
<b>Severity of stroke (perceived)</b> Mild (74) 37% Moderate (54) 27% Severe (64) 32% Not sure (8) 4%	39 20% 36 18% 45 23% 8 4%	35 18% 18 9% 19 10% 0	0.031
<b>Stroke type (personal knowledge)</b> Ischaemic (77) 39% Bleed (31) 15.8% Don't know (88) 44.9%	48 24% 16 8% 61 31%	29 15% 15 8% 27 14%	0.249
<b>Trial type considered</b> Real (72) 36% Mock (128) 64%	62 31% 66 33%	10 5% 62 31%	

\*Percentages may not total 100 due to missing responses



#### 4.2.1 Ethnicity

The 2011 census showed that non-white minority ethnic groups comprised 14% of the UK population (Office for National Statistics, 2011). This proportion was the same across the West Midlands region, but this study saw a higher proportion of respondents with non-white ethnicity than both the national and regional average (18%, n=36). A comparison of this variation is shown in Table 4.3.

**Table 4.3 Comparison of Ethnic Diversity**

Ethnicity	England&Wales* 2011 (%)	WestMidlands* 2011 (%)	This Study 2012 (%)
White	87	86	82
Mixed / Multiple Ethnic Groups	2	1	1
Asian: Indian	3	4	3
Asian: Pakistani	2	4	8
Asian: Bangladeshi	1	1	1
Asian: Other	1	1	4
Black: African	2	1	1
Black: Caribbean	1	2	4
Black: Other	0	-	-
Other Ethnic Groups	1	-	-

\*Source: Office for National Statistics, 2011 Census data from KS201EW.

#### 4.2.2 Educational level

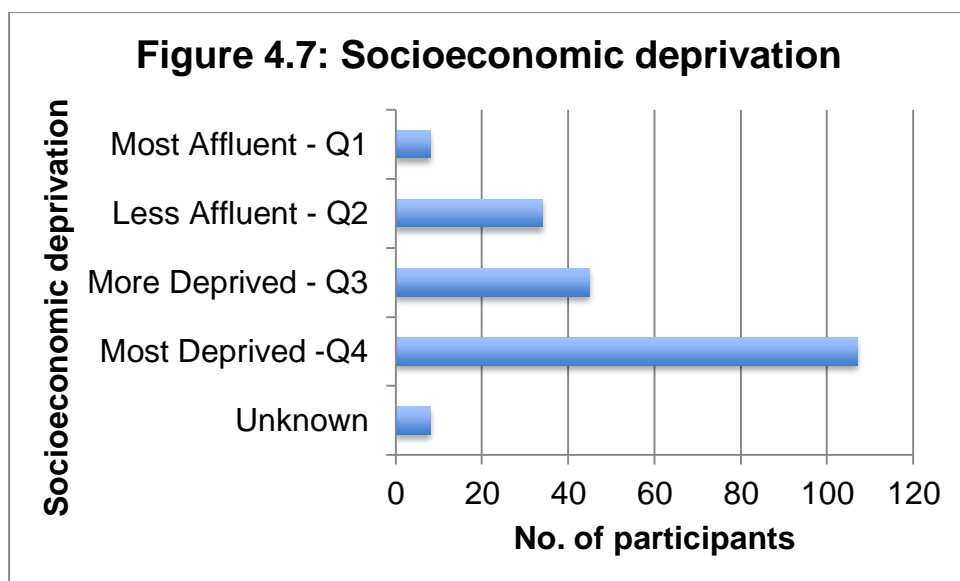
The highest level of taught education received by respondents was recorded within five sub categories ranging from: no formal qualifications (including school leavers certificate); GCSE / CSE / O level; A level or equivalent; Degree or vocational qualifications and postgraduate studies. For comparison of proportions analysis, a binary grouping was created, comparing those with degree or higher-level education to those with A-Level/GCSE level education and below. No significant association

was found between an individual's level of education and whether or not they agreed to participate in a trial.

#### 4.2.3 Socioeconomic deprivation

Deprivation quartiles were derived using the online tool GeoConvert. This tool uses residential postcodes to associate each individual with their specific electoral ward, with each ward (n=32,482 across England) ranked according to its position in the 2010 Index of Multiple Deprivation (IMD). This allows each individual to be assigned a deprivation quartile on the basis of his or her place of residence. Quartile 1 represents the most affluent group, and quartile 4 the most deprived group.

Six of the 200 study respondents could not be assigned a deprivation quartile. Of the remaining 194 respondents, over half (n=107) lived in areas within the most deprived quartile (Figure 4.7). No association was found between trial participation and socioeconomic deprivation.

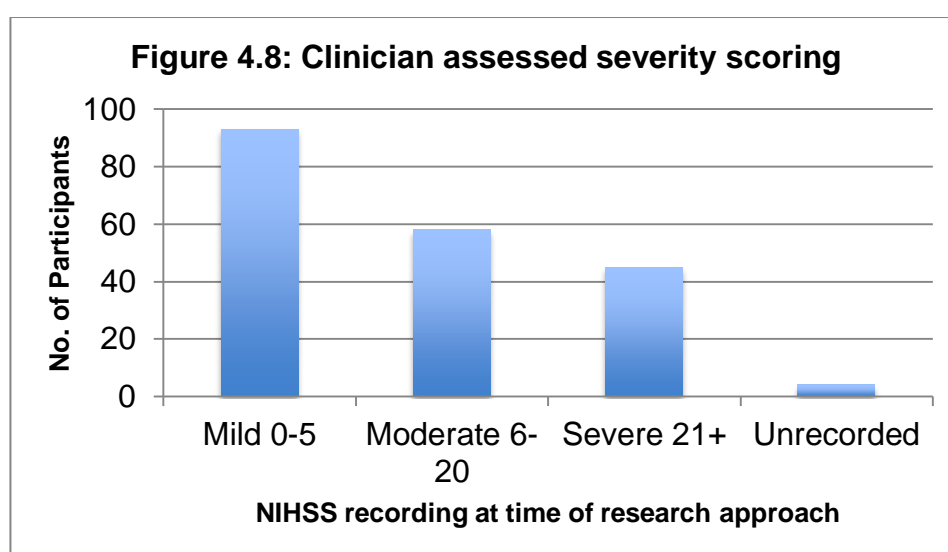


#### 4.2.4 Stroke Severity measures

Stroke severity was measured using the National institute of Health Stroke Scale (NIHSS) at the time of the research approach either prospectively or extracted from a patient's medical records +/- one day either side of that date.

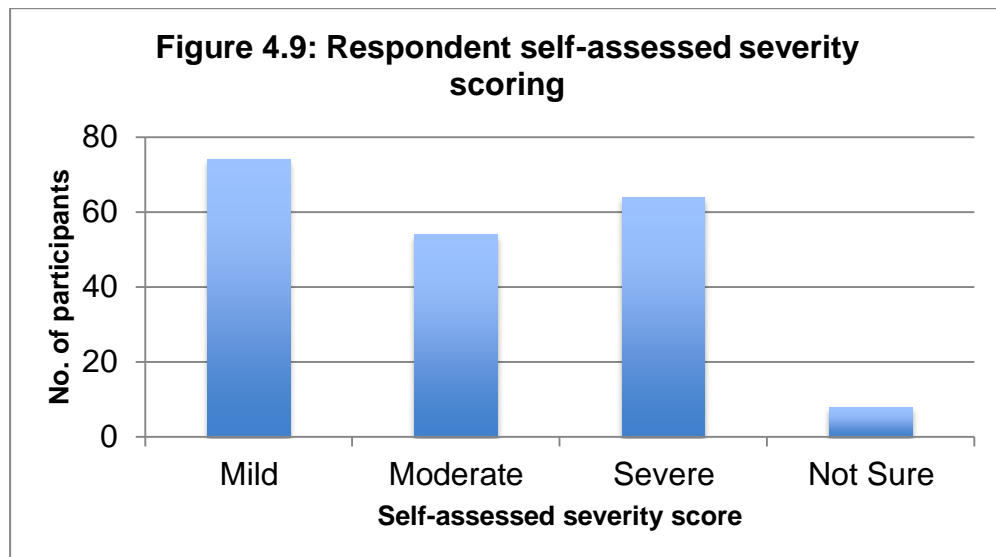
This was compared to a self-assessed severity measure made by the person giving consent to the study (patient or consultee). Figure 4.8 shows the distribution of NIHSS scoring recorded for patients as part of this study, in comparison to Figure 4.9 that shows the distribution of self-assessed stroke severity by respondents (decision-makers).

In Figure 4.8, 93 (46.5%) patients were assessed as having had a mild stroke (NIHSS 0-5), 58 (29%) were assessed as moderate (NIHSS 6-20) and 45 (22.5%) were assessed as severe (NIHSS >20). Four respondents did not have a NIHSS score recorded.



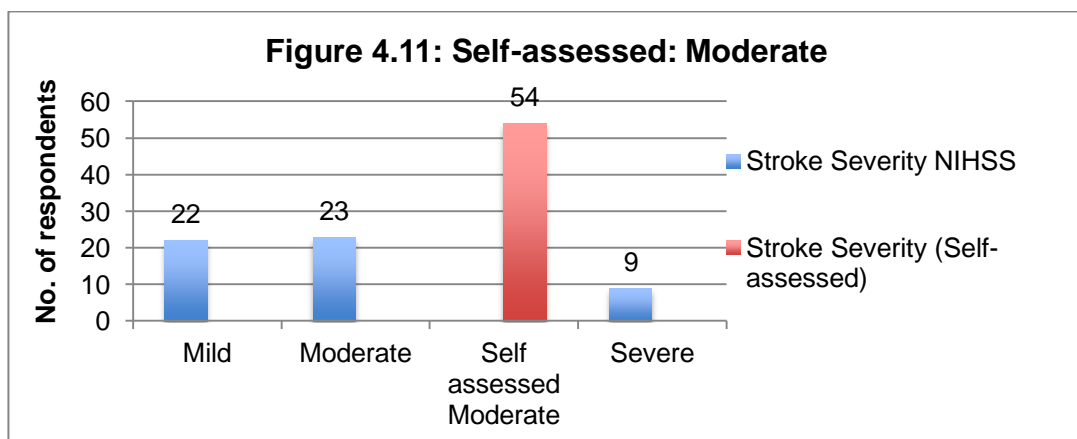
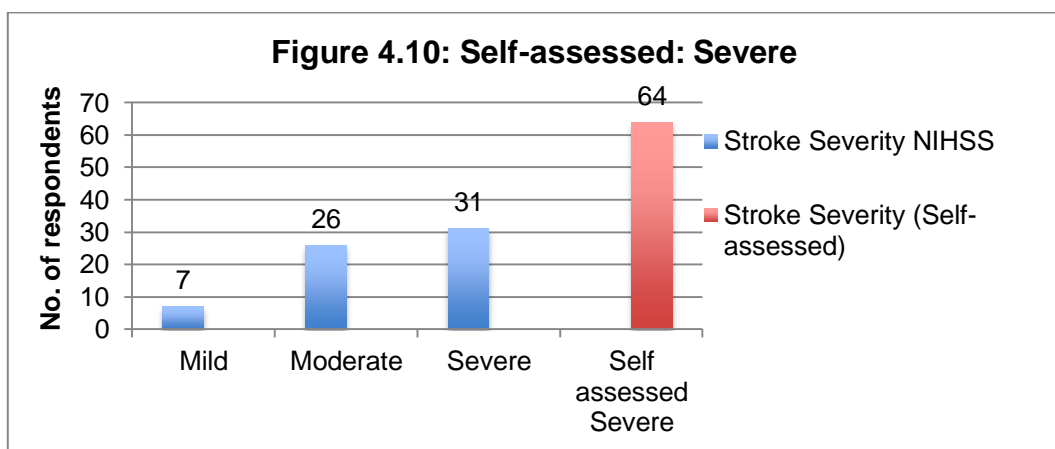
\*Mild, moderate and severe categories of NIHSS scoring defined by Ver Hage (2011).

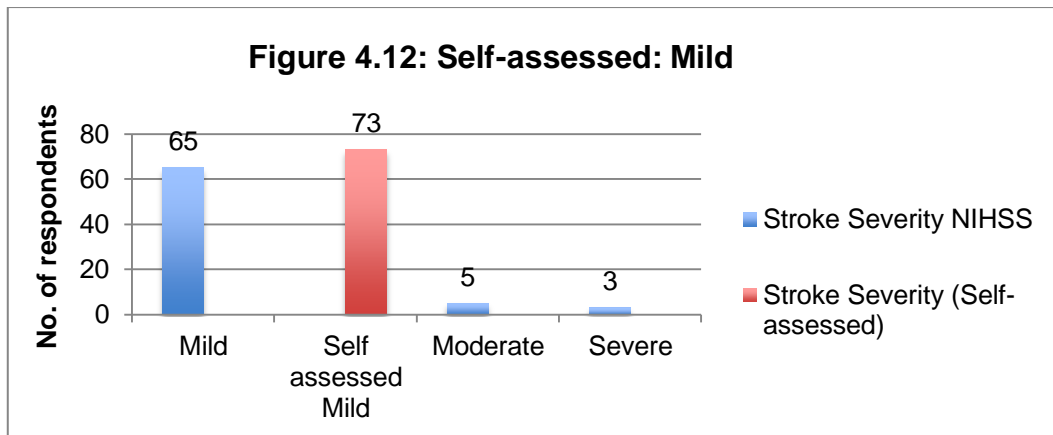
By comparison (in Figure 4.9), 74 (37%) patients were self / consultee rated as having had a mild stroke, 54 (27%) were self / consultee rated as moderate and 64 (32%) were self / consultee rated as severe. Eight respondents were unsure as to how to rate the current condition.



Although respondents were more likely to view the stroke as more severe than the NIHSS score, there was no statistically significant difference between clinician and self-assessed stroke severity scoring although the p value approaches significance ( $X^2 = 5.58$ ,  $p=0.061$ ). There was no statistically significant difference between whether or not a respondent agreed to participate in a trial on the basis of NIHSS scoring. However, respondents who self-rated stroke severity as moderate or severe were significantly more likely to participate in a trial than those who considered the stroke to be mild ( $X^2 = 9.87$ ,  $p=0.031$ ). The likelihood of agreeing to participate in a trial was increased as perceived stroke severity increased using Chi square for trend ( $X^2 = 4.674$ ,  $p=0.031$ ).

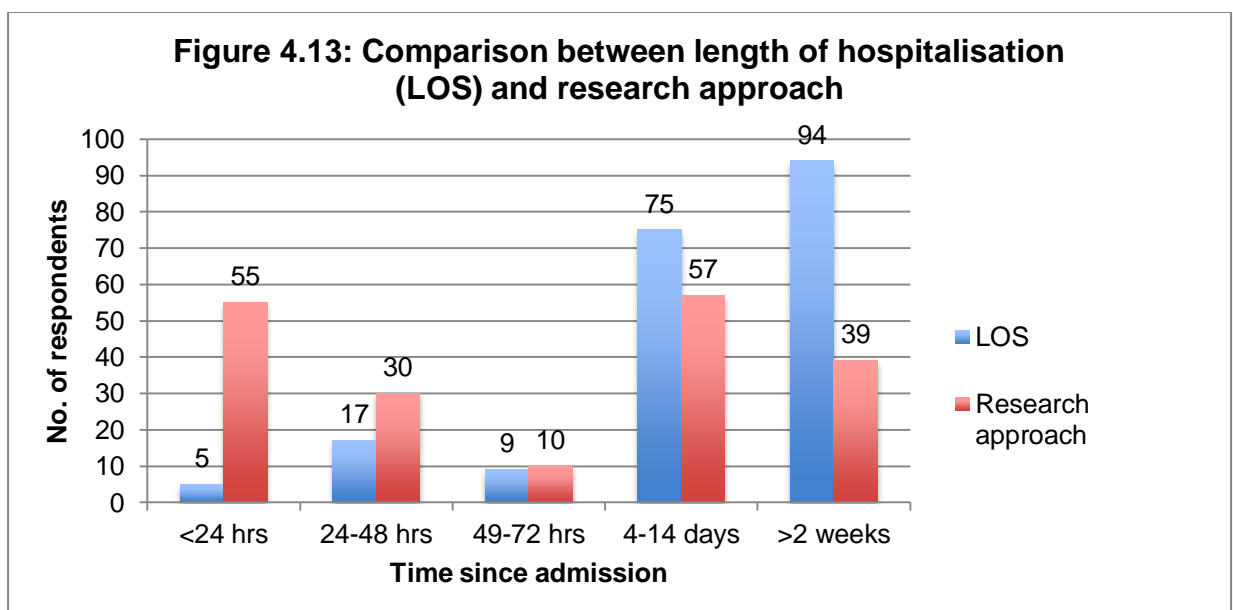
From the data, some patients reported stroke severity as severe and yet clinician scoring on NIHSS was mild. This is illustrated in Figures 4.10-4.12. The red column represents the total numbers of respondents rating themselves as that particular severity. The blue columns alongside are not additional respondents but a disaggregation of the tall red bar. For each self assessed severity (red, tall bar), the corresponding NIHSS rating is shown (blue bars).





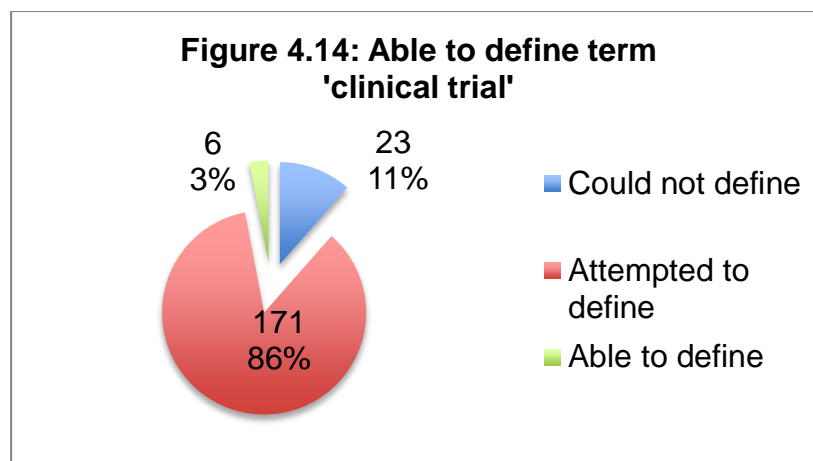
#### 4.2.5 Length of Hospitalisation

A comparison was made between the timing of the research approach and the length of time a patient remained in hospital (Figure 4.13). 42% of respondents were approached within 48 hours of admission (n=85). A delayed approach (i.e. approached more than 48 hours after admission) occurred where respondents were initially 'too unwell', awaiting a consultee, busy with treatment, delay in presentation and out of hours presentation in some cases i.e. over a bank holiday weekend.



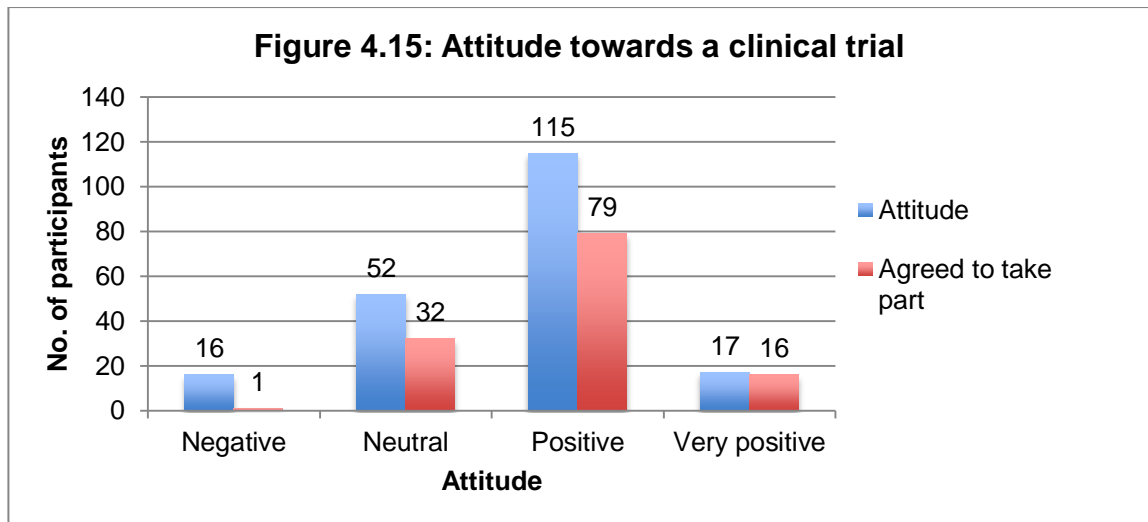
### 4.3 Questionnaire responses

At the beginning of the survey, respondents were asked to define the term 'clinical trial'. Three per cent were able to define the term in line with the DH official definition. Eighty-five per cent made an attempt using one-two key words from the official DH definition. Eleven per cent (n=23) were unable to proffer any answer as highlighted in Figure 4.14.



#### 4.3.1 Attitudes and opinions

Seventeen respondents (8.5%) rated their general attitude to clinical trials as being 'very positive', and 115 (57.5%) rated their attitude as 'positive'. Of these 132 patients who rated their attitude as positive and very positive, 94 (71%) agreed to participate in a trial. A neutral attitude was expressed by 26% (n=52), although over half of these (61.5%) still agreed to trial participation. A negative attitude was reported by 16 respondents (8%), although one of these went on to agree to a trial (Figure 4.15).

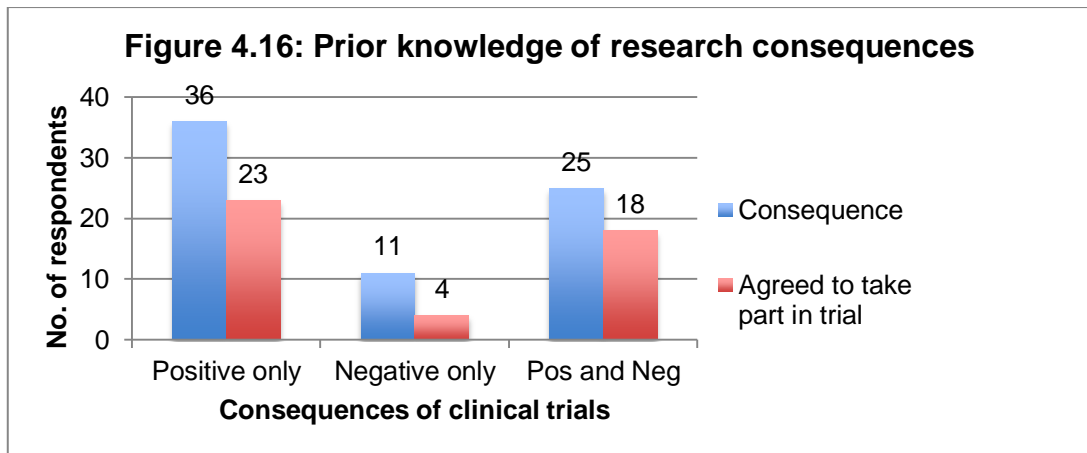


Attitude to clinical trials was strongly associated with participation in the clinical trial ( $p$  for trend  $<0.0001$ ). Respondents who had a positive or very positive attitude to clinical trials were significantly more likely to participate in a trial than those who had a neutral or negative attitude (74% vs 26%,  $p<0.0001$ ).

#### 4.3.2 Prior knowledge of research consequences

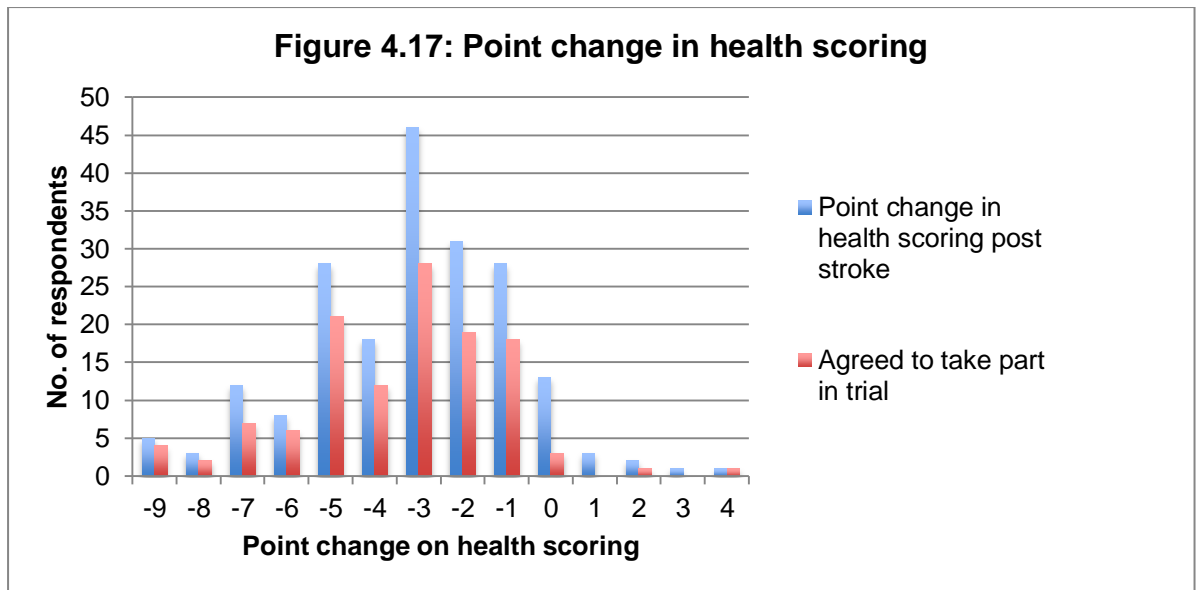
Over one third of respondents ( $n=72$ ) were aware of having heard a consequence of participating in a clinical trial (whether positive, negative or both) as shown in Figure 4.16. Overall, 18% ( $n=36$ ) of total respondents were aware of having heard positive consequences of clinical trials previously from an outside source (i.e. media, newspapers or friends) whilst 5.5% ( $n=11$ ) reported having heard negative consequences from an outside source. 12.5% ( $n=25$ ) of respondents were aware of having heard both positive and negative consequences of clinical trials previously.



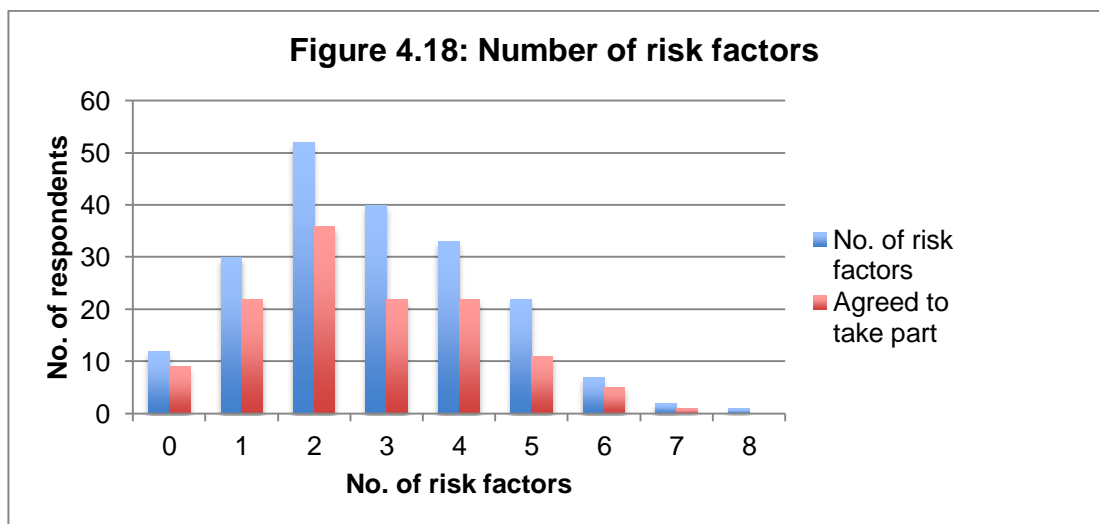


### 4.3.3 Health Status

Respondents were asked to score their level of health pre-stroke and post event (at the time of the study approach) with a top score of 10 reflecting excellent health and a drop in points denoting a decline in perceived health status following stroke. A drop in self-reported health scoring post stroke compared to their pre-stroke rated health was reported by 179 respondents – with a 1 point drop represented as -1 on Figure 4.17 up to a 9 point drop in health scoring, represented as -9; 13 respondents reported the same level of overall health (a zero point drop) and 7 reported an improvement, – citing the treatment of co-morbidities (represented as a positive number on the horizontal axis). Negative numbers on the horizontal axis correspond to the number of points dropped in health scoring since stroke event. The mean and mode was a 3-point drop in overall health state due to stroke (52%) as seen in Figure 4.17.



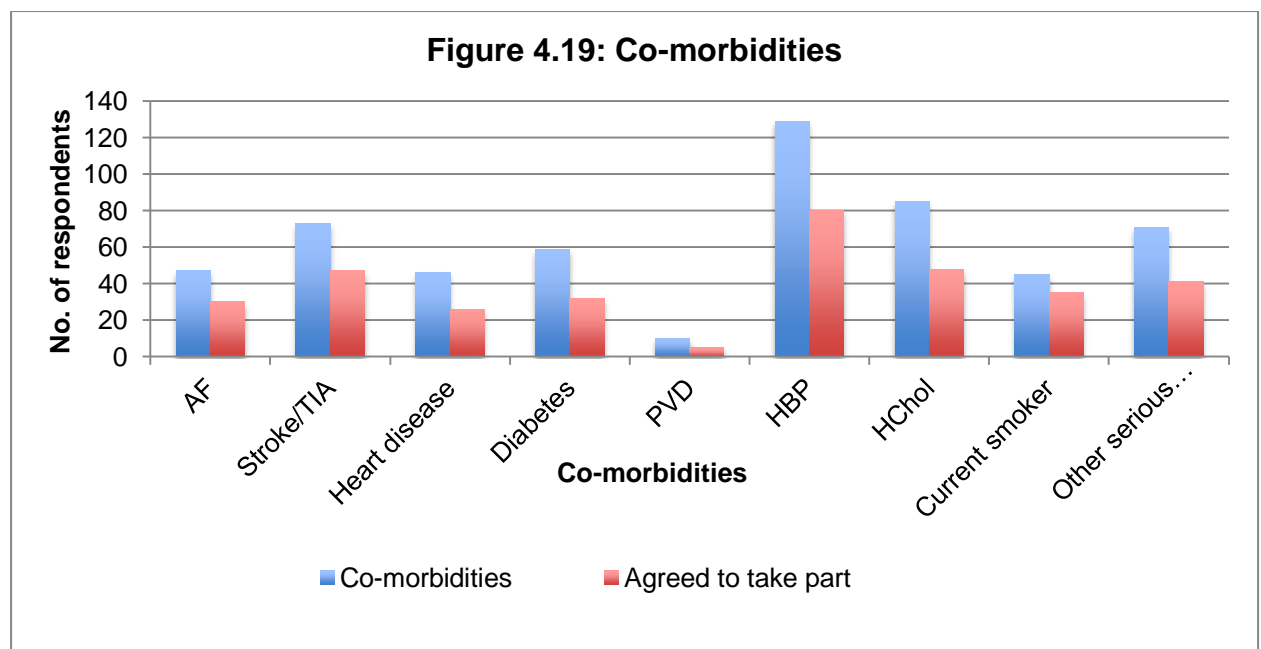
188 respondents had risk factors associated with stroke in their past medical history with two risk factors being most common. Three quarters of the respondents had at least two risk factors increasing their risk of having a stroke or second stroke (Figure 4.18).



The most common co-morbidity was high blood pressure (HBP). The proportion of respondents with HBP that agreed to take part in a clinical trial was higher than

expected in comparison to other co-morbidities although this was not statistically significant ( $p=0.322$ ). Of the total respondents with high blood pressure ( $n=129$ ), 80 agreed to take part in a trial (Figure 4.19).

In addition to one of the real trials being a blood pressure drug trial, the mock trial was also a blood pressure, drug trial and was considered by 128 respondents of the total 200.



12% of respondents ( $n=24$ ) had been approached about taking part in research before (prior to this admission). Of these 24 approached, 20 had consented and participated in a research trial before. Of these 20, half ( $n=11$ ) agreed to a clinical trial as part of this study.

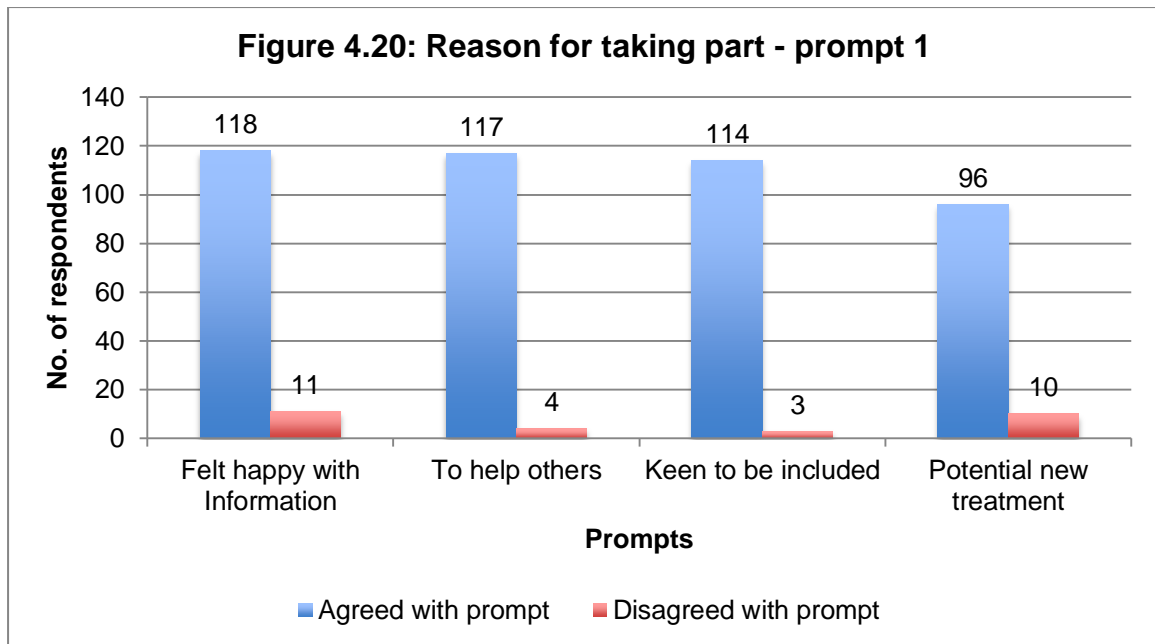
#### 4.3.4 Decision

Sixty per cent (n=120) of respondents made a decision regarding participation without consulting anyone else. Of these, almost half (43%, n = 52) stated that they would have liked to have discussed it with a family member if the opportunity had been available.

In terms of what influenced people in their decision as to whether or not to participate in a trial, 'self-determined decision' was cited as the biggest influence on decision to take part, with 174 respondents (87%) citing that 'self' was a 'strong' or 'very strong' influence on their decision-making. The next most commonly cited influence on decision-making was family or friends, which was mentioned by 66 respondents as being a 'strong' or 'very strong' influence.

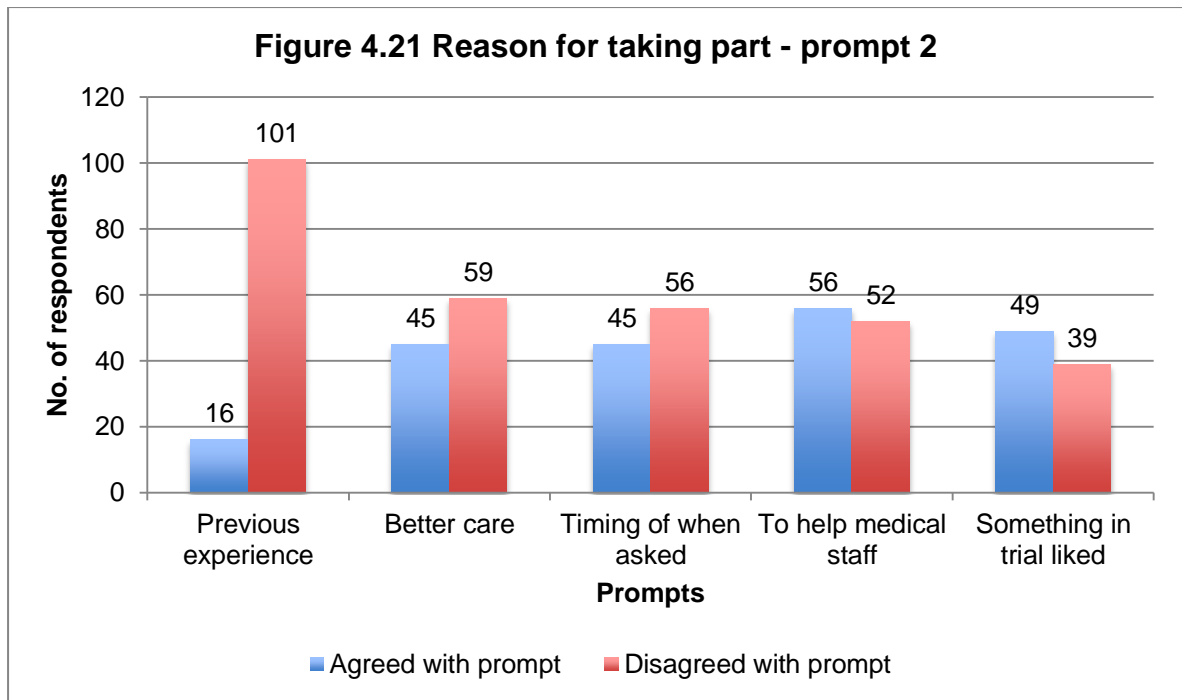
The questionnaire included some open questions in which respondents were asked to elaborate on the reasoning behind their decision-making on accepting or declining trial participation. These responses to open questions were analysed thematically (see section 4.5). Subsequently, prompts as to the reasoning behind the decision to participate were categorised (Kasner et al 2009; NIH 2012, 2015; Healthtalk 2012, 2015)

Figures 4.20 and 4.21 highlight the prompts used following agreement to participate in a trial. The majority of those agreeing to participate in a trial, did so based on feeling happy with the information, to help others, keen to be included and potential for a new treatment.



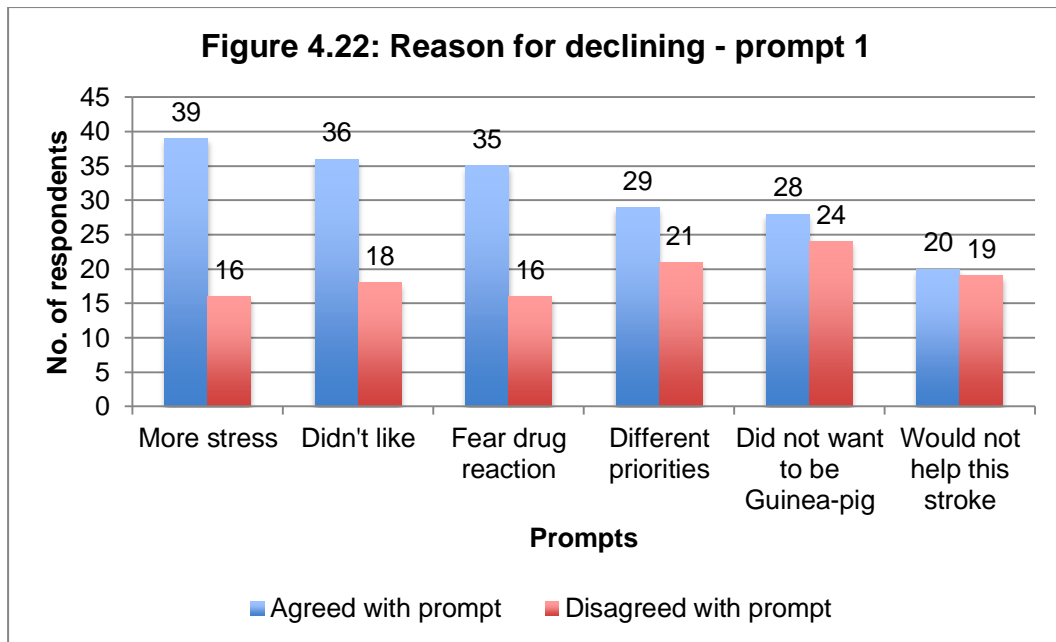
The majority of respondents agreeing to take part in a trial, did not agree based on previous experience (which correlates to the small number (n=24) of those respondents having considered research prior to admission).

Respondents were split more evenly on prompts regarding possibility of better care, timing of when asked, to help medical staff who asked them and something in the trial that was liked (Figure 4.21).

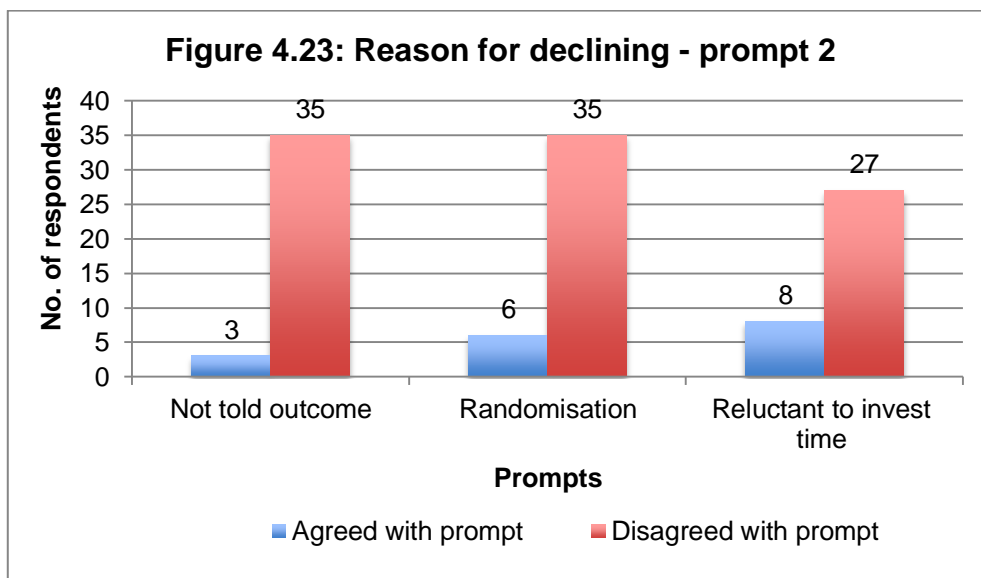


Figures 4.22-4.24 highlight those prompts used following a decline to participate in a trial. More respondents declined a trial citing it to add more stress, there was something in trial they didn't like, a fear of a drug reaction or adverse reaction and having different priorities at the time of asking.

A much closer split (almost 50:50) was found with those declining due to not wanting to be a 'guinea-pig' (self-perceived) and that it might not help the current stroke (Figure 4.22).

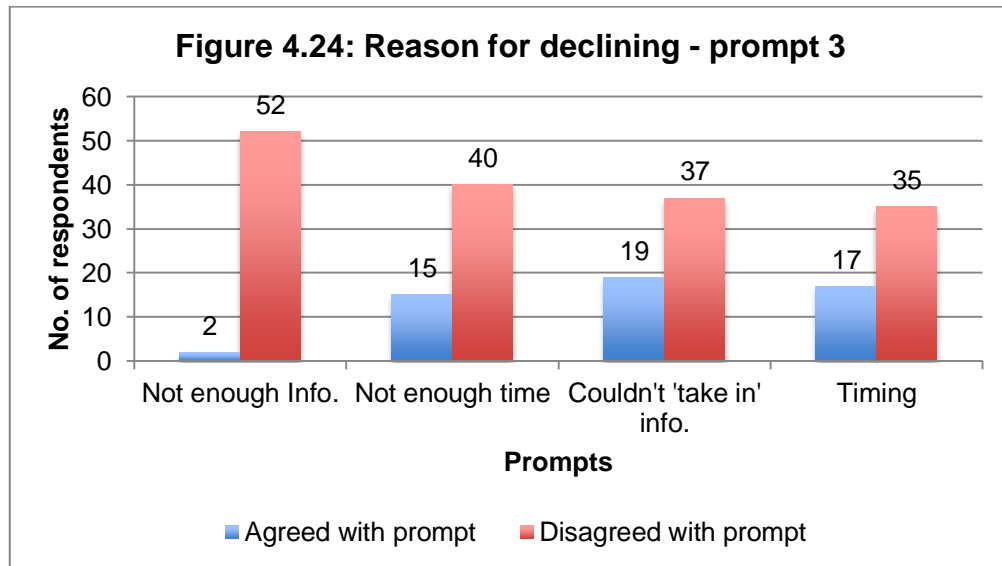


For those respondents who declined participation in a trial, the majority did not decline because of not being told the outcome of the research, randomisation or reluctance to invest the time (Figure 4.23).



For those respondents who declined participation in a trial, more respondents stated they did not decline due to reasons such as not having enough information, enough

time to make a decision, that they couldn't take in the information or the timing they were asked (although a small numbers did quote these on prompting as possible reasons (n=15, 19 and 17 respectively – Figure 4.24).



Of those declining a trial, three respondents were happy to agree to participation at a later date citing wrong timing earlier on in admission when originally approached as they 'did not know what was going on'.

One consultee had a choice of two real trials and reported: "...a terrible dilemma in the choice, more than just the research – which was bad enough". The consultee went on to choose the second trial involving interventional scans (real trial) stating clear rationale as to declining the first due to specific interventional drugs, "... I don't like the thought of agreeing for him to have medication, I don't like medication". (Consultee – Patient's daughter, aged 33 years).



#### **4.4 Univariate and multivariate analyses**

Univariate and multivariate binary logistic regression analyses were carried out to assess which variables were associated with agreement to participate in a trial (real or mock) – the result of which are summarised in Tables 4.4 and 4.5 respectively.

##### **4.4.1 Univariate analysis**

Respondents who perceived their stroke as mild were around half as likely to agree to participate in a trial than patients who perceived their stroke as severe (odds ratio (OR) 0.47, 95% confidence interval (CI) 0.23-0.95;  $p = 0.036$ ). Respondents who were offered a real trial were almost six times more likely to participate in a trial than those who were offered a mock trial. (OR 5.73, 95% CI 2.70-12.17;  $p < 0.0001$ ).

**Table 4.4 Univariate analyses**

<b>Variable</b>	<b>Variable</b>	<b>P value</b>	<b>Odds ratio</b>	<b>95% CI</b>
Gender	Male	0.277	1.38	0.77 to 2.47
	Female	Reference	-	-
Age	<50	0.148	2.00	0.78 to 5.11
	50-59	0.335	1.60	0.62 to 4.16
	60-69	0.910	1.05	0.43 to 2.56
	70-79	0.170	1.93	0.76 to 4.95
	80+	Reference	-	-
Ethnicity	White	0.842	1.08	0.51 to 2.30
	Non-white	Reference	-	-
Education	Lower attainment	Reference	-	-
	Higher attainment	0.336	1.48	0.67 to 3.29
Deprivation	Affluent	0.356	0.51	0.12 to 2.15
	Less affluent	0.220	0.61	0.28 to 1.35
	More deprived	0.567	1.25	0.58 to 2.67
	Most deprived	Reference	-	-
<b>Perceived stroke severity</b>	Mild	<b>0.036</b>	0.47	0.23 to 0.95
	Moderate	0.781	0.89	0.41 to 1.97
	Severe	Reference	-	-
NIHSS stroke score	Mild	0.789	1.11	0.53 to 2.29
	Moderate	0.345	1.48	0.66 to 3.35
	Severe	Reference	-	-
Respondent type	Patient	0.358	1.34	0.72 to 2.48
	Consultee	Reference	-	-
<b>Trial offered</b>	Real	<b>&lt;0.0001</b>	5.73	2.70 to 12.17
	Mock	Reference	-	-

\*Bold entries denote statistically significant p values

#### 4.4.2 Multivariate analysis

Findings from the multivariate analyses are highlighted in Table 4.5. The following univariate variables were included in the model: gender, age, ethnicity, education, deprivation, perceived stroke severity, NIHSS stroke score, respondent type and trial offered.

Once other variables had been controlled for, ethnicity was statistically significant with respondents of white ethnicity being around three times more likely than non-white respondents to agree to participate in a trial (OR 3.29, 95% CI 1.03-10.51;  $p = 0.045$ ).

Respondents whose stroke severity was mild on NIHSS scoring were significantly more likely than those who were severe on the NIHSS to agree to trial participation (OR 4.97, 95% CI: 1.10-22.51;  $p = 0.037$ ), although this result should be interpreted with caution due to small numbers and the large confidence interval.

Similarly, as found in the univariate model, the type of trial that a respondent was offered was a significant predictor of their likelihood of agreeing to participate. Respondents offered a real trial were almost ten times more likely to agree to participate than those who had been offered a mock trial (OR 9.45, 95% CI: 3.70-24.16;  $p < 0.0001$ ).

**Table 4.5 Multivariate analyses**

<b>Variable</b>	<b>Variable</b>	<b>P value</b>	<b>Odds ratio</b>	<b>95% CI</b>
Gender	Male	0.302	1.51	0.69 to 3.30
	Female	Reference	-	-
Age	<50	0.382	1.74	0.50 to 6.02
	50-59	0.770	1.20	0.35 to 4.08
	60-69	0.532	0.69	0.22 to 2.19
	70-79	0.148	2.40	0.73 to 7.85
	80+	Reference	-	-
<b>Ethnicity</b>	White	<b>0.045</b>	3.29	1.03 to 10.51
	Non-white	Reference	-	-
Education	Lower attainment	Reference	-	-
	Higher attainment	0.156	2.03	0.76 to 5.41
Deprivation	Affluent	0.602	0.57	0.70 to 4.67
	Less affluent	0.061	0.37	0.13 to 1.05
	More deprived	0.476	1.38	0.57 to 3.37
	Most deprived	Reference	-	-
<b>Perceived stroke severity</b>	Mild	<b>0.001</b>	0.12	0.04 to 0.42
	Moderate	0.055	0.34	0.12 to 1.03
	Severe	Reference	-	-
<b>NIHSS stroke score</b>	Mild	<b>0.037</b>	4.97	1.10 to 22.51
	Moderate	0.250	2.17	0.58 to 8.13
	Severe	Reference	-	-
Respondent type	Patient	0.999	1.00	0.32 to 3.09
	Consultee	Reference	-	-
<b>Trial offered</b>	Real	<b>&lt;0.0001</b>	9.45	3.70 to 24.16
	Mock	Reference	-	-

\*Bold entries denote statistically significant p values

## 4.5 Thematic analysis

Of those respondents agreeing and declining a trial, the factors stated in the open questions for decision-making (prior to any prompt) were analysed thematically.

### 4.5.1 Agreed to participate

During the thematic analysis, codes emerged for respondents agreeing to participate in a clinical trial (64% of respondents) and from these, two common themes arose:

- Altruism - of self and for others in the future with altruism expressed as well as self-concern.
- Ambivalence - within which inevitability was also cited.

#### 4.5.1.1 Altruism

Respondents who were happy with the trial and keen to take part were included in this theme. An example of responses included the following:

*“...was so pleased to do it, to help people the same as me”.* (Patient, aged 65 years – became very emotional);

*“...if it will do me any good...”* (Patient, aged 83 years).

Altruism for the greater good and wanting to help others in the future was cited by respondents in a large number of cases, in isolation and amongst a group of reasons given for a decision to participate. Self-concern incorporated a rationale for decision-making of better care and respondents highlighted ‘extras’ in a trial as being influential in reasoning behind the decision i.e. an ultrasound scan being available when it is not part of routine clinical care and a perception of receiving more

monitoring by the hospital if choosing to take part in research trial. An example of responses included the following:

*“...Information from nurse was very positive. Keen for anything that would help him, that he would be monitored, regular scans, less likely to get clots because of it...”*

(Consultee, aged 52 years);

*“...thought it would help me and others in a situation like mine at a later stage in the future. I'm an example. So many things we don't know about. I had been asking the question myself about oxygen...”*. (Patient, aged 52 years in regard to the Oxygen trial).

#### 4.5.1.2 Ambivalence

This included the perception that research was necessary, respondents who felt there was nothing to lose or were ‘not bothered’, for example:

*“...As long as doesn't interfere with current meds. Provided Dr was in support of it”*.

(Patient, aged 88 years);

*“...I don't know why actually...”* (Patient, aged 74 years).

A series of reasons were given by some respondents which overlapped these themes such that ambivalence was expressed prior to altruism, for example:

*“...younger person may say no but at 87, I've lived my life so if my body is in a fit state, I'd do it, keen to give something, happy if it might help someone else.”* (Patient, aged 87 years).

There was a perception that things could not be worse or trial was harmless, Learning and where new knowledge could be gained or work to prevent future strokes was also within this theme. One response being:

*“... no reason to say no, good explanation by the nurse...”* (Consultee, aged 54 years, agreed to patient participating in a clinical trial).

#### 4.5.2 Declined to participate

During the thematic analysis, codes emerged for respondents declining patient participation in a clinical trial (36% of respondents) and from these, three common themes arose:

- Trial related
- Disinterest
- Overwhelmed

##### 4.5.2.1 Trial related

Trial related issues included concern regarding the trial medication (drug study), follow-up regime, concerns regarding comorbidities and concomitant medication, risk of making things worse, no guarantee and worry about side effects'. For example:

*“...Because patient would refuse if able to self consent. Doesn't like taking medication - irrelevant of patch...”*. (Consultee – patient's daughter, aged 54 years).

Six respondents volunteered information, unprompted in hindsight, regarding timing of research trial approach for example:

*“...if you’d have asked me in A&E, I would have said no as I didn’t know what was going on .... but today is better... so yes”.* (Patient, agreed to clinical trial, aged 72 years).

*“...I will do anything I think will help. If 100 years ago, nobody had said yes to anything, where would we be now? Would say no to drug trial though until I know what is really going on with this stroke, I wouldn’t. It’s the unknown of how the stroke will keep affecting me.”* (Patient, declined a clinical trial, aged 65 years).

#### *4.5.2.2 Disinterest*

Disinterest included those directly expressing “not interested” and reporting an unclear recovery pathway; those ineligible, unsuitable or too unwell were incorporated here. Age responses were also incorporated here and were highlighted by both patients and consultees.

*“...I believe in research, if I was younger...now set in my ways. If it was just questions and answers then would say yes but due to age...no”.* (Patient, aged 72 years);

*“...Not to say wouldn’t if he was more improved. Not fit enough because of what’s happened to him. Perhaps slightly younger people less than 70...”* (Consultee – patient’s wife, aged 81 years);

*“...I think I’m too old, I think it’s a good thing. Not at the moment...”.* (Patient, aged 90 years);

*“...she’s old school, if it’s not broke, don’t try and fix it...”* (Relative’s perspective of patient’s approach to life. Consultee – Patient’s son, aged 47 years, declining



patient's participation in a clinical trial. Patient had a reported stroke severity as severe by consultee and severe category of NIH Stroke scoring by clinician).

#### *4.5.2.3 Overwhelmed*

Feeling overwhelmed was a common theme relating to: 'too much on' (overall) and 'too much to take in', 'been through enough', 'got enough on already'. A response of being 'too unwell' and related to 'stroke severity' was also incorporated here. For example:

"...At that time (acute stroke) I was 'not in the right place' to make a decision. You don't hear about it (research) so you're not prepared. Unfamiliarity. Felt patient was too poorly - saying no meant one less thing to worry about. Knew needed to make a quick decision, not ready to make that decision". (Consultee - daughter, aged 52 years, consulted with six family members).

The results of this study have been presented using descriptive statistics and a thematic analysis. These results will now be discussed in the next chapter.

## CHAPTER 5

### DISCUSSION

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#### Overview

Difficulties exist with carrying out clinical trials in the NHS. These difficulties are compounded in the acute environment and even more so in the context of an acute neurological injury within emergency care. Patients in the acute setting have the most to benefit from research and yet the least amount of time to consider it. An already challenging time for a research opportunity to be considered, is further complicated in the presence of an acute event with associated fluctuating symptoms, unclear diagnosis, uncertain prognosis and potential variation in mental capacity requiring the need for a consultee.

This study set out to document the willingness to participate in acute stroke studies by patients or their consultees and has captured public opinion prospectively in regard to a clinical trial participation decision in an acute setting, for 200 respondents acutely affected by stroke.

The findings of this study are considered in the first two sections of this chapter and are discussed in reference to recruitment and influencing factors on decision-making. Comparison with the current literature is made throughout the chapter. Section 5.3 considers the strengths and limitations of the chosen methodology in light of the research findings. In the final section, the potential impact on evolving trial design and recruitment strategies is discussed in light of the original aim and objectives of this study.

In summary, the findings of the study include a comparison of site characteristics and participant characteristics. Results suggest a disparity in participation-decision outcome depending on: whether patients consent themselves and if an affinity to a trial is perceived. A difference was found in participant's willingness to join a trial based on whether it was real or hypothetical. Self assessed stroke severity differed from clinician assessment using an assessment tool and was statistically significant in that worsening severity (as self-assessed), increased the likelihood of trial participation. Results from multivariate analysis include some additional significance for ethnic minority representation. Quotes were used from a thematic analysis that reflects the common themes determined for trial participation-decision outcomes.

## **5.1 Recruitment**

### **5.1.1 Site characteristics**

Recruiting sites admitted stroke patients in keeping with national data sets for basic demographic details and stroke type. Both offered similar clinical services (RCP 2014b). Both sites accepted a similar catchment number of patients from their local population and were six miles apart. The first recruiting site had an onsite rehabilitation ward for treatment after the acute phase and had a thrombolysis service operating during weekday office hours only, diverting stroke admissions for assessment outside of these times to a partner hospital within the same trust seven miles away. Patients were transferred following the hyperacute phase to spend the acute phase in the recruiting site if their registered GP was in the 'catchment' area for that site.

The second recruiting site had an on-call thrombolysis service for out of hours with all patients received at that site at any time. Patients were transferred to a community trust for further rehabilitation (six miles away) after the acute phase and once a bed became available. This resulted in a length of stay variation between the two recruiting trusts but consistency was maintained in the research approach since the acute phase was the focus for this study and both recruiting sites treated the patients during this phase.

If a research contact was missed during admission, patients re-attended at a 6 week follow-up clinic appointment which was a potential opportunity to increase recruitment. However, this was after a considerable length of stay in some cases and patients were not able to recall sufficient details about their time in the acute environment to take part in the study. The mock trial was not appropriate at this time point as it reflected acute treatment and this would have been a retrospective decision, opposing the prospective nature of the study design. As a result, any patients discharged before a research contact, were not recruited. MacNeill et al (2013) found patients didn't distinguish between clinical care and research study. This was confirmed in ad hoc discussions with patients outside of the formal study.

#### 5.1.2 Participation

The study population was diverse and the study achieved higher ethnic minority representation than regional and national population figures (Office for National Statistics, Census 2011). The stroke population studied typically reflected national statistics in all other respects, i.e. age, gender and educational level (RCP 2014a).

Research in the literature suggests willingness to participate in a hypothetical (mock) trial to be a valid predictor of actual participation (Halpern et al 2001). Assessing responses in a hypothetical situation as opposed to an emergency may reflect true opinions and preferences. However, the researcher for this study noted initial confusion in some respondents, with the concept of a hypothetical trial in itself being the focus of consideration as opposed to the details of the trial. Of the 200 respondents in this study, 36% (n=72) considered a real trial and 64% (n=128) considered a hypothetical trial.

Univariate analysis found respondents were six times more likely to participate in a real trial than a mock trial (OR 5.73, 95% CI 2.70-12.17;  $p < 0.0001$ ). Using multivariate analysis (controlling for the effects of other variables) respondents were ten times more likely to participate in a real trial than a mock trial (OR 9.45, 95% CI 3.70-24.16;  $p < 0.0001$ ). This was found to be statistically significant for this study but not by Kasner who found no difference in the likelihood of participating in the real and mock trials. This may indicate a difference in attitude and opinions in clinical trials cross-culturally but may be due to a researcher factor or due to the nature of the mock trial itself - being hypothetical. This result was interpreted with caution due to small participant numbers for this analysis and the large confidence interval although the mock trials were almost identical to their respective real trial counterpart.

Overall, 128 respondents (68%) agreed to participate in a clinical trial of any sort (real or hypothetical) despite only a third of patients with known stroke onset time (n=47 of 141) during the working hours of 9am – 5pm, Monday-Friday. This adds support to the case for expansion of the clinical service to become a seven day service with

extended hours - which acute research would benefit from being aligned with. A potential time delay after admission but prior to research approach was inevitable with one researcher and out of hours presentation for many patients. As a result, an early contact time-point with consultees was potentially missed. For this study, since the acute phase was considered to be 1-7 days (Rocco et al 2007) and commonly within the first 72 hours), any impact was perceived to be minimal.

Unwitnessed stroke events accounts for >25% of all strokes (Maas and Singhal 2013). Terminology in secondary care uses terms such as: 'last seen well, 'first known unwell' or 'wake-up' stroke to indicate an uncertain event onset time. Clarity of onset time can be assisted by advanced imaging (where this is available) but waiting for confirmation of diagnosis may delay beyond the time window for recruitment.

#### *5.1.2.1 Study decision-maker*

Stroke patients were able to make the participation decision themselves in 69% of cases, higher than in previous studies noted in the literature such as Flaherty et al (2008) which reported 30% and Kasner et al (2009) with 47%. In Kasner's study, the majority of consents were secured within the first 24 hours post event. During this early phase, stroke symptoms are often most pronounced and as such, fewer patients may be able to consent themselves.

Consultees were used for the remaining respondents in line with current practice and following the process for clinical trials where a consultee is approached when patients are not able to satisfy the consent process requirements fully.

Notably, when presented with a trial participation decision, patients were more inclined to agree to participate than consultees were to agree on a patient's behalf, for the patient's participation. This may be due to patients being more worried about the impact of the stroke itself and their wellbeing and therefore being more willing to take risks to improve it. Conversely, consultees may be concerned about the risks of any side effects and making the current situation worse with an unproven treatment. There is a burden of psychological stress perceived by consultees despite the decision-making role being beneficence on behalf of the patient (Rose and Kasner 2011). In research, a consultee is approached to pass an opinion (as they know the patient best), as to whether the patient would be likely to agree or decline to participate, should they be able to consent themselves.

Consent sought from a consultee, should represent the patients best interests. However, reasoning given for clinical trial participation decision by consultees, centred around the consultee's own perception as opposed to the patient's likely opinion. Consultees often appeared unable to detach themselves from a perceived responsibility. There was likely too little time to process all the necessary information for a well-considered decision to be made on someone else's behalf. This is highlighted in the results chapter, section 4.1.2 where responses of 'barely' and 'not enough' time for trial consideration were reported and in section 4.3.4 where reasons for trial decision are shown (Figures 4.22-4.24).

### *5.1.2.2 Respondent Demographics*

There appeared to be no impact of demographic factors on trial participation, despite suggestions of possible influence of age, gender, ethnicity and educational level, in previous studies (Corbie-Smith et al 2003; Ding et al 2007 and Glickman et al 2008).

Where stroke patients decided on trial participation for themselves (n= 138, 69%), the age of the patient was recorded with a mean age of 66 years. This is younger than figures quoted in the three month national stroke audit in 2013 of 77 years (RCP 2014a) and may be a reflection of stroke incidence, reclassification of TIAs as strokes, and advanced imaging (Easton et al 2009). Age remains the single most important risk factor for stroke since the risk of a stroke doubles every decade after the age of 55 years (Wolf et al 1992). Within the study population older patients may have been excluded if unable to consent themselves and had no consultee available or fell within the category of too unwell to approach (with probable mortality). These patients were not deemed approachable for this study by the clinical care team.

There was variation in age when all 'respondents' (including both patients and consultees) were analysed with a mean age of the decision-maker of 63.39 years since some responders were consultees whose ages varied from that of the patient. Some consultees were patient's children whilst others were a spouse and had a closer age to the patient's.

A large proportion of the study population were from the most socioeconomically deprived quartile. The study population achieved representation across the socioeconomic groupings and reflected regional and national statistics for the area



studied. People from the most socioeconomically deprived areas of the UK, are twice as likely to have a stroke than those from the least deprived areas (Public Health England 2015), however, no statistical difference was found between socioeconomic deprivation scoring and likelihood of trial participation. Whilst socioeconomic status (SES) was found to affect early phase cancer trial referrals (Mohd Noor et al 2012), once reviewed, deprivation did not affect enrolment.

McLean et al (2006) support the continued existence of the inverse care law (as defined by Julian Tudor Hart in 1971 who described the availability of good medical care as varying “*inversely with the need for it in the population served*” (Hart 1971). This may warrant further exploration in terms of research participation since the current literature (as regards research) focuses on socioeconomic deprivation linked to ill health or responsible for a lack of access to resources including trials (Sateren et al 2002, Pell et al 2000). This is opposed to socioeconomic deprivation influencing or not, the willingness to participate in trials.

Publicity of research in the community could raise the profile, awareness to and understanding of research such that in the event of ill health, a research approach in secondary care is not so unexpected or foreign. For example the ‘ok to ask’ campaign of recent years by NIHR. Areas of known high risk for particular health conditions are likely to benefit from research information, in advance of an ill-health event, if communities are within reach.

In multivariate analysis, once the effect of other variables had been controlled for, white ethnicity was found to be statistically significant with patients in this group being

around three times more likely than non-white respondents to agree to participate in a trial (95% CI: 1.03-10.51). This is in contrast to the data on deprivation and maybe due to participant factors such as cultural, gender and language barriers if English was not a first language or an individual was unable to read English. Trust of medical doctor and gender roles in society may also play a part although this was not tested within this study.

There is a higher risk of stroke in ethnic minority populations according to the findings of Wang et al (2013), Hajat et al (2004) and Scarborough et al (2009). Projections from Lievesley (Runnymede report -2010), report the number of older people in the UK from ethnic minority backgrounds as increasing as first generation immigrants and their families age. Variations in access to healthcare have been highlighted by Szczepura (2005) with patients at risk of triple jeopardy (Norman 1985) in the form of assumed family support, inequalities in access to healthcare and ill-health - with Norman's early work on older immigrants. Cultural variations may include an 'acceptance' of what has happened and a contentment in being looked after by relatives (Salway et al 2007). For others, it may be the expectation of being given medication to improve (although this is not unique to patients from ethnic minority backgrounds). The research concept therefore that medication, may or may not be given and that there is equipoise from a medical perspective may be a barrier for trial participation for some minority populations (Scheppers 2006).

Asian elders could experience a loss of status following a stroke and therefore feel difficulties with motivation to engage. For another, it was considered to be the "*will of*

*Allah” and “any improvements were in the hands of Allah”* (Patient, declined study and clinical trial outright, with permission given for use of this comment).

Researcher factors in connection with ethnic minority recruitment are not so well documented either in the current literature or within this study, although this study did achieve representation from ethnic minority groups above regional and national data figures.

## **5.2 Study process**

### 5.2.1 Communication

In response to a request to define the term ‘clinical trial’ in the study survey, a large proportion of respondents hesitated and struggled to explain the term (see chapter 4, section 4.3 regarding the questionnaire response). Six of 200 respondents (3%) were able to correctly define the term ‘clinical trial’ using concepts such as randomization, placebo and comparison. Twenty-three (11%) were unable to proffer any answer at all. The remaining respondents, all made a fair attempt at the definition with the most common answers being “... *looking into something*”; “*testing*” and “*experiment*” being mentioned. The definition of a clinical trial from the DH NHS website, was subsequently given as part of this study so no misconceptions were held from the outset and the survey was then continued to completion.

The implications of 11% of respondents not being able to define the term is a concern in the context of gaining valid informed consent for a research trial (Rose and Kasner 2011). Research consent without understanding may rely more on trust of the respondent in the medical professional and absence of coercion (Davies 1997; Wing

1999), especially in a time sensitive environment. An explanation of general research information, incorporating a definition of the term, could be delivered prior to ill-health and be community based – as opposed to extending the consenting process, when a trial opportunity presents with the onset of illness. The impact this may have had in trials is not clear and a potential area to further explore.

In terms of communication, 52% of participants stated they would have liked to have conferred with someone about the trial if they had been available (stating a family member in most cases). This was similar to a 57% finding by Kasner et al (2009) in a similar study. It was noted on the secondary care wards that visiting was restricted to a two hour visit time late in the afternoon plus one hour in the evenings. This was reduced further during outbreaks of infectious disease (Norovirus) - when ward areas would be effectively 'closed', accepting no new ward admissions and stricter visiting. This happened on two separate occasions at the first recruiting site, a few weeks apart making it difficult to approach relatives to act as consultees if needed or for participants to be able to confer with family members. Also, family members did not visit every day or due to work commitments, visited in the evening when the researcher was unlikely to be present.

The impact that conferring may have had on recruitment is unclear but potentially far-reaching, beyond recruitment. Within the questionnaire, respondents were asked whom they had conferred with, if anyone. In the absence of a family member to confer with, participants could have had contact with other medical staff, ward staff or other patients in general conversation, which they may have utilised in the decision-making process either consciously or subconsciously.

### 5.2.2 Cross-cultural comparison

A comparison was made between this study and findings by Kasner et al (2009) in Table 5.1 - both studies recruited 200 respondents using similar survey research methodology with a real and mock trial. A stipulation of the IRB (ethics board for US) meant Kasner did not use the NIHSS to score a patient's stroke severity but asked respondents to grade the stroke themselves. Kasner felt this to be a positive since their decision should be considered within their own perspective of stroke severity. In this study, by comparison, both scorings were recorded: a self-assessed scoring and a clinician assessed using the NIHSS.

**Table 5.1 Comparative data between USA and UK**

<b>Response</b>	<b>Kasner et al (2009) Hyperacute</b>	<b>This study (2013) Acute</b>
Total number of participants	200	200
Agreed to a clinical trial	57% n=114	64% n=128
Stroke patient consent for study	47% n=94	69% n=138
Agreed to a real trial	22% n=44	36% n=72
Sufficient time to consider trial	56%	85.5% n=171
Insufficient time to consider trial	38%	9% n=18
Prior knowledge of consequences		
Positive	30% n=60	30.5% n=61
Negative	12% n=24	18% n=36
Overlap of both	33% n=66	12.5% n=25
<b>Total:</b>	75% n=150	61% n=121
General attitude		
Very positive	5%	8.5%
Positive	45%	57.5%
Neutral	44%	26%
Negative	5%	8%
Very Negative	2%	
Decision made solely by respondent	72% n=144	60% n=120
Sole decision-makers who would have liked to have conferred with someone	57% n= 82	43% n=52

From Kasner's study, American respondents had been more aware of consequences of research generally, prior to the research contact - with over double having heard something both positive and negative about research previously, in comparison to UK respondents.

Kasner used a 'hyperacute' stroke research trial and mock, whereas in comparison, an 'acute' phase stroke research trial and mock was used in this study due to the service advancements in hyperacute still being under development in large parts of the UK. From this respect, caution needs to be applied with a direct comparison of

data with Kasner. The hyperacute phase of a stroke although only recently separated from the acute phase and only a matter of hours earlier, could hold sufficient difference to make any comparison speculative.

More UK respondents agreed to participate in an acute stroke trial than their American counterparts, in a hyperacute stroke trial. It is not clear whether British respondents were more likely to participate in trials but they reported a positive attitude towards trials, having heard less about trials overall. By comparison, American respondents appeared more cautious with fewer agreeing to participate and a larger number of respondents having heard about research previously.

More respondents in Kasner's sample in the hyperacute phase felt they had insufficient time to make a decision, compared to this study, conducted in the acute phase (38% vs 9%), Reflecting possible differences in the phases of stroke. Urgency is fundamental in acute stroke research trials, however, respondents should not feel hurried. Sen Biswas et al (2007) suggested support for research from medical staff and family may improve recruitment. More research contact points may prove beneficial especially if the concept of research is new to potential participants, either by telephone or in person and the role of pre-hospital staff raising the possibility early and discussion en-route to the emergency department have a potential to increase recruitment (Leira et al 2009).

In common with Kasner et al, this study found consultees less likely to agree to participation, than patients themselves. Highlighting this to consultees who may have felt the burden of responsibility in decision-making, might reassure and ease the

decision-making process. Exploring a patient's affinity, perceptions and attitudes to guide the research opportunity presented might also reassure consultees that the trial is tailored to the individual e.g. they have high blood pressure and the trial being offered is to manage high blood pressure.

Kasner et al (2009) found no association with participants self-graded level of stroke severity. However, in this study those participants with more severe strokes were statistically more likely to participate in a research study (as noted in chapter 4, section 4.2.4). In relation to the stroke itself, disparity was found between clinician assessments of stroke severity using NIHSS versus respondent self-assessed stroke severity. Self-assessed stroke severity was determined on an individual level, by the individual themselves. Any attempts of explanation to account for this difference in rating would be purely speculative and it was not the aim of this study to explore disparity between participants and clinician's assessments of stroke severity.

Assessment of stroke severity did coincide with a reported points-drop on a health scale from previous wellness, which was captured on the study questionnaire. Self-assessed stroke severity was a statistically significant finding. Patients who assessed their own level of stroke severity as moderate or severe were significantly more likely to agree to participate in a trial than those who considered their stroke to be mild ( $X^2 = 9.87$ ,  $p=0.031$ ). Using Chi-square for trend, the likelihood of agreeing to participate in a trial was increased as perceived stroke severity increased ( $X^2 = 4.674$ ,  $p=0.031$ ).



### **5.3 Potential Influences on participation**

Not knowing a patient's affinity, perceptions and attitudes to research, medical staff consider the eligibility criteria for a research opportunity for patients as opposed to what trial the patient might be most interested in. Personal affinity may play a part in decision-making and retention in research trial. For instance, high blood pressure was a common risk factors reported by respondents and the proportion that agreed to take part in a trial was higher than any other risk factor (although not statistically significant). The mock trial was a drug trial related to blood pressure and several respondents commented that there was something about the trial that they liked as an influence in their participation decision and a 'blood pressure trial' was named positively on three occasions in regard to participation.

Where multiple or competing trials are open at a site, medical bias for one trial being offered over another may conceivably exist with factors such as the 70 day national NIHR target to meet; a financial incentive from pharmaceutical industry sponsored study or a home-grown site-sponsored study being a recruitment pressure. As a result, a trial opportunity may therefore be presented in a skewed fashion as opposed to consideration from the patient perspective of what they would be keen to participate in, limiting patient's choice. Trials are often opened due to a personal interest from medical teams. Local populations whilst considered for recruitment target numbers are not necessarily canvassed for what they want to be available in research in the local or regional secondary care Trust.

Once a patient has declined to take part in research, the reason for that decision is not always noted in the patient records. A second research opportunity may not be

presented due to the limited resource of researchers or trial time restrictions leading to failed screening no longer meeting eligibility. Also, patients may then have a preconditioned response to what they understand to be research, which may be misinformed. Researchers conversely may assume patients to have already made up their mind against research and be hesitant to reapproach a patient when in fact the previous decision was trial specific. Three respondents agreed to a trial when they had declined a different one initially.

Giving a choice of trials may not be appropriate and could complicate a decision on participation. The added choice of deciding between trials could be too much to ask of the acutely unwell, neurologically affected patients and their close relatives. Whilst not within the remit and scope of this study, future work could inform practice.

### 5.3.1. Motivators

Motivators and barriers to clinical trial recruitment are documented in the literature (Prescott et al 1999, McDonald et al 2006 and Treweek et al 2011). Within the current literature perceived personal benefit (to help self, better care and access to the latest treatments) and altruism are frequently cited motivators for participation in prevention and chronic disease trials (Corbie-Smith et al 2003; Cassileth et al 1982). Also mentioned is doctor's recommendation, hope for a therapeutic benefit, only option and curiosity (NIH 2002). Although motivators have been less frequently researched than obstacles and barriers. Cross-culturally motivators may vary for instance in USA, literature cites free drugs (NIH 2002) as motivational factors for participation and by comparison, healthcare regimes in the UK are different with excess treatment costs

for drugs being covered traditionally by the NHS (particularly cancer studies until recently).

The content of the trial offered might have contributed towards motivation to participate. Blood pressure is a contributing factor to over half of all the strokes in the UK (RCP 2014a). This was also the commonest risk factor for respondents in this study and a high proportion of respondents with high blood pressure agreed to participate in a trial. A real trial offered at one recruiting site was a blood pressure study and the mock trial was a blood pressure trial at both sites. Due to small numbers, it was not possible to ascertain significance between an individual's blood pressure status and trial participation at a statistical level.

The most common motivating factors from the thematic analysis in this study were cited to be altruism and ambivalence.

### 5.3.2 Barriers

Barriers lead to trials either failing to meet targets and thus their objectives, with financial and resource waste. Limited resources may be diverted for trial extensions to meet recruitment targets and therefore distract or limit the support for new trial work. Barriers to recruitment have been a focus in clinical research, historically documenting issues surrounding consent (in the ethics literature) and more recently focusing on recruitment as targets are analysed at a national level.

Potential negative external influences include: rigid entry criteria; perception of costs in both time or monetary value and no suitable trial. Fear and mistrust are equally

cited in the literature with limited attention given to benefit / burden balance for participant. Within this study, personal fears of being a “guinea pig”, of side effects and of the unknown were cited for refusal (see chapter 4 results, section 4.3.4 on the participation decision, Figures 4.22-4.24) supporting previous work by Corbie–Smith et al 2003 and Madsen et al 1999 which also found feeling overwhelmed, perceived risk outweighed perceived benefit or participants had a preference for outcome (of randomisation).

Whilst participant barriers have been noted in the previous literature, less well noted are clinician barriers to recruitment. These can include time due to the pressures of normal clinical practice and the time demands of recruitment and follow-up; perceived importance of the trial; the doctor-patient relationship- in particular clinicians’ declaring equipoise and Incompatibility of the trial protocol with normal clinical care.

The reasons for recruitment failure are rarely documented in medical records and thus add an uncertainty to identifying barriers and putting strategies in place to facilitate and ultimately increase recruitment. The most common barriers from the thematic analysis in this study, was cited to be: something trial related, disinterest in the trial topic and feeling overwhelmed.

Additional points of contact for research may assist in addressing patients and consultees feeling overwhelmed at the prospect of research participation. Raising awareness about research in the community may help reduce disinterest and increasing the choice of trials available and tailoring a choice to a patient’s affinity, may assist in addressing trial related negatives.

Further work may also be needed on the information exchanged by medical personnel in regard to stroke to enable patients and their families to give fully informed consent. For example patients were more likely to say yes when asked themselves (Section 4.1.2; Figures 4.4-4.5). Also more respondents rated the stroke as severe, than the clinician scoring rated them (section 4.2.4; Figures 4.8-4.9) and more people want to take part in trials if they perceive themselves as severely affected. These findings, if conveyed to potential respondents of future trials may alleviate some burden of responsibility for consultees and reassure both consultees and patients.

#### **5.4 Strengths and limitations of this study**

Survey research methodology – the chosen methodology for this study, is open to critique in the literature due to data that may lack detail or depth. Also, one particular research technique in isolation may not be ideal to allow for multicultural variations of participants and strategies for improved recruitment maybe required (Hussain-Gambles et al (2004).

Not all stroke admissions were captured by the research approach used in this study, largely due to only one researcher being available (section 4.1.1; Figures 4.2-4.3 and section 5.1.2). Potential respondents, 'eligible but missed' from a research approach were lost to research. A limitation of the data is recognised in that it captures only those approached and consented.

A questionnaire developed for US patients may not be applicable to the UK population. A PPI group reviewed the trial paperwork; the questionnaire was piloted and was subsequently adapted for use in the UK. It may, however, not have allowed for all potentially influencing organisational factors, particularly if these were not apparent.

Cross-continental and different ethnic cultures may affect direct comparison of the data. Whilst the mock trial was fully integrated in clinical care, the real trial was delivered without the study researcher necessarily being available. As such, the study details were completed in retrospect for some respondents. Any time delay was minimised, where possible, as it was recognised that recall of details may be poor for some respondents, particularly over time.

Thematic analysis is inherently interpretive research open to biases, values and judgements of researchers (Creswell 1994). The limitations of the analysis were recognised. Whilst the qualitative element of the study was a small thematic analysis, in terms of recruitment a physical aspect to the findings was for new knowledge and better care with self-actualisation, to help self and others in the future.

#### 5.4.1 Strengths

In terms of strengths, the study design was prospective. Respondents were able to verbalise a reason supporting the participation decision and did so prior to any prompt.

Prompt responses were interpreted with caution since they may not have had a role in decision-making but sounded plausible when considered subsequently. Responses to prompts largely supported the reasoning verbalised by respondents for trial outcome decision adding credence to the initial rationale.

With one researcher, there was consistency in approach, explanation and delivery of the survey, minimising influencing factors which may otherwise have arisen. One researcher would not necessarily have improved trial agreement but did provide consistency across the 200 respondents. This was at the expense of lack of available researcher at times.

#### 5.4.2 Limitations

A proportion of the stroke admissions at each recruiting site were 'lost to research' beyond those originally predicted, due to limited researcher time – although recruitment numbers were met within the time frame of the study. Respondents were not always approached at the earliest possible opportunity, often due to clinical care requirements or a delay due to the need for a consultee to be present. The variation in timings of the research approach may have introduced bias but reflected the usual process for trial recruitment, on sites, for acute trials. Also at times, there was limited researcher availability. This was a result of not achieving NIHR recognition, an accreditation which would have enabled access to NIHR resources (research staff) and in the absence of alternative financial support over and above the studentship.

The study population was too small for a robust analysis of the effect of 'timing of research approach' to be undertaken. Kasner et al (2009) achieved a higher

proportion of approaches in the first 24 hours but fewer respondents agreed (although a high proportion (85%) felt happy with the time given to consider the opportunity). Symptoms can vary a lot in the first 24-48 hours of a stroke and this might explain variations in personal perception of stroke severity to an extent and the decision taken in light of the complications of stroke.

This study approach was not as integrated for the real trial consideration as the mock - the latter of which was integral to the initial research approach. A slight time delay was noted between the real trial and completion of the survey although this was recognised from the outset of the study and minimised as much as possible. This was in contrast to Kasner et al (2009) who used the initial study approach prior to any clinical trial presentation (real or mock).

Real trial opportunities were offered with and without the presence of this study's researcher. It is recognised that more decliners could have been captured by this study if more personnel had been available – Kasner reporting that he used a team of researchers whilst this study used only the author.

It was not always documented in the medical records when a patient declined a real trial approach. Recording of the rationale behind this decline could have provided informative data. This study would also have benefited from exact alignment with clinical research opportunities offered and more real trials being open at recruiting sites (trial offered being statistically significant in terms of participation). At the outset of this study, nine real trials were open at recruiting sites. This dropped to 3-4



following commencement of the study and lead to reduced research participation opportunities for patients.

Several timings of initial study approach were noted (section 4.2.5). It is possible that the same participants approached at certain times during stroke admission may have had a different response (section 4.5.2.1).

Limited thematic analysis was undertaken but should be recognised for its limitations. Comments cited during the thematic analysis as verbalised by consultees, reflected an inseparable influence of personal perception. It is highly possible that responses may have been time sensitive with influence of how the patient was clinically, felt or looked, if they were sleeping or showing any change in condition. An example of comments given include the following:

*“...it could help him or someone else, monitored all the time”.* (Consultee, aged 49 years, agreed for patient to take part).

*“...don't really want to put her through anything else because of what she's been through already”.* (Consultee, aged 79 years, declined for patient to participate).

*“...reluctant as not clear diagnosis but agreed because of blood pressure. Important to do these things, if got something yourself, doing a trial in that would help others in the future.”* (Patient, aged 42 years, agreed to take part).

Consultees were those available at visiting hours, which were restricted in the number of visitors allowed and timing of visiting hours. It was possible that it was not necessarily the most suitable family member who was approached although this was

verbally checked on initiating the approach. Family disputes, argument and lack of agreement between different consultees were noted to some extent for a small number of respondents. On a particular day, less close relatives or non-family members might have been visiting and it is possible that the consultee approached did not necessarily feel best placed to make a research decision. Attempts were made to establish this at the outset of each approach and the consultee's relationship to the patient (if used as decision-maker) was noted on the questionnaire. This relied upon limited information and the confidence of the consultee to act on their relative's behalf. Having no close family also challenged recruitment.

## **5.5 Summary**

The aim of this study was to answer the research question of what influences decision making for clinical trial participation in the context of acute stroke and whether there are any identifiable factors indicative of participation.

This chapter has aimed to discuss the characteristics of recruiting sites and of respondents to clinical trials in the acute stroke phase. Demographic factors, level of education, prior research experience and issues related to the stroke experience itself have been explored. There is no suggestion of any impact on the decision to participate in acute stroke trials with the exception of self-assessed stroke severity.

Decision-making by potential participants in stroke trials is complicated by an unexpected decision needed in a short time frame requiring information to be read, understood and acted upon in someone else's best interest with unclear diagnosis and uncertain prognosis in an acute secondary care environment with a genuine rate

of stroke mortality or permanent disability. As such, stroke presents unique research challenges (Carman et al 2014).

General attitudes towards clinical trials were found to be largely positive with little recognition or weighting placed on external factors (whether this is due to a lack of awareness to any influence, denial or subtlety is still unclear). Differences were found in the rationale behind patients and consultees decision-making. Participation for both groups was most likely with a real trial as opposed to a hypothetical (mock) trial.

Having reflected on these points, it is possible to acknowledge the achievements of this study and also recognise areas for future work. These conclusions are presented in the final chapter.

## CHAPTER 6

### CONCLUSION

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This study set out to determine the factors associated with stroke patients' willingness to participate in acute stroke trials. Influences, attitudes and perceptions regarding participation were explored, alongside health status and demographics. The study has successfully documented prospective findings from 200 respondents completing a survey and considering a clinical trial, during admission for an acute stroke. In this chapter, the key findings of this study will be reviewed and areas of further work will be highlighted with implications for CRN policy.

Recruitment to clinical trials continues to be a focus in the UK but this study is one of only a small number to emerge in recent times within stroke care. Whilst those choosing to decline a study are often lost to research and the rationale unrecorded, potential participants were successfully engaged and a verbatim response recorded.

Findings reveal that sociodemographic factors such as age, gender or ethnicity did not explain decision-making about clinical trial participation in acute stroke research, in its entirety. Decisions about participation in trial research are more likely to be strongly influenced by a potential participant's attitudes, perceptions and prior knowledge or experience of clinical trials. Therefore, more could be done to recruit to trials centred around the individual potential participant.

This study found that agreement to participate was more likely in a real trial than a mock (hypothetical) trial in the context of an acute stroke. Views expressed by respondents regarding the rationale for their participation decision suggest that trials with a focus on a particular clinical condition or co-morbidity such as blood pressure, or those focused on a particular patient cohort (e.g. a specific ethnic group) were more likely to be perceived favourably by stroke patients or their consultees.

Patients who were able to consent for themselves were more likely to agree to trial participation than consultees considering trial participation on behalf of a patient who was unable to consent. Some consultees reported a 'burden of responsibility' in decision making for an acute stroke clinical trial. Presenting a trial for consideration by reviewing not only eligibility but also knowledge of the patient as to whether this would be a trial they would feel an affinity towards, may improve recruitment rates further and reassure consultees of an individualised plan of care. This could provide reassurance and ease any decision burden by informing of a more individualised recruitment strategy.

There are challenges associated with presenting individuals with a choice of trial within which to participate (to maximise recruitment), weighed against the choice being perceived as an added burden -to the detriment of potential participants who may decline due to feeling overwhelmed.

In this study, a personal perception of the stroke being severe (by the respondent) was more likely to result in trial participation. It is not evident how a patient or consultee deduces severity and there was disparity in personal perception and

clinician scoring on a severity assessment tool (NIHSS). More respondents considered themselves as severely affected than clinicians did. Where alternative consent is sought for trial participation, this disparity could be highlighted as it may lessen the perceived 'burden of responsibility' yet further.

The terminology in research is not always clearly understood by participants and misconceptions may exist with an inability to define the term clinical trial at the outset of the research opportunity. Potential participants may benefit from additional research contacts and increased community awareness to understand a definition prior to a hospital admission.

The rationale behind trial participation decisions is not easily elicited but due to challenges of recall in the acute setting, in the context of stroke, would be best placed immediately alongside a research opportunity. Recall after an acute neurological event would be best placed as fully integrated within real trials opportunities at the earliest opportunity. If questioned at a later date, the trial may not be easily recalled suggesting informed consent may not be truly informed (Rose and Kasner 2011) and remembering the rationale behind a trial decision maybe even more vague.

### **6.1 Recommendations for future work**

A question as to what influences perceptions of event severity with acute stroke remains and warrants further work due to a disparity in the perception by those affected and in that measured by health care professionals using a validated clinical

assessment tool (NIHSS). In addition, the participation of ethnic minority groups needs continued exploration and potential participants across all groups may benefit from additional research contact points during admission. White ethnicity was found to increase the likelihood of trial participation. Whilst the respondents for this study were ethnically diverse and non-white patients responded to the survey in greater numbers than the regional and national average, the likelihood of agreement to take part in a clinical trial within the survey was statistically lower in the non-white ethnic group. The explanation behind this is still not clear and would benefit from future work.

Trials embedded within an overarching programme which tests recruitment strategies prospectively - whilst recruiting to a 'live' study could improve recruitment strategies and design approaches for disease, cohort or institutional specifics (MRC START 2012). Future work would also benefit from focusing not only on the reasons that patients agree or decline trial participation, but understanding the reasons why clinicians may not focus resources on enhancing trial recruitment.

Many actively recruiting research studies on the NIHR portfolio and other commercial studies currently have an international reach. International collaboration is recommended as a result of this study to enable larger sample size analysis and cross-cultural comparison for variance in order for global studies to increase recruitment efficiency.

Similarities with Kasner et al (2009) - who used similar methodology - include the fact that approximately half of respondents in both studies would have liked to have

conferred with someone prior to decision-making. This did not prevent a decision being made but the decision itself may have been open to influence (positive or negative) if another person had been available. Having heard only positive or negative consequences of research previously had similar numbers across both studies, however, those respondents having heard both positive and negative reports previously, were potentially more research aware and those respondents in the US sample were double the number compared to the UK.

Differences were noticeable in those agreeing to participate in a clinical trial with statistical significance in the UK but not the US for self assessed stroke severity and whether the trial was real or mock. A different ethnic group was studied in the UK and found significance in the likelihood of those of white British as opposed to other ethnicities, in agreeing to participate in a trial. However, because of sample sizes some sub-analysis was not possible but could be enabled in the future with collaboration and potential meta-analysis of similar studies.

## **6.2 Recommendations for future policy**

As Britain continues to move towards further ethnic diversity and with the increase in the number of internationally recruiting trials, representation requires a concerted effort. The emphasis applied by the NIH in the US in 1990s to this end has not been replicated in the UK to date and maybe necessary to make sufficient strides towards inclusive representation (Redwood and Gill 2013).

Recruitment continues to be a focus and representative, timely recruitment is fundamental for trial success. The CRN has produced guidance, which emphasises



efficiency and timely processes. Whilst this is necessary for maximising potential research opportunities, Trusts must also be aware of potential financial implications from the NIHR when self-setting targets, with an expectation of 100% achievement. National league tables rank Trusts in terms of meeting a 70 day recruitment target and consequently Trusts would do well to work with recruitment strategies to a greater extent.

Much of the research training available locally is provided by the CRN. Perception of stroke severity has implications for communicating in clinical trials and the training requirements to successfully recruit to time and target (high level objectives of the CRN). Whilst consent training is available, due to the crucial role of recruitment, much could be gained from teaching recruitment strategies to generic researchers.

Previously, research on barriers to recruitment has been speculated on by members of the general public as opposed to prospective on actual patients who have declined a clinical trial or were ineligible. This study has enabled non-responders and decliners to be analysed prospectively, alongside those agreeing to participate in a clinical trial, filling a knowledge gap of why some UK acute stroke patients are willing to participate in acute stroke trials and why others decline or it is declined on their behalf. This study has achieved its objectives in studying the willingness to participate in acute stroke research trials, but its impact on future trial design has yet to be realised.

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## APPENDICES

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## APPENDIX 1

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Definition of Clinical trial from NHS Choices. <http://www.nhs.uk/Conditions/Clinical-trials/Pages/Definition.aspx>



## Clinical trials and medical research - Definition

### What are clinical trials?

A clinical trial is a type of clinical research that compares one treatment with another. It may involve patients or healthy people, or both.

Small studies produce less reliable results than large ones, so studies often have to be carried out on a large number of people before the results are considered sufficiently reliable.

### Why clinical trials are important

Doctors and other healthcare professionals and patients need evidence from clinical trials to know which treatments work best. Without this evidence, there's a risk that people could be given treatments that have no advantage, waste NHS resources, and might even be harmful.

Clinical trials help to find out if:

- treatments are safe
- treatments have any side effects
- new treatments are better than the standard available treatments

Many NHS treatments have been tested in clinical trials. But the evidence for some treatments is incomplete. Read more about [what we don't know](#).

The NHS aims to inform patients about research relevant to them and offer more patients the opportunity to take part in clinical trials if they want to.

### What clinical trials can find out

Clinical trials can help:

- prevent illnesses by testing a vaccine
- detect or diagnose illnesses by testing a scan or blood test
- treat illnesses by testing new or existing medicines
- find out how best to provide psychological support
- find out how people can control their symptoms or improve their quality of life – for example, by testing how a particular diet affects a condition

Trials follow a set of rules, known as a protocol, to ensure they're well designed and as safe as possible, they measure the right things in the right way, and the results are meaningful. A full protocol should be available to anyone who's considering taking part in a trial and wants to see it.

Many clinical trials are designed to show whether new medicines work as expected. These results are sent to the [Medicines and Healthcare Products Regulatory Agency \(MHRA\)](#). The MHRA then decides whether to allow the company making the medicine to market it for a particular use.

Read more about [safety and regulation](#).

### Entering a trial

If you're receiving treatment for a medical condition, you may be asked if you would like to be part of a trial. You might be interested in finding out about trials taking place so you can volunteer to join one.

Read more about [taking part in clinical trials](#), including how to join a trial.

### Testing Treatments interactive


The [Testing Treatments interactive \(TTi\)](#) website contains video and audio material, and cartoons and games explaining how fair tests are carried out.


If you want to find out more about medical research, you can also download the Testing Treatments book for free from the TTI website.


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Next review due: 05/01/2017

Healthy Evidence forum

 **TriGlycerides on the high**  
My Report: LIPID PROFILE Serum Appearance : Clear Clear S Cholesterol : 129...  
19 replies

 **Is there any evidence for the bullet-proof coffee craze?**  
It's made from filter coffee, two tablespoons of grass-fed butter and two...  
20 replies

 **Acupuncture?**  
I've had back pain for several years now. At first, I believed that it was...  
28 replies

## Clinical trials and medical research - Fair tests

### About fair tests

Not only do unproven treatments need to be tested, but the tests also need to be fair.

Without a fair test, the findings from any research may not mean very much.

Even worse, an unfair test could give healthcare professionals and patients the wrong idea, and people may be given a treatment that doesn't work or is actually harmful. They may also not be given a treatment that could be helpful.

This page explains:

- [making comparisons](#)
- [placebo effect](#)
- [control groups](#)
- [randomisation](#)
- [blinding](#)
- [size of trials](#)

### Making comparisons

If someone who's ill takes a treatment and then gets better, it could be the result of a natural recovery that would have happened anyway.

To tell if the treatment has worked, it needs to be compared with another treatment or a placebo. The two results have to be different enough to indicate a difference hasn't occurred by chance.

#### Comparing a treatment with a placebo

The treatment may be compared with a placebo (a dummy treatment), such as a sugar pill, that looks the same as the treatment.

If there are fewer symptoms or other problems after a treatment than after taking a placebo, this suggests the treatment works.

#### Comparing a treatment with a standard treatment

Where a treatment is already known to be effective from previous research, it's usually not considered right (ethical) to compare the new treatment with a placebo. The new treatment usually needs to be compared with a standard treatment that's already known to be helpful.

This makes it possible to assess whether the new treatment works better than the treatment already being used. New treatments are as likely to be worse as they are to be better than existing treatments.

### Placebo effect

The placebo effect is the phenomenon of someone's symptoms improving when they've only been given a dummy treatment, or even after they've just seen a doctor.

Sometimes a doctor's or other healthcare professional's reassurance, and their confident way of communicating with people who are feeling ill, helps some people feel better. The placebo effect is a largely mysterious and fascinating effect that can be quite powerful.

If you think and believe you're going to get better, you're much more likely to. However, this doesn't work in all situations and for all conditions.

Dummy treatments may be given to people in clinical trials. A placebo medicine looks the same as the medicine being studied, so you don't know which one you're taking. Some people may feel better after taking the placebo medicine because they think they're being given real medication. This is the placebo effect.

Placebos are particularly powerful in conditions where symptoms are important. For example, people feel pain differently and respond better to treatments they think are going to work. In extreme circumstances, some people who are in severe pain respond to a placebo as well as they would to a powerful painkiller.

But placebos don't work for all conditions. [High blood pressure](#) (hypertension) can be lowered by active medicines, but placebos have no detectable effect. Similarly, placebo treatments don't lower blood cholesterol, but [statin medicines](#) do.

### Sham treatments that work

Researchers have designed ways of creating placebos for complementary medicine treatments, such as [acupuncture](#).

It's possible to carry out sham acupuncture where needles are inserted to a different depth and in different places from those used in real Chinese acupuncture. In recent trials, both types of acupuncture appeared to be better than doing nothing.

Studies have also carried out placebo surgery on people with knee pain, and these have shown the placebo surgery often has good results.

Examples of the placebo effect include:

- four placebo tablets work better than two in gastric ulcers
- pink dummy pills are better at maintaining concentration than blue ones
- placebo injections are more effective than placebo pills
- painkillers work better if they're believed to be costly than if they're believed to be cheap

(Source: *Bad Science*, Ben Goldacre, *Fourth Estate*, 2008)

### Control groups

Participants in a clinical trial will usually be put into one of two groups. They may be put in a group where they're given:

- the unevaluated treatment being assessed
- an existing standard treatment, or a placebo if no proven standard treatment exists (known as the control group)

The aim is to compare what happens in these groups. Participants are randomly assigned to one of these groups.

While the treatments are different in the two groups, researchers try to keep as many of the other conditions the same as possible. For example, both groups should have people of a similar age, with a similar proportion of men and women, who are in similar overall health.

### Randomisation

The best way to get similar groups is to allocate individuals to one of the groups in the trial in an unpredictable, random way. This increases the likelihood that the two groups will be similar. This process is called random allocation or randomisation.

In most trials, a computer will be used to decide which group each patient will be allocated to. This allocation will be concealed until after each eligible patient has been accepted for the trial.

These precautions mean the people who decide whether a patient is eligible to participate in the trial can't influence which treatment a patient is allocated to receive. This protects the study from conscious or unconscious bias, which would make the test unreliable.

### Blinding

Many trials are set up so nobody knows who's been allocated to receive which treatment. This is known as blinding, and it helps reduce the effects of bias when comparing the outcomes of the treatments.

Many people feel better if they think they're getting a better new treatment, even if the treatment is ineffective and their underlying health problem hasn't really changed at all.

When both the medical staff organising treatment and those taking part in the trial don't know who's receiving which treatment, it's called a double-blind trial.

Blinding is easier when testing medicines, but more difficult when testing other types of treatments or methods of caring for people. For example, it may be impossible to blind a trial comparing two types of surgery.

### Why blinding is important

Some clinical trials measure hard outcomes such as survival, so outcome measurement is unlikely to be biased.

However, most trials measure outcomes that are more open to biased assessment. For example, patients and researchers may have to make some sort of judgement about how bad symptoms are.

If either researchers or participants know – or think they know – who is receiving which treatment (including placebos), that knowledge may influence what they report.

Participants who think they're taking an active treatment may not want to let down the researcher, and may exaggerate benefits and minimise side effects. Researchers also may allow their hopes about a new treatment to unconsciously influence their recording of symptoms.

The result of these biases is often to overestimate how effective a treatment is. To reduce these possible sources of bias, many trials are double-blind.

### Size of trials

For a trial to be a fair test, the number of people taking part needs to be large enough. For example, in a small trial of 20 people, with 10 people taking each treatment, seven people may improve on the new treatment and five on the standard treatment.

Most of us would not think of that as a fair test because, while the new treatment may be better, the finding could easily have occurred by chance.

If the trial was bigger, with 700 out of 1,000 people improving on the new treatment and 500 out of 1,000 on the standard treatment, the result means researchers can be very confident that the new treatment was better.

The degree of this confidence in the difference can be estimated. Researchers can provide ranges called confidence intervals to show you how certain their results are.

Researchers can also test how "statistically significant" a result is. This can help to show where differences between treatments are unlikely to be the result of chance.

### More information

Read more about fair tests on the [Testing Treatments interactive \(TTI\)](#) and the [James Lind Library](#) websites, where you can also download books for free, including how to make smart health choices and understanding health statistics.

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Healthy Evidence forum



TnGlycides on the high

My Report: LIPID PROFILE Serum Appearance - Clear Clear S Cholesterol - 129

19 replies

## APPENDIX 2

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### **Survey tool and study documentation**

- Participant information sheet and consent form.
- Survey tool
- Mock Patient information sheet and consent form
- Mock Consultee information sheet and consent form



**START Study**



**Studying the recruitment  
of stroke patients into  
research trials**



**Birmingham Heartlands Hospital**

Bordesley Green East  
Birmingham B9 5SS

Tel: 0121 424 2000

Fax: 0121 424 2200

## **The START Questionnaire Study**

### **Participant Information Sheet**

#### **INVITATION TO TAKE PART**

Please read this information sheet and discuss with your doctor, friends and relatives if you wish. If there is anything that is not clear or if you would like more information please ask the researcher or call the number at the end of this information sheet.

#### **WHAT IS THE PURPOSE OF THIS STUDY?**

The purpose of the study is to find out patients and relatives views on taking part in stroke research. Your opinions and information may help us improve stroke care for other patients in future. We also want to make sure everyone can take part in research who wants to.

#### **WHY HAVE I BEEN CHOSEN AND DO I HAVE TO TAKE PART?**

We plan to offer this study to all stroke patients admitted to this hospital within one year, or their relatives. Participation is entirely voluntary and it is up to you whether or not you decide to take part. If you **do** take part, you will be given this information sheet to keep and will be asked to sign a consent form. You can contact us at any time to withdraw from the study without giving a reason. Whether you take part or not, the care you or your relative receives will not be affected in any way.

#### **WHAT WILL I HAVE TO DO?**

If you are a patient, you will be asked to give permission for us to collect information from medical records about the type of stroke you have suffered. We will also ask you to complete a questionnaire with one of our researchers. The questionnaire should take about 20 minutes to complete.

#### **WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?**

Yes. If you join the study and are a patient, some parts of your medical records will be viewed by an authorised researcher and information collected. This will be analysed at the University of Birmingham. Records may also be looked at by representatives of regulatory authorities and by authorised people from the trust to check that the study is being carried out correctly. Nothing that can reveal your identity will be disclosed outside of the Hospital. At the end of the



research, confidential records will be kept securely for 5 years before being destroyed. Access to any information stored electronically will be protected by passwords and restricted to the researcher working on the study.

**WHAT WILL HAPPEN TO THE RESULTS OF THE STUDY?**

The findings will be used to improve the design of studies in the future. The results will be presented in a way that will not identify individuals. Copies of the research findings will be available by post on request and accessible on a website.

**WHO HAS APPROVED THIS STUDY?**

All research in the NHS is assessed by an independent group of people called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been approved by a local Research Ethics Committee. The University of Birmingham is sponsoring this study. The Florence Nightingale Foundation is funding this study.

**WHO CAN I CONTACT FOR FURTHER INFORMATION?**

Jo McCormack

Elizabeth Adey

Researcher

R&D Manager, Heartlands Hospital

Primary Care Clinical Sciences

Bordesley Green East

University of Birmingham

Birmingham



Email: [Redacted]

Email: [Redacted]

**THANK YOU FOR TAKING THE TIME TO READ THIS INFORMATION ABOUT OUR STUDY**



## START Study



Studying the  
recruitment of stroke  
patients into  
research trials



**Birmingham Heartlands Hospital**

Bordesley Green East  
Birmingham B9 5SS

Tel: 0121 424 2000

Fax: 0121 424 2200

# Participant Consent Form

Investigator Name: Jo McCormack

Centre Number: BHH

Patient Initials:.....

Patient Number: .....

Please initial box

1. I confirm that I have read and understood the information sheet dated 20<sup>th</sup> March 2012 (version 1.1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without any medical care or legal rights being affected.
3. **Patients only:** I understand that relevant sections of medical notes and data collected during the study, may be looked at by an individual from the University of Birmingham, regulatory authorities or from the NHS Trust, where it is relevant to taking part in this research. I give permission for these individuals to have access to my medical records.
4. I agree to take part in the above study.

\_\_\_\_\_  
Name of Participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

If verbal agreement is given but participant is unable to sign for any reason, a witness to this should sign below

\_\_\_\_\_  
Name of witness

to verbal consent (if applicable)

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Researcher

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

When completed, 1 for patient; 1 for site file, 1 (original) to be kept in medical notes.



# Questionnaire

# 1 \_ \_ \_

## \*Researcher administered Questionnaire

-Questions will be posed face:face and the answers filled in by the researcher

Q1 Date of Questionnaire completion \_\_\_/\_\_\_/\_\_\_(dd/mmm/yy) Time \_\_\_:\_\_\_(24hr)

Q2 Respondent:

Stroke patient <sup>0</sup>	*Consultee <sup>1</sup>
-----------------------------	-------------------------

\*Relationship to patient:

Q3 How severe do you perceive the current condition?

Mild <sup>0</sup>	Moderate <sup>1</sup>	Severe <sup>2</sup>	Not sure <sup>888</sup>
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Q4 Trial offered:

Real <sup>0</sup>	Mock Trial <sup>1</sup>
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### DEMOGRAPHIC

Q5 Age \_\_\_\_\_yrs

Q6 Gender:

M <sup>0</sup>	F <sup>1</sup>
----------------	----------------

Q7 Ethnicity

White <sup>0</sup>	Pakistani <sup>1</sup>	Indian <sup>2</sup>	Bangladeshi <sup>3</sup>	Black Carribean <sup>4</sup>	Black-African <sup>5</sup>	Other <sup>6</sup>
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Q8 Highest level of education completed

No formal qualifications <sup>0</sup>	GCSEs/ CSEs/ 'O' Level equivalent <sup>1</sup>	'A' levels / equivalent <sup>2</sup>	Degree <sup>3</sup>	Postgraduate/ professional qualification <sup>4</sup>
---------------------------------------	--	--------------------------------------	---------------------	---

Q9 Postcode\_\_\_\_\_

### PRIOR RESEARCH RELATED EXPERIENCE

Q10 What do you understand by the term 'clinical trial'? \_\_\_\_\_

Q11 What do you think about clinical trials?

Very negative <sup>0</sup>	Negative <sup>1</sup>	Neutral <sup>2</sup>	Positive <sup>3</sup>	Very positive <sup>4</sup>
----------------------------	-----------------------	----------------------	-----------------------	----------------------------

Q12 Have you heard any positive consequences of clinical trials?

No <sup>0</sup>	Yes <sup>1</sup>	Don't Know <sup>888</sup>
-----------------	------------------	---------------------------

Q13 Have you heard any negative consequences of clinical trials?

No <sup>0</sup>	Yes <sup>1</sup>	Don't Know <sup>888</sup>
-----------------	------------------	---------------------------





## Questionnaire

# 1 \_ \_ \_

### \*Researcher administered Questionnaire

-Questions will be posed face:face and the answers filled in by the researcher

Q14a Prior to this hospitalisation, have you ever been asked to take part in a clinical trial

No <sup>0</sup>	Yes <sup>1</sup>	Don't Know <sup>888</sup>
-----------------	------------------	---------------------------

Q14b If 'yes', did you choose to participate?

No <sup>0</sup>	Yes <sup>1</sup>	NA <sup>888</sup>
-----------------	------------------	-------------------

Q15 Do you know if anyone in your immediate family has ever been asked to take part in a clinical Trial?

No <sup>0</sup>	Yes <sup>1</sup>	Don't Know <sup>888</sup>
-----------------	------------------	---------------------------

(by immediate we mean parent/ partner/ child/ brother/sister)

Q16 Has anyone in your immediate family ever participated in a clinical Trial?

No <sup>0</sup>	Yes <sup>1</sup>	Don't Know <sup>888</sup>
-----------------	------------------	---------------------------

#### PERSONAL HEALTH

Q17 On a scale of 1-10, where 1 is the worst possible state of health imaginable, and 10 is the best, how would you rate your current state of health **NOW**?: \_\_\_\_\_

Q18 On a scale of 1-10, where 1 is the worst possible state of health imaginable, and 10 is the best, how would you rate your state of health **BEFORE THE STROKE**?: \_\_\_\_\_

#### STROKE DIAGNOSIS

##### Personal opinion

Q19 Date of stroke \_\_\_/\_\_\_/\_\_\_ (dd/mmm/yyyy) Time of Stroke \_\_\_:\_\_\_ (24 hr)

\*If 'wake-up stroke', time of wake up \_\_\_:\_. Time of last seen well \_\_\_:\_\_\_

Q20 What type of stroke occurred? (personal knowledge)

Ischaemic <sup>0</sup>	Bleed <sup>1</sup>	Don't know <sup>888</sup>
------------------------	--------------------	---------------------------

Q21 Has patient consented to allow researcher access to their medical records?

No <sup>0</sup>	Yes <sup>1</sup>
-----------------	------------------

**From medical records (\*patient consent only)**



# Questionnaire

# 1\_ \_ \_

## \*Researcher administered Questionnaire

-Questions will be posed face:face and the answers filled in by the researcher

Q22\* Date of stroke \_\_\_/\_\_\_/\_\_\_(dd/mmm/yyyy) Time of Stroke \_\_\_:\_\_\_(24 hr)

**From medical records (\*patient consent only)**

Q23\* Date of arrival in A&E \_\_\_/\_\_\_/\_\_\_(dd/mmm/yy) Time of arrival \_\_\_:\_\_\_(24 hr)

**From medical records (\*patient consent only)**

Q24\* Stroke diagnosis from CT scan (from medical records)

Ischaemic <sup>0</sup>	Bleed <sup>1</sup>	Unclear <sup>999</sup>
------------------------	--------------------	------------------------

Q25 Have you been approached about a research trial since admission?

No <sup>0</sup>	Yes <sup>1</sup>	Don't Know <sup>888</sup>
-----------------	------------------	---------------------------

If yes,

Q26 At what stage of your hospital stay were you approached about research?

i.e. admission (prior to ward ), day 1, 2, 3 /week 1, 2, 3 etc. \_\_\_\_\_

Q27a Should we have approached you at a different stage of recovery?

No <sup>0</sup>	Yes <sup>1</sup>	Don't Know <sup>888</sup>
-----------------	------------------	---------------------------

Q27b If 'yes', When? \_\_\_\_\_

### PAST MEDICAL HISTORY

Q28 Do you have or have you had:

a. Atrial Fibrillation	No <sup>0</sup>	Yes <sup>1</sup>	N/K <sup>888</sup>	
b. Previous Stroke / TIA	No <sup>0</sup>	Yes <sup>1</sup>	N/K <sup>888</sup>	
c. Previous heart attack or coronary artery disease	No <sup>0</sup>	Yes <sup>1</sup>	N/K <sup>888</sup>	
d. Diabetes	No <sup>0</sup>	Yes <sup>1</sup>	N/K <sup>888</sup>	
e. Peripheral vascular disease	No <sup>0</sup>	Yes <sup>1</sup>	N/K <sup>888</sup>	
f. High blood pressure (hypertension)	No <sup>0</sup>	Yes <sup>1</sup>	N/K <sup>888</sup>	
g. High cholesterol (hyperlipidemia)	No <sup>0</sup>	Yes <sup>1</sup>	N/K <sup>888</sup>	
h. Smoking	Never <sup>0</sup>	Former <sup>1</sup>	Current <sup>2</sup>	N/K <sup>888</sup>
i. Other serious medical condition _____	No <sup>0</sup>	Yes <sup>1</sup>	N/K <sup>888</sup>	



# Questionnaire

# 1\_ \_ \_

## \*Researcher administered Questionnaire

-Questions will be posed face:face and the answers filled in by the researcher

**If the patient has been offered a research trial, familiarise patient with details.**

Name of trial offered: CLARHC/ SOS/ ENOS/ CLOTS3/ DARS/ BRAINS /MOCK\*

**\*If the patient has not been approached on this admission with research option, administer the mock trial for opinion now.**

Q29 Agreed to participate to real trial?

No <sup>0</sup>	Yes <sup>1</sup>
-----------------	------------------

or

Q30 Agreed to participate in mock trial?

No <sup>0</sup>	Yes <sup>1</sup>
-----------------	------------------

### CLINICAL TRIALS

Q31 Who or what influenced your decision about participating and to what extent?

	No influence	Weak influence	Moderate	Strong Influence	Very Strong Influence
a. GP	0	1	2	3	4
b. Hospital Doctor	0	1	2	3	4
c. Nurse	0	1	2	3	4
d. Family or friends	0	1	2	3	4
e. Religion	0	1	2	3	4
f. Previous knowledge of clinical trials	0	1	2	3	4
g. Self	0	1	2	3	4
h. Others (please state) _____	0	1	2	3	4



# Questionnaire

1\_ \_ \_

## \*Researcher administered Questionnaire

-Questions will be posed face:face and the answers filled in by the researcher

Q32 Was the written information you were given sufficient to make a decision about the trial?

Not enough <sup>0</sup>	Barely enough <sup>1</sup>	Enough <sup>2</sup>	Too much <sup>3</sup>
-------------------------	----------------------------	---------------------	-----------------------

Q33a Did you discuss the decision about participating or not, with anyone?

No <sup>0</sup>	Yes <sup>1</sup>
-----------------	------------------

Q33b If yes, who? \_\_\_\_\_

Q34 Is there anyone else who you would have liked to discuss your decision with? \_\_\_\_\_

No <sup>0</sup>	Yes <sup>1</sup>	Don't Know <sup>888</sup>
-----------------	------------------	---------------------------

Q35 How much time were you given to make your decision? \_\_\_\_\_

Q36 Was the time you were given to make your decision:

Not enough <sup>0</sup>	Barely enough <sup>1</sup>	Enough <sup>2</sup>	More than enough <sup>3</sup>
-------------------------	----------------------------	---------------------	-------------------------------

Q37a What factors do you think influenced your decision (whether you agreed to participate in this study or not)?

---



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**Prompt:**

If agreed to trial, please use this table only	Strongly disagree	Disagree	Not sure	Agree	Strongly agree
b. Previous experience	0	1	2	3	4
c. Felt happy with the information	0	1	2	3	4
d. Keen to be included	0	1	2	3	4
e. Something in the trial I liked	0	1	2	3	4





# Questionnaire

# 1\_ \_ \_

## \*Researcher administered Questionnaire

-Questions will be posed face:face and the answers filled in by the researcher

-please specify _____					
f. Timing of when I was asked	0	1	2	3	4
g. Better care than normal	0	1	2	3	4
h. Potential benefit from a new treatment	0	1	2	3	4
i. Taking part would help others in the future	0	1	2	3	4
j. To help the doctor or nurses who asked me	0	1	2	3	4

### Prompt:

If declined a trial, please use this table only	Strongly disagree	Disagree	Not sure	Agree	Strongly agree
n. Not enough information to make the decision	0	1	2	3	4
o. Not enough time to make the decision	0	1	2	3	4
p. Something in the trial I didn't like	0	1	2	3	4
Please specify _____					
q. Timing of when I was asked	0	1	2	3	4
r. Didn't want to be a guinea pig	0	1	2	3	4
s. Fear of adverse drug reaction	0	1	2	3	4
t. Didn't want to take on more stress / too much on	0	1	2	3	4
u. Different priorities at time of asking	0	1	2	3	4
v. Makes no difference to stroke now	0	1	2	3	4
w. Won't be told the outcome of research	0	1	2	3	4
x. Didn't feel able to 'take in' the information	0	1	2	3	4
y. Randomisation, no definite treatment	0	1	2	3	4
z. Reluctant to invest time	0	1	2	3	4



## Questionnaire

1\_ \_ \_

### \*Researcher administered Questionnaire

-Questions will be posed face:face and the answers filled in by the researcher

Q38 How do you think your decision will affect your family and friends?

Very negative <sup>0</sup>	Negative <sup>1</sup>	Neutral <sup>2</sup>	Positive <sup>3</sup>	Very positive <sup>4</sup>
----------------------------	-----------------------	----------------------	-----------------------	----------------------------

Q39 Is there anything else you would like to add that may help us with recruiting patients to future trials?

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Q40 What research should we be doing for stroke? What is important to you?

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**Thank you for taking the time to answer these questions**

# **Mock Trial**

## **Patient Information Sheet**

**This information sheet is for your opinion only.**

**No treatment will be started as a result of considering this information sheet.**

**Local Investigator:** Jo McCormack

You are being invited to take part in a research trial. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear to you, or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

### **What is the purpose of the study?**

Lowering blood pressure reduces the risk of further strokes in patients who have already had one or more strokes. High blood pressure is common in the first hours and days following a stroke and increases the risk of the patient not recovering fully and being left with some disability. Lowering blood pressure in the first hours and days after stroke with medications may help patients to recover. Although at present we routinely treat high blood pressure long term after a stroke, we do not do so immediately after the stroke.

We aim to assess in a trial what effect Drug X has on how well people recover from strokes. Drug X is a tried and tested drug for other medical conditions and acts quickly to relax blood vessels and lowers blood pressure. The data will help doctors decide whether blood pressure lowering treatments like Drug X can be used in patients with acute strokes to improve recovery.

### **Why have I been chosen?**

You have been chosen because you have had a stroke and are over the age of 18 and because your blood pressure is high.

### **Do I have to take part?**

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason.

Deciding to withdraw from the study will not affect the standard of care you receive.

**What will happen to me if I take part?**

Your involvement in the study will last for 3 months. If you decide to take part in this study the study doctor or nurse will ask you about your medical history and take your blood pressure.

In this study Drug X is given in a patch much like the patches people use to help stop smoking. A computer will decide at random whether you will receive the treatment patch or nothing. We are doing this because we don't know which way of treating patients is best. To find out, we need to make a comparison between Drug X or no Drug X. We put people into groups and give each group a different treatment and the results are compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). In this study half the patients will receive the active patch and half will have no patch.

Once you have been assigned a treatment, the nurse will come and put a dressing on your arm or chest. You will not know if there is a treatment patch under the dressing or not, but the nurses and doctors will know. This will need to be changed once a day for 7 days, and then the treatment will stop.

During the next 7 days a doctor will check your condition looking in particular for signs of any side effects of the treatment.

You will be contacted 3 months after your stroke for a short talk on the telephone (or by post) by a member of the research team. This is to check your condition at that time. In order to make the final evaluation of the study as objective as possible, the person who telephones you will not know if you received the active treatment or not.

Other than described here, your treatment will be exactly the same as for all stroke patients.

**Expenses and payments**

Volunteers will not receive payment for participating in this study. There will be no charge for the trial medication.

**What is the drug, device or procedure that is being tested?**

Drug X is a medicine which has been used for many years to treat heart problems. It is not used as a long-term blood pressure medicine but does lower blood pressure quickly and effectively for short periods in patients with a stroke and that is why we are using it in this study.

**What are the alternatives for diagnosis or treatment?**



There are various licensed medications used to lower blood pressure sometime after a stroke. You do not need to take part in this study to receive blood pressure treatment. You should discuss the options with your doctor before deciding whether to take part in the study.

If you decide to take part in the study, this will not affect your right to receive appropriate medical care from your doctor.

**What are the side effects of any treatment received when taking part?**

All drugs have the possibility of side effects. The side effects from Drug X are generally mild. They can include headache, low blood pressure and dizziness.

You **MUST** inform your GP or member of the research team if you feel you have had a reaction to the medication.

**What are the other possible disadvantages and risks of taking part?**

You will need to be followed up by the research team for 3 months after starting the study.

**What are the possible benefits of taking part?**

Your participation in this study may reduce the symptoms of your stroke or improve your long-term recovery. However, we cannot guarantee the study will help you, and your participation is voluntary. The information we get from your involvement may benefit other people who may have a stroke in the future.

**What happens when the research study stops?**

We aim to treat 5,000 patients in this study. When it has finished we will look at the data and decide if this is a useful treatment for stroke. We will not tell you directly the results of the study, but they will be published in a journal where they can be viewed.

**Will my taking part in the study be kept confidential?**

If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons organising the research.

They may also be looked at by representatives of regulatory authorities and by authorised people from the Trust, or other NHS bodies to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site.

Your contact details, and those of a relative or friend that you provided, will be passed to the National Coordinating Centre. This will enable the three month telephone follow up to take place.

Our procedures for handling, processing, storage and destruction of patient's data are compliant with the Data Protection Act 1998.

**Contact Details:**

If you have any questions or concerns do not hesitate to contact the research team.

**What if relevant new information becomes available?**

Sometimes during the course of a research project new information becomes available about the treatment/drug that is being studied. If this happens, your research doctor will tell you about it and discuss whether you want to or should continue in the study, although after the first 7 days you will no longer be receiving Drug X. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. They will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

**What will happen if I don't want to carry on with the study?**

If you withdraw from the study, we will destroy all your identifiable samples, but we would like to use the data collected up to your withdrawal.

**What if there is a problem?**

If you had a reaction to the medication we would stop the medication and appropriate medical care would be given. Any adverse events are monitored.

**Complaints**

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions on: 07719 898 730 If you remain unhappy and wish to complain formally, you can do this through the formal complaints procedure.

**Harm**

If you are harmed during the research and this *is* due to someone's negligence then you may have grounds for legal action for compensation, but you may have to pay your legal costs. The normal hospital complaints mechanisms will be available to you.

If you are harmed during the research and this is *not* due to someone's negligence then there are no special compensation arrangements, but you may still follow the normal hospital complaints mechanisms. Again you may have to pay your legal costs.

The University of Birmingham maintains clinical trials insurance to cover legal liability.

**Involvement of the General Practitioner/Family doctor (GP)**

If you are enrolled in the study we will inform your General Practitioner.

**What will happen to the results of the research study?**

The results of the research may be published. If so, this will be in a medical journal. You will not be identified in any report.

**Who is organising and funding the research?**

This study has been funded by Florence Nightingale Foundation. The University of Birmingham is sponsor for the study.

**Who has reviewed the study?**

A local research ethics committee has reviewed the research.

*1 copy in medical notes, 1 to patient & 1 to trial folder*

# Mock Trial

## Patient Consent Form

A prospective, randomised, parallel-group, blinded, controlled, collaborative, mock trial to investigate the safety and efficacy of Drug X, in patients with acute stroke.

Investigator Name: Jo McCormack

Centre Number: ..... Patient Initials: ..... Patient Number: .....

Please initial box

1. I confirm that I have read and understood the information sheet dated 30<sup>th</sup> October 2011(version 1.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that participation is voluntary and that everyone would be free to withdraw at any time without giving a reason, without my medical care or legal rights being affected.
3. I understand that relevant sections of medical notes and data collected during the study, may be looked at by an individual from the University of Birmingham, regulatory authorities or from the NHS Trust, where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. I understand that information held by the NHS and records maintained by the NHS Information Centre may be used to keep in touch with me and follow up my health status.
4. I would agree to take part in the above study, if this were a real trial.

\_\_\_\_\_  
Name of Patient

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Name of Person  
Taking Consent

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

When completed, 1 for patient; 1 for patient site file, 1 (original) to be kept in medical notes.

**This form does not relate to a real trial.**

# Mock Trial

## Consultee Information Sheet

**This patient information sheet is for your opinion only.**

**No treatment will be started as a result of considering this information sheet.**

**Local Investigators:** Jo McCormack

Your relative is being invited to take part in a research trial. We are asking you to read the information and make a decision about whether or not your relative would like to be involved, as they are unable to make the decision for themselves at present. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear to you, or if you would like more information. Take time to decide whether or not you wish your relative to take part. Thank you for reading this.

### **What is the purpose of the study?**

Lowering blood pressure reduces the risk of further strokes in patients who have already had one or more strokes. High blood pressure is common in the first hours and days following a stroke and increases the risk of the patient not recovering fully and being left with some disability. Lowering blood pressure in the first hours and days after stroke with medications may help patients to recover. Although at present we routinely treat high blood pressure long term after a stroke, we do not do so immediately after the stroke.

We aim to assess in a trial what effects Drug X has on how well people recover from strokes. Drug X is a tried and tested drug for other medical conditions and acts quickly to relax blood vessels and lowers blood pressure. The data will help doctors decide whether blood pressure lowering treatments like Drug X can be used in patients with acute strokes to improve recovery.

### **Why has your relative been chosen?**

Your relative has been chosen because they have had a stroke and are over the age of 18 and because their blood pressure is high.

### **Does your relative have to take part?**

It is up to you to decide whether or not your relative takes part. If you do decide for them to take part, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw your relative at any time and without giving a reason. If your relative gets better and is able to make decisions again, they can withdraw from the study if they wish.

Deciding to withdraw from the study would not affect the standard of care your relative receives.

### **What will happen to your relative if they take part?**

Your relative's involvement in the study will last for 3 months. If you decide to take part in this study the study doctor or nurse will ask you about your relative's medical history and take their blood pressure.

In this study Drug X is given in a patch much like the patches people use to help stop smoking. A computer will decide at random whether your relative receives the treatment patch or nothing. We are doing this because we don't know which way of treating patients is best. To find out, we need to make a comparison between Drug X or no Drug X. We put people into groups and give each group a different treatment and then the results are compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). In this study half the patients will receive the active patch and half will have no patch.

Once a treatment has been assigned, the nurse will come and put a dressing on your relative's arm, chest or back. You and your relative will not know if there is a treatment patch under the dressing or not, but the nurses and doctors will know. This will need to be changed once a day for 7 days, and then the treatment will stop.

During the next 7 days a doctor will check your relative's condition, looking in particular for signs of any side effects of the treatment.

Your relative, or their representative, will be contacted 3 months after their stroke for a short talk on the telephone (or by post) by a member of the research team. This is to check their condition at that time. In order to make the final evaluation of the study as objective as possible, the person who telephones will not know if your relative received the active treatment or not.

Other than described here, your relative's treatment will be exactly the same as for all stroke patients.

### **Expenses and payments**

Volunteers will not receive payment for participating in this study. There will be no charge for the trial medication.

### **What is the drug, device or procedure that is being tested?**

Drug X is a medicine which has been used for many years to treat heart problems. It is not used as a long-term blood pressure medicine, but does lower blood pressure quickly and effectively for short periods in patients with a stroke and that is why we are using it in this study.

### **What are the alternatives for diagnosis or treatment?**

There are various licensed medications used to lower blood pressure sometime after a stroke. Your relative does not need to take part in this study to receive blood pressure treatment. You should discuss the options with your doctor before deciding whether your relative should take part in the study.

If you decide for your relative to take part in the study, this will not affect their right to receive appropriate medical care from their doctor.

**What are the side effects of any treatment received when taking part?**

All drugs have the possibility of side effects. The side effects from Drug X are generally mild. They can include headache, low blood pressure and dizziness.

You and your relative **MUST** inform your GP or member of the research team if you feel there has been a reaction to the medication.

**What are the other possible disadvantages and risks of taking part?**

Your relative will need to be followed up by the research team for 3 months after starting the study.

**What are the possible benefits of taking part?**

Participation in this study may reduce the symptoms of the stroke or improve long-term recovery. However, we cannot guarantee the study will help your relative, and participation is voluntary. The information we get from your relative's involvement may benefit other people who have a stroke in the future.

**What happens when the research study stops?**

We aim to treat 5,000 patients in this study. When it has finished we will look at the data and decide if this is a useful treatment for stroke. We will not tell you or your relative directly the results of the study, but they will be published in a journal, where they can be viewed.

**Will my relative's involvement in the study be kept confidential?**

If your relative joins the study, some parts of their medical records and the data collected for the study will be looked at by authorised persons organising the research.

They may also be looked at by representatives of regulatory authorities and by authorised people from the Trust, or other NHS bodies to check that the study is being carried out correctly. All will have a duty of confidentiality to research participants and nothing that could reveal your relative's identity will be disclosed outside the research site.

Your relatives contact details, and those of one other relative or friend that is provided, will be passed to the National Coordinating Centre. This will enable the three month telephone follow up to take place.

Our procedures for handling, processing, storage and destruction of the patient's data are compliant with the Data Protection Act 1998.

**Contact Details:**

If you have any questions or concerns do not hesitate to contact: Jo McCormack. Tel: 07719 898 730

### **What if relevant new information becomes available?**

Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your research doctor will tell you and/or your relative about it and discuss whether your relative wants to or should continue in the study, although after the first 7 days they will no longer be receiving Drug X. If the decision was not to carry on, the research doctor would make arrangements for your relative's care to continue. If the decision was to continue in the study you or your relative would be asked to sign an updated consent form.

Also, on receiving new information your research doctor might consider it to be in your relative's best interests to withdraw from the study. They would explain the reasons and arrange for their care to continue.

If the study is stopped for any other reason, you will be told why and your relative's continuing care will be arranged.

### **What will happen if your relative doesn't want to carry on with the study?**

If your relative withdraws or is withdrawn from the study, we will destroy all identifiable samples, but we would like to use the data collected up to their withdrawal.

### **What if there is a problem?**

If your relative had a reaction to the medication, we would stop the medication and appropriate medical care would be given. Any adverse events are monitored.

### **Complaints**

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions: Jo McCormack. Tel: 07719 898 730. If you remain unhappy and wish to complain formally, you can do this through the complaints procedures.

### **Harm**

If your relative is harmed during the research and this *is* due to someone's negligence then your relative may have grounds for legal action for compensation, but they may have to pay legal costs. The normal hospital complaints mechanisms will be available to your relative.

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The University of Birmingham maintains Clinical Trials Insurance to cover the University's legal liability.

### **Involvement of the General Practitioner/Family doctor (GP)**

If your relative is enrolled in the study we will inform your relative's General Practitioner.



**What will happen to the results of the research study?**

The results of the research may be published. If so, this will be in a medical journal. Your relative will not be identified in any report.

**Who is organising and funding the research?**

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**Who has reviewed the study?**

A local research ethics committee has reviewed the research.

*1 copy in medical notes, 1 to patient & 1 to trial folder*

# Mock Trial

## Consultee Consent Form

A prospective, randomised, parallel-group, blinded, controlled, collaborative, mock trial to investigate the safety and efficacy of Drug X in patients with acute stroke.

Investigator Name: Jo McCormack

Centre Number: ..... Patient Initials: ..... Patient Number: .....

Please initial box

1. I confirm that I have read and understood the information sheet dated 30<sup>th</sup> October 2011 (version 1.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that my relative's participation is voluntary and that they are free to withdraw at any time without giving any reason, without their medical care or legal rights being affected.
3. I understand that relevant sections of my relative's medical notes and data collected during the study, may be looked at by an individual from the University of Birmingham, regulatory authorities or from the NHS Trust, where it is relevant to my relative taking part in this research. I give permission for these individuals to have access to my relative's records. I understand that information held by the NHS and records maintained by the NHS Information Centre may be used to keep in touch and follow up on my relative's health status.
4. I would agree for my relative to take part in the above study, if this were a real trial.

\_\_\_\_\_  
Name of Relative

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Relationship to Patient

\_\_\_\_\_  
Name of Person  
taking consent

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

When completed, 1 for patient/relative; 1 for patient site file, 1 (original) to be kept in medical notes.

**This form does not relate to a real trial.**

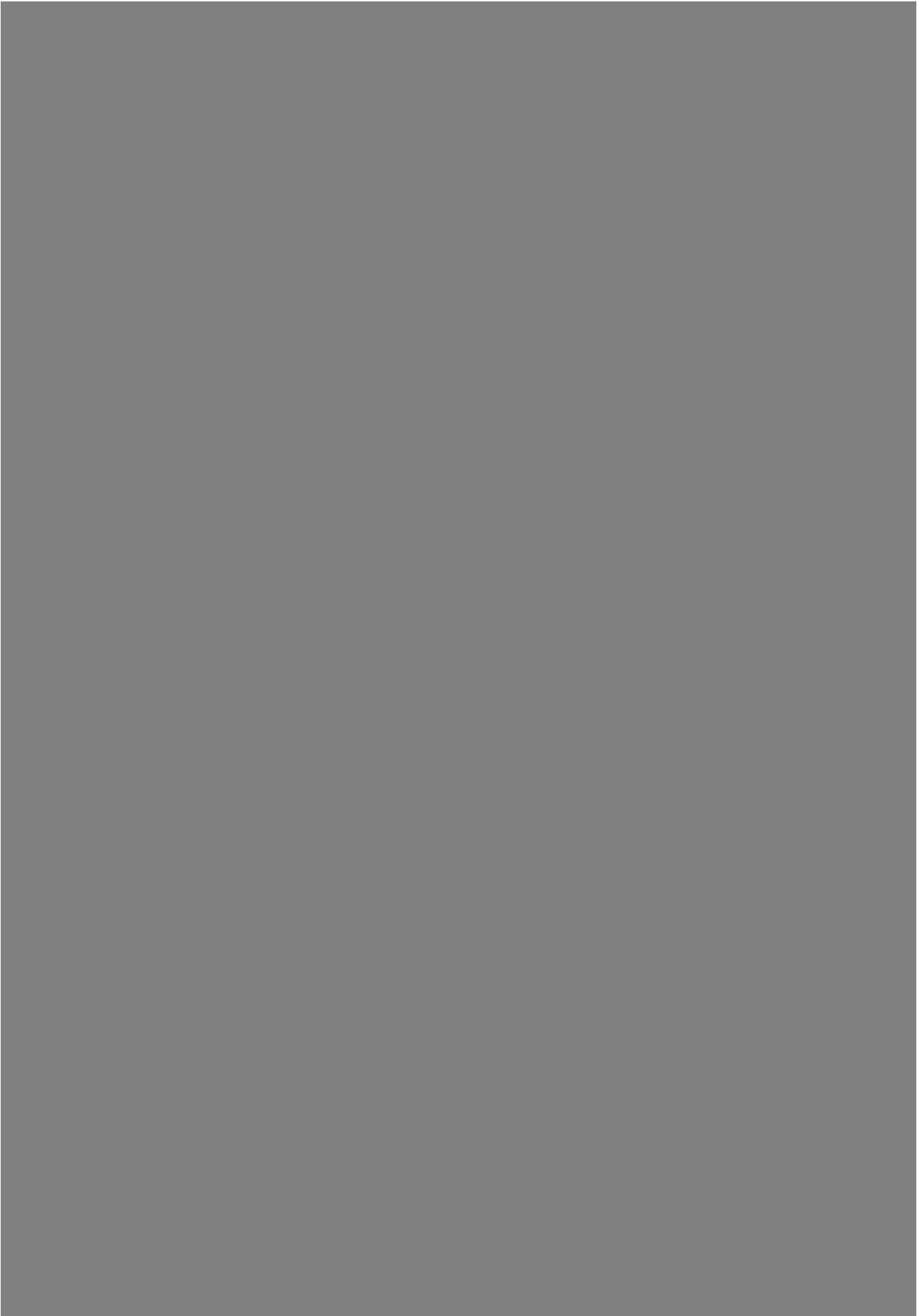
## APPENDIX 3

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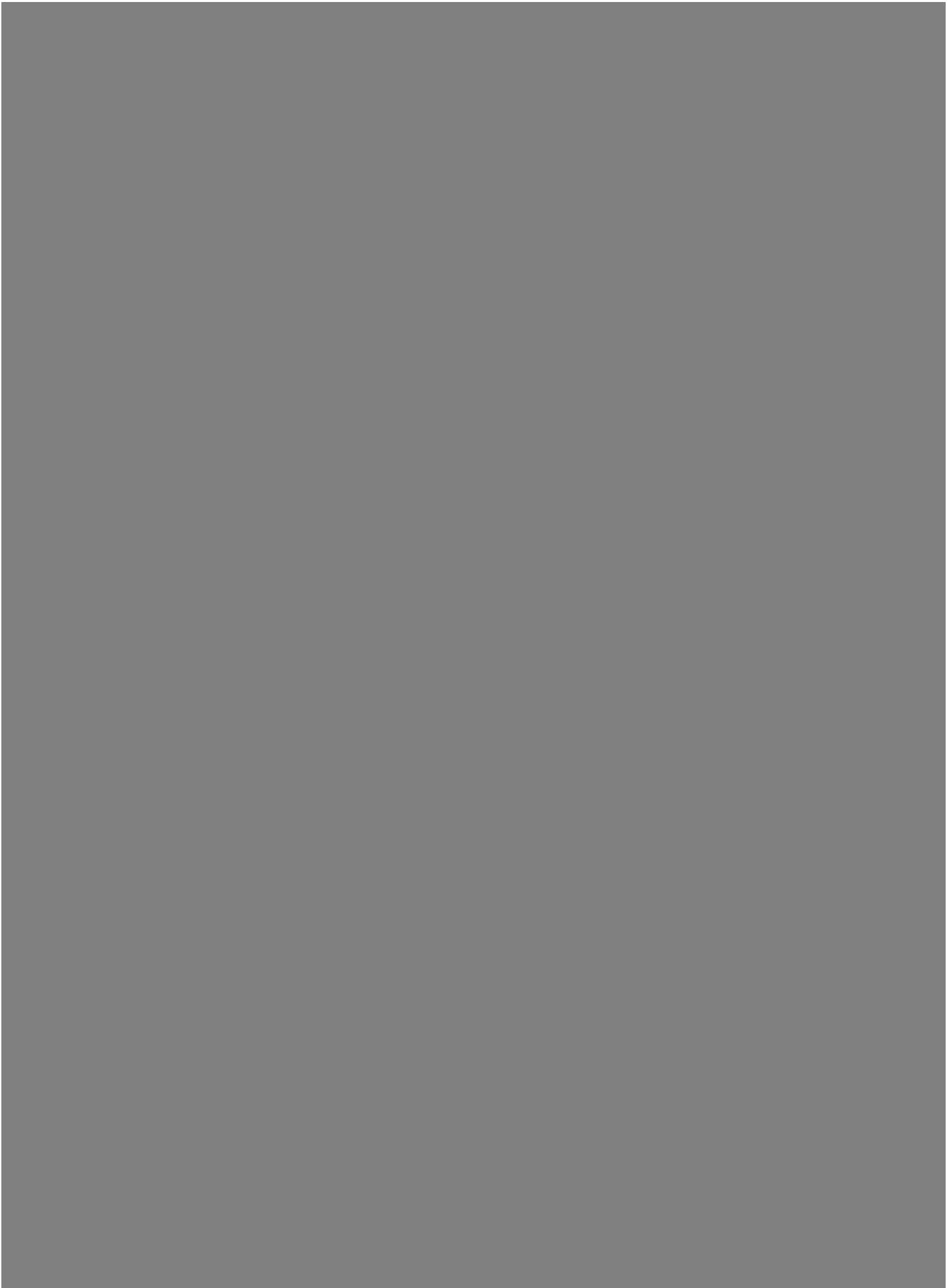
NIH Stroke Scale (NIHSS)



















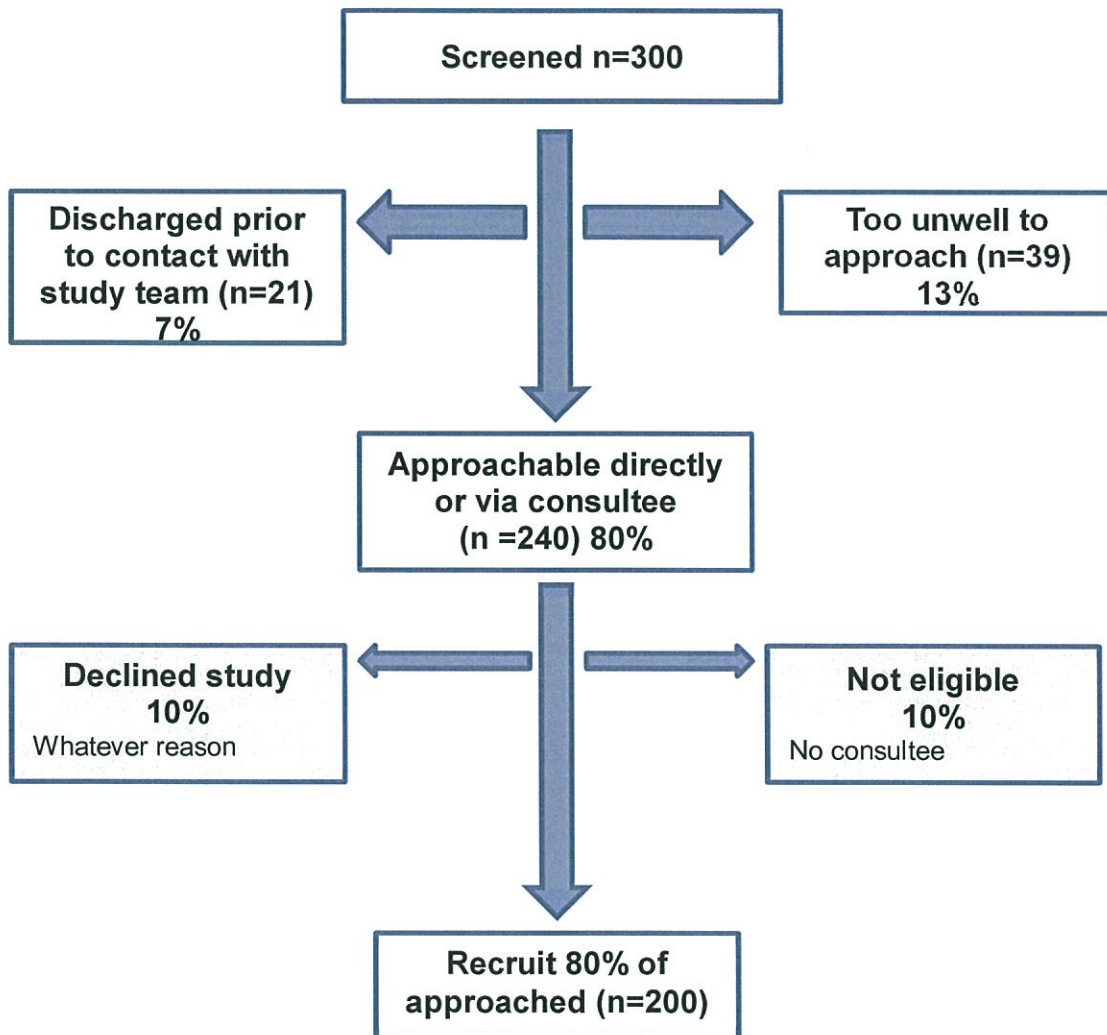




## APPENDIX 4

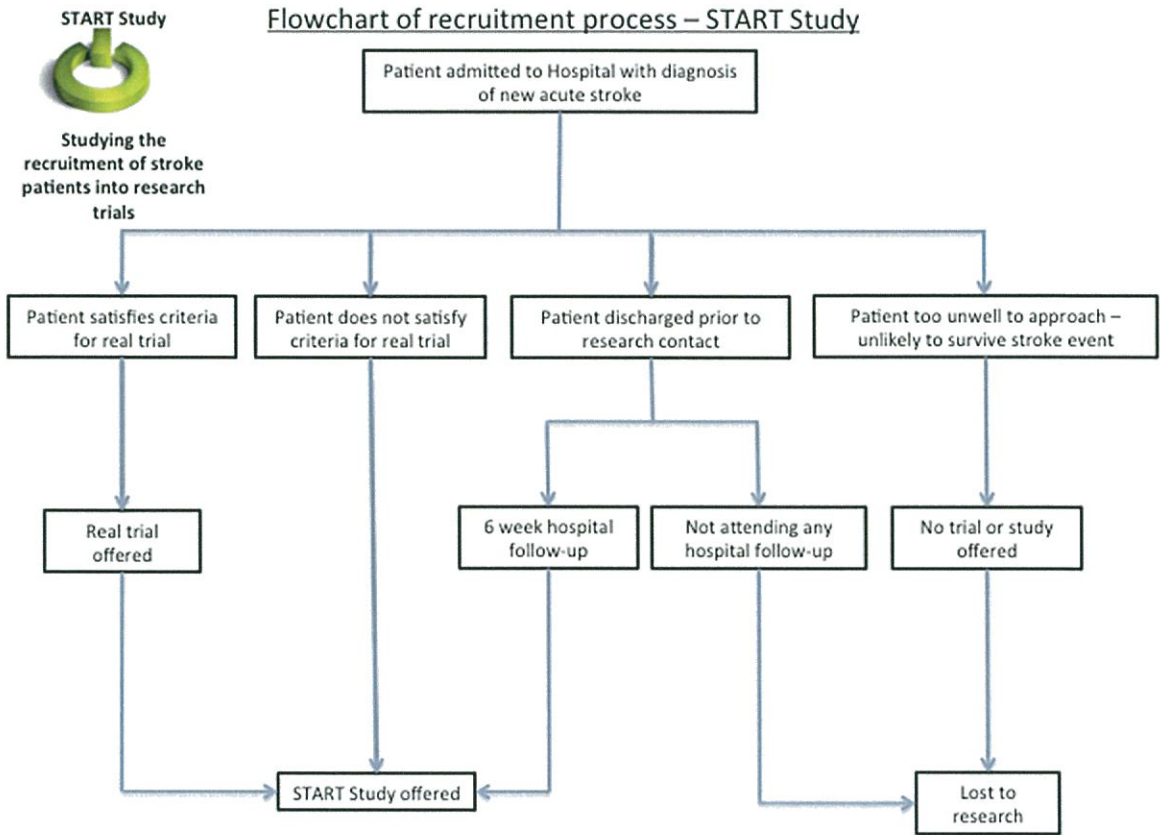
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### Predicted recruitment with a consort diagram format



## APPENDIX 5

### Flowchart of recruitment process



Summary Flowchart START Study, 30<sup>th</sup> August 2011 Version 1.0