Delirium and Acute Stroke

The occurrence of delirium and its association with long term outcomes for patients post-stroke

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Declaration

The candidate confirms that the work submitted is his/her own and that appropriate credit has been given where reference has been made to the work of others.

Dedication

In the memory of my beloved sister, Aisha Ahmed.

Acknowledgments

I would, first of all like to thank my supervisors, Dr John D. Holmes and Professor John B. Young for their support, input and guidance throughout this project. Their positive feedback and kindness towards me throughout my PhD was greatly appreciated.

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Abstract

Introduction

Delirium is an acute generalised impairment of brain function and a common complication of illness in older people. However it is commonly overlooked or misdiagnosed in clinical practice. Previous studies have found that delirium is linked to longer hospital stays, an increased need for institutionalisation and future complications e.g. increased risk of dementia and mortality. Delirium onset may be associated with an acute stroke, although few studies have investigated this association. The aims of this study were to identify delirium incidence in stroke, compare long term patient outcomes and identify confounding variables that may affect delirium onset.

Methods

Based on the findings from the systematic review, a UK based prospective cohort study with a one year follow up period was designed to recruit stroke patients with and without delirium. Additional assessments were administered within 72 hours of admission to assess physical function, mood, risk of dementia and cognitive impairment. These assessments were repeated six months post-stroke as well as monitoring outcomes such as mortality, length of stay and discharge destination.

Results

A total of 298 patients were recruited from the stroke unit at the Leeds Teaching Hospitals Trust, with a delirium incidence of 32.9%. Patients with delirium were associated with longer hospital stays, higher mortality rates at one and six months and an increased need for institutionalisation, as well as positive associations with a number of predisposing factors. Delirium patients also had lower assessment scores for physical function and dementia risk at six months.

Conclusion

The results of this study show that delirium has a significant effect on outcomes for stroke patients. Increased emphasis and awareness of delirium on the stroke units could help increase detection rates of delirium. Suggestions for the implementation of better education programmes and screening protocols may aid delirium management and these require further research.

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List of Abbreviations

A&E	Accident and Emergency
ACE-R	Addenbrooke's Cognitive Examination - Revised
AD8	Ascertain Dementia 8
ADL	Activities of Daily Living
AMTS	Abbreviated Mental Test Score
ASU	Acute Stroke Unit
BFHT	Bradford Foundation Hospitals Trust
BI	Barthel Index
BMI	Body Mass Index
BRI	Bradford Royal Infirmary
BST	Brain Attack Team
CAH	Chapel Allerton Hospital
CAM	Confusion Assessment Method
CAMDEX	Cambridge Mental Disorder of the Elderly Examination
CAM-ICU	Confusion Assessment Method - Intensive Care Unit
CANTAB	Cambridge Neuropsychological Test Automated Battery
CASP	Clinical Appraisal Skills Programme
CCSE	Cognitive Capacity Screening Examination
CDR	Clinical Dementia Rating

CI	Cerebral infarction
CLAHRC	Collaboration for Leadership in Applied Health Research and Care
CLRN	Comprehensive Local Research Network
CRF	Case Report Form
CST	Community Stroke Team
CT	Computerised Tomography
CTD	Cognitive Test for Delirium
DI	Delirium Index
DoH	Department of Health
DOS	Delirium Observation Screening Scale
DRS	Delirium Rating Scale
DRS – R98	Delirium Rating Scale – Revised 98
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders IV
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
EEG	Electroencephalogram
FIM	Functional Independence Measure
GCS	Glasgow Coma Scale
GDS	Geriatric Depression Scale
GMC	General Medical Council
GP	General Practitioner

HASU	Hyper Acute Stroke Unit
HES	Hospital Episode Statistics
HPA	Hypothalamic Pituitary Adrenal
ICD-10	International Classification of Diseases 10
ICDS	Intensive Care Delirium Screening
ICU	Intensive Care Unit
IH	Intracerebral haemorrhage
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
LGI	Leeds General Infirmary
LOS	Length Of Stay
LTHT	Leeds Teaching Hospitals Trust
LYBRA	Leeds, York and Bradford Research Association
MCA	Middle Cerebral Artery
MDAS	Memorial Delirium Assessment Scale
MEWS	Modified Early Warning Score
MMSE	Mini Mental State Exam
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
MRS	Modified Rankin Scale
MTS	Mental Test Score
MUST	Malnutrition Universal Screening Tool
NDS	National Dementia Strategy

NEADL	Nottingham Extended Activities of Daily Living
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHSS	National Institute of Health Stroke Scale
NSSA	National Sentinel Stroke Audit
OBS	Organic Brain Syndrome
ONS	Official National Statistics
PE	Pulmonary Embolism
PET	Positron Emission Tomography
RASS	Richmond Agitation and Sedation Scale
RCT	Randomised Control Trial
SAH	Subarachnoid Haemorrhage
SINAP	Stroke Improvement National Audit Programme
SIPSO	Subjective Index for Physical and Social Outcome
SJUH	St James University Hospital
SLH	St Luke's Hospital
SMMSE	Standardised Mini Mental State Exam
SPECT	Single Photon Emission Computed Tomography
SPMSQ	Short Portable Mental Status Questionnaire
SSD	Sub-syndromal Delirium
SSNAP	Sentinel Stroke National Audit Programme
TIA	Transient Ischaemic Attack

TICS	Telephone Interview for Cognitive Status
UoL	University of Leeds
WHO	World Health Organisation

Introduction

This purpose of this thesis was to investigate the clinical condition of delirium in the acute stroke population. The last decade has seen a rise in the number of elderly living longer. The latest projections estimate that in 20 years time, the elderly population in the UK will almost double to around 19 million by the year 2050[1]. This ever increasing population is a testament to our dedicated healthcare services, better research and improvements in daily living and care of the general public.

Historically stroke was regarded as a disease of old age and the majority of strokes tend to occur in the elderly population (over 65 years). Currently there are 10 million people in the UK aged over 65 years old[1] and each year there are approximately 152,000 strokes in the UK. In developing countries, the implementation of primary prevention initiatives focusing on smoking cessation and lowering blood pressure have helped to decrease stroke incidence and stroke mortality rates have also halved over the last 20 years[2]. However due to an ageing population, the overall rate of stroke remains high worldwide. In comparison to other chronic diseases, stroke has a large range of disabilities with many stroke survivors requiring long term care[2]. Quality of life is also affected as this population will unavoidably have an increased incidence and prevalence of illness, placing an increased strain on healthcare systems and providers such as the NHS, who are already under immense pressure.

Currently half of the general hospital beds are thought to be occupied by older people for whom the management of illnesses such as stroke may be more complex. This may be due to increased sensitivity to the adverse events of treatment and the presence of more than one disorder/ multiple co-morbidities. Delirium is a clinical condition that when combined with multiple co-morbidities in the elderly can lead to higher rates of hospitalisation, increased use of community resources and poorer patient outcomes. This complex clinical syndrome has been a topic of interest to researchers and clinicians for centuries[3], as evidenced by collections of scientific medical descriptions of delirium during this period by writers such as Hippocrates. In fact it was thought to be a common occurrence in people of that time and the existence of delirium can be traced as far back as 1400 in the literature. More easily recognised descriptions can found in plays such as Shakespeare's King Lear, where the king emerges from his delirium to recognise his daughter Cordelia.

In the present day, delirium has been described as a ‘cognitive superbug’ penetrating healthcare environments and complicating the course of hospitalisation and treatment, especially in the elderly[4]. Over time, a body of work on delirium has slowly started to build describing the various risk factors, highly susceptible patient populations, possible effects on prognosis and possible theories on the pathophysiology that may be responsible for delirium occurrence. However delirium has been historically understudied. As the average age of the population rises globally, a future parallel rise in stroke, delirium occurrence and an increased care burden is also likely be witnessed. Delirium will be a major concern to consider whilst tending to an increasingly aged population. It is clear that with time, the study of older adults and illnesses such as stroke are becoming gradually more significant as we look to ways to promote awareness and reduce the burden on our healthcare systems.

As mentioned previously, the purpose of this thesis was to investigate delirium within the acute stroke population. The first chapter aims to give an overview, discussing the degree of co-morbidity in terms of the occurrence of delirium in susceptible populations and the effect on patient outcomes. The following chapter will briefly discuss stroke incidence, pathology and patient prognosis post-stroke. Chapter three will examine the current literature available on delirium and stroke and discuss the impact these conditions have on patient outcomes. Any potential gaps in the published literature will be identified by conducting a systematic review and a meta-analysis will also be performed on the studies included in the systematic review. The conclusions from Chapter three will be used to help form the research questions described in Chapter four and define the aims and objectives of the study.

The study design and patient protocol will be designed to fulfil the research questions that have been selected. Any methodological, ethical and statistical considerations in addition to any amendments made to the study prior to patient recruitment, will be discussed in Chapter five. Chapter six will discuss the finalised study methodology by clarifying the details of the assessments methods and time periods. The results of the data collected will be analysed and presented in Chapter seven with any study limitations and areas for improvement to be discussed in Chapter eight. The final chapter will provide the study conclusions and summarise the key points of this thesis.

1 Delirium

In the Oxford English dictionary, delirium is described as “an acutely disturbed state of mind characterised by restlessness, illusions, and incoherence, occurring in intoxication, fever, and other disorders”[5]. The origin of the word delirium is from the Latin word ‘delirare’ which literally means to deviate from or go out of the furrow (de- ‘away’ and lira ‘ridge between furrows’) and was first used by the Roman physician, Celsius. Although delirium is now the accepted term, there have been numerous alternatives for the syndrome such as; ‘acute confusional state’, ‘acute brain syndrome/ failure’, ‘metabolic encephalopathy’, ‘organic brain syndrome’ and ‘ICU psychosis’[6]. This collection of terms was the result of different aetiologies and populations in which delirium was observed, and to some extent it illustrates the complex nature of the syndrome. Consequently this has been reflected in issues such as lack of recognition, low detection rates and misdiagnosis. There is a need for further investigation within this area.

1.1 The clinical profile

Delirium is a complex neuropsychiatric disorder caused by an underlying physical illness, resulting in functional disturbances in the central nervous system. This multifactorial clinical syndrome has several well defined predisposing and precipitating factors and has a broad range of physiological and psychological manifestations. The definition of delirium has changed over time and was classically described as a ‘clouding of consciousness’ to describe this state of confusion and attempts were made to distinguish it from dementia. Eventually it was defined as a transient disorder of cognitive function.

Delirium is characterised by a disturbance of consciousness and generalised impairment of cognitive function, resulting in instability of the autonomic nervous system and detrimental psychological symptoms[7, 8]. It is a characteristic syndrome, which has a distinct but variable presentation in relation to its cause. Its acute onset and fluctuating nature are good diagnostic indicators and other associated key features include; inattention/ distractibility, restlessness, anxiety, irritability, disorientation, perceptual disturbances, changes in thought processes and psychomotor activity and disturbances in the sleep wake cycle[9].

1.1.1 **Features**

The clinical features of delirium are as follows;

1. **Altered levels of consciousness –** Levels of consciousness may fluctuate between extremes such as unconsciousness or milder presentations such as inattention, drowsiness and inability to focus, the latter of which may be easily missed. Impaired cognition may mask changes in consciousness whilst a dementia patient may be drowsy due to sedation, reversal of sleep patterns or boredom. Because of this impairment of consciousness is not a reliable diagnostic indicator for delirium as it is intermittent and not easy to determine.

2. **Attention deficits –** Patients have problems in concentrating, sustaining or shifting attention and thinking clearly. They are unable to process information (e.g. remembering instructions) and focus (e.g. they may have to ask for directions and ask questions as they are easily distracted). Inattention often increases during the latter part of the day due to fatigue and this is known as ‘sun downing’. Inattention is useful in screening and can be tested by asking patient to spell a word backwards or perform simple subtractions.

3. **Memory impairment –** The ability to retain information is impacted by the altered levels of consciousness, inattention and lack of focus. Short term memory such as remembering recent events (e.g. reason for hospitalisation) are more heavily affected and contribute towards disorientation. These memory deficits, although short lived, are a constant sign in delirium diagnosis and can be tested using brief cognitive tests such as the Mini Mental State Exam (MMSE)[10] or the Abbreviated Mental Test Score (AMTS)[11].

4. **Disorientation –** Inability to register recent information partly due to inattentiveness. The patient’s ability to remember date, time, place and situation are decreased, leading to a reduced awareness of their environment. It can remain undetected if the patient is not asked directly for such information.

5. **Disorganised thinking –** The patients present as being confused and are unable to relay clear and coherent thoughts. Patients lack reason, logic and judgement and so content of thought is of very little relevance and is dysphasic and rambling in nature. They may also have an altered rate of speech that is rapid and at times repetitive, stammering, hesitant and dysarthic.

6. **Disturbance of perception –** Perceptual disturbances fluctuate with the symptoms and are usually related to memory impairment and disorientation. They arise due to sensory discrimination and patients have difficulty making sense of what is real and what is unrelated to them. They manifest as misperceptions, illusions, hallucinations and delusions. Visual hallucinations (e.g. peculiar images, seeing animals or strange people) and illusions (patterns are misinterpreted as insects moving) are most common. Auditory hallucinations or sensory disturbances (taste and smell) can also occur. Patients may also suffer from paranoid delusions which involve suspicious or persecutory beliefs (e.g. staff intend to cause them harm), but often may not report them as they are afraid they will be perceived as 'insane'.

7. **Emotional disturbances –** Patients may exhibit a diverse range of rapidly changing emotions and more than one emotion can be prominent or intermittent during an episode. Responses may be dependent on the nature of any hallucinations and emotional lability is a key feature where euphoria may lead to sadness, fear, anger and then to euphoria. Symptoms of anxiety, fear, irritability, anger, depression, sadness apathy or euphoria may be noted. Patients may display apathy and withdrawal and may appear depressed due to disrupted sleep and decreased motivation and appetite. Suicidal thoughts may be expressed. Agitation may occur as a result of confusion and disorientation and can lead to a patient being non-compliant. The emotional disturbances can be problematic but they do not remain for long periods of time.

8. **Disturb sleep wake cycle –** Sleep disorders include insomnia, fragmented/ reduced sleep, excessive drowsiness during the day, increased nocturnal agitation and reversal of the day and night sleep cycle. Reversal of the circadian sleep cycle combined with decreased environmental cues at night and the aforementioned symptoms previously discussed can make patient management difficult.

9. **Neurological signs –** Higher integrative functions such as problem solving, planning, reading and writing, visuospatial functions (copying designs and finding words) and praxis of actions may be affected. Neurological signs and symptoms such as tremors (asterixis), involuntary twitching (myoclonus), urinary incontinence, language disorders (receptive/ expressive dysphasia) and data impairment are more frequent in older people suffering from delirium.

10. **Disturbances of psychomotor activity –** Psychomotor activity is altered in patients with delirium and it is this motor behaviour upon which the different clinical

presentations can be based. These clinical presentations will now be discussed in further detail.

1.1.2 **Clinical presentations**

Lipowski (1990)[9] argued that there were different 'types' of delirium based on motor presentation; hyperactive, hypoactive and mixed and these subtypes were further studied by Liptzin and Levkoff[12]. Hyperactive patients exhibit an increased alertness and overactivity of the sympathetic nervous system. This may include autonomic features such as dry mouth, dilated pupils, sweating, raised blood pressure, rapid pulse and breathing, and tremors. It has been linked to adverse effects of drug intoxication and withdrawal. Hyperactive delirium is the most easily recognised presentation[13], but can be misdiagnosed as anxiety, schizophrenia, agitated dementia or a psychotic disorder. On the other hand, hypoactive patients exhibit subdued concentration, inattention, psychotic features such as delusions or disturbances of perception and may be frequently incontinent[14]. This presentation is not as easily detected, often remains unrecognised and is more common in elderly patients[15]. These cases are often dismissed as transient, or insignificant due to the lack of disruptive and odd behaviour. They can also be misdiagnosed as depression or dementia.

There are a small proportion of delirium patients that have an unclassified presentation as they do not exhibit any changes in psychomotor behaviour at all[16]. However, most patients tend to experience mixed delirium, due to rapid unpredictable shifts between the hypo and hyper states. This may be due to the multiple aetiological factors, individual co-morbidities, fluctuating nature of the syndrome and it is suggested that mixed delirium may put patients most at risk of substantial morbidity and mortality[17-19, 14]. There is also another clinical presentation of delirium known as 'sub-syndromal delirium' (SSD)[20, 21], the presence of which may precede or follow an actual episode of delirium. The clinical profile and experiences of outcome are similar to the other presentations and in some cases it may not even progress to a full episode. It occurs when a patient displays two or more features of delirium, but they do not match all the features stated in the Diagnostic and Statistical Manual of Mental Disorders (DSM)[22, 23] criteria. Some studies have suggested that a broader definition of delirium is needed as the current criteria may be too narrow[24, 25] and the DSM criteria have recently been revised to reflect some of these changes[26]. Overall these different clinical presentations of delirium may have differences in aetiology and pathophysiology, which may make them more associative with a particular disease state[27].

Their differences in clinical features means that there is no single pattern of delirium and this can lead to variations in detection, treatment responses and possibly even outcomes[28, 29]. However that does not make them exclusive to a specific condition or predictive of a certain aetiological cause. They are simply a clinical descriptor of the different presentations of delirium.

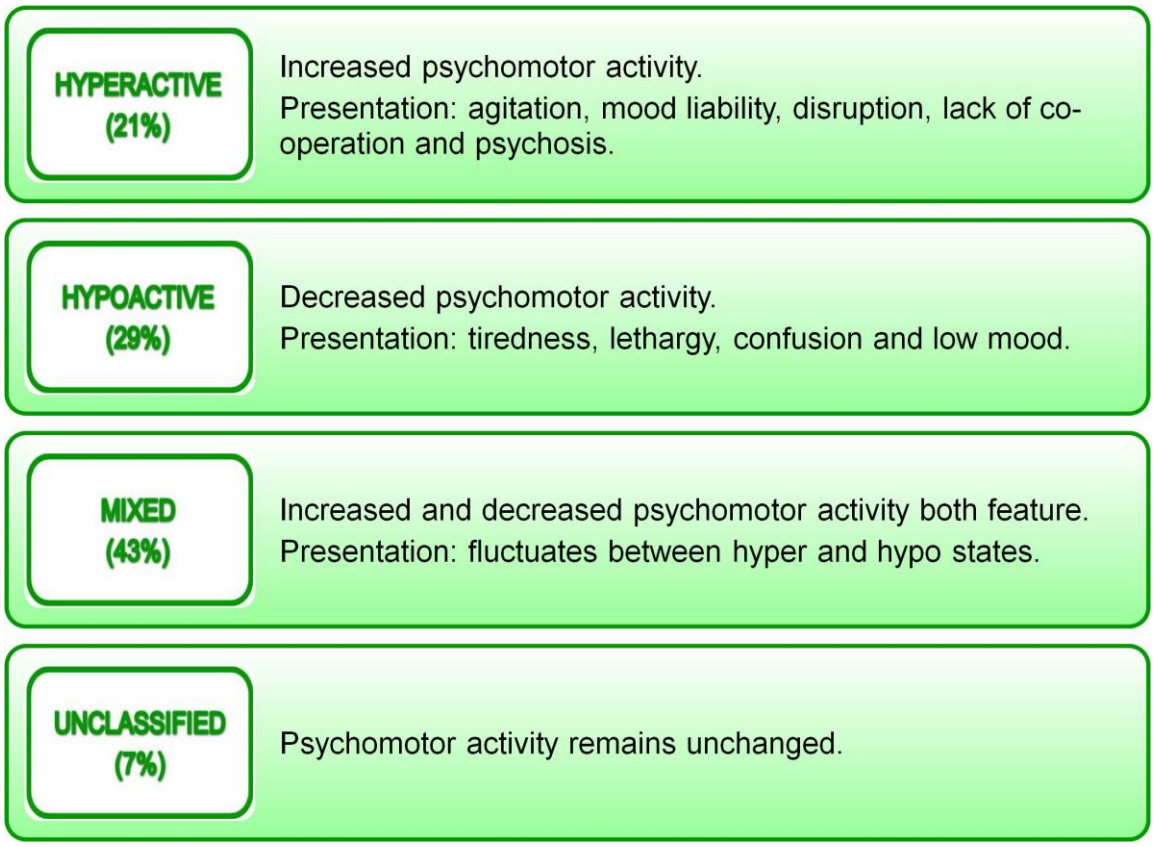

Image adapted from icudelirium.co.uk

Figure 1.1: Clinical presentations of delirium.

From the literature, the figure above summarises the different clinical presentations of delirium based on psychomotor activity and/or differences in arousal i.e. changes in attention and alertness.

1.1.3 Onset, severity and duration

The onset of delirium is acute meaning it can develop abruptly and be present one day and absent the next[30]. The symptoms are of a fluctuating nature as they wax and wane over of a period of time and often worsen at night[31, 32]. The majority of delirium within a general

medical or surgical setting tends to occur within 48 to 72 hours of admission, whereas in ICU, this onset may begin at an average of 2 to 3 days[33]. Severity of a delirium can be assessed with rating scales and studies show that patients with severe delirium have been associated with increased mortality, functional decline and a need for institutionalisation post-discharge[33, 34]. Around 22 to 51% of patients suffer from an episode of delirium that is classed as severe[35] and dementia has been suggested as a risk factor for severe delirium[36]. With regards to duration of delirium[37, 38], the reported literature for medical settings ranges from resolution of delirium in 24 to 48 hours, whilst others report delirium lasting up to 7 to 14 days[27, 39, 30].

Delirium was traditionally considered to be a transient condition in which most cases resolve within days or weeks as the physical illness subsides. However reviews and recent studies have suggested that in some people, delirium can be persistent[40-42], ranging from 5 to 39% of patients for a number of months subsequently[41]. The overlap between delirium, persisting delirium and onset of dementia has emerged as an important topic in the reviewed literature.

1.2 Aetiology and pathophysiology of delirium

In order to detect and manage delirium, a sound understanding of the syndrome and its causation is essential. In hospital settings underlying predisposing factors can combine with acute predicating insults leading to multiple aetiologies. These risk factors have a sequential multiplicative rather than an additive affect[43] and so single aetiology delirium is rare. Attempting to identify and treat a single cause is overly simplistic because in nearly half of elderly patients, there are usually two or more underlying conditions that contribute to an episode[44, 45]. Delirium risk factors will now be discussed in further detail.

1.2.1 **Risk factors for the development of delirium**

There are a number of risk factors associated with delirium, which can be present upon admission or develop during hospitalisation. Age (65 years and over)[46], pre-existing cognitive impairment[47], severe co-morbidity (deteriorating or risk of deterioration)[48], current hip fracture[49] and exposure to certain medications[50] are strong predictors of delirium onset. Risk factors can be related to the patient's condition (e.g. infection), a clinical intervention (e.g. urinary catheter) or their surroundings (e.g. numerous ward

transfers). Some of these risk factors (e.g. medications or change in environment) can be modified to prevent delirium onset[51], whilst other factors (e.g. age or gender) are non-modifiable[52].

It has been suggested that certain patients may be more susceptible to delirium than others[53]. When vulnerability at baseline is low, the patient remains resistant to delirium despite exposure to significant risk factors. However when vulnerability is high, exposure to even mild risk factors can trigger the onset of delirium. Based on this theory by Inouye et al, it would be logical to closely monitor patients with a high susceptibility to delirium onset. As a result, models of causation that quantify the role of numerous risk factors have been developed[54]. The risk of delirium can be predicted by observing the cumulative interactions of risk factors with baseline susceptibility.

Inouye et al, formed the concept that delirium risk factors can be divided into either the predisposing group or the precipitating group[55, 53]. Predisposing factors can be present upon hospital admission and these reflect the baseline vulnerability of the patient. Aside from age, pre-existing cognitive decline[56] is perhaps the most predictive risk factor for delirium as an increased risk has been reported in those with a prior history of delirium and poor cognition. Primary cerebral diseases such as Parkinson's disease and psychiatric illness, have also been shown to be significant[57]. Precipitating risk factors on the other hand, are hospital related factors that contribute to the development of delirium. These can be a result of stress such as lack of familiarity with surroundings or more harmful input such as invasive urinary catheters. In the elderly, incontinence, urinary retention and faecal impaction have also been shown to be significant risk factors[58, 59].

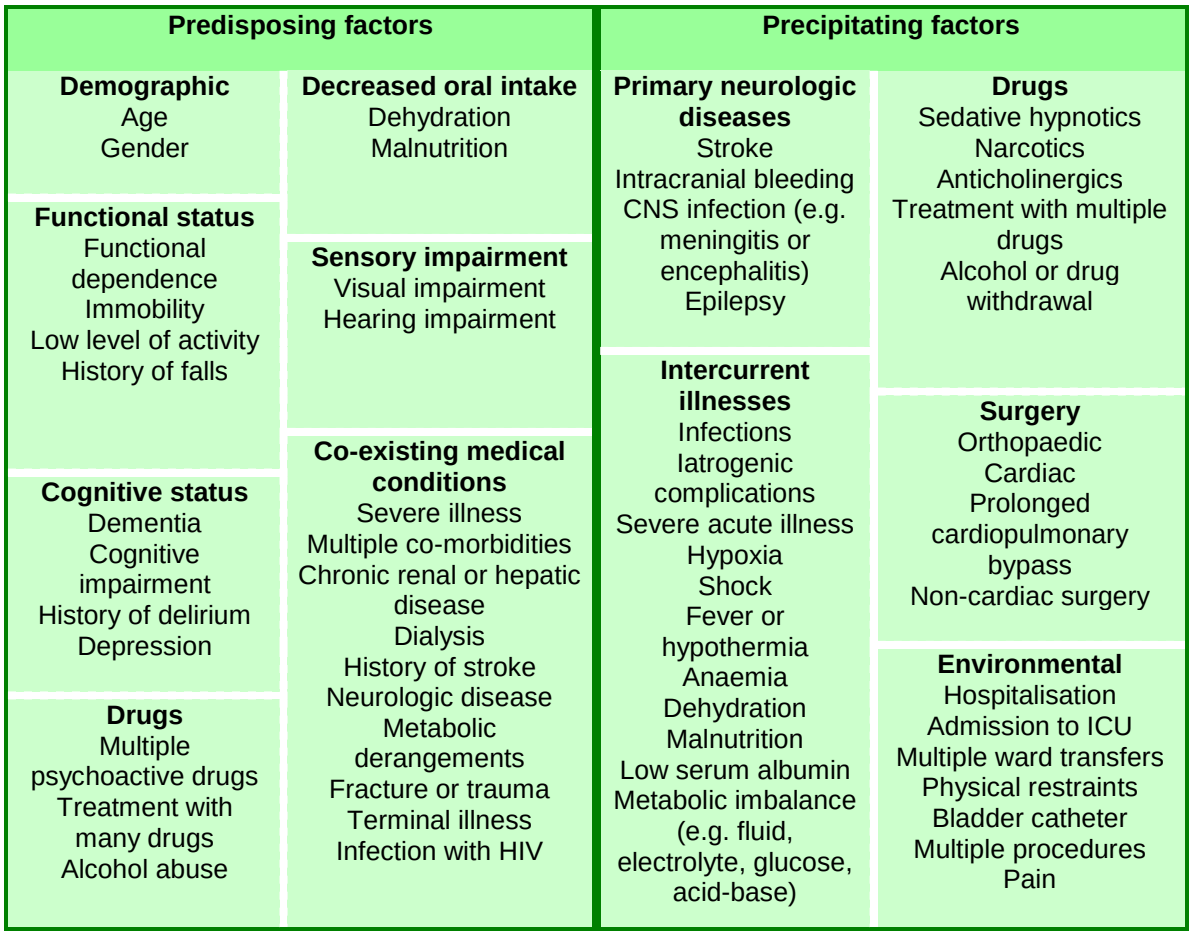

Image adapted from icudelirium.co.uk

Figure 1.2: Associated risk factors for delirium.

There are a vast range of delirium risk factors and one high risk groups is medications. Medications are implicated in 20 to 40% of cases[60] and almost every class of drug has the potential to cause delirium. Exposure to benzodiazepines, antipsychotics, tricyclic antidepressants, opiates, narcotics, anxiolytics, antihypertensives and anti inflammatories have all been implicated as predictors of delirium across different study populations. Anticholinergic medications have been not only been shown to increase risk but also increase the severity of symptoms after onset[61, 62] . Therefore it would be wise to minimise exposure to certain medications, especially during high risk periods such as post-operatively.

Figure 1.2 presents variables which have been clearly defined as predisposing or precipitating factors, producing a collection of modifiable and non-modifiable variables[46]. However, defining whether certain conditions are confounders or risk factors for delirium is not as straightforward. This lack of clarity suggests the need for more comprehensive risk factor studies, similar to those by Inouye et al[54] and Carrasco et al[63], upon which risk score models could be based in order to identify high risk patients. A risk factor study was

considered for this thesis and this is something that will be discussed in further detail in Chapters eight and nine.

1.2.2 **Studies addressing causation**

Causation is commonly the focus of epidemiological studies. Various studies have been conducted to try and find possible causes of delirium and some of these include deficiencies in the vitamin B12[64], lack of oxygen[65] and the use of medications such as anticholinergics[61]. As previously mentioned, most of the risk factor literature is based on a variety of different hospital settings. These range from the general medical population[66], the impact of a setting such as ICU[67, 68], the presence of risk factors for certain illnesses such as vascular disease[69] or cancer[70]or a specific patient population such as post-operative patients[71, 72].

There are a number of issues regarding the methodology of such studies and their reported findings may not be generalisable to other study populations. Examples of methodological considerations include: inadequate statistical analysis of risk factors (univariate analysis compared to multivariate analysis), small sample sizes (risk factor studies tend to have large numbers so that the results are statistically significant) and lack of consideration for confounding variables (as these could affect the outcome of results).

1.2.3 **Prevention measures for delirium**

Many risk factors may simply be markers of general morbidity; some are protective whilst others are causative factors, depending on the amount of exposure and the circumstances[58, 73]. Delirium risk factors can be modified by preventative interventions and reviews have highlighted that studies investigating the preventative impact of modifying these risk factors are of importance[74]. Preliminary evidence indicates that multicomponent interventions for modifiable clinical factors, tailored to the patient's needs and care settings, can reduce the frequency and severity of delirium.[75] This has been illustrated by a review of trials in medical and post-operative patients, which reported an absolute risk reduction ranging from 13 to 19%[76, 77]. In another study, active preventative interventions and early detection resulted in an economic benefit by decreasing long term nursing home costs by 15.7%[78].

Delirium prevention strategies can be simple and these are most effective when delivered by a competent multidisciplinary team who are adequately trained and experienced in delirium prevention. Education of health care professionals is essential so that they are familiar with identifying high risk patients and psychiatrists can help with training and identifying predisposing and precipitating factors for delirium. As well as the staff, it is important that family members are informed of the fluctuating and acute onset of delirium features so that they too can be involved in improving detection within community settings. Family members may also be able to provide insight into subtle changes in cognitive function, physical function, perception and social behaviour; all of which could be indicative of delirium onset.

Those at high risk should be regularly monitored and disruptions to surroundings should be minimised (i.e. no excessive staff changes and ward transfers). Other common elements that can be modified with substantial clinical benefit include regular review of medications and elimination of unnecessary drugs, adequate hydration and nutrition, careful and effective prescribing of pain relief, monitoring for signs of infection or hypoxia, avoiding the use of catheterisation and physical restraints, correction of sensory deficits, reorientation, clear communication with the patient, non-pharmacological approaches to anxiety, sleep enhancement, early mobilisation and cognitive stimulation.

It is worth noting that once delirium had developed, these interventions were found to be less effective and efficient[79, 80]**.** There is a clear need for more trials in the prevention of delirium[81-85]. Specific areas of interest include the use of psychotropic medications, the impact on psychological morbidity, activities of daily living, quality of life, cost of intervention and mortality.

1.2.4 **The pathophysiology of delirium**

The pathophysiology of delirium is poorly understood. O'Keeffe[86] summaries it best as a manifestation of diffuse, non-specific and non-psychiatric generalised disorder of cerebral oxidative metabolism and neurotransmission. It can also include the dysregulation of inflammatory agents in the cerebrum and any other neuro-biologic factors that are involved in neurotransmitter function. It is clear that further research is needed[87-90] and these changes in pathology could be used as potential biomarkers for the detection of delirium[91-95, 88]. There are a number of theories which will now be briefly described.

1. **Cerebral oxidative metabolism –** This is the most well known theory and is still under research[96, 97]. Using electroencephalographs of delirious patients, it was theorised that delirium was due to oxidative metabolism in the brain leading to dysfunction of the cerebral cortex[98]. However since its initial conception, it has been proposed that neurotransmitters may also be a contributory factor.

2. **Disruption of neurotransmitters –** Acetylcholine, dopamine, serotonin, γ aminobutyric acid, glutamate, melatonin and histamine have all been implicated in delirium pathology.

   a) Acetylcholine: is involved in the complex regulation of attention, arousal, cognition and consciousness and cholinergic neurones often undergo degenerative changes during ageing. Therefore decreased levels of acetylcholine could be responsible for delirium features such as inattention and impaired cognition. Studies have also shown that multiple anticholinergic medications can cause an 'anticholinergic burden' increasing the risk of delirium[99] and the reversal of this could form the basis of a potential treatment for delirium.

   b) Dopamine: works in combination with acetylcholine as high levels of dopamine lead to lower levels of acetylcholine and so dopamine excess can cause delirium[100]. For example, opiates and also drugs used to treat Parkinson's disease (Levodopa) can increase risk levels of dopamine, whilst dopamine antagonists such as antipsychotics can be used to treat delirium[101].

   c) Others substrates: such as serotonin, GABA, noradrenalin and glutamate may have a role as they interact with cholinergic and dopaminergic pathways[102]. GABA medications have also been linked to both the improvement and deterioration of delirium[103].

3. **Inflammatory agents –** Both cortical and subcortical structures have been implicated and it has been suggested that cytokines such as interleukins, interferons and tumour necrosis factors may also be involved[104-106]. Studies have reported elevated levels of cytokines in delirious patients[107] whilst in other studies, specific interleukin levels were found to be lower in non-delirious patients[108], suggesting that they may be neuroprotective.

4. **Stress response or drug induced –** Stress is an important modulator in brain function as it induces a rapid response in the sympathetic nervous system, increasing delivery of oxygen and glucose thus enhancing cognitive function. The Hypothalamic Pituitary

Adrenal (HPA) axis affects neuronal integrity and produces a slower sustained response that can last for days or even weeks. However excessive stimulation of the HPA axis leads to increased levels of glucocorticoids and this can have an adverse effect on the amygdala, prefrontal cortex and the hippocampus[109]. Studies have reported elevated cortical levels, resulting in hypercortisolism in stroke patients[110, 111].

1.3 Prevalence of delirium

Delirium is a serious health issue, particularly in the older population as it has a high incidence and prevalence in community and hospital settings. It is frequently not recognised, poorly detected and badly managed[112]. Poor recognition is a well known issue as studies have reported that between a third and two thirds of cases remain undetected in clinical practice[113]. In a survey of US physicians, 89% considered delirium to be an important outcome, 40% routinely screened for delirium but only 16% used a specific tool for detection[114]. These identification problems exist across all clinical settings[115]. The rates of non-detection (43% to 66%) reflect the poor understanding and under appreciation of delirium as a serious independent condition.

1.3.1 **The occurrence of delirium**

Care home delirium is poorly recognised and there are only a few population based studies for delirium occurrence in the community. The majority of the delirium occurrence estimates are derived from hospital settings. In a paper by Meagher[32] incidence rates were reported as general population (0.4%), general population over 55 years of age (1.1%), general hospital admissions (9 to 30%) and elderly hospital admissions (5 to 55%). In the elderly, rates can range from 15% to 62% in post-operative patients[116, 117] and up to 70 to 87% in elderly patients in intensive care[118]. Delirium has been reported to be present in 10 to 24% of older adults upon admission to hospital (prevalent cases)[119]. This can then develop in a further 5 to 35% of elderly patients during hospitalisation (incident cases) and often this number can be as high as up to 50%[67, 120, 121]. The prevalence in intensive care units has been reported as up to 60 to 85%[122], up to 62% in hip fracture[123] and over 50% in post-operative patients[124, 125] and the terminally ill[126, 127]. The occurrence of delirium within nursing home residents (over 75 years) has also been shown to have a wide variation ranging from 15% to 60%[30].

Study population	Delirium rates
Community dwelling older adults (prevalence)	
- aged 55 years and over	< 0.5 to 1.1%
- aged 85 years and older	< 0.5 to 13.6%
N.B. Small number of cases in both studies	
- incidence of delirium in non-demented (over 3 year period)	10%
Skilled nursing facilities and long term care settings (prevalence)	0.5 to 39%
Frail older adults receiving Health Care Services:	
- Nursing homes	58%
- Assisted living facilities	35%
- Elders living at home with Home Care Services	35%
Hospitalised older adults:	
- Admission to medical wards (prevalence)	5 to 31%
- Subsequent incidence during hospitalization	3 to 55%
Elderly admissions to Accident and Emergency (prevalence)	5% to 10%
Elderly accident and emergency attendees	16%
Patients with AIDS	17 to 40%
Hospitalised patients with HIV	30 to 40 %
Cancer patient	25 to 40%
Cancer patient in the terminal stages	28 to 85%
Intensive care unit patients (overall)	12 to 50%
ICU setting	11 to 31%
Sub ICU setting	29.2%
N.B. In sub ICU setting, this was split into;	
- present at admission (prevalence)	15.5%
- developed during stay	13.7%
Post-operative patients (overall)	5 to 75%
- Elective non-cardiac surgeries	5 to 26%
- Elective vascular surgery	29 to 52.2%
- Major abdominal surgery	60%
- Cardiac surgery	8 to 50%
Elderly surgical patients with hip fracture (prevalence)	4.4 to 61%
Elderly surgical patients with hip fracture post-operative (incidence)	4 to 53.3%
Other studies:	
- patients with hip fracture	50%
- people with hip fractures	40 to 60%
- hip fracture in the elderly	16 to 62 %

Image adapted from the paper by Meagher et al[31]

Figure 1.3: Rates of delirium in different clinical settings.

The figure above summaries the delirium rates observed in various study populations. The highest rates of delirium are seen in the ICU and surgical hip fracture patients. The delirium rates for the elderly hip fracture population are relatively high, the reason for which is unknown. Some literature suggests that the occurrence of delirium in the hip fracture may be a separate entity[71], compared to the delirium observed in the general medical population. With regards to cardiac surgery, it is dependent on population and type of procedure being performed. It has been suggested that improvements in surgical, cardiopulmonary bypass and anaesthesia technique may have lowered this incidence rate[124, 128, 129], however this has not yet been confirmed.

Figure 1.3 summaries the delirium rates (unless otherwise stated) across some of the different clinical settings. We can see that the rates can vary and this can be due to the population under assessment, the nature of the study setting, the patient procedures being administered and the detection methods employed. Furthermore the definition of occurrence may change as different studies may choose different time periods for delirium detection ranging from acute admissions to the entire length of hospital stay. In some studies the presence of delirium may be assumed to be zero upon hospital admission, thus combining prevalence and new incidences of delirium to calculate a cumulative delirium incidence, which would produce inaccurate estimates.

To summarise although the table may illustrate well defined rates, it may not be as accurate due to variations in methodology and definition. A standardised protocol for research studies in delirium may help to eliminate some of these issues and would allow for accurate and reliable comparisons to be made. For the purposes of this overview, overall delirium is more frequent in older populations, those with certain medical or surgical problems and those with pre-existing dementia.

1.3.2 **Detection of delirium (case ascertainment)**

A clear understanding of baseline cognition is essential to delirium detection and families can help identify subtle changes in mental state. A cognitive screening tool such as the MMSE or AMTS should be used to confirm this. The literature shows that routine cognitive assessment when used in combination with Confusion Assessment Method (CAM)[130] can help to increase delirium detection[32, 131]. Considering that delirium is an indicator for serious illness, any sudden deterioration in mental state should be treated as delirium specifically for elderly patients, who should be screened and regularly reviewed for risk factors. Once delirium has been detected, the search for the underlying causes and precipitants should begin[132, 133].

The clinical diagnosis and initial evaluation should involve history of alcohol and drug use, a review of medication and background history from the patient, family, carers and GP's. Delirium cases are often prevalent upon hospital admission[76] and a thorough history can help identify when the condition developed and what triggered it, the duration of symptoms and identification of the risk factors[132, 133].

1.3.3 **Diagnosis of delirium (case definition)**

Physical and neurological examinations are performed to help identify the underlying cause but this may not be straightforward as patients can be resistant and uncooperative. Investigations should be conducted to determine the aetiology of delirium which can include; blood tests, oxygen saturation, ECG, chest X-ray, urine analysis, liver enzyme and function tests, lumbar puncture and cerebral imaging scans[134-137]. Careful consideration of the results can help to distinguish delirium from other disorders.

Once delirium has been identified, a clinical assessment should be carried out using the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V)[23] or the International Classification of Diseases 10 (ICD-10)[138] which are considered the international standards for delirium diagnosis. Substantial developments in neuropsychology have been made in the past 20 years and this is of particular benefit to the elderly population[139-141]. These include; clearer definitions for delirium, a range of tools to identify, diagnose and assess delirium symptoms and the gradual recognition that delirium is associated with a significant independent morbidity. Figure 4.1 illustrates the range of diagnostic tools that can be used for delirium detection. It should be noted that some of the tools listed in Figure 1.4 are not specifically designed to detect and diagnose delirium. Therefore it is possible that certain tools may only focus on specific areas such as cognitive impairment, which is only one feature of a delirium episode. The use of delirium tools will be discussed in further detail later in Chapter five (Section 5.4.2). Consideration for choosing a suitable tool should be: (1) why is the instrument being used? (2) Who will be conducting the assessments, within what time frame and how often? (3) Is the tool suited to the setting and the population being studied?

	Scale	Presence of delirium	Characteristics
MINIMAL TRAINING	**Mini-Mental State Exam**	≤ 20	5 domains/ 30 points; 10-20 minutes; widely used by most clinicians; requires verbal communication from patient; not suitable in ICU setting; not delirium specific.
	Cognitive Capacity Screening Exam	≤ 19	7 domains/ 31 points; 10-20 minutes; cognitive screen, differentiation between 'functional psychoses' and diffuse organic brain syndrome
	Short Portable Mental Status Questionnaire	≥ 3	10 items/ 10 points; 3-5 minutes; cognitive screen; verbal; determines organic brain deficit; affected by education levels
	Clock Drawing Test	Depends on completion	Quick and easy; cognitive screen; psychomotor skills tested; useful in Alzheimer's disease
HIGH TRAINING	**Memorial Delirium Assessment Scale**	≥ 7	10 items/ 30 points; especially useful for repeated assessments, severity; does not include items for diagnosis
	Confusion Assessment Method	Positive	9 items; 20 minutes; best diagnostic tool; no rating of severity; not suitable in ICU setting
	Confusion Assessment Method ICU	Positive	4 features only; 2-3 minutes; very quick; useful in ICU setting
	Delirium Rating Scale	≥ 12	10 items/32 points; useful in screening, diagnosis and symptom severity; widely validated and available in different languages
	Delirium Rating Scale Revised 98	≥ 15	16 items/ 46 points; 13 severity items and 3 diagnostic items; ideal for longitudinal studies
	NEECHAM Confusion Scale	≤ 24	3 subscales/ 9 items/ 54 points; 10 minutes; useful at delirium onset and in patients with 'quiet' manifestations; suitable in ICU setting
	Cognitive Test for Delirium	≤ 22	5 domains/ 30 points; 10-15 minutes; developed for ICU setting; 100% sensitivity
	Abbreviated Cognitive Test for Delirium	≤ 10	28 points; visual attention span and recognition memory for pictures only; more practical for use by ICU Clinicians
	Intensive Care Delirium Screening Checklist	≥ 4	8 items/ 8 points; suitable for ICU setting; especially for patients with language disturbance
	Delirium Observation Screening Scale	≥ 3	25 items/ 5 point Likert scale per item; easy to use; observational scale; assesses severity; developed for use by nurses

Image adapted from the paper by Pae et al[55] and Adamis et al[142]

Figure 1.4: Summary of the tools used to detect delirium.

The figure above provides an overview of the current tools that are used to screen for delirium and the areas that they focus on. It should be noted that not all the tools listed above such as the MMSE, have been designed to specifically detect delirium [143].

1.3.4 **Differential diagnosis of delirium**

The medical differential diagnoses for delirium is extensive and in order to treat delirium, a large number of aetiologies must be differentiated and investigated[144, 44, 145]. Differential diagnoses to consider in delirium are dementia and depression (common), dementia with Lewy Body, functional psychosis and mania (less common) and post-ictal confusion and dysphasia (rare), the latter of which are common post-stroke[146, 147]. Figure 1.5 illustrates the key differences between delirium and some of the aforementioned disorders.

Dementia: The traditional distinction between delirium and dementia is the acute onset, fluctuating nature and reversibility of delirium[148-150]. However this aspect of reversibility can be complicated in some patients. This can include Lewy Body dementia (which has a slow fluctuating nature with psychosis)[151, 152], exposure to a prolonged delirious state (which leads to subsequent cognitive decline)[153] or often the persistence of delirium symptoms months after discharge[41]. It has been suggested that delirium may be an indicator of undiagnosed or evolving dementia[154, 150]. Recognition rates for dementia are considerably low in the community (estimated to be at around 40%) resulting in a rising prevalence of dementia in acute hospital settings[155].

Diagnoses can become complicated as patients with pre-existing dementia can develop superimposed delirium[156, 157] (as evidenced by up to two thirds of superimposed delirium cases), which can result in worse outcomes for the patient[156, 158]. In cases where both dementia and delirium occur, the presentation of delirium remains the same as delirium symptoms are clinically dominant. Therefore when diagnosing between delirium, dementia and delirium combined with dementia, careful history taking with emphasis on the onset, attention and fluctuation of key features is essential[159].

Depression: The symptoms of depression (low mood, suicidal ideation, apathy, demotivation, withdrawn) occur frequently in delirium[160, 161]. The emotional and behavioural changes in delirium are often mistaken for adjustment reactions for cancer or trauma patients[162], however true onset of depression is often less acute and sustained. Cognitive impairment is occasionally seen in depression, known as depressive pseudo-dementia[163], can be mistaken as a confusional state. Therefore careful history is needed for an accurate diagnosis. A study showed that up to 40% of psychiatry referrals for suspected depression were actually found to be delirious[164]. It is important to distinguish between delirium and depression[165] as many antidepressants have anticholinergic properties[62] which in turn could worsen a delirium episode if incorrectly treated.

	Delirium	Dementia	Depression	Psychosis
Onset	Acute	Insidious	Variable	Variable
Duration	Short	Lengthy	Variable, recurrent	Variable, recurrent
Course	Fluctuating	Steadily progressive	Diurnal variation	Variable
Consciousness	Clouded	Clear until late stages	Generally unimpaired	Unimpaired
Orientation	Poor	Poor	Usually good	Good
Attention	Poor	Preserved in early stages	Poor	Poor
Cognition	Impaired	Impaired	Variable	Normal
Short term memory	Reduced	Reduced	Normal	Normal
Hallucinations	Common (visual)	Infrequent	Rare	Common (auditory)
Delusions	Common psychotic ideas are unstructured, fleeting and simple in content	Uncommon	Occasional psychotic symptoms are complex and in keeping with prevailing mood	Frequent psychotic symptoms are complex and paranoid
Speech	Incoherent	Dysphasia	Normal	Normal
Involuntary movements	Present	Absent	Absent	Absent
Physical illness	Present	Absent	Variable	Absent
Electroencephalogram (EEG)	Abnormal in 80 – 90%; generalised diffused slowing in 80%	Abnormal in 80 – 90%; generalised diffused slowing in 80%	Generally normal	Generally normal

Image adapted from the paper by Meagher et al[165]

Figure 1.5: Differential diagnosis of delirium.

The figure above summarises the difference between different psychiatric symptoms. Delirium can frequently coexist with other disorders, which means that making a diagnosis can be more complicated. Principal disorders from which delirium must be distinguished are dementia and depression especially in hypoactive patients. The presentation of delirium can also mimic functional psychiatric disorders such as agitated depression or mania and hyperactive delirium can be mistaken for schizophrenia due to the auditory and visual hallucinations.

1.3.5 **Considerations for prevalence studies**

Prevalence studies may be conducted in different settings and with different patient groups, for example: community settings, hospices, nursing homes and hospitals. The rates of occurrence listed in Figure 1.5 may not actually be a true representation of the populations studied due to lack of recognition or detection. There are a number of reasons for under-diagnosis which will now be discussed[112].

Non-detection is a major obstacle in delirium research. The stereotypical image of delirium is that of delirium tremens (agitated and disturbed) which is a separate entity in itself and only accounts for a small minority of care. Due to this stereotype, somnolent or hypoactive presentations of the conditions are often ignored[133]. Paradoxically hypoactive is the most prevalent subtype in the elderly[167] and these are the cases that are often left unidentified upon examination of patients.

Delirium prevalence in the community is low[168] and is not the focus of many epidemiological studies. Even in general hospital settings, upon admission the prevalence of dementia is usually higher than that of delirium. It is only upon hospitalisation that the incidence of delirium begins to increase due to the presence of multiple risk factors. This raises a few questions about future research. Firstly are prevalence rates in the community underestimated and do we need to conduct more studies to counteract this? And secondly are the current incidence studies sufficiently informative for delirium research? This leads onto my final point regarding the under diagnosis of delirium in clinical settings[169].

The clinical manifestations of delirium itself can lead to under diagnosis but the fluctuating nature of the delirium means that cases may present themselves between assessment periods. As a result patients with delirium may be classed as not having delirium and cases are therefore missed. Also with regards to certain subtypes (e.g. hypoactive), cases are not a cause for concern as previously mentioned so these cases may also be missed. Those that are hypoactive may be more compliant than hyperactive patients and this compliance may incorrectly be perceived as intact cognitive function. Misdiagnosis may occur as changes in cognition may be masked by conditions such as pre-existing dementia or psychomotor retarded depression[145]. The use of different diagnostic terms, as listed in the beginning of Chapter one, may also lead to uncertainty over what is being diagnosed.

Methodologically, in certain settings screening for delirium or even cognitive impairment is not a routine procedure despite some studies suggesting that early recognition is helpful[170, 171, 169, 172-175]. The minority of clinical settings that do screen for delirium often use tools that

assess cognitive function rather than those specifically designed for delirium detection. Furthermore, the delirium tools developed to screen and assess delirium vary in sensitivity and specificity (this will be discussed in Chapter four) which can have an impact on the reported findings. The timing and frequency of repeat assessments for delirium is also likely to have an effect on the occurrence rates reported[39].

Screening for delirium alone is not sufficient and interviews with carers are required to detect subtle changes in behaviour. There is often a lack of informant history regarding the patient's prior baseline cognitive and physical function. Unfortunately a formal cognitive assessment routine is often lacking in the technological world of medicine. Frequent and continuous monitoring of patient cognitive function is required to highlight any deterioration in mental state, an indicator of delirium. Symptoms of delirium can often to be attributed to sensory deprivation of the hospital environment rather than delirium itself. There is also the issue of the lack of appreciation of delirium as a distinct entity and an indicator for serious morbidity and mortality[176]. This may in part be due to technological focus and rapid pace of modern hospital care and partly due to the inattentive or ageist attitudes towards helpless patients, older adults or those that present with confusion. These attitudes can lead to people normalising such behaviour when in fact these features of delirium are of medical significance.

The shift pattern of staff and system and communication problems between numerous ward transfers can also lead to information not being relayed correctly and diagnoses being missed[177, 178]. Nurses spend a significant amount of time with patients and their families so they are well placed to detect delirium[179, 180]. However if nurses are not adequately trained, then they may be overly reliant on monitoring cognition or use of orientation cues[181]. Therefore decreased levels of skilled nursing staff could contribute to low levels of detection. Similarly other medical staff that may not have any experience of delirium diagnosis could lead to inaccuracies in the assessments. Compared to psychiatrists, doctors are more likely to use their own clinical diagnosis as they are less familiar with methods to assess cognition and inattention[114]. Possible solutions would be the introduction of educational programmes, routine cognitive testing, using delirium screening tools and more frequent involvement of psychiatrists for delirium management[32, 25, 166, 180].

Considering these reasons, the occurrence of delirium reported in the elderly could possibly be an underestimation. This wide variation illustrates the differences in patient groups, potential confounders, methodology and lack of consensus regarding delirium definition. Errors in delirium diagnosis impact upon management of delirium and the long term outcomes which will now be discussed.

1.4 Management of delirium

The management of delirium requires a multifaceted bio-psychosocial approach using a competent and well trained multidisciplinary team[132, 133]. Firstly the cause of the physical underlying disorder needs to be identified and treated. Diagnosis and treatment work side by side so regular progress reviews are good practice and can also help detect and treat any additional risk factors that may appear at later stages[182].

Keeping the family as well as the patient up to date on the progress is beneficial. Delirium can be a terrifying experience so adequate information, reassurance that the symptoms are temporary and should resolve and clear effective communication can help both the patient and their families. Reorientation should be facilitated by the presence of relatives, consistency in staff members, familiar possessions, frequent verbal reminders and multiple cues with regards to their settings and circumstances.

Furthermore good communication within teams from primary healthcare (home) or general medical team (hospital) is a key component to successful management[166]. The mental health team can help to clarify differential diagnosis patients, deal with problem behaviours and assess symptoms competency. Studies have found that there is a referral bias towards hyperactive patients who are seen as having severe delirium and so benefit from a higher rate of psychiatric consultations and pharmacological interventions[32]. Hypoactive cases should also receive the same level of treatment and it is suggested that psychiatry services could contribute their skills in identifying these cases[32]. Often the involvement of the mental health team occurs much later in the treatment process and it has been suggested that an earlier involvement could be advantageous[25, 166].

1.4.1 **Environmental measures**

Efforts should be made to provide a safe environment and minimise the potential for complications (e.g. falls). A good therapeutic environment should maintain good nutrition and fluids intake, maintain mobility, avoid under and over stimulation, ensures surroundings are bright, well lit, quiet and comfortable, correct sensory deficits (e.g. glasses, hearing aids, dentures), promote adequate levels of sleep with sedation, avoid use of physical restraints where possible. The environmental strategies such as a ‘delirium room’[83, 183, 184] or those described above[185, 183] are underutilised despite being free from adverse reactions. Studies have found that these strategies are not applied in response to changes in cognition but rather in response to disruptive behaviour (hyperactive delirium)[27, 186, 187].

The literature reports that there have been some positive responses with regards to delirium prevention[188, 82, 80, 189-191] but the effectiveness of these measures remains mixed[77, 192]. For example a recent RCT of the use of a specialist delirium/ dementia ward concluded that even though patient and carer satisfaction was improved, there was no convincing benefit in health status or service use[193].

1.4.2 **Pharmacological intervention**

Medication as a cause has been implicated in a large number of delirium cases (>30%) so excessive medication use or compounds that may aggravate delirium are best minimised[194, 195]. Certain antipsychotics can modify neurotransmitter dysfunction[196] and there have been trials to treat delirium using cholinesterase inhibitors such as rivastigmine[197]. Medications are often used to alleviate delirium symptoms by controlling disruptive or distressing behaviour such as hallucinations or agitation. Consideration should be given to severity of symptoms, the clinical setting, dose and administration, patient age and risk of side effects[198]. Timely intervention, regular review using the Richmond Agitation and Sedation Scale (RASS)[199, 200] and input from psychiatry regarding the appropriateness of the treatment plan are considered good practice.

There are a range of medications used to manage delirium symptoms and their use is briefly discussed. The use of psychotropic drugs should be stopped as it can interfere with the patient's cognitive status[201]. Sedatives can be used to control agitation and restlessness but again they can worsen cognitive function. Antipsychotics are the most frequently used as they help to control agitation and psychosis but also help to improve attention and orientation[202]. It has been suggested treatment should continue until the symptoms are fully resolved as initial improvements may just be a fluctuation of the delirium[203, 204]. When the patient does stabilise, then the dosing of antipsychotics should be gradually tapered and discontinued rather than an abrupt stop. Antipsychotics such as haloperidol are the most studied[205, 206] but atypical antipsychotics such as risperidone and olanzapine are also being evaluated for use in delirium[207]. Benzodiazepines such as lorazepam (also known as tranquillisers) are the first choice of drug to mitigate delirium associated with alcohol withdrawal symptoms. There are also studies looking at the use of procholinergic drugs to help in the treatment of delirium[208].

1.4.3 **Follow up treatment**

Symptoms of delirium can persist beyond the acute phase of treatment and this must be accounted for when planning a patient's discharge from hospital. Follow up visits are recommended following hospital discharge as they can help to identify residual cognitive, functional or social problems as well as reducing the risk of delirium reoccurring[133]. Simple education and clear communication with the patient and their families is important as delirium can be a distressing experience for both.

Communication with the patient's family can help explain the delay period that often occurs between the acute treatment of the underlying physical disorder and the return to normal mental function which can take days, weeks or even months to normalise[41]. Careful explanation of the diagnosis can help avoid families misinterpreting delirium as evidence of brain damage. Disorientation and inattention can be persistent problems and carers can help provide reorientation cues for patients[43]. In addition to this, families can prevent future episodes of delirium by early recognition of the signs and possible causes such as sensory impairment which can easily be corrected at home[209].

Many patients do not feel comfortable discussing their experience of delirium. Some patients may feel that the delirium is a sign of future events and could be an indication of a psychiatric disturbance. As a result patients undergo 'silent delirium' where they suffer in silence and are afraid or ashamed to acknowledge their symptoms and ask for help[210]. The psychological aftermath of delirium is understudied[32], but depression and post-traumatic stress disorder has been associated with delirium[211]. The development in geriatric neuroscience and the accessibility of psychiatry services, both in the community as well as the hospital means that psychiatrists can remain involved with the patient's treatment and facilitate future research. Delirium may also be an indicator of dementia[211]. It has therefore been suggested as good practice to utilise the multidisciplinary teams in the hospital and the community and request referrals for continued social support or further assessments[133].

1.4.4 **Future emerging therapies**

Given that delirium may be a disturbance of brain function some studies are investigating patients with hypoglycaemia[212] and hypoxia[65] associated with cholinergic metabolism whilst other groups have investigated traumatic brain injury[213] and stroke[214, 215, 38, 46, 216-218].

There is also the possibility of using medication to help treat rather than just manage the effects of delirium e.g. using procholinergic medication to normalise acetylcholine levels in the brain[196]. Other medication classes have also been tested such as using low doses of antidepressants (e.g. trazodone[219] and mianserin[220]) to help alleviate cognitive symptoms as well as alterations in mood. Oddly, smoking has been identified as a possible protective factor against the risk of developing delirium [221]. However a trial testing nicotine replacement therapy is lacking.

Other studies have reported the application of light therapy[222] and more recently music therapy[223, 224] can help prevent under and over stimulation of noise levels. However both of these potential therapies need to be correctly evaluated before routine use. If regularly used, then prevention interventions and standardised detection and management protocols can help to improve delirium care by reducing severity, duration and recurrence of episodes. Therefore efforts are being made to introduce a common delirium screening method in clinical settings as part of the regular admissions process. All these interventions have the ultimate aim of improving patient outcomes which will now be discussed.

1.5 Effect of delirium outcomes

Delirium has been associated with an overall poor prognosis. An increased mortality risk has been reported among older adults both during, and after, hospitalisation with estimates ranging from 22 to 76%[225, 226]. High mortality rates have also been reported at one month, six months and one year with a reported mortality rate of 35 to 40%[227-229, 226, 230]. This high rate is most likely due to the severe underlying medical pathology. However, once illness severity and confounding variables have been adjusted for, the rate of mortality directly attributed to delirium may actually be lower.

Significant independent co-morbidity has been strongly associated with delirium[231, 232], especially in certain populations such as post-operative patients[233, 234, 28, 235]. In the elderly population overall high morbidity levels were associated with risk of falls, pressure sores, incontinence, malnutrition, dehydration and pneumonia[236, 237]. This increase in complications means that the average length of stay in hospital is significantly longer for patients with delirium (21 days) compared to those without delirium (9 days)[19]. Although there is a lag phase between acute treatment and return to normalised mental function, most patients do experience complete resolution of their delirium symptoms. However certain groups such as the elderly are less likely to make a full recovery[238, 239].

Studies have found that, post-discharge delirium has a strong independent impact on functional ability and cognitive decline[18]. Studies have shown that at the time of discharge, patients still had significant cognitive decline which then persisted for many months leading to long term memory impairment[40, 41, 240]. It is thought that delirium may actually highlight patients that have a decreased brain reserve making them more susceptible to long term cognitive illnesses. Therefore it is possible that delirium could actually be used as an indicator for evolving dementia[241, 150]. Patients with delirium have an increased need for institutionalisation at one and six months and overall have a higher rate (47%) compared to non-delirium patients (18%)[40].

Inyoue et al[55, 53, 242], reported that there is a seven fold increase in mortality risk for delirious patients discharged from the emergency department. Delirium present at discharge was associated with a 2.6 fold increase in risk of death or nursing home placement. Delirium that persisted beyond discharge from acute treatment was highly associated with rehospitalisation, prolonged institutionalisation and death[40]. For almost a third of cases delirium was persistent after discharge and as delirium can last for several months, the long term prognosis has shown to be worse for this group of patients[41]. Another study reported that almost two years post-discharge, the risk of mortality, functional decline and institutionalisation was almost double in patients diagnosed with delirium[243]. Some studies suggest that delirium results in prolonged hospitalisation which leads to an indirect decline in functional ability[18, 19, 244], whilst others believe that irreversible brain damage is caused as a direct result of delirium[241, 245]. There is also a psychological and social impact[145, 246, 113] associated with the distress that delirium causes for patients and their families. However this has been severely understudied and so the full effect post-discharge is unknown.

Delirium places a large strain on patients, their families and social and health services. The cost of delirium to the NHS is substantial and healthcare costs are typically doubled in delirious patients[78]. Delirium is associated with higher hospital costs due to prolonged hospitalisation. There is the cost of increased nursing time per patient due to the frequency of more medical complications as a result of delirium[247]. The total estimated additional cost is £1500 for every delirious patient[78]. Additional costs still continue to accrue after hospital discharge due to; increased need for institutionalisation, rehabilitation, follow up visits, home care and rehospitalisation due to high remission rates in delirium[247]. Inyoue and colleagues estimated that 2.3 million older people each year have their hospital stay complicated by delirium, resulting in 17.5 billion hospital days and medical expenditure of over $6.9 billion[56]. The economic cost of delirium in a US study has been shown to range

from $38 to $152 billion each year[78]. It is estimated that people with delirium have a greater than two fold increase in costs than for people without delirium and its economic impact is similar to the cost of diabetes mellitus[248], hip fracture[249] and falls[250] in older people. Despite high morbidity and mortality and economic burden, delirium is still a poorly recognised syndrome.

1.5.1 **Considerations for prognostic studies**

The present knowledge base of delirium is lacking in many areas, but there are many opportunities for important research. Issues with delirium have included poor rates of recognition and detection, identifying causation and appropriate treatment, the presence of disruptive behaviour and dealing with the aftermath of a delirium episode. As a result there are wide variations in clinical practice (e.g. geriatricians compared to psychiatrists) and inconsistent treatment guidelines. In order to produce good quality evidence, future studies require careful consideration of issues such as: informed consent which may be problematic due to the nature of delirium[251-253], the methodologies employed and identification of a suitable study population.

When planning a prognostic study, study sample, case ascertainment and case definition should be clearly defined with justification of the selection criteria used. From the onset, studies should have well defined clinically significant outcomes, the results of which should be clearly documented. This also includes taking into consideration important confounding variables when measuring outcomes (e.g. accounting for the presence and relevance of dementia in a study sample). With regards to confounding variables, a suitably representative number should be chosen in accordance to the size of the study sample and these should be recorded at the time of assessment in order to minimise error. When examining the possible effects of confounding variables on the chosen study outcomes, appropriate statistical techniques (e.g. multivariate approach) should be applied and results should be presented in a clinically relevant context (e.g. use of confidence intervals and odds ratios). Considering the association between delirium and mortality, survival analysis (e.g. Cox proportional hazards model) would also be an appropriate statistic test to consider conducting.

With regards to methodology, any follow up period should be clearly defined and justified. For example, would one month post-discharge be suitable to assess dementia or would a six month period be better suited. Assessment tools should be carefully selected with consideration given to what will the instrument be used for, who will conduct the

assessments, in what time frame and how often and is the tool suited to the population being studied.

Other areas to consider include increasing knowledge of phenomenonology and its impact on outcomes as well as the long term psychological impact on patients after a delirium episode. Currently the pharmacological management of delirium is based on theoretical knowledge as opposed to well designed efficacy studies. Due the fluctuating nature of delirium, it is important to evaluate the efficacy of interventions using a placebo controlled study. However problems of consent (patient may be incapacitous during certain periods) and withholding treatment in a clinical situation would be the ethical sticking points. Outcome predictors need to be identified to assess the effectiveness of delirium interventions. With this in place, pharmacological interventions can then be tailored to treat the clinical presentations of delirium and their psychological impact, in order to be most effective and efficient. The combination of pharmacological treatment with environmental therapies also needs to be evaluated, in order to identify what treatments are most effective.

1.6 Conclusion

Delirium is an understudied neuropsychiatric condition that is associated with significant morbidity, increased need for hospitalisation and long term institutionalisation and a subsequent decline in cognitive and physical function. Delirium also carries a serious risk of mortality that is much higher in comparison to an illness like dementia. The management of delirium is primarily dictated by the setting and the population in which it occurs. However issues of non-detection, under diagnosis, misdiagnosis and lack of management and treatment experience are a cause for concern. No single speciality has assumed responsibility for the clinical management or study of delirium. This has subsequently resulted in inconsistent definitions, wide variation in research methodologies, inadequate consideration of confounding variables and heterogeneity of the populations studied making it difficult to interpret and compare findings. Fundamentally it has resulted in the under appreciation of delirium as a serious clinical indicator of significant morbidity and mortality. One study population that needs further investigation regarding its association with delirium is acute stroke. Chapter two will now provide a brief overview of stroke and its associated outcomes.

1.6.1 **Key points**

- Delirium is a neuropsychiatric disorder that is accompanied by an underlying physical illness.
- It is a common occurrence in the elderly; however delirium is often overlooked or misdiagnosed in clinical practice.
- Undetected delirium can delay patient recovery and have an adverse effect on outcomes due to increased rates of morbidity and mortality.
- Better staff awareness, efficient and effective detection methods and early interventions may help patients at high risk of delirium, but basic research is lacking.
- A possible high risk group that has been identified as needing further investigation is the acute stroke population.

2 Stroke

In more economically developed countries, stroke has been reported as one of the most important causes of ill health, disability and death and it was ranked as the third most common cause of death worldwide. Stroke has recently transitioned to the fourth leading cause of death globally, demonstrating the healthcare improvements and commitment to decrease cerebrovascular illnesses[254]. The World Health Organisation (WHO) defined stroke as; 'rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin'[255, 256].

The current data indicates that in developed countries; the economic burden of stroke is responsible for 2 to 4% of the total health expenditure[257] and it has the highest cost to society in the Western Hemisphere[258]. This economic burden includes both direct and indirect costs such as; the cost of hospitalisation, specialised care staff, rehabilitation, treatment/ management of subsequent medical complications, lost productivity and the caregiver burden and costs associated with loss of independence[259, 260]. Due to differences in the use of resources and units cost, the cost of stroke, length of stay and the survival rate varies across countries[261-263].

Considering the significant burden caused by stroke, research expenditure for stroke is comparatively less than the amount spent on heart disease and cancer research[264]. Awareness and recognition of stroke symptoms was found to be low in the general public[265], however the launch of recent media campaigns such as 'FAST' aimed to change this[266]. Stroke is strongly associated with an increase in age and with an impending ageing population, this disease requires more attention. The following chapter aims to give a brief overview of the epidemiology, risk factors and outcomes associated with stroke. This provides some context for the work conducted in this thesis.

2.1 Clinical symptoms and subtypes

Stroke is a clinical syndrome and can be caused by the interruption of blood supply to the brain due to a blood vessel ruptured (intracerebral haemorrhage), or an occluded blood vessel (cerebral infarction). Transient ischaemic attacks (TIA's) are sometimes referred to as 'mini strokes' and are caused by temporary occlusions such that symptoms resolve

within 24 hours. A series of TIA's can increase the likelihood of an acute stroke occurring and treatments such as thrombolysis[267] are administered to avoid future poorer outcomes for patients. Adverse outcomes post-stroke can vary between patients and may include increased mortality risk, prolonged hospitalisation or a decrease in cognitive function[268, 269]. A stroke can be identified by sudden numbness or weakness in one half of the body or a single limb, incoherent/ slurred speech, confusion, changes in gait, problems with balance or coordination and blurred or double vision[270, 271, 216]. Non-specific presentations such as confusion, immobility, incontinence or falls may also be present but these can also be attributed to conditions other than stroke[272, 273]. The symptoms of stroke can have a similar presentation to features of a delirium, which were previously described in Chapter one.

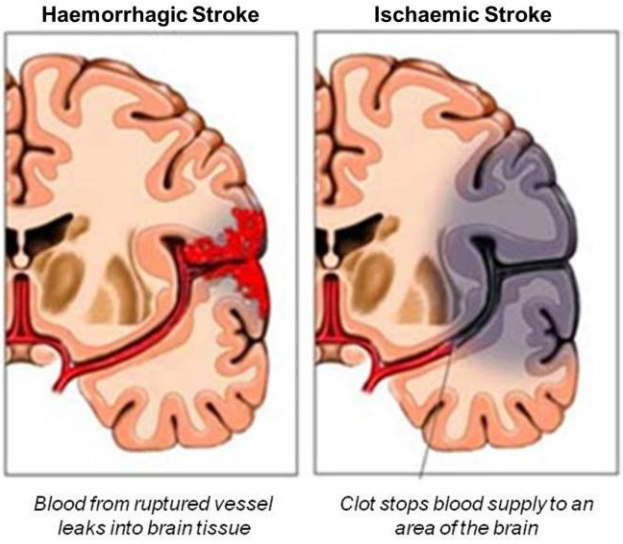

Image obtained from aurorahealthcare.com

Figure 2.1: Types of stroke.

An ischaemic stroke is caused by a lack of blood flow to certain brain areas due to hypoperfusion, the presence of emboli or the formation of thrombi[255]. A decrease or lack in blood flow means that certain brain areas become deprived of oxygen. If there is a lack of oxygen for approximately 60 to 90 seconds, the brain will cease to function and a lack of oxygen for over three hours can lead to irreversible brain damage[273]. Haemorrhagic strokes on the other hand, are caused by weakened blood vessels which can rupture causing blood to accumulate in certain brain areas. In these types of strokes, the brain area is damaged by tissue compression due to the accumulation of blood in that area. The site and severity of the damage determines the fatality of the stroke and whether the subsequent disabilities are temporary or more permanent. The territory supplied by the middle cerebral artery (MCA) is where most strokes usually occur[255].

Clinical subtypes of stroke include intracerebral bleeding, subarachnoid haemorrhage (SAH) and infarctions. An infarct can be further divided between large vessel disease, small vessel disease (lacunar), cardioembolism and rare causes such as venous infarction, vasculitis, and infective endocarditis[275]. Subarachnoid haemorrhages are consistent with the clinical definition for a stroke, but are regarded as a separate entity due to the different clinical presentation and distinctive management[276]. Vascular dementia, silent infarctions and TIA's are examples of cerebrovascular conditions that do not readily fit the WHO definition of stroke[277, 278]. This is an especially common problem in the elderly population for whom the diagnosis of an acute stroke may be more problematic[279]. Correct characterisation of the stroke using classification scales[280] can help determine information such as treatment plans, risk of recurrence and long term prognosis.

2.2 Epidemiology of stroke

Stroke is a debilitating disease with significant long term consequences. Its high prevalence indicates that it is accompanied by significant economic and social burden[260]. Approximately 150,000 people suffer from stroke each year in the UK[281] and 200,000 deaths per annum in the USA and Europe can be attributed to stroke[281].

Over 80% of strokes occur in people aged over 65 years and the annual incidence of stroke rises 1% with each year in this group of people[282]. After the age of 85 years, 25% of men and 20% of women can be expected to suffer a stroke[283, 284]. According to estimates from The National Service Framework for Older People, each year over 100,000 people in England and Wales people suffer a first stroke[285, 286]. Based on a review of epidemiological study data, it was estimated that in a population of one million people, 1800 patients will present with a first stroke, 600 patients with a recurrent stroke and 500 patients will present with a TIA[287].

In 1999 data from the Fourth National Morbidity Survey[288] in England and Wales was analysed for stroke incidence, workload and pattern of disease in general practice in relation to the patient's age, sex, socioeconomic status and aetiological contribution of identified risk factors for stroke. The one year prospective cohort study (1991-1992) surveyed 502,482 patients across 60 general practices in England and Wales. It was estimated that there were 87,700 people with a first ever stroke and 53,700 with a recurrent stroke, giving a total number of 133,700 strokes overall.

Although there has been a steady decline in stroke mortality over the past three decades, other measures of disease burden are needed[289, 290]. Incidence rates can help to identify if the case fatality is changing over time and measure the true burden of the disease[291, 292, 286]. National incidence data are limited due to the large amount of data, cost and time involved with such research[257]. Instead incidence studies are often localised to specific areas or communities[293-295, 283, 296, 297], which may not be an accurate representation of the general population[298, 299]. Such data are important for policy makers and health organisations e.g. Department of Health (DoH), National Institute for Health and Clinical Excellence (NICE), to plan for and organise stroke care nationally. Important considerations for economic studies for stroke include standardisation of stroke reporting[298] and maintaining stroke registers[300], longer duration of patient follow ups, inclusion of a broad range of services for patients post-discharge and social care and support provision[301, 302].

2.3 Aetiological causes of stroke

The causes of stroke include heart disease, small and large vessel disease, hypertension and venous thrombosis[303]. There are numerous risk factors that can also accumulate over time and contribute to the onset of a stroke but preventative treatment of these factors can help to reduce the risk of a stroke occurring[304-306].

Previous studies[307, 308] have identified a large number of possible risk factors, the evidence[309, 310] for which has been summarised in various reviews of the literature. Risk factors include; increasing age[311], male gender[312], certain ethnicities[313], cardiovascular disease[314], ischaemic heart disease[315], atrial fibrillation[316], carotid artery stenosis[317], diabetes mellitus[318], hypertension[319], hypercholesterolemia[320], hyperlipidaemia[321], sickle cell disease[322], previous TIA's or strokes[323], smoking[324], alcohol[325], drugs[326], inappropriate diet lacking fruit and vegetables[327], lack of exercise[328, 329] and social status[330].

The incidence of stroke increases with age and the risk of having a stroke are doubled every 10 years after 55 years of age[284]. Although stroke is more prevalent in the older population, 10% of strokes occur in younger adults under the age of 50 years[331]. Studies have found that males are more prone to strokes than females, but women have a higher risk of stroke mortality of over 60%[281]. Those with a family history of stroke may also be more susceptible to stroke. For example the presence of a genetic disorder such as

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)[332] can increase the risk.

People in the African-Caribbean and South Asian communities have a much higher risk of death from stroke and are twice as likely to have suffer a stroke compared to people who are Caucasian[333, 334]. A study found that after adjusting for age, the prevalence of stroke was 40% for African-Caribbean and 70% for South Asian men[335]. These groups are at a higher risk partly due to the high incidence of obesity, diabetes and hypertension. Other factors such as geographical location seem to increase the likelihood of having a stroke i.e. more common in south-eastern United States[336, 337]. Social status also seems to be a possible risk factor as analysis has shown that unskilled manual workers (low income socioeconomic group) have a 60% higher stroke risk in comparison to professionals (more affluent socioeconomic group). The mortality is also 50% in the low income group compared to the more affluent[338]. However these findings seem to vary between levels of economic development of specific countries[339].

As mentioned previously, TIA's are often seen as strong predictors of an impending stroke (ten times more likely than someone who has not had a TIA). Similarly history of a previous stroke also increases the chances of having another stroke in the future. The association between first strokes and recurrent strokes against the known risk factors was reviewed[303]. It was reported that increasing age, atrial fibrillation, diabetes, heart failure, ischaemic heart disease, hypertension, smoking and previous TIA's were strongly associated with first time strokes[303]. Similarly with recurrent strokes, there were strong associations with again increasing age, diabetes, hypertension and also a history of TIA's and previous stroke[340, 341].

Prevalence of stroke in England among minority ethnic groups in the year 1999

	Male %	Female %
Black	3.2	0.8
Indian	2.5	0.7
Pakistani	0.7	0.6
Bangladeshi	1.2	0.4
Chinese	0.7	0.2
Irish	2.0	2.0
General population	2.3	2.1

Image obtained from The Stroke Association

Figure 2.2: Prevalence of stroke according to ethnic groups.

The figure above lists the percentages of men and women that suffered a stroke, according to their ethnicity.

2.3.1 Prevention strategies

The phrase 'prevention is better than cure' is certainly appropriate for stroke when the economic and social burden and the long term impacts are considered. There is a significant effort being made to educate the general population and put preventative measures in place that address stroke risk factors[304, 305, 342, 306]. Government campaigns involving the promotion of a healthier lifestyle consisting of a better diet, regular exercise, decreased intake of alcohol and cessation of smoking are recommended and encouraged.

Studies have shown that increasing age, male gender and previous TIA's or stoke are important factors but these are unmodifiable. However some of the important modifiable risk factors and their effectiveness are as follows.

- **Cardiovascular disease –** This includes peripheral artery disease which is a narrowing of the blood vessels in the limbs, due to atherosclerosis. Peripheral artery

disease can increase the risk of carotid artery disease/ stenosis. In this condition, the carotid arteries that supply blood to the brain can develop atherosclerotic plaques from which a thrombus forms and may embolise within the cerebral circulation. Other conditions that increase stroke risk include coronary heart disease, heart failure, heart valve disease, dilated cardiomyopathy and possibly even congenital heart defects.

- **Diabetes mellitus –** In England, 4% of men and 3% of women suffer from diabetes which is an independent risk factor for stroke[309, 310]. People with diabetes are also often found to have hypertension and hypercholesterolemia which again further increases the level of stroke risk. The presence of diabetes means that sufferers are two to three times more likely to have a stroke than those without diabetes[343].

- **Atrial fibrillation –** An irregular heart rhythm means that the heart does not beat effectively and allows blood to pool and clot which can lead to the formation of emboli that travel in the blood and cause blockages in the arteries supplying blood to the brain. Atrial fibrillation is often found in 15% of stroke patients and increases risk of stroke[344].

- **Hypercholesterolemia –** Also known as hyperlipidemia. A typical blood reports the amount of total cholesterol, high density lipoproteins (HDL), low density lipoproteins (LDL) and triglycerides. LDL's sometimes referred to as 'bad' cholesterol can build up to form blockages on the inside of artery walls and have been reported as a risk factor for stroke. On the other hand HDL's, sometimes referred to as 'good' cholesterol are thought to lower risk stroke but the effects are not as clear and further investigation is needed in this area. However lowering the overall circulating levels of cholesterol in the blood is recommended[345]. Cholesterol target levels may differ for individuals and the level of risk can be affected by the addition of illnesses and other contributing factors.

- **Hypertension –** In England, 34% of men and 30% of women suffer from high blood pressure, however not everyone receives active treatment[343] for it (78% of men and 67% of women) despite it being the most controllable risk factor! 50% of ischaemic strokes are caused by hypertension and so it is important that blood pressure is maintained at a suitable level.

Some risk factors require no active medication or treatment and can be modified by simple life changes such as;

- **Smoking –** Studies have shown that the nicotine and carbon monoxide in cigarettes can cause significant damage to the cardiovascular system[346], leading to the conditions previously described. Smokers have a two to four time greater risk of stroke

compared to non-smokers[343]. 10% of stroke deaths are attributed to smoking and it is estimated that in the UK there approximately 12.5 million smokers[281]. However cessation of smoking decreases the level of risk back to a level that is comparable to that of a non-smoker[343]. As a result there number of services and recommendations available to the public to help them give up smoking.

- **Diet –** Food intake that is high in fat and salt content can lead to hypertension and hypercholesterolemia and excessive intake can lead to obesity, all of which can contribute to an increased risk of stroke. A healthy balanced diet with the recommended five portions of fruit and vegetables a day can help to decrease stroke risk by 6%[343, 327]. A healthy diet can also help decrease obesity which is a risk factor not just for stroke but for many other health issues such as heart disease and diabetes. Currently 25% of men and 24% of women have a BMI of over >30, which makes them clinically obese and puts them at an increased risk of stroke[329].

- **Physical activity –** Moderate exercise such as 30 minutes of activity a day can help with a healthy lifestyle and decrease the occurrence of health issues such as hypertension, hypercholesterolemia and obesity. Moderate physical exercise has been shown to reduce the risk of stroke by up to 27%[328].

- **Substance abuse –** Alcohol abuse can lead to a number of complications and there is a strong association between heavy drinking and stroke. A study showed that males who drank over 35 units per week doubled their risk of mortality from stroke[325]. Similarly drug abuse can lead to a number of health and social problems and drug abuse is often reported as a cause for stroke in younger adults[326]. Drugs such as heroin[347], amphetamines and cocaine[348] have been reported as a stroke risk. Medications such as oral contraceptives when combined with smoking have also been shown to be a possible stroke risk[349].

There are also a number of environmental aspects and confounding variables that can impact on these risk factors, influencing the incidence and outcomes post-stroke, which will be discussed later in the chapter.

2.4 Hospital management of stroke

A person suspected of stroke is commonly admitted to the Accident and Emergency Department either by GP referral[350] or brought in by the Ambulance Service. An initial

assessment is then conducted in the Emergency Department. The diagnosis of stroke involves taking a careful history either from the patient or a family member or carer. Information about the events, symptoms, time onset and duration and past medical and family history help to determine the path of the diagnostic process[351, 352].

In 10 to 20% of suspected strokes are found to have an alternative diagnosis, although this can vary[353]. Stroke 'mimics' can include an old stroke with an increase in weakness due to a current illness, subdural haematomas, cerebral tumours, cerebral abscesses, encephalitis, venous thrombosis, cerebral vasculitis, hypoglycaemia or fits[354, 353, 277]. The cardiovascular system is examined to identify possible aetiological causes. Neurological deficits after a stroke are time dependent and are often unstable prone to sudden improvements or deterioration in the first few hours after a stroke. Beyond 6 to 10 hours, these deficits do not change as suddenly as the effects of the injury have increased. Due to potential beneficial effects of early neuroplasticity, some patients may experience modest improvements in the neurological deficits in the sub-acute period (12 hours to 7 days) post-stroke[355]. The clinical stroke syndrome can be identified using descriptors such as the National Institute of Health Stroke Scale (NIHSS), ICD 10[138] (codes 430-434 and 436-438) or the Bamford stroke classification scale[280]. Confirmation of diagnosis and pathology (infarct or haemorrhage) is often confirmed by brain imaging scans such as a Computerised Tomography (CT) or Magnetic Resonance Imaging (MRI) (Figure 2.3). The aim is to perform CT scans for suspected strokes within 24 hours of admission to hospital, to exclude the possibility of a haemorrhage which presents itself as white areas on the scan image. Further tests may be conducted to identify other causes[134] and an MRI scan may be done to identify an ischaemic stroke and/ or old stroke sites. Time is critical factor in the management of stroke and often the stroke patient are seen within 10 to 15 minutes upon hospital arrival, the CT scan is performed and interpreted in less than one hour and the patient is transferred to the appropriate inpatient ward within four hours from the point of hospital admission.

Type of Stroke	CT scan		MRI scan	
	Sensitivity	Specificity	Sensitivity	Specificity
Ischaemic stroke	16%	96%	83%	98%
Haemorrhagic stroke	89%	100%	81%	100%

Image adapted from the paper by Chalela et al[354].

Figure 2.3: The sensitivities and specificities of CT and MRI scans.

Studies have shown that MRI scans are a far more sensitive technique compared to CT scans[355, 356]; however they do have some limitations. For example MRI's do not tolerate patient movement well and so a successful scan requires the patient to co-operate for a longer period of time. Also those patients that have pacemakers cannot have an MRI. Techniques such as Positron Emission Tomography (PET) scans which when combined with certain isotopes (FDG) can track the metabolic activity of specific neurons[354] whilst Single Photon Emission Computed Tomography (SPECT) scans can monitor the cerebral blood flow (CBF) which can help to determine the aetiology[135].

It is beneficial to conduct a simple cognitive test to determine baseline cognition post-stroke. Often the AMTS is administered upon hospital admission to determine the patient's orientation to time and place. This is then subsequently followed up by tests such as the MMSE and/ or the MoCA to gain a better understanding of the patient's cognitive level. Tests can also help to identify any special issues that require attention such as dysphasia. As secondary deterioration is common in the first week post-stroke, the neurological exam can help to document a baseline activity for the patient so that any subsequent deterioration can be detected. Given that stroke is a disease that is prevalent in the older population, the significant co-morbidity associated with this group should be considered when making a stroke diagnosis[358, 359, 279]. Differential diagnoses in the elderly include; Parkinson's disease, dementia, psychiatric illness, metabolic disturbances and intoxication[278].

Patients are often transferred to stroke units[360] for further management which might include thrombolysis treatment to dissolve blood clots causing cerebral infarction. In clinical practice, despite a comprehensive work-up, sometimes the cause of the stroke can remain undetermined. This is true of 20 to 40% of cases[307]. Once an accurate diagnosis of stroke has been made, clinicians are able to tailor treatments to each individual patient and estimate the patient's long term prognosis. All this can have an impact on the post-stroke outcomes will now be discussed.

2.4.1 **Outcomes linked to stroke**

With an impending ageing population, the improvement of geriatric medicine is an important consideration for future healthcare[359] and this includes the development of stroke medicine. Studies have shown that once a stroke has occurred, admission to a stroke unit is associated with improved outcomes compared to general wards[361, 362]. Studies have found that the earlier rehabilitation is started after a stroke, the better the functional outcomes for the patient in the long term[363, 361, 364].

Over the last decade or so, there have been a number of initiatives that have helped to make the stroke treatment and rehabilitation process more efficient[365-367]. These include; the introduction of acute and (more recently) Hyper Acute Stroke Units (HASU) and dedicated rehabilitation stroke units, speedier transfers to and between the stroke units, provision of thrombolysis treatment and CT scans within a few hours of stroke, specialised stroke teams, use of multidisciplinary teams to plan patient care across the hospital, adequately trained staff, implementation of nursing 'critical care pathway' systems and standardised stroke protocols, reducing length of stay by efficient diagnostic evaluation and good communication and discharge planning with the patient's future care providers. Overall this has led to the delivery of good individual patient care and the overall care package for stroke is continually being improved[361, 368, 369, 342, 370, 371].

In a general hospital serving a population of 250,000 people, 4% of beds of the general medical beds will be occupied by stroke patients (25 to 35 individuals)[281]. As strokes are a common occurrence, a large proportion of the NHS financial budget is spent on providing prevention interventions, acute treatment and long term care associated with stroke. Mortality is the worst outcome of stroke and over 60,000 deaths in the UK are due to stroke[281], the detailed results of which can be seen in Figure 2.4a and 2.4b. Although stroke mortality and incidence has declined in recent years, the risk of mortality has remained constant. It is reported that in the first year after a stroke 30% of patients will die, usually within the first 10 days post-stroke[372]. Of those that survive, a third are likely to make good recovery progress within one month and a third will be left with significant disabilities that require long term care[260, 373, 374].

Breakdown of the number of deaths caused by stroke in the UK, by age and gender, in the year 2004

	Males	Females	Total
Under 35	109	100	209
35 to 44 years	263	207	470
45 to 54 years	613	530	1,143
55 to 64 years	1,434	1,085	2,519
65 to 74 years	3,955	3,289	7,244
Over 75 years	16,596	32,277	48,873
Total	22,970	37,488	60,458

Image obtained from The Stroke Association

Figure 2.4a: Stroke mortality according to age and gender.

The figure above lists the number of men and women that suffered a stroke, according to their age and gender.

Breakdown of deaths from stroke by country, in the year 2004

	Males	Females	Total
England	18,940	30,621	49,561
Wales	1,195	2,112	3,307
Scotland	2,294	3,861	6,155
Northern Ireland	541	894	1,435
UK	22,970	37,488	60,458

Image obtained from The Stroke Association

Figure 2.4b: Stroke mortality according to geographical location.

The figure above lists the number of men and women that suffered a stroke, according to their location.

With regards to patient outcomes, studies have shown that several complications can develop interfering with common stroke complications such as pneumonia, Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE) with neurological features, after a stroke. Figure 2.5 illustrates the frequency of some of the post-stroke patient outcomes.

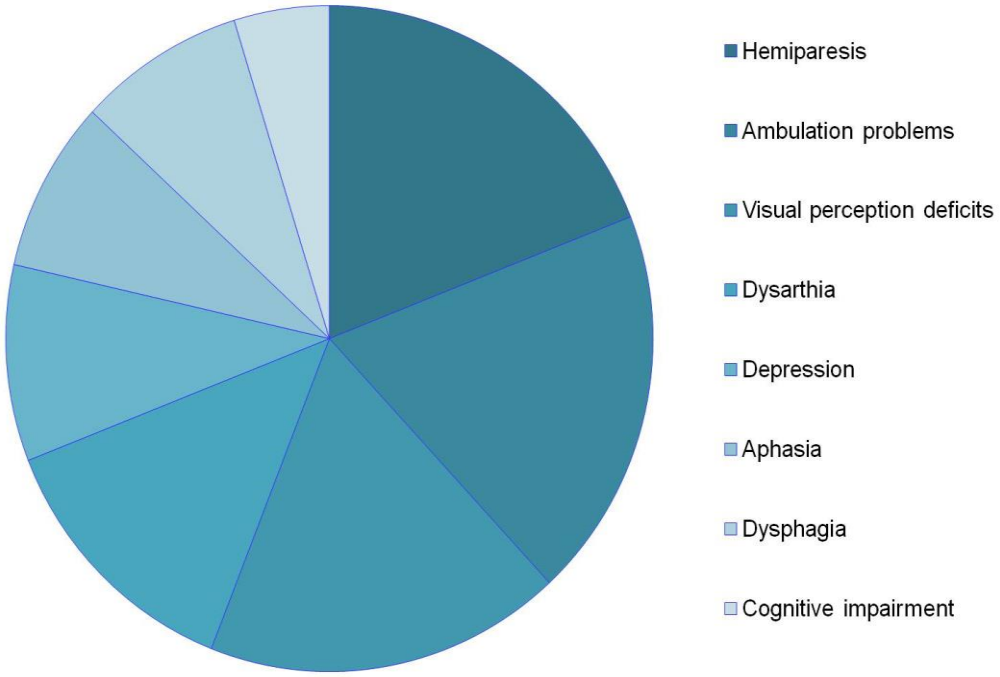

Image produced from data from The Stroke Association.

Figure 2.5: Post-stroke patient outcomes.

The figure above lists the frequency of some of the outcomes patients experience after a stroke. Percentages given are the maximum values of the ranges provided in the data.

Aside from the significant mortality risk post-stroke, other medical complications[374] include: the onset of dementia[375-381], depression[382-386], epilepsy [387], seizures[388], increased risk of falls[389], fatigue[390] and changes in attention[391], cognition[392, 393, 214, 394, 395], emotional behaviour[396, 397], mood[398] and affective disorders[161, 399, 400] and self esteem[401-404]. One year on and 65% of patients will be living independently whilst the remaining 35% will need help with activities of daily living[405, 406, 301]. This specialised care and attention can be in the form of, moving in with family members, requesting home help, using rehabilitation centres and some may require long term institutionalisation[368]. Statistics show that of the post-

stroke survivors at twelve months; 80% are back home, 12% live in a residential/ nursing home whilst 8% are totally dependent on others[281].

2.5 Considerations for further stroke research

Evidence based medicine is essential both for clinical practice but also as the course and outcomes related to stroke can be used by policy makers (e.g. GMC, NICE, WHO) to standardise and organise future stroke care[407-409]. The design of an audit means that there is no adjustment for potential bias and so aetiological and prognostic studies are needed Important considerations for economic studies for stroke[298, 299] include standardisation of studies reporting on stroke, larger incidence studies and maintenance of stroke registers globally, longer duration of patient follow ups, standardisation of outcome measures, inclusion of a broad range of services for patients post-discharge and social status and support provision[410, 290, 301, 411].

Studies in stroke (both aetiological and prognostic) have variable methodologies. Aetiological studies use different definitions and measures to record risk factors, which makes the results between studies difficult to compare. Many aetiological studies are also retrospective in design and rely on data that has been collected for other purposes such as mortality. This means that the subsequent data collected is susceptible to recall error as a significant amount of patients may be suffering from memory impairment and hospital data records are not always reliable. Also figures for stroke mortality and incidence have declined over the last few decades, but the risk of mortality remains constant which indicates that mortality may not be a suitable measure due to changes in other factors (e.g. case fatality).

Some studies do not account for confounding variables in their statistical analysis, which makes their results questionable. Some studies do not have case matched controls again leading to possibly questionable findings. Consideration must also be given to selection bias when recruiting participants for research[412]. Studies with low recruitment rates may lack adequate power, as to identify any meaningful confounders large patient groups are needed[413]. Studies that do not present findings within a clinical context and fail to provide odds and/ or relative risk ratios make comparisons between studies more difficult.

Despite this there have been a number of studies upon which successful stroke prevention measures have been based. However the evaluation of the effectiveness of these measures is another matter. The care process in stroke is full of variables such as different

stroke protocols, the training of the team members and variations in the standard of care they provide, the type of stroke and the physical and psychological condition of each individual patient all need to be taken into account. Many studies also fail to account for confounding variables by not including them in their analysis, using very few variables for analysis or using inappropriate statistics to analyse the effect of the variables.

For prognostic studies, well defined outcome measures that are clinically relevant need to be decided upon and defined at the beginning of the research. The duration of follow up and the justification for this time period should be made clear and not be a burden on the patient. Studies based across different institutions can also have an effect on the outcomes as there can be differences in the population specific to that geographic location, differences in stroke protocols and care pathways and differences in service provision (e.g. not all hospitals have acute stroke units or a certain number of beds allocated to stroke patients). These variables need to be considered when designing a study and prospective designs are most well suited as it decreases errors such as information recall as previously mentioned. Furthermore the majority of studies tend to focus on outcomes such as mortality and although this is clearly important, it may not be the best indicator. A better indicator would be the significant co-morbidity associated with stroke and the impact it has on patient outcomes. However challenges over how to quantify this, the effect of confounding variables and how this can be interpreted for clinical use needs to be considered so that the findings can be of use to the general population. In addition to the smaller population based studies, consideration should also be given to more large scale international studies that pool together global resources and data[409].

2.6 Conclusion

Stroke is an important cause of mortality and morbidity for the older population. Stroke diagnosis can be difficult due to other presence of other illnesses. Although stroke care has improved significantly over the last decade, further research is required into the aetiology and long term outcomes for patients post-stroke. In stroke the addition of complications in the older population can hinder rehabilitation and one such complication is delirium. Chapter one discussed the adverse effects delirium can have on patient outcomes and that certain patient groups may be at a higher risk of delirium. Stroke was identified as one such patient population that requires further investigation. In Chapter three the published literature available will be analysed by a systematic review to evaluate the incidence, patient outcomes and risk factors that arise when these two conditions concurrently occur.

2.6.1 **Key points**

- Stroke is an interruption of the brain's blood supply caused by an occlusion or a bleed in the blood vessels of the brain.
- It is now the fourth largest cause of death in the world, with the risk of dying at 12% in the first seven days, 19% at one month and 30% within one year from a first time stroke.
- Stroke has many complications and around half of stroke survivors will be dependent on long term care for day to day activities.
- It is common over 65 years of age and due to an ageing population, the number of stroke survivors and cost of care will also increase in the future.
- Delirium is a complication that when combined with stroke can have an adverse effect on patient recovery and this requires further investigation.

3 Delirium and acute stroke

3.1 Introduction: The clinical problem

Previous studies indicate that patients who develop delirium tend to have worse outcomes which include increased risk of complications, mortality, morbidity and worse physical, cognitive and psychological outcomes[228, 414, 230]. Delirium has also been associated with increased healthcare costs, which include longer hospital stays and the increased need for institutionalisation post-discharge[415, 164, 78, 186].

The patient populations observed in these previous studies included; surgical[234, 416, 84] and medical patients[417, 66, 418, 419, 153], hip fracture patients[420, 49, 421, 422] and people suffering from terminal illnesses[70, 423, 162]. In these studies, the clinical importance of delirium in patient care was highlighted and almost all of the studies concluded that further research on delirium was required. Recommendations were also made for the detection, prevention or management of delirium for those specific study populations. In comparison there is limited research on the epidemiology, prevention, management or outcomes of delirium in the stroke population.

3.1.1 **The detection of delirium**

The standardised research tools often employed to diagnose delirium have been developed and validated based on the DSM-IV and ICD-10 assessment criteria. However screening for delirium is not a routine procedure[56] and the hospital wards that do so, often use assessment tools that focus on cognitive function rather than the specifically designed delirium detection tools[424]. Furthermore, the research diagnostic tools developed for delirium often vary in sensitivity and specificity[142], thus affecting the reliability of delirium detection. This variation in results may also be due to lack of staff awareness[425], training or inexperience in detecting delirium[426], resulting in low inter-rater reliability. In addition to this, the temporary and fluctuating nature of delirium, and the different delirium subtypes, can make it difficult to detect[27]. Misdiagnosis may also occur as the symptoms of disorders such as dementia, depression and anxiety can overlap with the features of a delirium episode and so making a correct diagnosis can become challenging[145, 427, 428]. The early detection of delirium is recommended[429] and it is clear that more needs to be done to improve the detection and management of delirium[430].

3.1.2 **The complications of stroke**

Due to the multifactorial nature of delirium, a single case may have several risk factors contributing to the presence of delirium[431]. Stroke in itself can be a challenging diagnosis to make due to the presence of stroke mimics. The presentation of stroke symptoms is also variable dependent on the brain territory affected by the stroke[278, 432, 433]. Many stroke patients are often physically unwell due to a number of complications post-stroke. These complications are shared factors linking the stroke and delirium. Increased age is thought to be a risk factor for delirium[434, 113] and the majority of stroke patient tend to be over 65 years of age. It is known that stroke is a predisposing factor for the onset and/or development of delirium[228, 435] and yet few studies have been conducted in the stroke population to investigate delirium.

Symptoms of a stroke can include changes in mobility, blurred or double vision, slurred/ incoherent speech and confusion as described in Chapter two. These symptoms can overlap with the features of delirium, making the detection of delirium in stroke patients more challenging as is it difficult to ascertain whether the true nature of the patient's symptoms have been caused by the stroke itself or if in fact they are features of a possible delirium.

In addition to this when using tools to detect delirium, certain symptoms such as slurred or incoherent speech caused by the stroke may make the delirium instrument unreliable. Recent guidance issued by the National Institute for Clinical Excellence (NICE)[133] clearly stated the importance of identifying delirium as soon as possible, especially in patients over the age of 65 with significant illness. However at present, there are no clear guidelines being implemented regarding recommendations for multidisciplinary treatments, the best method to screen for delirium and if stroke patients should have a standard screening method in place for delirium detection.

3.2 Justification for further investigation

It is clear that further research is required to investigate the presence of delirium within the acute stroke population[436, 171, 120, 173, 38, 46, 175] and processes need to be put into place to help alleviate some of the aforementioned problems[112]. For possible interventions to be effective, a number of points need to be considered which include: the wide range of aetiology factors associated with delirium, the used of standardised diagnostic tools that are accurate and reliable, fixed measures to improve and evaluate delirium management in

order to improve patient outcomes and the quality of patient care and delivery of a standard and effective protocol.

In order to develop a standard screening protocol to manage delirium post-stroke, it is important to determine the occurrence and outcomes within the stroke population, which in turn will have an effect on the planning, delivery and evaluation of any future intervention. The occurrence of delirium post-stroke will influence the cost per case and the predictive value of screening for the syndrome. The type of intervention offered will also be affected by how common the syndrome is within the specific patient population. The patient outcomes associated with delirium post-stroke will determine whether it is feasible to plan a screening protocol or intervention strategy and whether its economic implications will make it cost effective in the long term.

3.2.1 **Objectives of the systematic review**

In contrast to traditional or narrative reviews, systematic reviews use a well defined rigorous approach to collect and analyse the available literature in a specific subject area[437]. Systematic reviews use strict criteria to identify a complete list of all published and unpublished studies. The literature is critically evaluated and synthesised in the least biased way to answer well focused questions about clinical practice.

Prior to planning any new investigations, a better understanding was required of the relationship between delirium and acute stroke and its impact on patient recovery. In order to do this, a systematic review was undertaken to investigate delirium and acute stroke. The aims of the review were to identify gaps in the available literature and to use the findings to help design new work. At the time of the original search conducted in June 2010, no systematic reviews on delirium after acute stroke had been published, to my knowledge. The objectives of this systematic review were to determine the following:

1) **The occurrence of delirium.** To analyse the incidence rates of delirium in stroke and determine the periods during which delirium screening is conducted.

2) **Evaluating the related outcomes.** To determine what outcome measures were chosen, the assessment tools employed and what were the durations of the follow up periods for the participants.

3) **Identify confounding variables and/or associated risk factors.** By highlighting key variables and their clinical utility risk on outcomes, future study designs could be

altered in order to avoid potential sources of bias and/ or producing inadequately powered studies.

The three key aims of the systematic review would help to plot a ‘natural history’ of delirium in order to identify when best to test for delirium onset and plan a predictive pathway with suitable time points for intervention and evaluation.

3.3 Points to consider when critically analysing studies

In order to inform discussion, a comprehensive search needs to be made of the topic areas to identify suitable studies. These studies are critically analysed to identify any limitations that could be potentially be improved upon in future investigations. During the process of critical analysis, the following general points should be considered.

a) **Composition of the cohort.** The study sample can greatly affect the outcomes of a study and attention should be given to how the sample was constructed. In this review, the age of the sample population should be generalisable to the elderly population, which for most studies is stated as 65+ years but a minimum age limit of 55+ years can be considered in this review. Those with a significantly young sample population may not be as representative. How were the participants recruited (consecutive or non-consecutive admissions), what sampling techniques were employed to reduce selection bias (systematic or random) and did the setting from which the sample was extracted have any unusual features that may prevent its generalisability to other similar settings? Were the inclusion and exclusion criteria clearly stated, were they applied uniformly to all potential participants and were all potential participants included? Did the sample size remain consistent throughout the study or where there fluctuations indicating that the sample may not have been treated in the same manner? And finally was there a high recruitment rate provided, indicating a comprehensive and inclusive study sample? If recruitment rates were low, was an adequate explanation given.

b) **Identifying the case (ascertainment).** Although there may be a number of instruments available, attention must be paid to the suitability and use. Were the chosen assessment tools suitable for detecting the cases intended/ specified, appropriate for the setting they were used in and had they been validated for use in that specific population?

c) **Defining the case (diagnosis).** Did the chosen diagnostic tools have a high sensitivity and specificity, good inter-rater reliability and test-retest accuracy? Were the tools rated against 'gold standard' reference criteria or other similar assessment tools? Do the tools require any specialist training or administration by a trained medical professional? Was the administration of the tool done by one investigator, multiple investigators or by the participant themselves, which may also introduce variation in the assessment scores? Were the tools administered on a regular basis or just at one specific time point as a single test can only provide a snapshot at a specific time point whereas repeat tests can build up a more accurate diagnosis? Furthermore certain scales may not be suitable to assess the outcomes in elderly and may require alterations in order to capture usable data. Are the chosen tools part of a larger test battery and do they work well together and are the selection of tools well tolerated by the elderly participant?

3.4 Methodological considerations

3.4.1 **Definitions of search terms**

Case ascertainment and case definition are of key importance when analysing epidemiology studies. For example the frequency of delirium detection assessments recorded could have a significant impact on the findings due to the fluctuating nature of delirium. Therefore it is important to determine whether incidence or prevalence was reported when interpreting the study findings, as there is a significant difference between the two terms. Incidence is defined as the frequency of new cases recorded within a certain time period e.g. during the follow up of a cohort over a one year period. In contrast, the term prevalence is used to define the number of existing cases recorded at a specific point in time for the cohort being studied. Essentially prevalence is the burden of a disease, where the numbers of new cases are added to the old cases to give a cumulative total at that time. Not all of the studies selected in the systematic review clearly defined whether they were recording incidence or prevalence and so a technique previously used in another systematic review was employed. For the purposes of this review, the term occurrence, as described by Siddiqi et al[121], was used to record the rates of delirium and a description and frequency of the recordings was also noted in the data extraction.

3.4.2 **Inclusion criteria**

The following types of studies were included; prospective cohort studies, longitudinal studies, case control studies and controlled trials. All adult participants over 18 years of age with a clear diagnosis of stroke and subarachnoid haemorrhage were included. As the patient population being investigated was acute stroke, studies in hospital general medical inpatients, stroke units, accident and emergency and intensive care units were considered. Articles that were written in languages other than English were included, provided that a suitable translation of the article could be obtained.

3.4.3 **Exclusion criteria**

The following types of studies were excluded;

a) **Retrospective studies –** Ward registers are regarded as poor sources of information as they are not regularly updated and so the recorded data may be unreliable. It is also unlikely that delirium will have been identified upon admission and often other conditions such as the stroke itself are given higher diagnostic priority. Therefore studies where the cohort data collection was done retrospectively were excluded.

b) **Specific patient case studies and small case series –** These were excluded as they were unlikely to provide any incidence data and such small sample numbers would be insufficient to draw conclusions that would be generalisable to the population under investigation.

c) **Review papers, editorials, opinion articles/ letters and conference proceedings –** These were unlikely to provide any new incidence data or provide statistical analysis or critical analysis of the available literature, to promote further understanding.

d) **Descriptions of service pathways, new technological detection methods, management/treatment techniques and investigations into the pathophysiology –** These were rejected as again they were unlikely to provide any new incidence data.

e) **Study samples derived from community and hospice settings, psychiatric units and surgical units –** The selected cohorts needed be generalisable to the chosen population. As the study population was acute stroke, the sample population would most likely be hospital based to reflect this and so any atypical settings were excluded.

f) **Study samples recruited solely based on a diagnosis of delirium –** The population should be relevant to the topic under investigation. Therefore studies where subjects were recruited only based on their delirium diagnosis with no attention given to their stroke diagnosis were excluded.

g) **Participant groups diagnosed with other conditions –** Subjects diagnosed with delirium tremens, neurological brain damage (e.g. neurodegenerative disorders) and brain injury were excluded as these may impact on the progression of the symptoms under investigation.

h) **Studies where the definition of delirium did not match the current consensus for delirium –** cases where the definition of delirium were not clear. Ideally cases should be identified and diagnosed using the DSM III R[22] or DSM IV[23] or ICD-10[138] criteria or standard scales and interviews. Those that did not were excluded.

i) **Articles not written in the English language –** Steps were taken to obtain translations of these papers. However in the event that no suitable translations could be obtained, then these papers were also excluded.

3.5 Systematic review methodology

3.5.1 **Initial search**

In June 2010, a general search on related terms for 'delirium' and 'acute stroke' (appendix 1) was performed in the selected databases which included; AMED, BIOSIS, Biological Sciences, CINAHL, Cochrane, CSA neurosciences, EMBASE, Global Health, MEDLINE, PsychINFO, TRIP and Web of Science/ Knowledge. This produced a broad set of results that were then analysed and the systematic data extraction and assessments of quality were carried out by one reviewer. A decision was made as to not narrow the search by using specific terms such as 'incidence', 'outcomes' and 'confounding variables and/or risk factors' as it was felt that this would compromise the sensitivity of the search. A complete list of the search terms used can be found in the appendix (see appendix 1 for search terms used).

Titles and abstracts were checked for their relevance to the chosen topic and a search for full text articles was conducted on all available databases for the citations that met the inclusion criteria, previously described in Section 3.4. A search for English translations was made and for those studies not written in the English language, attempts were made to

obtain suitable translations where possible. The bibliographies of each article were also checked to identify other studies that may not have been highlighted by the electronic searches. In addition to this, the authors of the selected studies were contacted for additional information not stated in articles, or for further clarification of the information presented. In April 2014, the systematic review search was subsequently refreshed for the purposes of publication and a meta-analysis was also performed, the details of which will be discussed in Chapter nine (Section 9.4).

3.5.2 **Study selection**

All the results identified by the database searches were reviewed by one reviewer (S. Ahmed). Titles and abstracts were identified from electronic database searches and any irrelevant studies were excluded by the reviewer. The reviewer sorted the citations into one of the following three groups; 'included', 'excluded' and 'possible'. The division of the citations into the groups and the reasons for the allocation were recorded on a paper form.

3.5.3 **Data extraction**

A paper form was used to extract data from the studies which met the inclusion criteria. The sections on the form were as follows;

a) Author, year of publication, country of origin and study design.

b) Sample size, characteristics of the sample, inclusion/ exclusion criteria applied and the number of people not recruited or included and the reasons why.

c) Assessment tools used to screen and diagnose delirium, frequency of assessments, suitability of the assessor, suitability of the tool and any subsequent adaptations that may have been made for any possible communication issues that may have been present in this study population.

d) Occurrence of delirium, the severity and duration of delirium episodes, reversibility of delirium and the time period over which the episodes were recorded.

e) Outcome measures including immediate, short term and long term outcomes. Up to discharge: mortality, length of stay, requirement for institutionalisation post-discharge and complications during stay i.e. infections, changes in functional capacity and

cognitive function and psychological distress. At one, six and twelve months: presence of delirium, mortality, changes in functional capacity and cognition, psychological distress and the requirement for institutionalisation.

f) Predictors for developing delirium, confounding variables and risk factors.

3.5.4 **Quality assessment**

The quality of the studies were assessed and compared to see if they were of a similar standard[438, 439]. Several checklists designed to assess methodological rigour against a set criteria were reviewed[437, 440-442]. These assessment criteria vary according to the type of study and so a range of checklists have been designed to produce a consistent approach to assessment and reporting. The Clinical Appraisal Skills Programme (CASP)[440, 441] has a number of checklists for the following study types; trials, systematic reviews, case control, cohort, qualitative research, economic evaluations, diagnostic test study and clinical predication rule. These checklists are easy to use, consistent and similar lengths of assessment questions are employed. Each selected study was scored using 'yes', 'no' or 'unclear' using the CASP checklist questions summarised in figure 3.1.

Trial	Cohort	Case control
1. Did the trial address a clearly focused issue?	1. Did the study address a clearly focused issue?	1. Did the study address a clearly focused issue?
2. Was the assignment of patients to treatment randomised?	2. Was the cohort recruited in an acceptable way?	2. Did the authors use appropriate method to answer their question?
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	3. Was the exposure accurately measured to minimise bias?	3. Were the cases recruited in an acceptable way?
4. Were patients, health workers and study personnel 'blind' to treatment?	4. Was the outcome accurately measured to minimise bias?	4. Were the controls selected in an acceptable way?
5. Were the groups similar at the start of the trial?	5a. Have the authors identified all important confounding factors? 5b. Have they taken account of the confounding factors in the design and/ or analysis?	5. Was the exposure accurately measured to minimise bias?
6. Aside from the experimental intervention, were the groups treated equally?	6a. Was the follow up of subjects complete enough? 6b. Was the follow up of subjects long enough?	6a. What confounding factors have the authors accounted for? 6b. Have the authors taken account of the potential confounding factors in the design and/ or in their analysis?
7. How large was the treatment effect?	7. What are the results of this study?	7. What are the results of this study?
8. How precise was the estimate of the treatment effect?	8. How precise are the results?	8. How precise are the results? How precise is the estimate of risk?
9. Can the results be applied in your context? (or to the local population?)	9. Do you believe the results?	9. Do you believe the results?
10. Were all clinically important outcomes considered?	10. Can the results be applied to the local population?	10. Can the results be applied to the local population?
11. Are the benefits worth the harms and costs?	11. Do the results of this study fit with other available evidence? 12. What are the implications of this study for practice?	11. Do the results of this study fit with other available evidence?

Image adapted from casp.co.uk

Figure 3.1: CASP quality assessment checklist.

The score allocations were as follows; 1-4 low quality, 5-8 medium quality and 9-12 high quality. Studies that scored highly were of high quality with a minimally biased methodology, making the outcomes of the study more reliable. Studies that did not score as

highly indicated that the methodology and outcomes may not be as reliable as compared to the other studies.

3.6 Results of the systematic review

In comparison to other clinical situations, the association between delirium and acute stroke has not been as thoroughly investigated which means that there were few studies available for analysis. The use of specific terms such as 'incidence', 'outcomes' and 'confounding variables and/or risk factors' would have further narrowed the search and so a broad search strategy was employed. Furthermore studies that reported occurrence did not always report outcomes. The reported outcomes also differed between the different cohorts and there was little consistency in the measures used. For the purposes of this review, the searches for occurrence and outcomes were combined together to make best use of the information available.

The initial search produced 1255 citations and after examination of the titles and abstracts by the reviewer, 188 articles were retrieved for further consideration. Of these articles, 174 were excluded as they did not meet the inclusion criteria specified for this systematic review. No new studies were highlighted from the bibliographies of the selected studies and so a total of fourteen reports/ studies[61, 443-447, 111, 448, 47, 449, 450, 197, 451, 452] that met the inclusion criteria were further examined. The schematic diagram in Figure 3.2 summaries the number of studies that were excluded in this review and the reasons why.

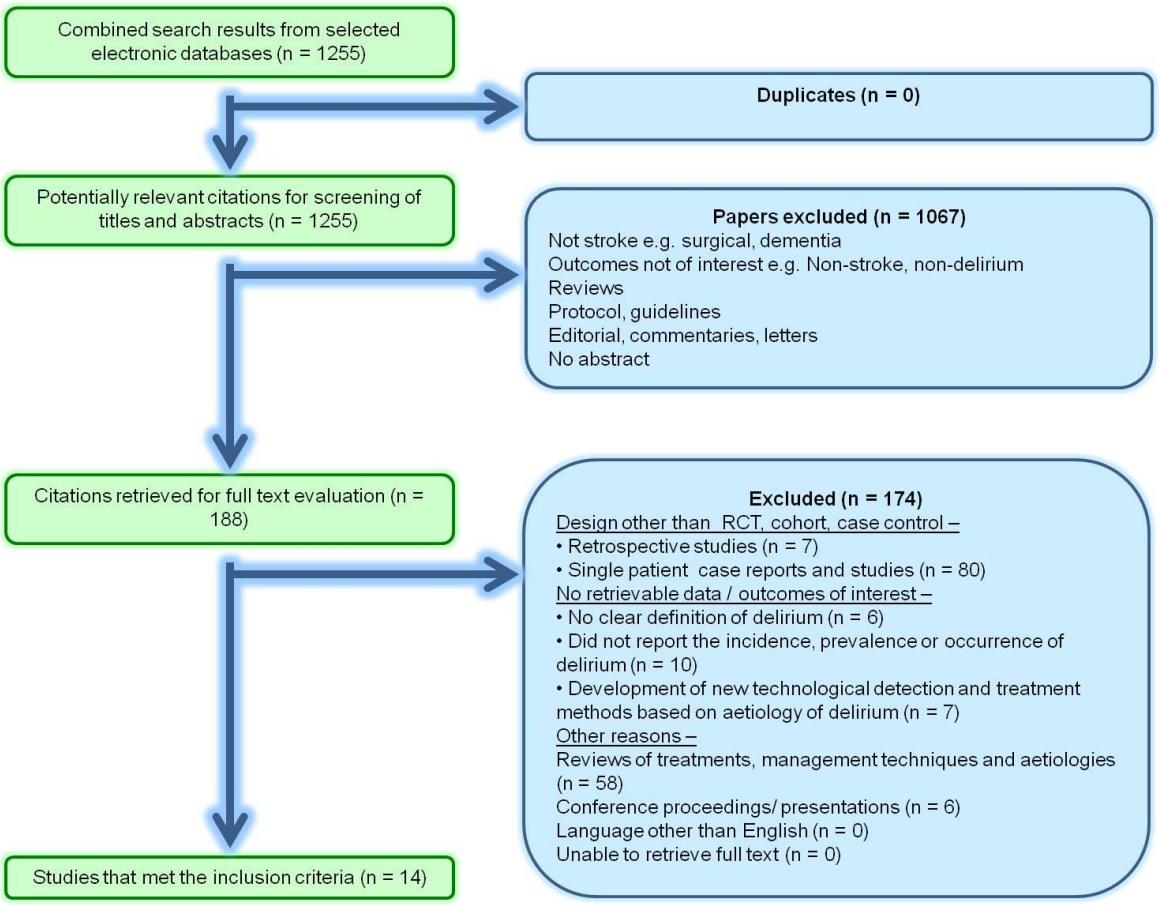

Figure 3.2: Schematic diagram of the systematic review conducted in June 2010.

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Fourteen reports/ studies[61, 443-447, 111, 448, 47, 449, 450, 197, 451, 452] met the inclusion criteria and these were further examined. Within this sample of selected studies, two of the research groups (McManus[449, 450] and Dostovic[446, 447]) used the same patient population for more than one paper. This means that although there are fourteen papers examined in this review, there were in fact only twelve distinct patient cohorts studied. Figure 3.3 and 3.4 summarise the specifics of each of the selected studies.

Author and country	Study design and setting	Sample (M = male, F = female, Age = mean age)	Recruitment criteria (I = Inclusion, E = Exclusion)	Assessments	Occurrence of delirium	Risk factors
Caeiro, 2004 *(Portugal)*	Prospective case control Stroke unit	231 admitted, 220 eligible 218 strokes recruited *(131M, 87F) Age = 57.3* 50 acute coronary controls *(38M, 12F) Age = 59.1*	I: Stroke (CI, IH, SAH), psych assessment within 4 days E: GCS score <5	DRS, DSM-IV (4 days) MRS (discharge)	13.3%	Infections and stroke increase the risk of delirium
Caeiro, 2004 *(Portugal)*	Case control Stroke unit	159 eligible, 74 recruited 22 delirium *(14M, 8F) Age = 63.6* 52 non-delirium *(Age/ sex match) Age = 60.9*	I: Stroke (CI, IH, SAH), psych assessment within 4 days E: GCS score <5	DRS, DSM-IV (4 days) MRS (discharge)	30%	Anticholinergic medications increase risk of delirium.
Caeiro, 2005 *(Portugal)*	Prospective cohort Stroke unit	68 strokes recruited *(28M, 40F) Age = 55.5* 11 delirium, 57 non-delirium	I: Consecutive patients with SAH E: GCS score <5	DSM-IV-R, DRS (admission)	16%	Older age, disturbance of alertness, aphasia and a Hunt and Hess score >2
Dahl, 2010 *(Norway)*	Prospective Stroke unit	200 admitted,178 recruited 18 delirium *(7M, 11F) Age = 79.4* 160 non-delirium *(95 M, 65 F) Age = 71.65*	I: CT to confirm stroke E: terminally ill or unconscious	MDAS, CAM (daily) MMSE, (3 days) ADL, MRS (3 days)	10%	Pre-stroke dementia, hemianopsia, apraxia, higher age and infection (UTI or pneumonia)
Dostovic, 2008, 2009 *(Bosnia and Herzegovina)*	Prospective Stroke unit	561 admitted, 233 recruited 59 delirium *(25M, 34F) Age = 70* 174 non-delirium	I: 1st stroke (CI, IH, SAH), neuropsych assessment in 4 days E: GCS score <5	DRS-R98, DSM-IV (24 hours & 3-4 days)	25.3%	65+ years, females, right sided lesions in ischaemic and left sided lesion in haemorrhagic strokes
Gustafson, 1991 *(Sweden)*	Prospective cohort Stroke unit	155 admitted, 145 recruited 69 delirium *(44 M, 25 F) Age = 76* 76 non-delirium *(46 M, 30 F) Age =69*	I: Stroke (CI, IH, SAH), E: GCS score <5	DSM-III-R (admission) MMSE, OBS scale (admission)	48%	Anticholinergic meds, pre-stroke dementia, previous delirium, cardiovascular illness and left sided lesions
Gustafson, 1993 *(Sweden)*	Prospective case control Stroke unit	83 delirious stroke (52 M, 31F) *Age = 74.7* 72 non-stroke controls (43M, 29F)	I: Dexamethasone suppression test done E: GCS score <5 (Sub-study of Gustafson, 1991)	DSM-III-R (admission)	42%	-

Figure 3.3: The incidence of delirium in studies based on the stroke population.

CI: Cerebral Infarction, IH: Intracerebral Haemorrhage, SAH: Subarachnoid Haemorrhage, TIA: Transient Ischaemic Attack, MMSE: Mini-Mental State Examination, CAM: Confusion Assessment Method, DRS: Delirium Rating Scale, DSM: Diagnostic and Statistical Manual, ADL: Activities of Daily Living, BI: Barthel Index, IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly, GCS: Glasgow Coma Scale, MRS: Modified Rankin Scale

Author and country	Study and setting	Sample (M = male, F = female, Age = mean age)	Recruitment criteria (I = Inclusion E = Exclusion)	Assessments	Occurrence of delirium	Risk factors
Henon, 1999 *(France)*	Prospective cohort Stroke unit	258 admitted, 202 recruited 49 delirium *(26M, 23F) Age = 78* 153 non-delirium *(71M, 82F) Age = 74*	I: Consecutive stroke (CI or IH), E: TIA, SAH, cerebral venous thrombosis stroke, head trauma , <40 yrs, not fluent in French, no informant, not local	DSM IV, DRS (48 hours) MMSE, IQCODE (48 hours) BI, Rankin scale (discharge) BI, MMSE, Rankin, Weintraub (6 month)	24%	Old age, non-smokers, metabolic or infectious disorders, high IQCODE scores, severe clinical deficits and high leukoaraiosis
McManus, 2008, 2009 *(UK)*	Prospective observational Stroke unit	110 eligible, 82 recruited 23 delirium *(15M, 8F) Age = 75* 59 non-delirium *(36M, 23F) Age = 63*	I: Stroke (CI or IH), delirium assessment within 4 days, E: SAH, GCS score <8, delirium < 24 hrs, English speaker	CAM (4 days & then weekly) IQCODE (admission)	28%	Unsafe swallow, BI score <10, poor vision pre-stroke and CRP>5
Oldenbeuving, 2008 *(The Netherlands)*	Pilot study of intervention Hospital based	527 admitted, 62 delirious 26 recruited 17 delirious treated *(11M, 6F) Age = 77*	I: Consecutive stroke (CI or IH), delirium 1st week of admission E: Delirium < 24 hrs	CAM (admission, day 2-4 & 5-7) IQCODE (admission)	11.8%	-
Sandberg, 2001 *(Sweden)*	Cross sectional Stroke unit	156 admitted, 133 recruited (55M, 78F), *Age* = 77	I: Consecutive stroke with 24 hrs, CT confirmed E: Refusal of consent	DSM-IV, MADRS (daily) MMSE (daily) BI (daily)	75% with apnoea 56% without apnoea	Risk factors related to sleep apnoea not delirium
Sheng, 2006 *(Australia)*	Prospective observational Hospital based	186 admitted, 156 recruited 39 delirium *(17M, 22F) Age = 81.5* 117 non-delirium *(66M, 51F) Age = 78.4*	I: stroke (CI or IH), 65yrs+ E: TIA, SAH, head trauma, neurosurgery, stroke due to tumour or cerebral venous thrombosis	DSM-IV (3 days) FIM, MMSE (1, 6 & 12 months)	25%	Old age, dysphagia, neglect, vision field loss, low blood pressure and low GCS scores

Figure 3.3: The incidence of delirium in studies based on the stroke population – continued.

CI: Cerebral Infarction, IH: Intracerebral Haemorrhage, SAH: Subarachnoid Haemorrhage, TIA: Transient Ischaemic Attack, MMSE: Mini-Mental State Examination, CAM: Confusion Assessment Method, DRS: Delirium Rating Scale, DSM: Diagnostic and Statistical Manual, ADL: Activities of Daily Living, BI: Barthel Index, IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly, GCS: Glasgow Coma Scale, MRS: Modified Rankin Scale

Author	Occurrence	Outcomes	Confounding variables	Quality of study
Caeiro, 2004 *(Portugal)*	13% delirium	52% hypoactive and 48% hyperactive High unfavourable outcome e.g. death or dependency (76% Vs 33%)	Education, medical complications, right sided infarcts and haemorrhagic strokes all contribute to delirium onset.	High
Caeiro, 2004 *(Portugal)*	30% delirium	Use of anticholinergic medications highly associated with delirium onset Risk prediction model produced	Hospitalisation medical complications, anticholinergic medication taken before stroke and intracerebral haemorrhage are all independent predictors of stroke.	Medium
Caeiro, 2005 *(Portugal)*	16% delirium	Pathology affects attention, memory and emotional behaviour	Older age, increased disturbance of alertness, and a Hunt and Hess score >2 were linked to high DRS scores. Intraventricular bleeding, hydrocephalus and basofrontal haematomas linked to pathology of delirium.	Medium
Dahl, 2010 *(Norway)*	10% delirium	Longer hospital stays (12.28 days Vs 8.5 days) Increased stroke severity and dysfunction.	-	High
Dostovic, 2008, 2009 *(Bosnia and Herzegovina)*	25.3% delirium	29.2% still delirious at discharge Delirium duration (mean 4 days, range 1 – 18 days) Higher mortality (18.6% Vs 1.7%)	Overall delirium more common in haemorrhages. Left sided lesions common in haemorrhagic stroke and right sided lesions in ischaemic stroke. Ischaemic strokes more common in the anterior circulation.	High
Gustafson, 1991 *(Sweden)*	48% delirium	Longer hospital stays (19 days Vs 13 days) Higher institutionalisation (43.5% Vs 15.8%) Higher mortality (15.9% Vs 2.6%)	Post-stroke myocardial infarctions, pneumonia, urinary tract infection, urinary retention and pulmonary embolism all linked to delirium. Extremity paresis, previous delirium, older age and anticholinergic meds all independent predictors for delirium development.	High
Gustafson, 1993 *(Sweden)*	42% delirium	Higher basal plasma cortisol levels Longer hospital stays (23.1 days Vs 15.6 days)	Hypercortisolism may be connected to the pathophysiology of delirium in acute stroke. High cortisol levels, severe motor impairment and left sided lesions were independent predictors of delirium. Old age had borderline significance.	High

Figure 3.4: The outcomes of stroke patients with delirium.

Author	Occurrence	Outcomes	Confounding variables	Quality of study
Henon, 1999 *(France)*	24% delirium	Decreased functional outcome at discharge and at 6 months Longer hospital stays (13 days Vs 12 days) Higher institutionalisation (61.2% Vs 43.8%) Higher mortality as inpatient (14.3% Vs 13.1%) and at 6 months (40.5% Vs 32.3%)	Metabolic or infectious disorders as independent variables. Right superficial lesions, cerebral atrophy, leukoaraiosis and pre-existing cognitive decline associated with delirium.	High
McManus, 2008, 2009 *(UK)*	28% delirium	Delirium common post-stroke and remains for up 1 month Longer hospital stays (62.2 days Vs 28.9 days) Higher institutionalisation (43.7% Vs 5.2%) Higher mortality (30.4% Vs 1.7%)	25.6% African group delirious compared to 29.2% non-African. Poor vision, poor hearing, high IQCODE scores, small vessel disease, atrial fibrillation, previous stroke/TIA and TACI stroke associated with delirium. Pre-cognitive decline independent predictor. Delirium may be a predictor of stroke. Low MMSE scores associated with delirium.	High
Oldenbeuving, 2008	11.8% delirium	Severity of delirium decreased in 94% of cases with Rivastigmine treatment	-	Medium
Sandberg, 2001 *(Sweden)*	75% delirium with sleep apnea 56% delirium without sleep apnea	52% of patients had sleep apnoea post-stroke 75% were delirious with sleep apnoea and 56% were delirious without sleep apnoea	Delirium is independently associated with vision impairment and minimal oxygen saturation. Delirium, depression, latent reactions to verbal stimuli and an impaired ADL linked to sleep apnoea.	Medium
Sheng, 2006 *(Australia)*	25% delirium	Increased disability and decreased cognition post-stroke Longer hospital stays (33.2 days Vs 25.3 days) Higher institutionalisation (38.5% Vs 12%) Higher mortality at 6 months (29.7% Vs 12.8%) and at 1 year (41% Vs 17%)	Older age, haemorrhagic stroke, pre-stroke dementia and GCS<15 independent predictors for delirium. TACI stroke and cardioembolic stroke highly associated with delirium. Delirium patients more likely to have complications such as urinary tract infections, urinary or faecal incontinence and metabolic disorders. Transient delirium had better long term outcomes compared to delirium lasting over 24 hours.	High

Figure 3.4: The outcomes of stroke patients with delirium – continued.

3.6.1 **Differences in sampling and methodology**

All the studies included in this review were based in a hospital setting e.g. general medical wards or stroke units and sampled consecutive stroke admissions. The inclusion and exclusion criteria were broadly similar. Most studies excluded subjects who were severely unwell and had a low GCS score or patients with TIA's, subarachnoid haemorrhages, head trauma, neurosurgery and those not competent in the English language. A less common exclusion criterion was the exclusion of patients below 40 years of age[47]. The majority of the studies sampled a cohort with an average age of over 65 years of age. However, there were exceptions. Studies by Caeiro et al,[61, 443, 444] had an average age of 55 to 65 years which meant that this study population was much younger in comparison to the other cohorts. Another less common exclusion criterion was the exclusion of patients who were not local or did not have an informant or carer[47].

Regarding the ethics of consent in delirium research, it is preferable to obtain the informed consent of a participant with capacity. If the participant lacks capacity, then the proxy consent of a carer is sought. If neither of these options is viable, then the consent of a professional is sought, as they would be appointed as a temporary consultee on the patient's behalf. With the exception of two studies[197, 452], the remaining cohorts did not specify how consent was taken.

The studies were prospective cohort studies with the exception of three studies[61, 197, 451]. Caerio et al, 2004 produced a preliminary study of the role of anticholinergic medications using a case control study with age and sex matched controls. Sandberg et al, 2001 used a cross sectional study to investigate the link between sleep apnoea, stroke and delirium. Finally, Oldenbeuving et al, 2008 used a subset of patients within a large epidemiological study to conduct a smaller pilot study looking at the effects of rigvastigmine in the treatment of delirium after stroke.

Screening and diagnostic methodology for delirium ascertainment varied greatly between cohorts. With regards to the use of diagnostic tools, previous studies and reviews have shown that the sensitivity and specificity of the tools used is dependent on the training and experience of the assessor[142, 424] and many of the studies varied with the use of qualified clinicians and/ or researchers. There were significant differences in the assessment tools used to measure delirium occurrences as well as processes of consent and the quality of the study data. The majority of the research groups relied on using the DSM III R, DSM-IV or ICD-10 criteria, alongside the CAM or DRS scales which are based on the aforementioned criterion. There were some exceptions such as the use of the Organic Brain Syndrome

(OBS) Scale[453], cognitive assessments such as the MMSE or relying on diagnoses based on clinical observation of the patient's behaviour. The CAM and DRS have been shown to have good sensitivity and specificity in detecting delirium. However it is worth noting that the screening tools employed in the studies had not been tested for use in the stroke population. Furthermore no pilot studies were conducted to assess the suitability of the selected tools within the chosen population.

With regards to delirium assessments, the timing and frequency of the assessments are of key importance. Incorrect timing of the assessments could result in missing potential cases of interest, as delirium often occurs near the time of admission. Similarly with regards to frequency, regular screening could help detect subsequent cases of delirium after the initial assessment. From the systematic review the majority of delirium assessments were conducted within a week of admission, with the timing of the delirium measurements ranging from less than 24 hours up to within 3 to 4 days of admission. These studies then repeated delirium assessments on a weekly basis dependent, on what time period they had specified for their follow up long term outcomes. The reporting of delirium rates varied between studies as Dahl et al,[445] and McManus et al,[449, 450] clearly stating the term prevalence whilst the remaining studies avoided using 'incidence' and 'prevalence' and opted for terms such as frequency instead. It was thought that the differences in the reporting procedures (i.e. variations in assessment timing and frequency) could alter the findings of the study; however this does not seem to be the case.

With regards to the outcomes and confounding variables, several different primary outcomes were recorded and many studies had clearly defined outcomes from the onset of the study. The reporting of co-morbidity, length of stay, discharge destination, duration of delirium and functional outcomes varied between cohorts. Nearly all studies reported some sort of confounding variables, but these were not always consistent as the methodological and/ or statistical adjustments for relevant confounding variables varied.

3.6.2 **Results: Occurrence of delirium in acute stroke**

The papers generated from the systematic review reported delirium occurrence rates of between 10 to 48%, details of which can be found in Figure 3.2 and 3.3. Two cohorts reported delirium occurrence within 24 hours or less[444, 446, 447], whilst the majority of studies reported delirium occurrence within 2 to 4 days. Two of the studies focused on evaluating medications that may contribute to the onset of delirium[61] and medications that could be used to decrease the severity of delirium[197]. Both of these studies[61, 197] analysed the

incidence, severity and duration of delirium in stroke patients but without any follow up on outcomes or associated risk factors. The purpose of the study by Gustafson et al,[448] was to determine if the pathology of delirium might be related to cortisol levels and so no follow up outcomes were recorded. Sandberg et al,[451] described the methods that they used to record the incidence of delirium in relation to sleep apnoea in stroke, however the frequency or timing of assessments was not described.

3.6.3 **Results: Outcomes associated with delirium in acute stroke**

Mortality rates were reported in four cohorts[443, 445-447, 47] with the data indicating that patients with delirium had an increased risk of mortality at discharge. A fifth cohort, Sheng et al,[452] reported that although there was not a significant difference in mortality at discharge or at one month, this became more distinct at six and twelve months. Sheng et al reported the rate of mortality at six months for the delirious patient group was 30% in comparison to the 13% reported in the group of non-delirious patients. Similarly at twelve months, mortality for the delirious group increased to 41% compared the non-delirious group which increased only slightly to 17% mortality.

The duration of delirium was recorded in four cohorts[446, 447, 449, 450, 197, 452] and the length of stay was also reported in four cohorts[445, 47, 449, 450, 452]. The studies that reported length of stay[445, 47, 449, 450, 452] showed that those with delirium had a longer period of hospitalisation, with an average stay of 30.3 days in comparison to non-delirious patients who only stayed an average of 18.7 days. Lastly data on discharge destination or the need for institutionalisation upon hospital discharge was only reported in four of the cohorts[448, 47, 449, 450, 452].

With regards to subsequent follow up periods, there was only one study[452] which explored the outcomes of delirium twelve months post-stroke. Henon et al,[47] conducted a six month follow up, whilst McManus et al,[449, 450] followed up till one month post-discharge. The remaining cohorts recorded outcomes at patient discharge but not all had consistent outcome measures. Subsequent cognitive decline or pre-stroke dementia was recorded in two studies[47, 452] and various functional outcomes such as changes in cognition (MMSE) or activities of daily living (ADL) scores were recorded for six cohorts[445-448, 47, 449, 450, 452].

Once discharged, four cohorts[448, 47, 449, 450, 452] suggested that the presence of delirium eventually led to the need for institutionalisation post-discharge. Dostovic et al,[446, 447] reported that a third of patients were still delirious at discharge and the average duration of

delirium was 3 to 4 days. Similarly Sheng et al,[452] reported that those with delirium that lasted for longer than 24 hours had worse outcomes at six months and an increased mortality risk at one and twelve months. Various functional outcomes were recorded for six cohorts, where two[449, 450] indicated a decrease in cognitive function as evidenced by changes in MMSE scores and four recorded a decrease in functional ability as evidenced by lower ADL scores[446-448, 47, 452].

In the study by Sandberg et al,[451] only follow up outcomes associated with the occurrence of sleep apnoea as opposed to the presence of delirium, were recorded and so this data was not included.

3.6.4 **Results: Confounding variables/ risk factors for developing delirium in acute stroke**

Five of the studies indicated that an increase in age increased the chance of developing delirium post-stroke[444-448, 452], whilst two cohorts identified that women were at higher risk of developing delirium[446, 447, 452]. Medical complications such as urinary infections and pneumonia were identified as key predictors for delirium[443, 445, 448, 47, 449, 450, 452] and subsequent cognitive decline or pre-stroke dementia was recorded in two studies[445, 47]. Of the studies that indicated that the presence of delirium was linked to the type of stroke, four cohorts suggested it was more common in haemorrhagic strokes[443, 446-448, 452] and three suggested that right sided lesions were better predictors for delirium onset[443, 446, 447, 47]. Only Gustafson et al[448] suggested that delirium was more common in left sided lesions.

As mentioned previously the study by Sandberg et al,[451] only recorded the occurrence of delirium in stroke patients that had sleep apnoea and follow up outcomes were associated with sleep apnoea as opposed to the presence of delirium. However this was the only study to assess the psychological impact on patients, an area which had not been reported in the remaining studies. Due to different assessment methodologies used in these cohorts and the low number of data sets, it was not feasible to pool together the results from the various studies for a combined meta-analysis.

3.7 Discussion of the systematic review

The results of the systematic review indicate that delirium after acute stroke has serious consequences for patient outcomes such as increased risk of mortality, length of stay and the need of institutionalisation. The studies in the systematic review reported an occurrence rate ranging between 10 to 48%. The findings of this review are in line with the previous literature reviews[120, 38, 46] that focused on giving an overall view of delirium in acute stroke whereas this systematic review focused purely on occurrence and outcomes with an aim to pool together the data for meta-analysis.

It is worth noting that the studies selected by this review included a number of heterogenic study populations. These populations were due to the considerable degree of variation between the selection criteria employed for each of the individual studies. The exclusion of certain patient subgroups could be source of bias. For example excluding those with a history of dementia means eliminating possible cases of delirium as dementia has been shown to be a risk factor for delirium onset[48, 454, 15]. Similarly excluding patients with aphasia or communication difficulties could have been avoided by considering the use of assessment tools that have been adapted for use in patients with communication issues. Furthermore the consent process for participants was not always described and this should have been clearly described for all studies[251, 252]. These amendments could have significantly decreased variations in participant selection and could have reduced or eliminated selection bias within the study population. For this systematic review it should also be noted that two of the research groups (McManus et al and Dostovic et al) used the same patient population for more than one paper. This means that although there are fourteen papers examined in this review, there were in fact only twelve different patient populations studied.

3.7.1 **Occurrence of delirium in acute stroke**

The studies included in the review reported the incidence of delirium in acute stroke which were consistent with delirium rates in other medical settings. These groups as previously mentioned included vascular surgery[234, 84], hip fracture patients[420, 49] and terminal illness[70, 423, 162]. The reported incidences of delirium varied greatly within the stroke population and so study findings may not allow for reliable comparisons to be made between studies. These variations could be due to a number of reasons. Consideration should be given to the variation in study methodologies when interpreting study findings and the impact it could have on the reported data. The frequency of the delirium assessments could have affected

the study findings as some groups conducted assessments daily[445], some weekly[449, 450] and some studies did not clearly state the frequency of assessments[451]. Whether the assessments were conducted on a busy ward or in a private side room should be considered, as any distractions could have affected the test subject and in turn the diagnostic outcome. The background of the assessors; ranging from clinical psychiatrists to those with very little psychiatry training[425], could also have affected the diagnostic process. It could also simply be attributed to geographic location or the variation in the sensitivity and specificity of the range of diagnostic tools that were employed in the studies.

The majority of studies used tools based on the DSM-IV or ICD-10 criteria such as the CAM or DRS scale. However it should be noted that these delirium tools have been validated for use in general medical patients and not specifically for use within the stroke population. None of the studies in the review stated that the tools were not designed to be used for delirium detection in the stroke population and no pilot studies were conducted to assess their validity. Some studies modified the scoring of their chosen assessment tools to accommodate the stroke patients. For example, applying their own cut off points[47], scoring 'not applicable' in certain sections due to patient communication issues[443] or excluding patients altogether if they were aphasic or had a reduced level of consciousness or alertness[47]. However it should be noted that McManus et al,[449, 450] was the only group that compared the use of CAM and DRS in the stroke population and stated the advantages and disadvantages of each method. They reported a high level of agreement between the two diagnostic tools and an association between the presence of delirium and a low MMSE score. The fluctuation of cognitive function and the associated language difficulties in acute stroke were also highlighted. The research group concluded that the CAM was more appropriate for use as it was easier to use, but it did require adequate training before use.

Other studies also used additional tools such as the OBS scale or the MMSE, rather than relying purely on clinical assessments based on the DSM or ICD criteria or by focusing on specific delirium features such as decreased consciousness or confusion. It should also be noted that scores of assessments such as the MMSE can be influenced by language, motor function and mood. By reviewing these studies it is clear that a standardised assessment protocol is required for the detection of delirium in acute stroke. The review also showed that the severity of delirium was only reported in selected studies[445-447], although this could have easily been analysed and recorded once the study sample had been selected. This is important because the severity and duration of delirium may be related to other issues and long term outcomes such as the risk of developing dementia[66, 172].

3.7.2 **Outcomes associated with delirium and confounding variables/ risk factors for developing delirium in acute stroke**

The outcomes associated with delirium after a stroke, are in line with the published literature in other clinical situations[41, 121, 230]. It is consistent with the conclusion that delirium after stroke is highly associated with an increased mortality, morbidity and length of stay in hospital. Regarding follow ups, out of the twelve populations studied, eight studies only reported short term hospital discharge outcomes. It is surprising that this short term follow up was omitted in the other four studies as information such as length of stay, mortality and discharge destination could have been easily obtained from the ward registers.

For long term outcomes, McManus et al, conducted a one month follow up for length of stay, mortality and discharge destination and Henon et al, conducted a six month follow up for functional measures, but both studies collected no other further data. It would have been advantageous to conduct additional tests for outcome measures such as the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) or Activities of Daily Living (ADL), to see if these had changed since discharge. The study by Sheng et al was the only study which conducted a thorough patient follow up at one, six and twelve months and reported a delirium incidence of 25%, placing this cohort in the middle of the reported incidence range.

Some of the confounding variables identified, are in line with the confounding variables found within the general medical literature for delirium. There are many risk factors for delirium but old age, severe illness and visual impairment are just three of the established risk factors that were mentioned in the included studies. The location and type of lesion was also mentioned in several of the included studies, as well as other stroke specific factors but these varied considerably between the different cohorts.

This review indicates that delirium in stroke patients is a cause for concern and further research is needed to improve the management and possible prevention of delirium post-stroke. Further information specifically on post-discharge patient follow ups and long term outcomes is required. Measures such as mortality risk, length of hospital stay and the need for institutionalisation post-discharge need to be recorded and analysed to determine the level of impact they may have on a patient's recovery. In order to conduct more informative long term studies, it is important that we produce more reliable incidence data sets with minimal variation, providing an improved foundation for better patient outcome studies.

3.7.3 **Clinical implications**

The research suggests that in order to improve the management and treatment of patients with delirium in stroke, better detection methods are needed. The routine use of diagnostic tools for delirium might increase detection rates thus improving the clinical management of the syndrome. It is worth mentioning that in order to use the existing delirium tools alterations or adaptations may need to be made so that they may be used within the stroke population. This systematic review reported that the occurrence of delirium ranged from 10 to 48%, therefore it would be safe to assume that this would increase the workload of the clinical staff. This would mean relying heavily on services such as psychiatry and / or the mental health team to deal with the large number of referrals, something which is not feasible for a prolonged period of time. Although the diagnostic tools require adequate training and experience for reliable use, the psychiatry services/ mental health team could provide the necessary training and advice needed for the ward staff to be trained in delirium detection. It would be particularly advantageous to train the nursing staff, as they interact with patients on a daily basis and would be able to pick up on any subtle changes in the patient's behaviour, thus leading to more efficient detection. Consequently in the long term, it would be more efficient and effective to train the clinical staff on the ward to screen, detect and manage delirium whilst allowing the psychiatry/ mental health team to deal with the more complex cases.

The use of a standard screening protocol which could be implemented across hospitals would help with the detection of delirium cases. Due to the multifactorial nature of delirium, a number of different disciplines may be involved in order to give a good inclusive overview of the case, but this can be a time consuming process. It is therefore essential to have a balance between having a detailed insight but at the same time the protocol needs to be quick and easy to administer. A protocol that is less time consuming would be more appealing to the staff as it would not significantly increase their workload and so the staff would be more likely to incorporate and adhere to the protocol in their daily routine. The introduction of delirium screening protocols on stroke units and the training of clinical staff could make a significant improvement and the regular screening procedures on stroke units would also help to trigger a more prompt and timely search for underlying causes. In some of the studies it was noted that delirium already present at admission was more common than delirium occurring after being admitted. Other studies have shown that admission from an institution is a risk factor for delirium in hospital and some studies have shown that delirium is common in nursing homes. It may be worth considering a preventative intervention that

could be used in institutions such as nursing homes and this in turn may help to possibly reduce the number of admissions.

3.7.4 **Research implications**

The variation in delirium occurrence could be attributed to a number of reasons and one of the reasons to consider are the study methodologies employed. The articles analysed in this review found that a number of studies varied with regards to how patients were recruited, the assessment methods that were used and the differences in applying the DMS-IV and ICD-10 diagnostic criteria. These issues suggest that a standardised screening and assessment protocol needs to be put into place, so that reliable cross comparisons can be made between studies. As it has been mentioned previously, the studies included in this systematic review did not employ delirium tools validated for use within the stroke population and no pilot studies were conducted to check the suitability of the tools for the chosen population. A follow up systematic review analysing how best to screen for delirium would highlight the tools available and specifically focus on the feasibility of the screening tools and their sensitivity and specificity in relation to assessing stroke patients. Following on from this, a validation study could be conducted to assess the use of these delirium tools in the stroke population. Consideration should also be given to the development and validation of a new delirium tool specifically for use in the stroke. This could be a future avenue of research and would help to overcome this particular methodological challenge in delirium research.

Due to fluctuating nature of delirium, it is important to clearly state whether study groups are reporting incidence or prevalence rates as the frequency of the results recorded could have a significant impact on the cohort findings. This would also limit cross comparisons between different studies making the reliability of results not comparable. In addition to this the study populations recruited in these cohorts varied in age, gender and stroke types. Many studies had strict exclusion criteria regarding stroke types, existing illnesses, patient capacity, language/ communication issues and specific age limits. Due to the nature of delirium it also meant that a significant number of patients may have lacked the capacity to consent to the study or indeed they may have even struggled to communicate or complete the assessments required to participate. As a result there is a possibility that a significant number of people who may have had delirium would not have been recruited and analysed as part of the study cohort. The excessive exclusion criteria in these studies therefore produced research that was based on a group of people that were not truly representative of the stroke population, which leads to issues of generalisability of results and other ethical

considerations. The increased mortality rates associated with the presence of delirium post-stroke means that any future long term outcomes studies may need to factor the mortality rate into their recruitment targets in order to have an adequately powered study. Furthermore there were many single case reports about the psychological aspect of delirium in stroke patients but ignored in the larger cohort studies, as there was no follow up on the patient's psychological status and this is something which may need to be considered for future studies.

3.7.5 **Limitations of the review**

The original systematic review was completed in June 2010 to identify gaps in the literature and help inform the design of a study for further investigation. However the search was subsequently refreshed and reviewed in April 2014 so that it was up to date for publication and the addition of new data meant that a meta-analysis could be performed. A summary of the April 2014 search is provided in the discussion chapter (Section 9.4). For the original review conducted in June 2010, studies that that involved surgical intervention or those that were primarily focused on developing methods based on biochemical markers for delirium were excluded. Studies where the definition of delirium was not made clear were also excluded as case ascertainment would be unreliable. Delirium tremens was also excluded from this review as it was considered to be a distinct condition that was not as closely related to acute stroke as the other subtypes.

The primary aim was to identify studies that investigated the incidence and outcomes of delirium post-stroke, which is why a broad search strategy was used in order to increase the sensitivity of the search thus compromising on search specificity. A secondary systematic review focused on investigating how best to screen for delirium, specifically the feasibility of the screening tools and their sensitivity and specificity in the stroke population was considered. However this second review was subsequently eliminated due to limitations in time and resources. Furthermore the data that had been collated from the published literature included information about the assessor background, types of assessments used and their timing and frequency, as summarised in Figure 3.3 and 3.4. It was decided that this information was sufficient to inform the study planning and design.

As resources were limited, studies not written in English were also excluded if the translations of the paper obtained were not of adequate quality. Furthermore the citations and abstracts produced by the initial search were not reviewed by an independent assessor. Ideally a second review would have been conducted by a separate author. The second

author would have independently screened for relevance and fulfilment of the inclusion criteria to see if the results were in agreement. However due to limitations in time and resources, this was not possible. Overall, I consider that this systematic review was sufficient to highlight the key findings in the area of delirium and acute stroke.

3.7.6 **Implications for the proposed study**

The results of the systematic review showed that there were very few studies that have investigated the effects of delirium in stroke and the studies that did, reported a wide variation in delirium incidence. Out of the twelve research groups highlighted by the systematic review, only one study[452] followed patients long term for twelve months and another research group[449, 450] investigated a UK based cohort.

The results of the systematic review indicated a need for the following; a UK based study, assessing long term outcomes study, employing reliable diagnostic tools (e.g. CAM and DRS) as well as a less strict exclusion policy so that the study sample is more representative of the general stroke population. Fulfilling these requirements would help in allowing comparisons to be made with other incidence studies and the research questions and design of the proposed study were developed to meet these requirements.

3.8 Conclusion

Delirium and acute stroke when combined have serious consequences for patient outcomes such as in increased risk of mortality, length of stay and the need of institutionalisation. To date, studies researching the association between acute stroke and delirium have been limited and the cross comparisons between the existing studies are not reliable, due to a number of various methodological and ethical considerations. The rate of delirium occurrence in the published literature ranges from 10 to 48%, with the meta-analysis producing an average incidence of 23.7%, suggesting that the presence of delirium and its impact is significant. The clinical importance of delirium in acute stroke has been highlighted by many studies suggesting that appropriate action needs to be taken.

3.8.1 **Key points**

- Delirium in acute stroke has been linked to increased mortality, length of stay and the need for future institutionalisation.
- Due to its high occurrence rate, delirium in acute stroke is of significant clinical importance and better detection methods need to be implemented.
- Clinical staff should be educated in delirium awareness and trained in how to detect and manage delirium rather than relying on the psychiatry/ mental health team.
- The number of studies conducted within the area of delirium and acute stroke is limited due to a range of ethical and methodological variations.
- Future studies need to employ a standardised delirium screening and assessment methodology so that more reliable cross comparisons can be made between studies.

4 Aims and hypotheses

4.1 Aims and objectives

The primary aim of this study was to investigate the association of delirium with patient mortality within the acute stroke population. Fulfilling the primary aim would also identify the incidence, severity and duration of delirium within this population of patients. This UK based prospective cohort study was designed with the following secondary aims:

1. To investigate the association of delirium with length of hospital stay in acute stroke patients.
2. To investigate the association of delirium with a patient's discharge destination after a stroke.
3. To investigate the association of delirium with a patient's physical functional capacity post-stroke.
4. To investigate the association of delirium with memory impairment in stroke patients.
5. To determine whether the type of stroke predicts the onset of delirium.
6. To identify possible key confounding variables or outcome predictors that may protect against the onset or decrease the duration of delirium in stroke.
7. To evaluate the accuracy and reliability of the delirium instruments, the CAM-ICU and the DRS-R98, for use in the stroke population.

4.2 Hypotheses

In a prospective sample of stroke patients admitted to the acute stroke units within West Yorkshire, the following hypothesis was investigated:

Compared to those patients without delirium, patients with delirium will have a worse outcome in terms of an increased risk of mortality.

For the prospective cohort study of stroke patients admitted to the Leeds Teaching Hospitals Trust, the following additional hypotheses were:

1. Compared to patients without delirium, those patients with delirium will have a poorer outcome in terms of a longer length of stay in hospital.

2. Compared to patients without delirium, those patients with delirium will have a poorer outcome in terms of an increased need for institutionalised care post-stroke.

3. Compared to patients without delirium, those patients with delirium will have a poorer outcome in terms of a decreased physical functional capacity post-stroke.

4. Compared to patients without delirium, those patients with delirium will have a poorer outcome in terms of decreased cognitive function in the long term.

5. The onset of delirium is dependent on the type of stroke, specifically the size, type and location of the stroke lesion.

6. There are certain key confounding variables or outcome predictors which when altered affect the onset or duration of a delirium episode.

7. The delirium instruments selected for this study, the CAM-ICU combined with the DRS-R98, are suitable for use within the stroke population.

5 Methodological considerations

Several important aspects need to be considered when designing and conducting a study, to investigate the effects of delirium in an acute stroke population. These important aspects are discussed in this chapter and include the following: the type of study, avoidance of bias in the study sample[455, 456], the inclusion and exclusion criteria applied to potential participants, unambiguous case definitions, a stringent case selection procedure during recruitment, the complete follow up of participants once recruited, clear definition and measurement of key confounding variables or outcome predictors, clinically relevant outcome measures and the selection of statistical methods used to analyse the study data.

5.1 Type of study

There are a number of study methodologies available, each with their own advantages and disadvantages. The types of study that were considered for this investigation are described below.

5.1.1 **Cross sectional study**

Cross sectional studies[457] are observational study designs which describe the absence or presence of a clinical feature. They observe a collection of different individuals (a cross section of the population) at a specific time point or interval. Exposure and outcome can be determined simultaneously, so the prevalence of an illness and the odds ratio or the relative/ absolute risks from an illness can be calculated. Cross sectional studies are advantageous in that they are shorter in length, quicker and easier to conduct in comparison to other methodologies. However this type of study does have disadvantages, as it usually relies on data collected for other purposes and the recall of events may be unreliable. Furthermore as the outcome and risk factors are identified at the same time, the direction of any effect cannot be easily determined as it can be a problem identifying which came first. A cross sectional design for the purposes of this study would not be suitable as it would not allow for the long term monitoring of delirium duration and the follow up assessment of outcomes after discharge.

5.1.2 **Case control study**

Case control studies[458] are retrospective study designs that avoid the problem of cause and effect as the disease is the outcome of interest and they are often used for the study of rare diseases. People with the disease (case) are matched to people without the disease (control) in order to compare their exposure to its associated risk factors. These types of studies are advantageous as they can be conducted by an individual researcher, are inexpensive and shorter in duration compared to other methodologies and can be completed without waiting for the outcome to develop. However a disadvantage is that participants can be prone to recall error, due to the recollection of past events. This may cause difficulties in obtaining reliable information about an individual's exposure over a certain time period, in order to establish the timeline of exposure to the disease outcome.

Case control studies are beneficial in that individuals in both groups can be matched for factors such as age or sex in order to minimise bias in the sample. Participant recruitment may take longer as each of the case and control participants have to be matched appropriately, but it does mean that a lower power can be sufficient to detect any exposure effects. As with any investigation, larger numbers would increase the statistical power of the study findings. However identifying and recruiting these cases may prove difficult as it is often easier to recruit controls rather than cases. This type of study is often used to study rare conditions.

For the purposes of this study, recruiting stroke participants as controls may be relatively straight forward, but finding delirium cases in the stroke group that were matched in terms of age and gender may be difficult, as it could be time consuming. A potential solution to overcome this issue would be to recruit many controls to one case, but choosing a suitable control group can also be problematic. Although there is no list of suitable or unsuitable controls, sound justification is required for choosing a specific control group. Unsuitable controls can also make findings hard to interpret, which is why researchers tend to use more than one type of control group to overcome this problem. Furthermore a case control design would not be suited to this study as there is more than one outcome proposed for this investigation. In order to assess the selected outcomes, a separate sub-study would need to be implemented for each outcome to determine the effect it may have on the participants. A study design of this nature would be time consuming and unnecessarily complicated.

5.1.3 **Retrospective cohort study**

For a retrospective methodology[459], the outcome is defined at the start of the study and the researcher looks at the data already collected to examine the exposure to certain risk factors linked to the chosen outcome. In effect the event or illness has already passed and the data is simply collected to analyse the relative risk or odds ratio. Retrospective cohort studies are less time consuming, allow multiple outcomes to be analysed and can be used to study rare occurrences. However they may require unfeasibly large numbers for rare outcomes and often rely on analysing data collected for other purposes.

A retrospective approach in this study could lead to an underestimation of delirium incidence. For example in this study, the study data analysed would be derived from ward based registers and medical notes which may contain incomplete entries or incorrect data. Also the use of diagnostic tools after a delirium episode has passed could introduce an element of error, as the assessments would rely on the information recorded in the ward registers. This information may not be the most accurate diagnosis of delirium as it would not be the primary focus of ward care. The aim of the ward register is to record information on the primary cause of admission, which is a stroke and not on the detection of delirium. This means that accurate comparisons may not be made as there may be uncertainty over the presence of delirium due to doubts over the diagnostic process and the data records. Furthermore any patient input regarding the case would be questionable as their recall of events may differ from what actually took place, again making the data unreliable.

5.1.4 **Prospective cohort study**

A prospective cohort study[460] involves recruiting, observing and assessing a sample of people over a certain period of time for a common outcome. As well monitoring the development of a disease, prospective studies can help to determine risk factors and uncover unanticipated outcomes. Compared to the other methodologies, prospective studies are expensive, time consuming and have a large workload as they require a large number of participants to be monitored over a long period of time. This methodology can also be prone to attrition bias depending on what outcome is being studied. For example in the case of stroke, an increased mortality rate could contribute to a steady decrease in participants over the length of the study. Cohort studies are also greatly susceptible to the effect of confounding variables and this is discussed in further detail later on in this chapter (Section 5.6). Prospective studies are valuable in that they tend to have fewer potential sources of bias as participant exposure is assessed at the start of the study and then regular repeat

observations are made using a standard protocol. This means that the use of retrospective data collection is avoided, potential participant errors are lower and the data collected is consistent and completed to the same standard for every participant. Furthermore comparison groups do not have to be selected in advance, as the assessment of risk exposure produces a good selection of exposed and unexposed groups for comparison. This type of study design seems to be the most suitable for this study to produce an accurate, reliable and representative data set.

5.1.5 **Implications for the proposed study**

For the purposes of this study, a prospective cohort study was selected as it allowed direct comparisons to be made between stroke patients with and without delirium. It would also ensure that all participants are subjected to the same procedure from the start, thus producing a consistent data set for analysis. The diagnostic criteria used for case ascertainment could be determined prior to the commencement of the study. Also time can be taken to ensure that the assessment tools used in the determination of the cases are valid and reliable for that chosen patient population.

5.2 Construction of the study sample

When designing a study, consideration should be given to the construction of the sample. It is important that the sample produced is representative of the population being studied and that steps have been taken to avoid or reduce error and improve the generalisability of the sample. The following section discusses certain aspects that were considered.

5.2.1 **The study setting**

The study was set to recruit patients from stroke units based in National Health Service (NHS) hospitals within West Yorkshire, specifically hospitals based in Leeds and Bradford. Prior to study commencement, the stroke services within the Leeds Teaching Hospitals Trust (LTHT) were distributed between two hospitals in Leeds; the Leeds General Infirmary (LGI) and St James University Hospital (SJUH). In December 2010, the elderly stroke ward at SJUH was relocated to the LGI (Ward 44 and 46 were subsequently renamed L26 and L27) to form the Acute Stroke Unit (ASU) and the Stroke Rehabilitation Unit was relocated to

SJUH (Ward 30) for patients over 65 years of age and Chapel Allerton Hospital (CAH) (Ward 1) for patients under 65 years of age. In December 2011, the Hyper Acute Stroke Unit (HASU) was set up at the LGI (Ward L21) increasing the number of stroke beds.

At the Bradford Foundation Hospitals Trust (BFHT), the combined HASU and ASU were originally based at the Bradford Royal Infirmary (BRI) with the Stroke Rehabilitation Unit situated at St Luke's Hospital (SLH) (Ward 6D). The BRI also relocated their combined HASU and ASU from Ward 24 to Ward 9 at the BRI, increasing the number of acute stroke beds in the process. In both hospitals, almost all the stroke patients arrived at the hospital's Accident and Emergency (A&E) Department either by the ambulance paramedics, or via a referral from their general practitioner and from there they were transferred to the stroke units. Due to the recent reallocation of stroke services, almost all stroke cases are now admitted directly to the stroke units.

Hospital Trust	Acute stroke unit Ward no	Beds	Rehab stroke unit Ward no	Beds
LEEDS				
Consultants:	LGI (Brotherton level B)		SJUH (Beckett Wing)	
P. Wanklyn	Ward L26 (male)	16	Ward J30 (mixed)	24
J. Cooper	Ward L27 (female)	18	*Older stroke patients*	
S. Limaye				
Hassan	LGI (Brotherton level G)		Chapel Allerton	
J.Bamford	Ward 21 (HASU)	10	Ward 1 (mixed)	22
Chandran			*Younger stroke patients*	
BRADFORD				
Consultants:	BRI (Neuro/ Stroke)		SLH (Horton wing)	
C. Patterson	Ward 9 (mixed)	24	Ward F6	24
S. Maguire	*N.B. Includes HASU*		*N.B. Includes neuro-rehab*	
HARROGATE				
Consultants:	Strayside wing		Strayside wing	
S. Brotheridge	Oakdale ward (mixed)	4	Oakdale ward (mixed)	22
	N.B. No HASU		*N.B. Includes neuro-rehab*	
CALDERDALE				
Consultants:	HDU	4	Ward 7A stroke (mixed)	14
I. Shakir	Ward 6D (male)	4	Ward 7B stroke (mixed)	12
P. Rana	Ward 6D (female)	4	Ward 7C neuro (mixed)	14
R. Mir	Side rooms	3	Ward 7D general (mixed)	12
YORK				
Consultants:	Ward 36 (mixed)	14	Ward 39 (mixed)	19
J. Coyle	Side rooms	5		
W. Iverson				
WAKEFIELD				
Consultants:	Gate 2		Gate 2	
M. Carpenter	Stroke/ neuro ward	34	Stroke/ neuro-rehab ward	28
A. Stanners	(mixed)			
P. Dhatta	Pinderfields stroke unit	10	Pinderfields rehab unit	12

Figure 5.1: Stroke services available in Yorkshire in 2011-2012.

The number of stroke beds available in hospitals within West Yorkshire in 2011 to 2012.

As these hospitals have larger stroke units, it is possible that patients from other districts may be referred. The sample was limited to stroke services within Leeds and Bradford, with hospitals in Harrogate and Calderdale selected as additional recruitment sites if the need arose. The use of more than one hospital ward increased the number of beds available and thus increasing the number of potential participants. By recruiting from more than one hospital ward, any procedural differences such as screening or discharge pathways, potential sources of bias or any other affecting factors specific to a particular ward will also have been reduced.

In the hospitals chosen, there is a ward clerk assigned to each ward who is responsible for the data input into the ward registers and electronic databases. The stroke units have good links with the stroke rehabilitation units, physiotherapy and occupational teams, community stroke team (CST), intermediate care team (ICT), mental health teams, clinical psychology, neuropsychiatry and liaison psychiatry. The admission rates for the chosen wards are illustrated in Figure 5.2 below. Information about stroke patient care during hospital admission is helped by national audit registers as stroke is a very well audited clinical condition. An example of such a register is the Sentinel Stroke National Audit Programme (SSNAP) which builds on the work of the National Sentinel Stroke Audit (NSSA) and the Stroke Improvement National Audit Programme (SINAP). These registers demonstrate that stroke has a high level of interest and is a worthwhile area for further investigation.

Location	Beds	Admissions		Deaths		No. of potential participants
		Per year	Per month	Per year	Per month	
Ward 37 – LGI relocated to ward L27	18	480	40	92	8	480 – 92 = **388 per year** Average of 32 a month
Ward 34 – SJUH relocated to ward L26	15	480	40	33	3	480 – 33 = **447 per year** Average of 37 a month
Ward 24 – BRI relocated to ward 9	14	400	35	56	5	400 – 56 = **344 per year** Average of 29 a month

Figure 5.2: Admission statistics for stroke units in Leeds and Bradford in 2011.

The stroke units predominately cater for patients over 65 years of age. They currently have an average of 2 admissions per day and an average of 40 new admissions per month, not including weekends. The average number of deaths per stroke unit has also been taken into account, producing a cumulative total of approximately 1179 admissions over a one year period. Since December 2010, the elderly stroke wards have undergone significant relocation and restructuring, but it was assumed that the wards will generate similar admission numbers.

5.2.2 **Identifying potential participants**

Patients with a suspected stroke were admitted to the hospital Accident and Emergency Department where they were seen by the clinicians and nursing staff. Stroke diagnosis was made by clinical assessment and a Computer Tomography (CT)[357] or Magnetic Resonance Imaging (MRI) [356] scan of the head. Patients with a confirmed stroke diagnosis were then transferred to HASU or an ASU depending on the time of stroke onset. Details of the stroke unit admissions recorded in the ward registers by the ward clerk were checked, as well as consulting with clinical staff to accurately identify patients with an acute stroke.

5.2.3 **Recruitment of the participants**

Once potential participants were identified, the following issues were considered with regards to the recruitment of the study sample.

a) The recruitment window (occurrence bias)[456]. Delirium is a clinical syndrome that has an acute onset and a fluctuating nature. If the participants are not recruited within a specific time period after admission, then certain cases may be missed. This may alter the study outcomes as not all possible cases are included and in effect this would not be a true representation of the occurrence.

b) The refusal of participants (non-respondent/ volunteer bias)[456]. The population who refused to participate in the study may differ from those who did participate and this could have a significant impact on the study outcomes e.g. cognitive impairment and communication problems. Patients with delirium may be unwilling to participate as they are already going through a traumatic time. Similarly patients without delirium may deem the assessment as unnecessary as the study is voluntary and they may not wish to undergo any additional investigations. This may mean that the recruited population may be more motivated or willing to complete assessments as they are more able or more concerned about their health.

5.3 Study participant criteria

The impact of recruitment is important, in order to produce a reliable and consistent data set from which accurate findings can be reported. To produce this it is necessary to set certain

guidelines for the recruitment of the patients. For potential participants to be involved in this study, the following criteria needed to be fulfilled.

5.3.1 **Inclusion criteria**

The inclusion criteria for the study were as follows:

a) New diagnosis of a stroke as confirmed by clinical and imaging assessment within 72 hours of admission to the acute stroke unit. The time period of 72 hours was chosen as it increased the maximum number of participants that could be recruited, without having to miss any potential participants or interfere in the clinical assessments that the patient would require upon admission. Patients diagnosed with Transient Ischaemic Attack (TIA), Subarachnoid Haemorrhage (SAH) and other neurological conditions and stroke 'mimics' were not included.

b) Aged 55 years and over. Age has been shown to be significant risk factor for delirium, when investigated in other patient populations[76].

5.3.2 **Exclusion criteria**

The exclusion criteria for the study were as follows:

a) Patients who are severely ill. The decisions were made in consultation with the clinical staff and the use of the MEWS and GCS scores. Those with a Modified Early Warning Score (MEWS)[461, 462] of 5 or more and a Glasgow Coma Scale (GCS)[463, 464] score of 8 or lower were excluded. Patients that initially had a high MEWS score or low GCS score but improved within the recruitment window were considered for participation. There is a possibility that some severely ill patients that were excluded may have had delirium, but it would not have been appropriate to include them due to the state of their health.

b) Patients whose first language was not English and where appropriate arrangements for translation could not be made.

c) Patients who did not have capacity to consent and did not have a carer or consultee to look after the participant's best interests and wellbeing, and provide consent to take part in the study.

d) Patients who had a home address outside of West Yorkshire were classed as non-residents. The non-residents were included in the analysis of the incidence data but excluded for the analysis of the prognostic outcomes if follow up proved to be difficult.

e) Patients that were already enrolled in other research studies. If these other studies did not allow for co-recruitment of patients, then the patients were excluded.

5.4 Case definition and selection process

As described in Chapter two, the onset of a stroke can be identified using a number of warning signs but the actual diagnosis of a stroke is made by a medical professional[465, 351]. Once within the care of a medical professional, the onset of a stroke is identified quickly so that the patient can receive the prompt treatment they need. The process of stroke diagnosis is well documented[466] and every hospital has a stroke care pathway in place. However this is not the case for the screening, diagnosis and treatment of delirium. There are no clinical tests or investigations used routinely for the detection of delirium.

With regards to delirium, previous studies have used a range of different assessment tools to detect delirium within a stroke population, as discussed in Chapter three. It is important that the instruments used to identify the study cases are easy to use and interpret, well tolerated by the participants and have a good sensitivity and specificity to detect delirium. The Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)[23], recently updated to DSM 5[26] and the International Classification of Diseases 10 (ICD-10)[138], are considered the international standards in the diagnosis of delirium and provide an accurate definition of the syndrome. Subsequently other diagnostic methods for delirium have been developed and validated based on these criteria. The following section discusses the measures used in the study for the identification of both stroke and delirium.

5.4.1 **Classification of stroke**

The diagnosis of stroke was made by the clinical staff on the stroke units. These assessments were supplemented by CT and/ or MRI scans which clarified the pathology of a stroke in relation to an infarct or a haemorrhage. In addition to this, the Bamford stroke classification[280] was used as clinical descriptor, to provide a prognostic grouping of the stroke subtypes, as illustrated in Figure 5.3.

Stroke type	Features
Total Anterior Circulation Stroke (TACS)	1. New higher cerebral function dysfunction: dysphasia/dyscalculia/apraxia/neglect/visuospatial problems plus 2. Homonymous visual field defect, plus 3. Ipsilateral motor and/or sensory deficit of at least two areas of face, arm and leg. In the presence of impaired consciousness, higher cerebral function and visual fields deficits are assumed.
Partial Anterior Circulation Stroke (PACS)	Two of the three components of TACS, or isolated dysphasia or other cortical dysfunction, or motor/sensory loss more limited than for a LACS.
Lacunar Stroke (LACS)	Pure motor or pure sensory deficit affecting two of three of face, arm, and leg, or sensorimotor stroke (basal ganglia and internal capsule), or ataxic hemiparesis (cerebellar-type ataxia with ipsilateral pyramidal signs—internal capsule or pons); or dysarthria plus clumsy hand, or acute onset movement disorders (hemi-chorea, hemiballismus—basal ganglia).
Posterior Circulation Stroke (POCS)	Cranial nerve deficit with contralateral hemiparesis or sensory deficit, or bilateral stroke, or disorders of conjugate eye movement, or isolated cerebellar stroke, or isolated homonymous hemianopia.

Image adapted from the paper by Bamford et al[279]

Figure 5.3: The Bamford stroke classification.

The Bamford stroke classification scale is based on the four key clinical features of stroke; brainstem signs, hemiparesis, hemianopia and higher cortical dysfunction which include language problems. PACS are mostly embolic, whilst LACS are mostly thrombotic occlusions of small deep end arteries. POCS and TACS however are spilt - 80% of POCS are thrombotic and 20% are embolic compared to LACS which are two thirds embolic and one third of them are due to in-situ thrombosis[280].

The Bamford classification is also known as the Oxford Stroke Classification[467, 280, 468]. The patient's clinical signs are used to classify the stroke into one of four possible categories and this relatively simple bedside method[469] can give the assessor[470] useful information on mortality risk, dependence outcome and risk of reoccurrence. During patient examinations, MEWS readings are often used to monitor physiological status and the GCS score is used to assess the patient's level of consciousness. In this study both the MEWS and GCS scores were used to assess the potential participant's state of health to determine if they were well enough to participate in the study, in addition to the clinical assessment of the stroke.

5.4.2 **Detection of delirium**

As previously mentioned, several diagnostic methods have been developed to operationalise the DMS-IV and ICD-10 criteria[471-475, 130, 476-481]. From the systematic review and other review articles[142, 33, 424], several tools that screen for and diagnose delirium were shortlisted, which had varying degrees of sensitivity and specificity when used in the general medical population. However, these tools were not designed to detect delirium in a stroke population. These shortlisted measures as illustrated in Figure 5.4a and 5.4b, were previously mentioned in Chapter one and will now be further discussed.

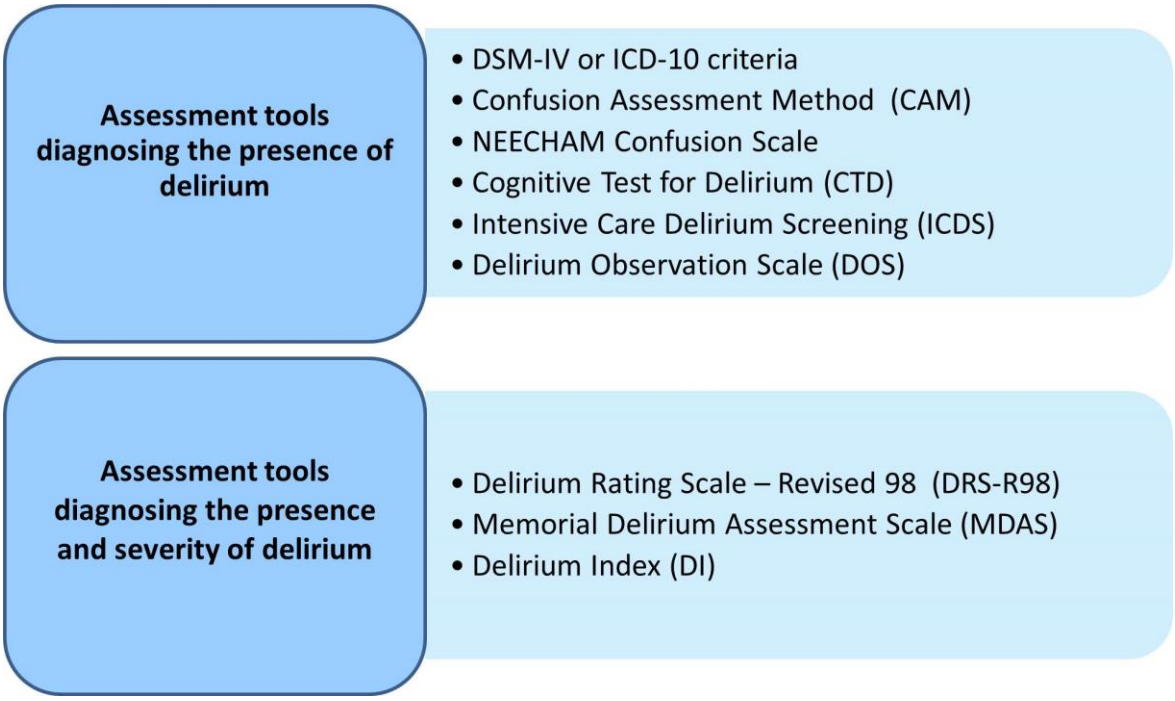


Figure 5.4a: A summary of the assessment tools available to diagnose delirium.

Many delirium diagnostic methods have been developed and validated based the DSM-IV or ICD-10 criteria, which are considered the reference "gold standard" in delirium. However they are not routinely used in clinical settings.

Delirium assessment tools	Features
Confusion Assessment Method (CAM)	Sensitivity: 94% Specificity: 89%
CAM for Intensive Care Unit (CAM-ICU)	Sensitivity: 94 - 100% Specificity: 90 - 95%
Cognitive Capacity Screening Examination (CCSE)	Sensitivity: 94 - 100% Specificity: 83 - 100%
Cognitive Test for Delirium (CTD)	Cut off 22; Sensitivity: 72%, Specificity: 71%
Delirium Observation Screening (DOS)	Sensitivity: 94.4% Specificity: 76.6%
Delirium Rating Scale (DRS)	Cut off 10; Sensitivity: 82%, Specificity: 94% Cut off 8; Sensitivity: 90%, Specificity: 82%
DRS – Revised 98 (DRS-R98)	Sensitivity: 91 - 100% Specificity: 85 - 100%
Intensive Care Delirium Screening (ICDS)	Sensitivity: 99% Specificity: 64%
Memorial Delirium Assessment Scale (MDAS)	Sensitivity: 68% Specificity: 94%
NEECHAM Confusion Scale	Sensitivity: 87% Specificity: 95%

Image adapted from the paper by Meagher et al[31]

Figure 5.4b: The sensitivity and specificity of delirium diagnostic tools.

Furthermore, many of these delirium tools vary in sensitivity and specificity in non-stroke settings, making the comparison of results between cases unreliable and problematic.

Diagnostic methods for delirium have been developed and validated based on the DSM-IV or ICD-10 criteria and one such tool is the Confusion Assessment Method (CAM)[130]. The CAM was originally developed in 1988-1990 to help non-psychiatrically trained clinicians to identify cases of delirium quickly and accurately. The CAM has the highest sensitivity and specificity in comparison to the other tools. Due to its ease of use and good validation results, the CAM is the mostly widely used tool for delirium detection[482] both in clinical and research settings. The tool includes two parts; firstly the screen for cognitive impairment and secondly the focus on the four core features of delirium that distinguish it from other forms of cognitive impairment. The four core features are acute onset or fluctuating nature, inattention, disorganised thinking and an altered level of consciousness. Each core feature is rated as positive if present or negative if absent and an overall score of three positive features indicates that delirium is present.

The Confusion Assessment Method for Intensive Care Units (CAM-ICU)[483] was further developed for use with patients in intensive care units who were unable to communicate verbally due to artificial ventilation or intubation. It is a well validated and frequently used tool. It requires minimal training, is quick to administer and has been translated into ten languages. The ability to translate the test was important in our study as the hospitals serve diverse communities and some of our participants may not be fluent in English. In addition to this, some of the study population may not be able communicate verbally due to the effects of stroke and so the use of the CAM-ICU may help to overcome this problem[484].

As the CAM-ICU does not determine the severity of a delirium episode, another measure was needed to meet this requirement. There are only a few tools that assess severity of delirium such as the Delirium Rating Scale – Revised 98 (DRS-R98)[485], the Memorial Delirium Assessment Scale (MDAS)[474] and the Delirium Index (DI)[476]. The DI depends solely on the observation of the patient without any input from other sources such as staff or carers[486]. The use of information from other sources would strength the diagnosis of delirium by decreasing potential sources of error and so the use of the DI was excluded on this basis. The MDAS showed a good specificity (94%) but lower sensitivity (68%) for the detection of delirium. Furthermore the MDAS had only been tested with one patient population consisting of cancer patients, whereas the Delirium Rating Scale (DRS)[481] had been tested in a range of different patient groups. The DRS also incorporates information from staff, carers and the medical notes as well as patient observations. Upon comparison of the sensitivity and specificity of the tools, the DRS also had a higher sensitivity and specificity compared to the MDAS and DI.

The DRS[481, 487] assesses 16 domains which include: sleep wake cycle, perceptual disturbances, delusions, lability of affect, language, thought process, motor agitation, motor retardation, orientation, attention, short and long term memory, visuospatial ability, temporal onset of symptoms, fluctuation of symptom severity and physical disorder. Each domain is allocated a score and the test has an overall maximum score of 32. The assessment tool also requires input from the staff involved with the patient's care.

The 1998 revised edition of the DRS, the DRS-R98[485] is based on 13 severity 'symptoms' and three 'diagnostic' items and is able to determine the severity of a delirium episode[488]. It is a well validated tool that is simple to administer, has a high inter-rater reliability, is ideal for longitudinal studies and has been translated into seven languages. The updated version of the DRS was chosen as the tool to assess delirium severity. From examining the literature and conducting the systematic review, it was considered that the combination of the CAM-ICU and the DRS-R98 was sufficient for the purposes of detecting the presence and assessing the severity and duration of delirium in this study.

5.4.3 **Selection of the study cases**

As delirium can be of a transient nature and the published literature has also shown a common inception point between 24 and 72 hours after admission[489], it is essential that the patients should be identified and recruited as quickly as possible. In the initial protocol, it was decided that patients should be recruited within 24 hours of hospital admission so that no potential cases were missed. Prior to the start of the study, a pilot study was conducted on the stroke units in which; the assessments tools, the Case Report Forms (CRF) and the study protocol were tested. The pilot study allowed the researcher to gain experience using the selected assessment tools, practice scoring and make protocol amendments.

The pilot study highlighted that the chosen recruitment window of 24 hours might prove problematic for the study recruitment. This is because as potential participants had suffered a stroke, they would be undergoing various clinical assessments upon their admission to the hospital within the first 24 hours. Therefore trying to conduct the study assessments correctly in amongst the initial clinical assessments would be difficult. As a result of this a recruitment window of 72 hours was chosen within which the diagnosis of stroke and initial delirium assessment would be made. The extension of the recruitment period meant there was less pressure in terms of assessments, on the participant during their first few days of hospital admission. This also meant that participant would be much more likely to consent once they had settled into the hospital environment.

5.5 Measurement of outcomes

This following section discusses the aspects related to the outcome measures, which were considered during the design of the study. These aspects include: selection of outcomes, the measurement of the selected outcomes, avoiding bias and error, and finally the follow up process.

5.5.1 **Mortality**

The risk of dying from a stroke is about 12% at seven days, 19% at one month and 30% at one year for a first-ever stroke[340, 490]. Studies indicate that delirium has also been associated with an increased risk of mortality[491] and so the combination of stroke and a delirium episode may greatly increase the mortality risk for patients.

It should also be considered that by extending the life of the patient, this could further increase costs associated with additional patient care and deplete already limited resources. In England alone, stroke is estimated to cost the economy £7 billion per year, of which £2.8 billion are direct costs to the NHS[331]. This indicates that stroke will become increasingly expensive as the number of people living with stroke increases. The stroke burden can be assessed by commonly applied health measures such as the gain of Life Years (LYs), Quality Adjusted Life Years (QALYs) and Disability Adjusted Life Years (DALYs)[492, 493]. However in determining priorities between individuals for limited resources, the General Medical Council (GMC) states that clinicians should have regard for three duties of care; to protect life and health, to respect autonomy and to treat justly. Therefore priority is given to the need to protect life and health and give priority to those who healthcare needs are greatest or most urgent.

Mortality is recorded by the issue of a death certificate by a clinician registered with the General Medical Council. For deaths that occur in the hospital, the death certificates are issued by one of the attending doctors and recorded in the Ward Register. The procedure is the same for deaths that occur once the patient has been discharged; however the procedure to access this data becomes less straightforward. Outside the hospital, the confirmation of death is made by the patient's general practitioner or any qualified and registered medical professional that may be on call. If the patient is in institutional care, then the staff at the institution can be contacted to confirm the patient's status. Similarly if the patient returns home, then the patient's local health authority or general practitioner can be contacted to confirm the patient's status.

Patients have their medical information stored in databases which are recorded using an NHS number that is unique to every patient. A request can be made to check these records to confirm the patient's survival status. An example of such a database is the Official National Statistics (ONS) which collects data on large scale studies using automatic tags for each patient, for which patient consent is required. For this study, mortality was monitored for up twelve months after the patient had suffered a stroke. The data was collected from ward registers, contacting staff based at the patient's institution or general practitioner. This procedure avoided the need for any further contact with patient's family, especially during a period of recent bereavement.

5.5.2 **Length of hospital stay**

According to the Hospital Episode Statistics (HES) for 2011 to 2012, stroke patients stay an average of 18.4 days in a general hospital ward after a stroke[494]. Over 2.6 million beds per year are occupied by stroke patients, which is the largest number of any patient population. 26% of patients do not spend any time in a dedicated stroke unit as not all hospitals have dedicated acute stroke units[365, 366]. In 2001, the average length of hospital stay in a general ward was around 34 days, however this has now significantly decreased[365]. In 2012 to 2013 the average length of stay in a dedicated stroke unit was calculated to be approximately 21 days but this can vary across hospitals[72, 73]. Research has shown that patients that have received care from a specialist stroke unit have a 50% reduced risk of death[364], better long term recovery and a decreased need for long term hospital or institutional care[495, 361, 366].

In addition to the resources and cost implications[367, 496], longer hospital stays also have an impact on the patient's health and may increase the risk of complications post-stroke. Longer hospital stays have been associated with an increased risk of hospital acquired infections[497] which would impact on the patient's prognosis. Studies in non-stroke populations have shown that delirium may independently increase the length of stay[19, 244], which would place increased pressure on NHS resources as well as impacting on the patient's health. Furthermore research has shown that early discharge for stroke care patients may aid a quicker recovery rate. Community stroke teams can help to decrease the length of stay and bridge the gap between hospital and home by continuing to provide vital rehabilitation services for patients after hospital discharge. From a psychological point of view, many patients are motivated to return to their own homes and limit their stay in hospital, as the hospital stay is most likely associated with an unfortunate event in their health.

The length of stay is defined by the combined time spent on the acute stroke unit, the rehabilitation unit and any other wards that the patient may have been transferred to for treatment during their stay in hospital. A patient's length of stay can be affected by a number of different factors such as post-stroke care needs, family support and NHS support services. In addition to being medically fit, the patient's degree of disability, their home environment and the needs of the carer are also taken into consideration. Some patients may need the help of Intermediate Care Teams (ICT) or spend some time in Community Intermediate Care (CIC) beds after hospital discharge. A patient's discharge from hospital can also be affected by future long term care arrangements not being put in place such as allocation of a place in institutional care, funding for home care nursing or contacting local authorities to arrange additional community support services for patients. In this study, length of stay was determined by monitoring the dates of admission and discharge or death as recorded in the Ward Registers.

5.5.3 **Discharge destination**

Upon hospital discharge, patients who are medically fit and independent are able to return to their homes as before or with care packages to provide additional support once they are home. However for some patients after a stroke, institutional care may have to be considered by the patient, the carers and the clinical staff responsible for the patient. In certain cases, patients may even request residential care in order to relieve pressure on their carers. At present, the cost of informal care after a stroke is £2.4 billion[331, 2]. The type of care required varies depending on the level of input a patient requires but approximately 20 to 40% of residents in care homes are there as a result of a stroke[2]. The average long term cost per patient ranges from £15,000 over the first five years after a stroke, but this can increase to £29,000 when informal care costs are added[498].

The presence of delirium can have an impact on a patient's need for institutionalisation post-discharge. Studies in populations such as hip fracture patients show that delirium increases the need for institutionalisation[499, 49]. Studies also estimate that the prevalence of delirium within a care home setting ranges from 6 to 60%[500] and these groups have NICE identified risk factors for delirium**.** An increase in the number of people with stroke coupled with delirium would mean that more patients would require some form of long term institutional care. This would impact on the costs, the patient's recovery rate and place more strain on care facilities.

Placement into an institutional care facility can be local authority means tested or privately funded by the patient. In order to secure placement, the needs of the patient are assessed by the staff and then matched to the appropriate institutions, so that the patient receives the best care possible for their specific needs[501]. The placement is then confirmed either through social services or directly by the patient and/ or their carers. However many patients and/ or their carers would prefer to avoid the use of an institutional care facility until it is absolutely necessary. This may be because in the past and at this moment in time, concerns have been raised about the quality of care provided for older people in long term care[502, 503]**.** These included factors such as; financial costs, care staff attitudes, poor living conditions and the mental wellbeing and health of other residents in care[503]. This is not an ideal situation to have, but changes are being made to improve the standards within care homes.

In this study, the patient's discharge destination and date of discharge were recorded in the ward registers. Discharge destinations included patients returning to their own home, moving in with a family member, sheltered housing, residential care homes, nursing homes and temporary Care in the Community (CIC) beds. Any other different destinations not listed were also noted. These patients were then further monitored for up to six months post-stroke to detect any changes in their residence, by contacting the patient's general practitioner or the local health authority.

5.5.4 **Physical function**

Up to 70% of stroke patients survive but are left with significant disability[281]. Stroke is the largest cause of adult disability in the UK[281]. Lost productivity and disability from strokes cost the economy around £1.8 billion[270]. After a stroke people lack independence and require more help with their needs and a longer recovery rate[405]. This increase in the patient's physical dependence will create a greater need for more institutionalised care placements, thus increasing the burden on community services provided by the local health authority as well as the care homes.

Studies in other patient populations have shown that delirium is linked to an increased risk of mortality and significant morbidity[38, 491]. An increase in morbidities means that patients may not be able to return to their pre-stroke functional ability and will therefore be more dependent on carers. The effect of delirium on the recovery process after a stroke can be assessed by measuring the patient's physical functional capacity as one of the outcomes. By monitoring functional capacity, it can be determined whether the presence of delirium delays

the patient's recovery and return to their pre-stroke functional capacity or if a complete recovery is no longer feasible.

In order to measure functional capacity, a suitable assessment tool needed to be selected that fulfilled a number of requirements. As patients will be undergoing a range of other assessments during their time in hospital, a tool that would be quick and easy to administer was required to decrease the burden on the participants. The tool should have good sensitivity to detect subtle function changes and be well tolerated by participants. Patient tolerance is crucial as any participants that do not react well to the assessments may withdraw from the study or refuse to participate at all.

From the systematic review conducted, it was apparent that several measures have been used, which have been summarised in Figure 5.5. Reviews have also been conducted to assess the feasibility of using these measures in the stroke population**,** but have provided no clear answer as to which was the best suited to measure functional ability outcomes[504, 410, 290, 505, 301, 506, 507]. The reason for this is not clear. It may be due to differences in the range of areas the different tools assess, the methodology of how the tool is administered to the patient or perhaps influenced by the profession and experience of the person employing the assessment tool.

One of the most commonly used measures in these studies is the Barthel Index[508], which measures activities of daily living. It is routinely used in clinical settings to measure functional ability, has also been used in many stroke based studies[509-511] and also has a postal version[512]. It is easy to administer and is based on 10 activities which are given a score of 1 to 4 to describe how well each activity is done. Although the basic functional tasks are covered, higher order functions are not assessed and the Barthel Index is not sensitive enough to detect subtle changes from normal function because there are only 2-4 categories per item. In addition to this, it has been shown to have inherent floor and ceiling effects[513, 514]. This means that the Barthel Index's sensitivity to change is limited at extremes of disability and those with a mild or moderate stroke have are likely to achieve a high score in activities of daily living, whilst still suffering from significant disability post-stroke.

Functional Measure	Features	Advantages and disadvantages
Barthel Index (BI)	**Assesses:** activities of daily living and mobility. **Structure**: 10 items **Scoring**: Scored 1 to 4 **Time**: 2-5 minutes self report or 20 minutes direct observation.	**Advantages:** 6 languages **Disadvantages:** significant ceiling effects
Modified Rankin Scale	**Assesses**: activities of daily living, post-stroke independence **Structure**: **Scoring**: scored 1 to 5 **Time**: 5-15 minutes	**Advantages:** adequate floor effect **Disadvantages:** Poor at detecting change. Categories are broad, poorly defined and left open to rater interpretation
Functional Independence Measure (FIM)	**Assesses**: physical and cognitive disability **Structure**: 18 items (13 physical domains, 3 cognition domains) **Scoring**: Scored 1 to 7 **Time**: 30 - 45 minutes	**Advantages:** developed in response to BI sensitivity issues. 10 languages **Disadvantages:** has ceiling effects with cognitive subscale.
National Institute of Health Stroke Scale (NIHSS)	**Assess**: level of consciousness, muscle function, **Structure**: 15 items **Scoring**: Scored 1 to 7 **Time**: 10 minutes	**Advantages:** 11 languages **Disadvantages:** low sensitivity. some scale items cannot be tested due to stroke severity
Subjective Index for Physical and Social Outcome (SIPSO)	**Assess**: functional ability post-stroke **Structure**: 10 items **Scoring**: Scored 1 to 4 **Time**: 15 minutes	**Advantages:** self report, can be administered quickly and cheaply **Disadvantages:** all subscales not fully validated
Nottingham Extended Activities of Daily Living (NEADL)	**Assess**: activities of daily living **Structure**: 16 items (4 domains) **Scoring**: Scored 1 to 4 **Time**: 15 minutes	**Advantages:** can be used as a postal questionnaire **Disadvantages:**

Image adapted from rehabmeasures.org

Figure 5.5: Summary of the tools used to measure functional capacity.

There are a number of functional measures used both in clinical settings and for research purposes. However there is no consensus on the instrument best suited to measure functional ability outcomes in the stroke population. Many of these tools vary in sensitivity and specificity and the table above summaries the features of some of these functional measures.

From the systematic review conducted and the reviews available, the Nottingham Extended Activities of Daily Living (NEADL)[515] was selected. Reviews[516, 517] have shown that it has good responsiveness and validity in comparison to other methods[518]. It is a more comprehensive measure, has better score representation, is easy to administer and is suitable for stroke patients[519]. The NEADL can also be used as a postal questionnaire[520], which may be completed by the patient and/ or the carer. For the purposes of this study, a measure of pre-stroke functional ability was obtained by extraction from the patient's medical admission notes and input from the patient's carers. The pre-stroke score was a retrospective assessment which may be susceptible to recall error from both the patients and/ or the carers. The NEADL was administered to the patient during their stay in hospital as part of the baseline assessments. It was then repeated at the one and six month post-stroke to assess changes in functional capacity.

5.5.5 **Cognitive function**

Cognitive impairment is common after a stroke[521, 522] and an increased age of 75 years and older has been shown to be significant risk factor, with an odds ratio of 2.5[435]. The combination of delirium after a stroke has the potential to significantly increase the later risk of dementia[376, 523]. Dementia currently costs the UK economy around £23 billion per year and one dementia patient costs about £27, 647 per year[524]. It is thought that up to one quarter of hospital beds are taken up by people with dementia, as they end up staying twice as long as other people who go in for the same procedure. Social care costs account for about 40% of this figure, due to the need for community care services and institutionalised care placements. The onset of dementia would mean a poorer prognosis for the patient due to the changes in quality of life, physical health, mental wellbeing and ultimately death[379, 525]. Dementia would also have a significant impact on the patient's family and their quality of life as well as increasing the burden on the NHS[526].

Initiatives such as the National Dementia Strategy (NDS) have promoted better diagnosis, management and support for people with dementia. Although currently there is no cure, it is estimated that delaying the onset of dementia by five years could help to reduce deaths directly linked to dementia by 30,000 a year[527, 528]. Assessing cognitive impairment is clinically relevant, as changes in cognitive impairment could be an early indicator for dementia[526]. There are a number of assessment tools[146, 147] that can be used to measure cognitive impairment which will now be discussed.

The Mini Mental State Examination (MMSE)[10] has been a commonly used instrument to detect cognitive problems. It focuses on the domains of language, immediate, short and long term memory, processing, attention and orientation and praxis. The scores are split into four bands from none; mild; moderate and severe cognitive impairment. The MMSE has a specificity of 80-100% and a sensitivity of 82-87% in detecting cognitive impairment. However it does have some disadvantages as the test can be influenced by the patient's age and education levels[529, 530]. This can create a variation in scores and as a result the standardised MMSE (SMMSE)[531, 532] was introduced to reduce inter-rater variability. The Telephone Interview for Cognitive Status (TICS)[533] is another cognition test that has been shown to have a high correlation with the MMSE and can be administered face to face as well, despite being designed to be administered over the phone[534]. The opportunity to test cognition using this method is advantageous when arranging follow up assessments for a large group of patients. Certain patients within the study sample may not want the researchers to come to their homes for further assessment. Furthermore some stroke patients may still be experiencing problems with their vision and reading and writing post-stroke. As a result they may not be able to fill out postal questionnaires but can still complete the TICS exam as it does not rely on visual clues.

The Addenbrooke's Cognitive Examination - Revised (ACE-R)[535] is a test that incorporates the MMSE. There are five subdomains that are tested: attention and orientation, memory, fluency, language and visuospatial. The ACE-R is a well validated and brief test that takes an average of 16 minutes to administer and score in a clinical setting. It is a sensitive and specific tool and the five sub-domain scores provide further details on which specific cognitive functions are affected. Another similar cognitive exam that is increasingly being used clinically in the UK is the Montreal Cognitive Assessment (MoCA)[536]. This is a shorter one page test that is scored out of 30, takes approximately 10 minutes to administer and is ideal for longitudinal studies. It has been translated into 35 languages and assesses the following domains: memory, attention and orientation, visuospatial abilities, language, fluency and executive function.

The ACE-R was chosen for this particular study population as it is sensitive to early cognitive dysfunction, which may be indicative of the early stages of dementia[537]. The ACE-R was administered during the patient's stay in hospital and then administered again at six months to investigate for changes in cognition. Consideration was given to the inevitable probability that a significant number of study sample may suffer from visual problems and difficulties with reading and writing post-stroke. Obviously this would be unavoidable, but if these problems affected the completeness of the data collected from the ACE-R exam, then an alternative method would be needed. The first option would be to eliminate specific parts of

the ACE-R that relied upon visual clues or reading or writing so that analysis was the same for each participant. A second option would be to extract the MMSE data from the ACE-R exam or use the much shorter SMMSE during hospital admission followed by the TICS at the six month follow up stage to obtain a measurement for cognitive impairment.

In addition to testing for cognitive impairment using the ACE-R, the addition of a specific dementia assessment tool was considered beneficial to detect dementia related changes at baseline and follow up. For the assessment of dementia, methods considered included the Clinical Dementia Rating (CDR)[538] which is able to detect mild impairment. However it is prone to subjective assessment. It also takes a long time to administer and it is not efficient at detecting changes over a longer period of time. Another commonly used method considered was the Cambridge Mental Disorder of the Elderly Examination (CAMDEX)[539] which consists of three separate sections: a structured patient clinical interview; a range of cognitive tests known as the CAMCOG; and a structured interview for the patient's informant.

The CAMDEX has a high inter-rater reliability and the CAMCOG has a good sensitivity and specificity, especially for a post-stroke assessment[540]. However the main disadvantage of this method was the time taken to complete the test, as the original version takes 60-90 minutes to administer whilst the shortened version takes 30 minutes. This would clearly increase the burden on the patient and may deter them from participating in the study. An alternative assessment tool was the Cambridge Neuropsychological Test Automated Battery (CANTAB)[541] which is based on the CAMCOG and is administered using a touch screen computer. However the use of a computer aided test was not be feasible for our chosen population, many of whom would be disabled due to their recent stroke. The presence of delirium may also impact their ability to understand and follow instructions on how to complete the computer based assessment.

Reviews have highlighted a number of interview methods as an alternative way of assessing dementia[542, 427, 543, 544]**.** These included the Short Portable Mental Status Questionnaire (SPMSQ)[545] which measures intellectual impairment. However, its sensitivity for detecting moderate and severe impairment is low[546]. Furthermore, the SPMSQ is similar to the Abbreviated Mental Test Score (AMTS)[11]. The AMTS is routinely administered on the wards and a more extensive assessment was considered necessary for this study. The Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE)[547] And the short form of the IQCODE[548] were also considered as they are easy to administer, culturally accepted and are not influenced by education or hearing or visual impairments[549, 550]. The IQCODE can give an impression of general decline rather than specific cognitive changes[551-553]. However,

it may be susceptible to informant bias depending on the carer-patient relationship[554]. Another assessment tool considered was the Ascertain Dementia-8 (AD-8)[555] which is a dementia interview that has a good sensitivity (>84%) and specificity (>80%)[556]. The AD-8 is advantageous in that, if the carer is not available for the interview, it can be administered solely to the patient[557] and can also be combined with a word list recall task[558].

For the purposes of this study, the AD-8 was used to assess for dementia as it is much shorter in length compared to the IQCODE and can be completed by either the informant or patient. If a carer was available, then the short form of the IQCODE was given to the carer to complete in order to compare comparisons between the different viewpoints between the carer and the patient. Again both the AD-8 and short form of the IQCODE were administered during the patient's stay in hospital and then repeated again at six months to monitor any changes that may predict the onset of dementia.

5.5.6 **Assessment of mood**

Mood disorders are common after a stroke[161, 451]. The Geriatric Depression Scale (GDS)[559] was used to monitor any changes in the patient's mood as it is easy to administer, requires very little training or prior psychiatric knowledge and is well validated[560, 561]. The GDS is a 30 item self-report assessment that is used to identify mood symptoms of depression but the formal diagnosis of depression requires a comprehensive clinical assessment. There are shorter versions of the scale that can be used to screen and exclude the presence of depression[562] but are of little clinical value in monitoring the severity of the depression. If depression is present then the longer list of questions can be used to determine the exact severity of the episode. The GDS was administered during the patient's stay in hospital and then repeated at six months to detect any possible changes in mood.

5.5.7 **The follow up process**

In order for reliable comparisons to be made for the outcome measures, the data set needed to be as complete as possible for every participant. During the participant's stay in hospital data was collected from medical notes, ward registers, databases and direct contact with the patient and carers. Once discharged from hospital, data was collected by contacting general practitioners and staff at institutionalised care facilities and local health authorities. Patients were also monitored by follow up assessments which were administered by home visits, telephone interviews or postal questionnaires, according to the participant's convenience.

5.5.8 **Avoiding bias in the outcome measures**

To avoid systematic errors in data collection, potential sources of bias should be considered when measuring outcomes[563, 455, 456].

a) The tools (instrument and insensitive measure bias)[456]. If the chosen assessment tools are not able to detect the presence of an illness (sensitivity) or the absence of the illness (specificity), then important differences in the chosen outcome may be missed. To avoid insensitive measure bias, the assessments chosen for this study e.g. the delirium tools, the activities of daily living and so forth, were selected after careful consideration and analysis of all available resources. The tools were chosen with the requirements of this study in mind to ensure that they were the best suited tools for this population of stroke patients. Following on from this point, if the carefully chosen assessment tools are not administered correctly, then this is also a potential source of error. If the researcher is not adequately trained in administering the various tests and assessment tools chosen, then this would lead to inaccurate data being collected and an incorrect representation of the sample population. For the purposes of this study, the tests were conducted by only one researcher to avoid differences in skill or training procedures so that all participants were assessed and scored in the same manner.

b) The protocol (verification bias or proficiency bias)[456]. If the measurement tool is restricted to test only those who have the illness, or is not applied equally to all participants, then this can lead to overestimations. For the purposes of this study, all participants had the same set of assessments conducted at exactly the same intervals, regardless of their diagnosis and whether they were delirium positive or negative.

c) The diagnoses (attention and expectation bias)[456]. Participants that are more aware of their involvement in a study, may be more motivated and give more positive responses compared to those participants that are unaware of their involvement in the study. In this study, some of the patients may lack capacity, which would impact on their understanding of why the assessments were being conducted. This lack of capacity may be due to confusion from the stroke, the presence of delirium or pre-existing long term conditions such as dementia. Although some variables such as lack of capacity cannot be controlled, for this study the researcher made an effort to keep the participants equally informed as to the purpose of these assessments with reminders and prompts given when necessary. With regards to expectation bias, researchers that are aware of a participant's diagnosis may unknowingly make a mistake in measuring outcomes towards the outcome they expect and in effect reinforce the diagnosis made. For

example a delirium positive person may be expected to score more poorly on cognitive assessments compared to someone without delirium. This may impact on the way the tests are administered as delirium negative patients may be given an opportunity to correct any mistakes they may have made, whereas a delirium positive patient may not receive a similar opportunity as it is assumed that they will score poorly in any case due to the presence of delirium. In this study, only one researcher conducted and scored all the assessments in the same manner to avoid potential differences in the methodology and thereby increasing the reliability of the scoring process. However this may also have been a potential source of bias, as the researcher was not blinded to the patient's diagnosis. Awareness of the patient's diagnosis may have influenced the scoring of the assessment and it is possible that this could have affected the generalisability of this study.

d) The participants (recall bias)[456]. Participants with delirium, or due to the effect of a stroke, may be confused. This may impact on their ability to recall events during the follow up assessments, especially if the events during their stay in hospital were of a negative nature. On the other hand, some participants may remember their involvement in the study and their previous responses or may be subjected to similar assessments from care teams in the community. Therefore when the assessments are repeated, the participants may no longer be unaware of the nature of the assessments as they may have the opportunity to 'learn' their responses. In this study, the researcher made an effort to contact community care teams post-discharge to determine if any similar assessments had been conducted and during which time period. If assessments were of a similar nature and the time period matched those stated in the protocol, then these results were used for the follow up assessments. This helped to avoid the problem of 'learned' responses from participants and it also meant that the participants did not have to undergo any unnecessary or additional assessments.

e) The outcomes (significance bias)[456]. In a prospective study, measuring outcomes that are not clinically significant would be waste of time and resources. Therefore time must be taken to ensure that the chosen outcomes are of clinical significance and the conclusions of the prospective study can be used to possibly make changes and develop strategies that can be employed in clinical practice. It is also important to have adequate participant numbers in order to avoid studies that are inadequately powered. Underpowered studies can lead to important effects not being detected whilst overpowered studies can be considered as unethical and a waste of resources. The appropriate power calculations for this study are discussed in further detail in Section 5.10. For this study, the outcomes chosen such as mortality, length of hospital stay, the

need for institutionalisation, physical functional capacity, cognitive function and changes in mood were chosen as they were of clinical significance and these have been discussed in detail earlier in this chapter at the start of Section 5.5.

f) The follow up (incomplete or withdrawal bias)[456]. Loss of follow up is a cause for concern in prospective studies. During their stay in hospital, the participants are a captive audience and so it is easier to complete the assessments. However once discharged, it is harder to contact participants and so it is better to maximise the use of resources that do not require as much patient contact such as using general practitioners and hospital databases. It is worth mentioning that these resources may not be as accurate or up-to-date as possible and the researchers have no way of checking each and every patient detail. However the use of these resources would allow for the completeness of data collection. It is also possible that once discharged from hospital, patients may no longer want to participate in the study and may withdraw from any further assessments. For the purposes of this study, the data collected in hospital was a combination of information extracted from the medical records as well as directly from the patients themselves. Once discharged from hospital, resources such as information from hospital databases, general practitioners and community care teams were employed to maximise the collection of data to ensure completeness of follow up. With regards to minimising loss to follow up, participants were given a range of options through which the follow up assessments could be conducted, at their convenience. The options included home visits, telephone interviews or postal questionnaires.

5.6 Potential confounding variables/ outcome predictors and risk factors

The literature suggests that delirium is associated with a number of confounding variables and risk factors such as age, gender and the patient's state of health and these are illustrated in Figure 5.6. From the research groups included in the systematic review in Chapter three, a list of confounding variables and risk factors was produced. These variables have also been discussed in further detail in certain reviews[120, 38, 46] investigating the occurrence of delirium in the acute stroke population.

Risk factors are variables that increase the risk of a certain outcome occurring[563]. For example in this study a risk factor such as age would increase the chances of a patient suffering from an episode of delirium. On the other hand, confounders are variables that may

have an effect on both the exposure and the outcomes in a prospective study in addition to the main risk factor being studied[563].

Confounders can cause problems in data analysis as it may seem that certain variables have a direct association with the outcome when they do not (positive confounding) or hide a genuine association with the outcome when they do (negative confounding). A solution to confounding variables would be to match each participant from the exposure group (delirium) to a participant from the non-exposure group (non-delirium) to account for this or to take a random sample of participants and adjust for the effects of confounders in the analysis phase of the study.

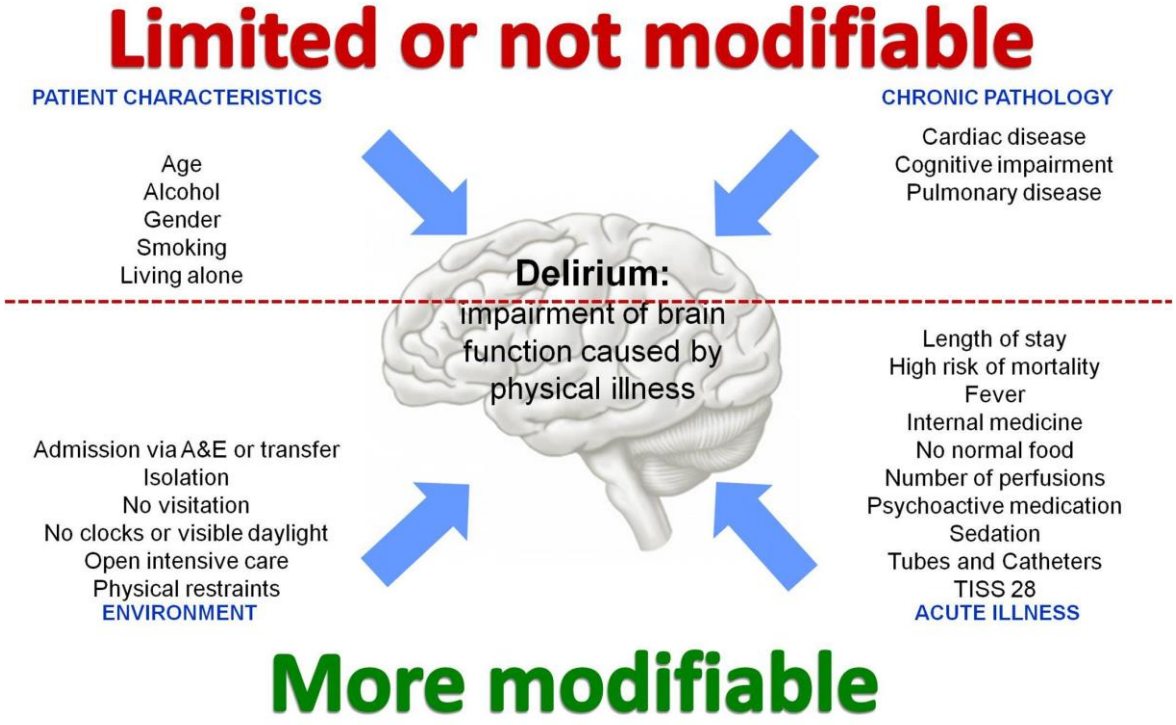


Image adapted from Van Rompaey et al[561]

Figure 5.6: Confounding variables/ risk factors that affect delirium in acute stroke.

There are a number of variables that are associated with delirium onset in the acute stroke population. Some variables such as age and sex are not modifiable and whilst other such as patient environment can be modified to a certain extent. The association between these variables and delirium in stroke patients requires further investigation.

In addition to the outcomes, supplementary data for confounding variables and/or risk factors was also collected to determine whether they had any effect on the outcomes. Patients recruited into the study were interviewed and a detailed medical history was collected that included social background, educational levels and type of employment. The medical history included information on prescribed medications, chronic illnesses, recent surgical procedures and previous mental health problems.

The variables investigated in this study were: incontinence, constipation, malnutrition, dehydration, electrolyte imbalance, infections, hypoxia, surgery and physical illness, number of medications, smoking, alcohol and changes in cognitive impairment. It is anticipated that these confounding variables and/ or risk factors may act as delirium predictors for outcomes[188]. The presence or absence of each variable was noted and then recorded according to various measurement scales used for the specific variable. Further details of these chosen measures are provided in the methodology (Section 6.6.2) which will be discussed in Chapter six.

5.7 Assessment of the delirium instruments

The delirium instruments chosen for this study are the CAM-ICU and DRS-R98 to screen for and assess the severity and duration of a delirium episode. Both of these instruments have been validated against the DSM-IV or ICD-10 criteria which are considered the "reference standard" for delirium diagnoses. Both the CAM-ICU and DRS-R98 have been tested and validated for use in populations such as general medical and surgical patients, patients with hip fracture and patients in intensive care. The instruments have shown good sensitivity and specificity in detecting delirium, are easy to administer and are well tolerated by patients.

The stroke population however differs significantly from the other populations previously tested. It should be noted that many of the features of delirium overlap with the symptoms of a stroke, which makes the detection of delirium more challenging. The accuracy and reliability of the CAM-ICU and DRS-R98 should be tested for use within the stroke population.

For this study, the source population were the stroke patients admitted to the stroke unit whilst the study population consisted of stroke patients with delirium. As the CAM-ICU and DRS-R98 had not been validated for use within the stroke population a few points needed to be considered, in order to make the study findings generalisable to the extended population. Firstly both assessment tools should be applied to all the stroke patients recruited regardless

of whether they had delirium or not. Secondly, the CAM-ICU and DRS-R98 should be administered at the same time points so that same set of symptoms are examined, as delirium has an acute onset and is susceptible to fluctuating symptoms. These points are worth mentioning to avoid any selection bias and ensure that it was a comprehensive exercise in testing the delirium instruments within an acute stroke population.

5.8 Ethical considerations

5.8.1 **Identification of potential participants**

The study protocol was reviewed and approved by certain consultants on the stroke units (Dr P. Wanklyn in Leeds and Dr C. Patterson in Bradford) based in West Yorkshire. Patients admitted to the stroke units were approached to participate in the study, after a consultation with clinical staff. The consultation with the clinical staff was necessary in order to correctly identify suitable participants and as well as safeguarding the interests of the patients, particularly as this study was based on a vulnerable population[252, 565]. Patients with delirium were expected to be in a poorer state of health as delirium is usually a sign of an underlying physical illness. Due to their vulnerable state, the researcher was careful not to approach patients where it was not appropriate, in order to avoid any additional distress to the patient and their families.

Potential participants were screened to see if they matched the recruitment criteria. A statistical power calculation, which is discussed in further detail in Section 5.10, was conducted to identify the recruitment numbers needed for this study. The aim was to screen 339 patients for the prospective cohort study, divided into 68 patients with delirium and 271 patients without delirium. These numbers also allowed for 15% contingency in both groups, to account for those who chose to withdraw from the study without affecting the feasibility of the study. The inclusion and exclusion criteria for this study had been carefully thought out in order to include as many patients and minimise recruitment bias[251]. For participants who did not match the study criteria or refused to participate, the exclusion CRF was completed detailing the reasons for exclusion.

5.8.2 **Capacity assessment**

Once the patients had satisfied the study criteria, the researcher assessed the capacity of the patient to obtain informed consent, according to the Mental Capacity Act 2005[566]. This

statutory framework aims to protect vulnerable people should they lose capacity to make their own decisions. When assessing capacity, consideration should be given to whether the patient has an impairment of the brain or disturbance of mental function and whether this impairment/ disturbance affects their ability to make decisions. A person with capacity should be able to understand, retain and process information that is relevant to the decision and then communicate their decision by speech, writing or any other means. The researcher received training from the LGI liaison psychiatry team and attendance at Comprehensive Clinical Research Network (CLRN) workshops. Assessing the patient's capacity was important in this study in order to identify the more vulnerable patients in the recruitment process. Gaining fully informed, voluntary consent is essential to all research.

The requirements are that the patient should be able to understand the information and without any coercion from the researcher, provide voluntary agreement to participate as a self-ruling agent. Where patients are not able to fully understand the situation, then rather than excluding them, proxy consent or assent is sought from someone who is appointed to safeguard the patient's interests. This is a legal requirement to avoid any unnecessary physical and mental suffering and/ or injury to the patient. For the purposes of this study the protocol stated that if the patient had capacity and could provide written consent, then they were included in the study. If the patient could not physically write as a result of their stroke, then verbal consent was obtained in the presence of a clinical staff member or the patient's carers. The patient's carers were also approached for written consent so that they could be interviewed as part of the study.

In cases where the patient lacked capacity, then proxy consent was sought from an appointed consultee for the patient. The appointed consultee was asked to sign a declaration form and kept informed of the patient's involvement in the study. Due to the nature of delirium, it was expected some of the patients would lose capacity after the initial consent process during the study. If this happened, then the patient would still be included provided that the appointed consultee was happy to continue. If the consultee refused proxy consent, then the patient would be excluded. It should be noted that regarding patient capacity, it is possible that the study findings could be susceptible to bias. Patients who lacked capacity or had been excluded from the study may have been suffering from delirium. This means that the final sample may not have included all the possible cases of delirium and therefore it may not be a true representation of the population being studied.

5.8.3 **Consent and recruitment process**

The participants that satisfied the study criteria were given a verbal explanation of the study and an opportunity to ask any questions they had. Both the patients and their carers were provided with information sheets describing the details of the study and the reasons as to why it was being done. The participants were then given adequate time to decide whether they would like to take part, without any coercion from the researcher. This time would allow them to appreciate the relevance of the study to their situation, use their own reasoning to make a decision and then make and communicate a choice based on this process. However it is important to remember that delirium is a temporary condition and it has an acute onset and fluctuating nature. Therefore it was crucial that the delirium baseline assessments should be conducted quickly, preferably within 72 hours of admission.

Once the participants understood the study information and had an opportunity to ask questions, they were then approached for written consent and asked to complete the appropriate consent forms according to their capacity. The researcher tried to build a rapport with the patients to develop a feeling of trust and minimise any unnecessary pressure. It was made clear to the participants that their involvement in the study was entirely voluntary and that they were free to withdraw from the study at any time. Furthermore, any information that they disclosed would be kept confidential and would not be shared with any unauthorised persons. Upon completing the consent forms and the baseline assessments, the participants were allocated a study number. The study number was used to anonymise the data collected by separating the study assessment data from any patient identifiable data.

In order to avoid any further feelings of being pressured, the consent forms were also structured in such a way that the patient and/ or their carers/ appointed consultee could choose the length of their participation in the study. At each assessment point during their stay in hospital, the participant was verbally re-consented prior to any assessments being administered. During the follow up stages of the study, the capacity of the participant was again re-assessed. All participants whether they previously lacked capacity or not, were requested to sign a second consent form, provided that they were happy to continue. Patients with delirium can display symptoms such as hallucinations or feelings of insecurity or not feeling safe. By regularly checking the patient’s consent, researcher avoided any potential situations where the patient may have felt distressed, threatened or pressured into completing the study assessments.

5.8.4 **Risk, benefits and burdens**

In order to conduct the study, ethical approval was acquired from the local research ethics committee. It was unlikely that the participants would have been harmed in any way during the study as the assessments being conducted by the researcher would not have interfered with the patient's existing clinical care. If the participants were unhappy or wished to make a complaint, then this was reported to the chief investigator and the research manager at the University of Leeds.

In terms of study numbers, between October 2009 and September 2010, approximately 200 patients were recruited to various stroke research studies on the LGI ward alone and many of these studies had strict exclusion criteria. In order to lessen the burden on patients and to help decrease any "research fatigue" for participants, patients recruited to other studies that did not allow for co-recruitment were not included in the study. Despite this, it was believed that the recruitment targets in this study were still achievable due to the large number of patients being admitted to the stroke units and the unrestrictive entry criteria for this study. The feasibility of recruitment numbers will be discussed further in Section 5.10.

During their stay in hospital, the patients had supplementary assessments administered as part of this study, in addition to their normal clinical care. The combination of assessments amounted to approximately 60 minutes of direct patient contact. This duration of assessment could potentially have added to the patient‘s stress of being in hospital. As a result, the various baseline assessments were staggered over the first 72 hours of hospital admission, to decrease the participant burden. It was expected that some participants would have severe communication disturbances. This may have affected their responses on certain assessments and so suitable assessment tools had been chosen to account for this. In addition to this, the researcher provided visual response/ cue cards to be used as communication aids during the assessment, for patients with communication difficulties. Nevertheless, there were participants who were unable to complete all parts of the assessments and so they were classed as ‘unable to score’ and analysed accordingly.

Once the patient had been discharged, the researcher completed the follow up assessments by contacting the patient to arrange a home visit, conduct a telephone interview or send out postal questionnaires. Prior to arranging the follow up assessments, the patient's general practitioner was contacted to determine the survival status of the participant. This was done in order to reduce any distress to carers that may be caused if the patient had died since their discharge from hospital. The data collected during the study consisted of the CRFs containing assessments results, clinical data, past medical history and patient and carer

interviews. The paper based documents were stored in a locked filing cabinet in the Charles Thackrah Building at the University of Leeds and were only accessible to the researcher and the supervisors. Two separate electronic databases were stored on a secure password protected server; one to pool the data together for analysis and the other to retain patient contact details.

The study data were analysed anonymously and confidential data kept to a minimum which was shredded if no longer required. Once recruitment and all follow up assessments had been completed, the data were analysed and a summary of the research findings were sent to the participants as well as thanking them for their involvement in the study. Although there was no immediate benefit to the participant in this study, it was anticipated that the research would lead to a better understanding in the area of stroke and delirium.

5.9 Financial considerations

The study was funded through a scholarship provided by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care (CLAHRC) for the Leeds, York and Bradford Research Association (LYBRA). The scholarship covered tuition fees, living allowances for the researcher and research costs which included; travel costs, conference fees, training, printing of the study material and so forth.

Aside from financial support, training and support was provided from a number of sources which included; academic support and training from the University of Leeds, training from the Liaison psychiatry team at the LGI and support from the clinical staff based at the acute and rehabilitation stroke units at the LGI and SJUH.

5.10 Statistical considerations

The largest loss to patient follow is often due to death and the combination of a stroke and delirium significantly increased the risk of mortality according to the literature reviewed previously. The sample size calculations for this study were generated using statistical power calculations and were based on mortality figures for patients with delirium in the stroke population. The prospective cohort study involved a comprehensive six month follow up and in essence would analyse two separate patient cohorts; delirium positive against

delirium negative. The patients were classed as independent meaning that they were not specifically age or sex matched for analysis. The type I error probability for this study was set at 0.05 with a power of 80%. The power calculation was calculated using the exact Fisher's test, where the alternative hypothesis was expressed as two proportions. The incidence figures for mortality were based on a paper by Sheng et al,[452] (2006) who investigated the effect of delirium on the stroke population and these figures are illustrated in Figure 5.7.

Cumulative mortality	Overall (n= 156)	With delirium (n = 39)	Without delirium (n = 117)
1 month mortality	9 (5.8)	4 (10.3)	5 (4.3)
6 month mortality	25 (17.1)	11 (29.7)	14 (12.8)
12 month mortality	34 (23.8)	16 (41.0)	18 (17.0)

Image adapted from the paper by Sheng et al[450]

Figure 5.7: Delirium incidence statistics for power calculations.

Sheng et al,[450] reported the incidence of delirium as 25%, which gives a ratio of 3:1, four delirium negative patients for every one delirium positive patient. The incidence of 6 month mortality was reported as delirium [29.7] against non-delirium [12.8]. The power calculations for this study were based on these figures given.

Based on the information in Figure 5.7, the minimum number of participants required was 59 people for the delirium positive group, and 236 people for the delirium negative group, giving a core total of 295 patients. Upon advice from a statistician (T. Munyombwe) a 15% contingency was included and so a minimum of 339 participants (68 delirium positive and 271 delirium negative) would need to be screened. Figure 5.8 illustrates the rate of patient turnover at the chosen study sites.

Recruitment period	Potential participants		People per month		People per week	
	Per site	Total sites	Per site	Total sites	Per site	Total sites
6 months	240	720	(16.4) **17**	(49.2) **50**	(4.1) **4**	(12.3) **12**
9 months	360	1080	(10.9) **11**	(32.8) **33**	(2.7) **3**	(8.2) **8**
12 months	480	1440	(8.2) **8**	(24.6) **25**	(2.0) **2**	(6.1) **6**

Figure 5.8: Breakdown of the study recruitment targets.

The figure above illustrates the number of potential participants available at the chosen study sites and the rate at which participants would need to be recruited in order to reach the study recruitment targets.

The recruitment schedule had originally been set out to a six month time scale. A review was conducted at the six month stage to see if interim recruitment targets had been met. Any issues or delays with the recruitment would mean that the recruitment period could be extended to twelve months with a review done every three months. This meant that there would be a six month overlap in the researcher's work schedule. During this six month period, the researcher would have split the weekdays equally between recruitment and follow up assessments to stay on target. Although this was a large workload, there are a few points that should be noted.

Firstly, it was anticipated that there would be a significant number of drop outs due to deaths and this in turn would result in a considerable drop in patient follow up visits. This decrease in follow up visits would allow the researcher to spend more time on the wards recruiting new patients. Secondly, the researcher only recruited during the weekdays and not at the weekends. This meant that the new stroke admissions admitted at the weekend would be added to start of the new week, thus increasing the number of potential participants that the researcher could screen. Based on these reasons and the numbers (Figure 5.7 and 5.8), it was believed that the patient recruitment figures were achievable in the allocated time frames.

5.11 Conclusion

There were a number of methodological and ethical issues to consider when designing the study to fulfil the chosen research aims. Poorly chosen study designs that are not suitable for the data being collected can create bias and errors in the data set. For example in this study choosing a retrospective cohort would mean relying on the patient's version of events which may be susceptible to recall error. This may produce inaccurate and unreliable findings which would also be a waste of time and resources. Due to the nature of conditions being investigated, a number of key issues were highlighted that that needed to be factored into the study design in order to avoid problems later in recruitment and assessment process. Details of the finalised study protocol will be discussed in Chapter six.

5.11.1 **Key points**

- Investigating clinical conditions such as delirium and stroke requires careful designing and planning.

- The study methodology of a prospective cohort was suitable for the type of data being collected and efforts were made to reduce potential sources of bias.
- The use of a pilot study helped to identify potential flaws in the proposed methodology and allowed for corrections to be made before active recruitment began.
- Eliminating potential flaws and reducing sources of bias and systematic errors would help to produce a completed data set that would be accurate and reliable.
- Due to the nature of the clinical conditions being studied, ethical considerations were of key importance when working with a vulnerable patient population.

6 Methodology

The following chapter discusses the detailed aspects of the methodology. These aspects include the following: study design, the study setting, the sample of participants recruited, the materials used, the baseline assessments, the time scale, the outcome measures and the data collection and analysis.

6.1 The study design

A prospective cohort study was conducted with stroke patients admitted to stroke units in West Yorkshire with a twelve month follow up period. Figure 6.1 summarises the study design.

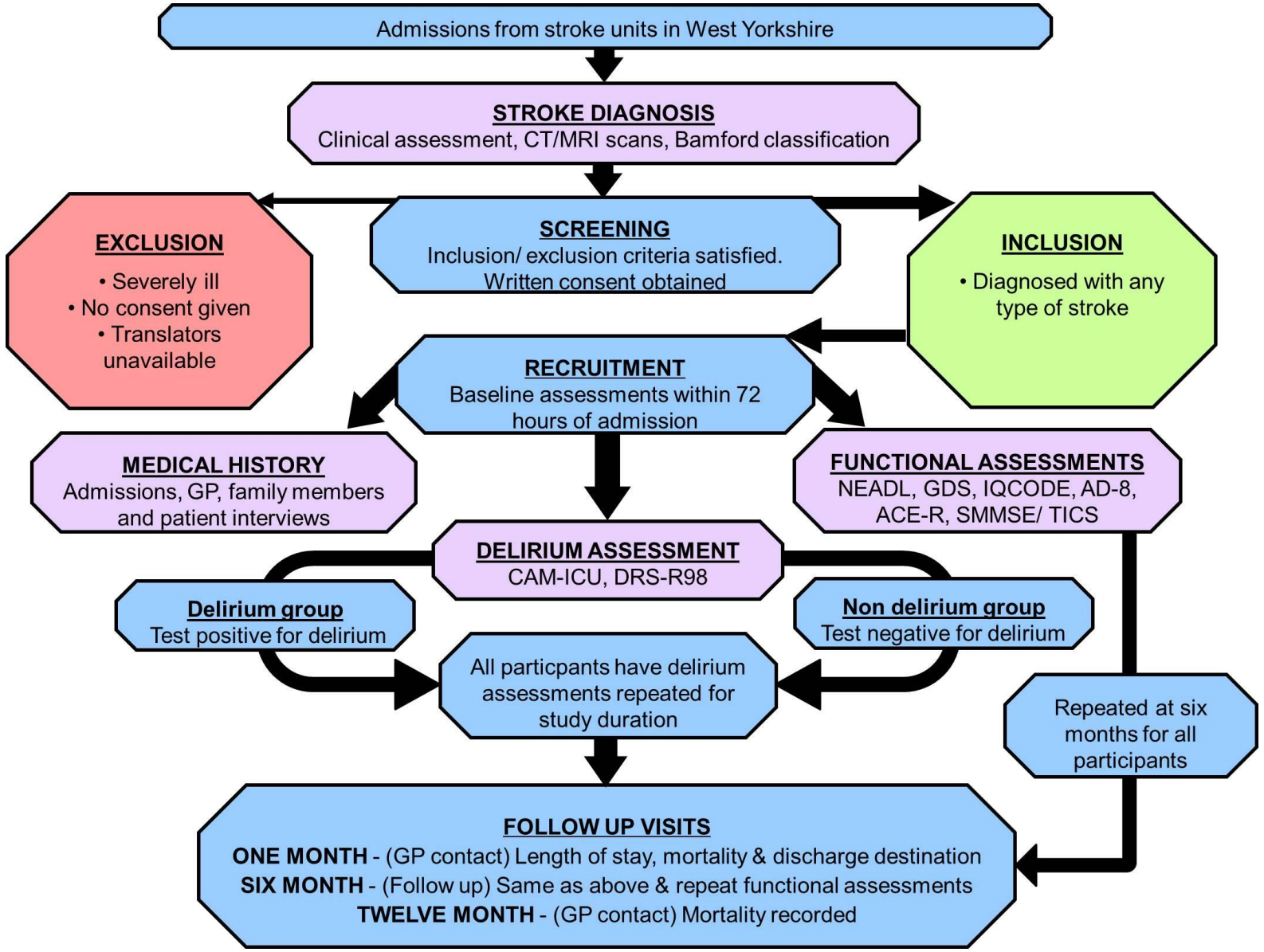


Figure 6.1: Study design for the prospective cohort study.

6.2 The study setting

The study was conducted at the Leeds Teaching Hospital Trust (LTHT) in the Acute Stroke Unit (ASU) based at the Leeds General Infirmary (LGI) and the stroke rehabilitation unit at St James University Hospital (SJUH) in Leeds, West Yorkshire. In addition to the acute stroke units for the male and female patients, patients were also recruited from the Hyper Acute Stroke Unit (HASU) based at the LGI after it was established in January 2012.

6.3 The study population

Patients were admitted to the LGI's Accident and Emergency Department either by ambulance or by referrals from their general practitioner. Stroke patients were then transferred to the HASU or the ASU depending on what was appropriate. As there was only one researcher with limited time and resources, patients that were not admitted to the stroke units were not approached for participation. The population for this study compromised consecutive stroke patients aged 55 years and over that were admitted to the stroke units at the LGI and SJUH, with a confirmed diagnosis of stroke.

6.4 The study materials used

Potential participants and carers that were interested in being involved with the study were provided with information sheets to read through. Examples of the information sheets distributed to the patients, carers and consultees are provided in the appendices 3, 4 and 5.

Once the patients and their carers indicated that they had understood the information, the participants were asked to provide written consent by completing the consent forms for the patients, carers and/ or consultees. Examples of the consent and declaration forms are provided in the appendices 7, 8 and 9.

Participants were also asked to consent to the researcher contacting their general practitioner in order to obtain any additional information that may be relevant to the research. The general practitioner was also sent an information sheet, as shown in appendix 6, informing them of their patient's involvement in the study.

The patient's initial diagnosis was augmented using the Bamford stroke classification, MEWS and GCS scores, as shown in appendix 11. Those participants who did not match

the recruitment criteria had an exclusion case report form completed to provide further details of the reasons for exclusion. The exclusion form is shown in appendix 10.

The study assessments administered in the study at baseline included the following;

1. Confusion Assessment Method for Intensive Care Unit (CAM-ICU) - appendix 12
2. Delirium Rating Scale - Revised 98 (DRS-R98) - appendix 13
3. The Nottingham Extended Activities of Daily Living (NEADL) - appendix 14
4. Geriatric Depression Scale (GDS) - appendix 15
5. Addenbrookes Cognitive Exam - Revised (ACE-R) - appendix 16
6. Ascertain Dementia (AD-8) - appendix 17
7. Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) - appendix 18
8. Standardised Mini Mental State Examination (SMMSE) – appendix 19

6.5 The recruitment of the sample

The researcher was based on the stroke units at the LGI where the ward registers were monitored to identify potential participants, with consultation from clinical staff on the ward. The source population were stroke patients aged 55 years and over, that had a confirmed diagnosis of stroke. The stroke diagnosis was confirmed using the CT/ MRI scans and classified using Bamford stroke classification. The MEWS and GCS scores along with input from the clinical staff were used to determine if it was clinically appropriate to approach the patient.

Once these criteria had been satisfied, the researcher approached the patient and their carers to introduce herself and provide a verbal explanation of the study and its purpose. This was done at the patient's bedside for the patients, or in the relatives' room for the carers. Both the patients and the carers were provided with information sheets about the study and left to read through the information in their own time. Patients who fulfilled the study inclusion criteria were asked to provide written consent in order to participate in the study. Participants who did not fulfil the inclusion criteria or who did not wish to take part were thanked for their time and the exclusion CRF was completed detailing the reasons for exclusion.

An assessment of capacity was made by the doctors on the Ward and recorded in the medical notes. Patients who lacked capacity and were not considered able to provide informed written consent were still included in the study, provided that proxy consent could be sought from an appointed consultee. Although this type of consent was not a replacement for the patient's written consent, it was felt that an appointed consultee could oversee the patient's involvement in the study and safeguard the patient's interest. A consultee could be the patient's family member, legal carer or, if no one else was available, then the patient's consultant during their stay in hospital. If the consultee declined to provide written consent, then the patient was not included in the study.

Patients that were recruited into the study were allocated a study number so that the data analysed would be done so anonymously. The study assessments were then administered to the patient within the first 72 hours of admission to the stroke unit.

6.6 The study assessments administered

The initial baseline assessments were conducted within 72 hours of hospital admission by the researcher. As the patients had suffered a recent stroke, the majority of the assessments were done at the patient’s bedside. However attempts were made to conduct the assessments in private where possible. Prior to starting the assessment, patients were asked if they usually wore glasses or a hearing aid so that the patient was not at a disadvantage during the assessment. The patient protocol for the study is illustrated in Figure 6.2 and is described in the following sections.

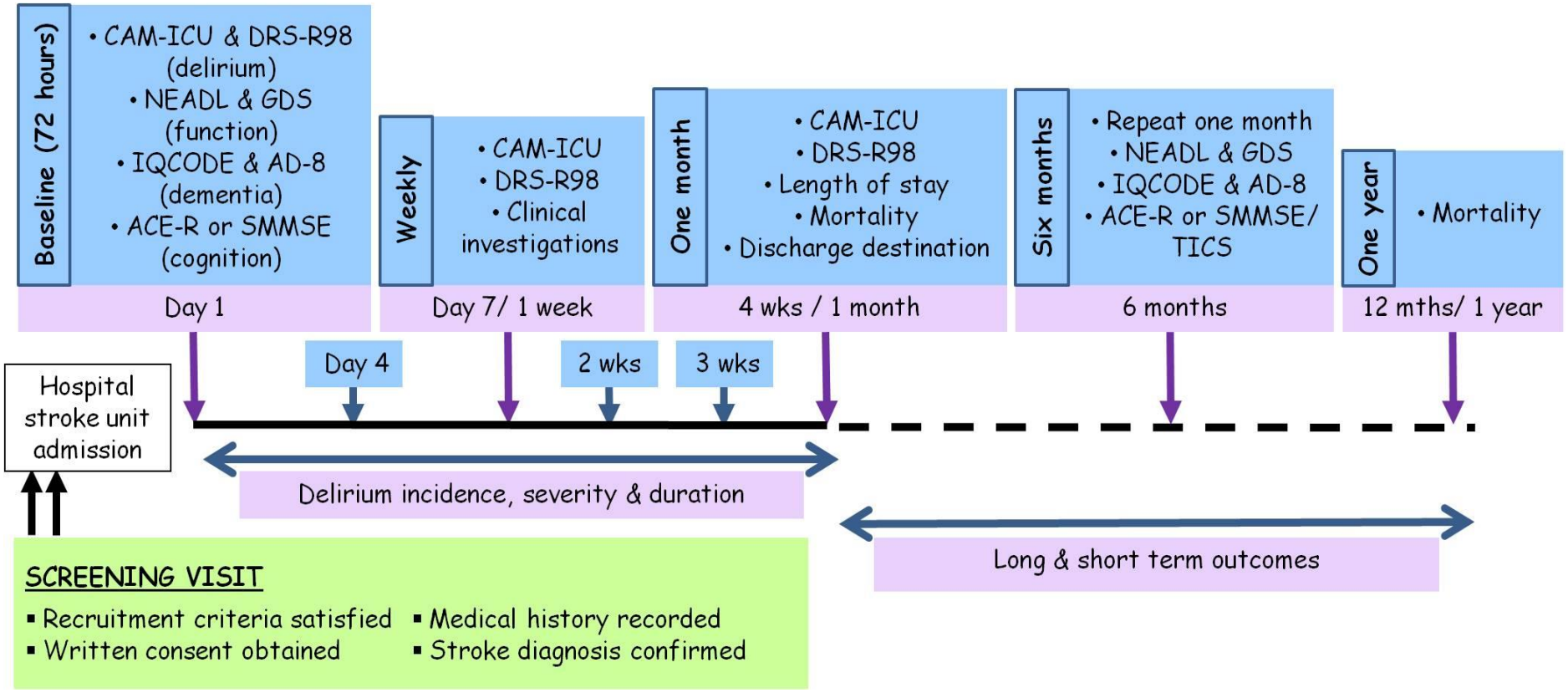


Figure 6.2: Patient protocol for the prospective cohort study.

6.6.1 **Introductory interview**

During an introductory interview, patient information on the following areas was collected and recorded in the patient's CRF. Data on physical variables was also collected and this information was extracted from the patient's medical notes and clerking information. The information collected was as follows:

1. Age
2. Date of birth
3. NHS number
4. Contact details for their general practitioner
5. Contact details for the patient
6. Contact details of the patient's carer
7. Patient's medical history
8. Patient's social background
9. Hospital location and place of referral
10. Data and time of admission to the stroke unit
11. Date and time of CT/ MRI scan if performed
12. Assessment of mental capacity
13. Pre-stroke functional capacity e.g. pre-stroke Modified Rankin score
14. Clinical examination results e.g. power and tone of limbs, changes in gait and vision, examination of all systems, nutritional status, clinical observations, blood results

Patients were thanked for their time at the end of the interview and reminded that they would be contacted at a later stage for their follow up assessments.

6.6.2 **Measurement of the confounding variables and risk factors**

Clinical data were collected to assess the effects of specific confounding variables, which were previously described in Chapter five. The confounding variables or predictors were

measured and recorded throughout the patient's stay in hospital. The variables were as follows:

1. **Incontinence** – defined as the involuntary excretion of urine or inability to control the bowel. Confirmation of incontinence was made by monitoring the nursing observations and any episodes that lasted more than 5 days were classed as positive for incontinence. Details of the type of incontinence, the aids use and the duration were recorded.

2. **Constipation** – defined as infrequent bowel movements of which there are two types; obstructed defaecation or colonic slow transit (hypomobility). Confirmation of incontinence was made by monitoring the nursing observations and any episodes that lasted more than 5 days were classed as positive for constipation. The Bristol stool chart[567] was used to record the type, severity and duration of the episode.

3. **Malnutrition –** defined as the incorrect intake of nutrients which can be too low, high or not in the correct proportions, due to an unbalanced diet. Confirmation of malnutrition was made by monitoring the Malnutrition Universal Screening Tool (MUST)[568] scores recorded in the nursing observations. Upon admission, the patient's height and weight were measured by the nursing staff. The Body Mass Index (BMI)[569] readings were calculated and recorded in the nursing notes and a MUST score of 1 and above was classed as positive for malnutrition. The duration of the episode, total weight loss during this period and the need for additional supplements were also recorded.

4. **Dehydration** – defined as the excessive loss of body water of which there are three types; hypotonic (loss of electrolytes e.g. Sodium), hypertonic (loss of water) and isotonic (equal loss of water and electrolytes). Confirmation of dehydration was made by monitoring the blood results and any electrolyte imbalances, changes in the urea to creatinine ratio or the need for paraenteral fluids (intravenous or subcutaneous) that lasted for longer than 5 days were classed as positive for dehydration. The duration, cause (e.g. poor intake, rapid loss rate) of the episode as well as the need for additional supplements were also recorded.

5. **Infections** – defined as a clinically evident illness that arises from infection, presence or growth of pathological biological agents. Confirmation of an infectious disease was made by monitoring the blood results and changes in the CRP or white cell count. The cause and duration of the episode as well as any previous history of infectious diseases were also recorded.

6. **Hypoxia** – defined as when the whole body or a specific region of the body is deprived of an adequate oxygen supply. Confirmation of hypoxia was made by monitoring the oxygen saturation results recorded in the nursing observations and the need for supplementary oxygen for longer than 5 days was classed as positive for hypoxia. The changes in oxygen saturation and duration of the episode were also recorded.

7. **Physical illness** – delirium onset has been to specific chronic pathology which includes; cardiac disease, pulmonary disease, cognitive impairment and any recent surgical procedure preceding their admission to hospital, as well as mental health problems and changes in the patient's memory. The number of physical illnesses were recorded.

8. **Stroke** - the pathology (infarct or haemorrhage) was established by the CT/ MRI scans and the Bamford classification was used as a clinical descriptor to classify the type of stroke into one of the four categories previously mentioned in Chapter five.

9. **Medication** - the details of medications taken were recorded. Details included the number of medications, types and dosages of drugs taken.

10. **Smoking** – the frequency (e.g. per day) and years spent smoking was recorded.

11. **Alcohol** – the frequency (e.g. unit per week) and type of drinking (e.g. casual, heavy), were recorded.

12. **Social background** – the marital status of the patient, living arrangements, type of accommodation, level of social care and support the patient receives such as home care or placement in an institutional care facility were recorded. The information was extracted from the responses for the Modified Rankin Score and background information recorded in the nursing notes.

13. **Education** – the patient's level of education was recorded by interviewing the patient or their carer. The responses were classed according to the scale in appendix 21.

14. **Employment** – the patient's first job and main occupation, type of employment and duration was recorded by interviewing the patient or their carer. The responses were classed according to the scale in appendix 22.

Once these details had been extracted, the study assessments were administered to the patient at the following time points:

6.6.3 **Within 72 hours of admission (baseline assessments)**

Patients were screened using the CAM-ICU to detect whether they had prevalent delirium and were then assessed using the DRS-R98 to determine the severity of delirium. The following baseline assessments were also conducted:

1. The Nottingham Extended Activities of Daily Living (NEADL)
2. Geriatric Depression Scale (GDS)
3. Addenbrookes Cognitive Exam - Revised (ACE-R)
4. Standardised Mini Mental State Examination (SMMSE)
5. Ascertain Dementia (AD-8)

Only one of the cognitive tests, either the ACE-R or the SMMSE, was administered depending on the patient's communication abilities and compliance. In addition to this, the patient's carers were also interviewed and asked to complete the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) as well verify the information provided by the patient during the interview.

6.6.4 **Day four and day seven**

On day four and day seven, the CAM-ICU was repeated on all patients to determine if any new cases of delirium had occurred and the DRS-R98 was used to determine the severity of the episode. If incident delirium was detected, then the patient's care team were informed. Any clinical investigations that had been carried out during the patient's stay in hospital were also recorded in their CRF's.

6.6.5 **Weeks two and three**

The CAM-ICU was repeated for all patients regardless of whether they had been delirium positive or negative in past assessments and the DRS-R98 was used to assess the severity of the episode. The use of the CAM-ICU, DRS-R98 and the recording of any new clinical investigations was done weekly. If any patients were discharged from hospital before the one month stage, then a pre-discharge delirium screen of both the CAM-ICU and DRS-R98

was administered before the patient was discharged. The date of hospital discharge and their discharge destination was also recorded in their CRF's.

6.6.6 **One month**

As we anticipated a high mortality rate at one month, the survival status of all patients' was reviewed after four weeks of recruitment. If the patient had been discharged prior to the one month stage, then the patient's general practitioner or care institution was contacted to determine survival status. If the patient had not survived, then the cause of death was recorded in the patient's CRF.

The remaining patients had their length of hospital stay, including additional NHS care recorded. Those patients that were still in hospital either at the acute stroke unit or at the stroke rehabilitation unit underwent assessments for the following: delirium (including both the CAM-ICU and DRS-R98), activities of daily living using the NEADL and the SMMSE (appendix 19) or the ACE-R to test their cognition.

A pre-discharge delirium screen of both the CAM-ICU and DRS-R98 was administered to patients due to be discharged at or before the one month stage. The date of hospital discharge and their discharge destination was also recorded in their CRF's. They were then contacted by telephone to review their activities of daily living using the NEADL and their cognitive function was tested using the Telephone Interview for Cognitive Status (TICS) assessment, as shown in appendix 20.

6.6.7 **Six months**

Patient outcomes were assessed at six months via home visits, telephone interviews or postal questionnaires as previously described. Prior to contacting the participants, general practitioners were contacted to confirm any patient deaths. This was done to avoid potential distress to the patient's families and carers. If the patient had been discharged to a care institution, then the appropriate staff members were contacted to confirm the patient's survival status.

The patient's length of stay in hospital was recorded by regularly monitoring the ward registers. Length of stay included the time spent in the acute stroke unit, the stroke

rehabilitation unit and any other NHS wards that the patient may have been transferred to, for subsequent treatment.

The discharge destination was also recorded along with the date of discharge. Discharge destination included patients returning to their homes, moving to a residential home or being placed in institutional care such as a nursing home or a hospice.

Where it was appropriate, the researcher arranged to meet with the participant and conduct the follow up interviews and assessments. Patients were assessed to determine how they were coping post-stroke and hospital discharge. The assessments administered during their stay in hospital were repeated and the scores were recorded in the patient's CRF. The assessments included the following;

1. Confusion Assessment Method for Intensive Care Unit (CAM-ICU)
2. Delirium Rating Scale - Revised 98 (DRS-R98)
3. The Nottingham Extended Activities of Daily Living (NEADL)
4. Geriatric Depression Scale (GDS)
5. Addenbrookes Cognitive Exam - Revised (ACE-R)
6. Telephone Interview for Cognitive Status (TICS)
7. Ascertain Dementia (AD-8)
8. Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)

Again, the carers were also interviewed to verify the information provided by the patient. The six month assessments marked the end of the participant's study involvement and the participants were thanked for their co-operation.

6.6.8 **One year**

The final stage of the study was to determine the survival status of all stroke patients one year after their first initial admission to hospital. The patient's general practitioner or care institution was contacted to determine survival status. If the patient had not survived, then the cause of death was recorded in the patient’s CRF. The one year stage marked the end of data collection for the study.

6.7 Data handling and analysis

The participant data collected was coded for anonymity and was entered into two separate electronic databases; one to pool the data together for analysis and the other to retain the participant contact details. The data was analysed using Microsoft Office Excel, IBM SPSS version 15 and STATA version 13.

6.8 Statistical analysis

For this study, the aim was to compare outcomes for stroke patients with delirium and stroke patients without delirium. For the analysis it was decided that the study cohort would be further divided into the following subgroups: delirium positive patients with and without dementia and delirium negative patients with and without dementia. However after careful consideration it was decided that this would not be suitable for reliable comparisons, as there were insufficient numbers in each subgroup. Therefore the analysis focused on the comparisons between the delirium and non-delirium groups. The specific areas of interest were;

1. The incidence and duration of delirium within the stroke group selected for the study.
2. The incidence of mortality in the delirium group compared to the non-delirium group.
3. The evaluation of outcomes such as; length of hospital stay, discharge destination, functional capacity, cognitive function and risk of dementia. These individual values would then be compared between delirium and non-delirium groups.
4. To analyse whether there is a relationship between the type of stroke and/or potential confounding variables and the duration of a delirium episode.

For the statistical analysis of the data, Microsoft Office Excel, IBM SPSS version 15 and STATA version 13 were used to analyse the data as follows;

1. The incidence of mortality for both the delirium and non-delirium groups was conducted using the Pearson chi-squared test and the Log Rank test.
2. For continuous variables, an independent samples t-test was used to compare differences between the delirium group and the non-delirium group.

3. For the categorical data, the Pearson chi-squared test was used to compare differences between the delirium group and the non-delirium group.

4. The mean difference and P values for continuous variables for both delirium and non-delirium groups were calculated using binary logistic regression.

5. Odds ratios and confidence intervals for categorical data associated to delirium were calculated using binary logistic regression.

6. The comparison between the outcomes at baseline and six months were analysed using the Wilcoxon Signed Ranks test. The difference between the delirium and non-delirium outcome scores were then further analysed using the Mann Whitney U test.

7. Factors that showed a significant association with delirium were subjected to binary logistic regression analysis to identify independent predictors for delirium.

6.9 Conclusion

A prospective cohort study was used to recruit stroke patients from the stroke units based at the Leeds Teaching Hospitals Trust. Patients with and without delirium were recruited into the study and followed up for a one year period. During their initial stay in hospital, all patients underwent a delirium screen and the data for a selection of confounders was also recorded. The study data generated were stratified according to the participant's delirium diagnosis. Participants also underwent a number of assessments to establish a baseline score so that a comparison of outcomes could be made at the six month follow up. Admission outcomes were also compared and checks for participant mortality were made throughout the study up until the one year stage.

6.9.1 **Key points**

- A prospective cohort study was used to recruit and assess stroke patients over a one year follow up period.
- All stroke patients recruited were screened for delirium using the assessment tools CAM-ICU and DRS-R98.
- Data for a selection of confounders was recorded and adjusted for in the analysis.

- Admission outcomes included mortality, length of stay and discharge destination.
- Six month outcomes included assessment of physical function, mood, risk of dementia and cognitive impairment.

7 Results

7.1 The study sample

The study recruitment was carried out in two separate phases (period one: 18th July 2011 to 23rd Dec 2011, period two: 23rd Feb 2012 to 18th November 2012), producing a cumulative 14 month recruitment period. During this period 1,253 patients were admitted to the stroke unit at the LGI either through transfer from A&E, other hospital wards or direct admission via a GP referral. Figure 7.1 illustrates the admissions and exclusions of the participants at each stage of the study.

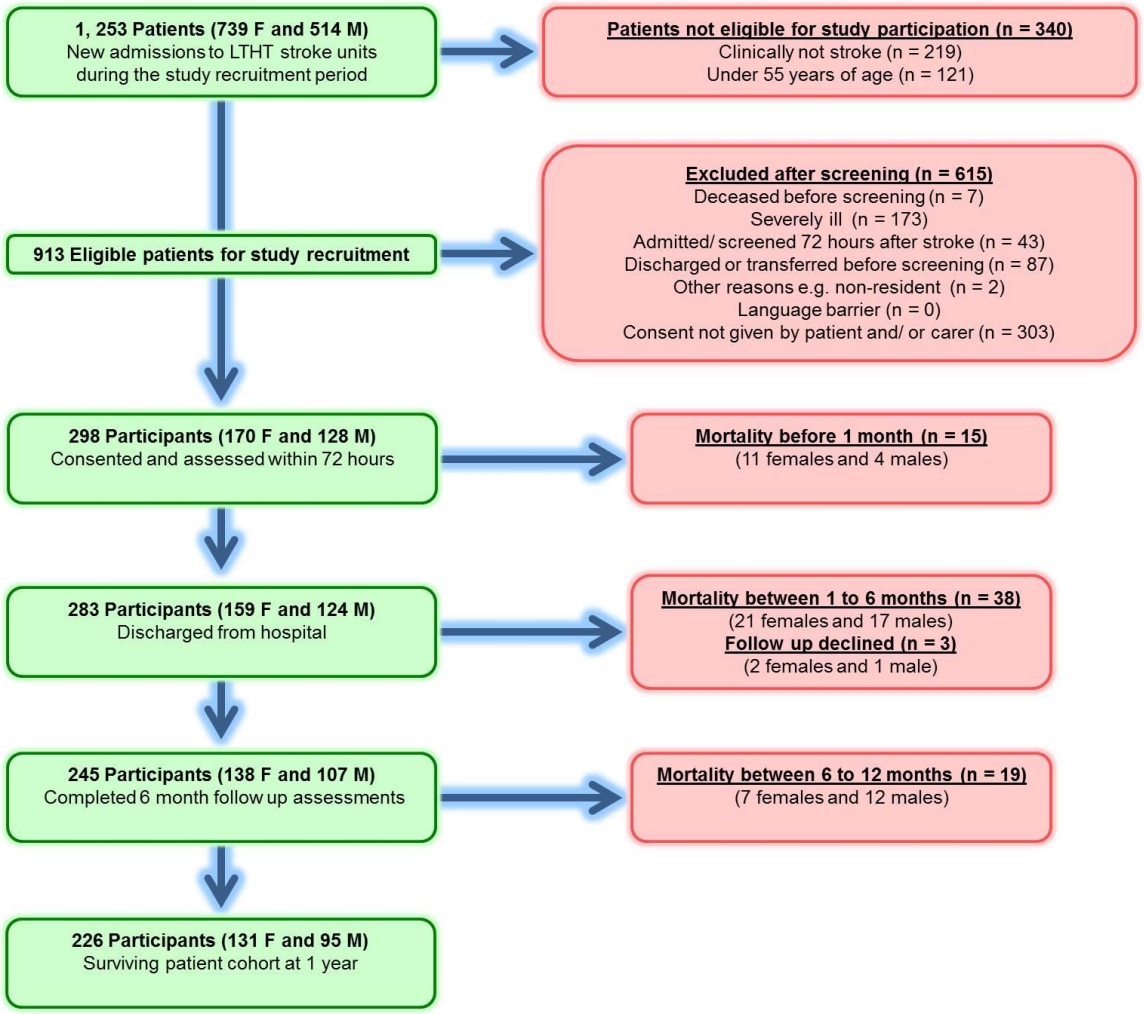


Figure 7.1: Schematic diagram of the number of admissions and exclusions.

Of the 1,253 admissions, 17% (219 patients) were clinically not an acute stoke consisting of TIA's, SAH, stroke mimics or other neurological conditions that have similar stroke type symptoms. Due to the restructuring of the stroke services within Leeds and the addition of a HASU unit in January 2012, the stroke unit no longer separated stroke patients according to age. All acute stroke cases were admitted solely to the LGI regardless of age and therefore a further 10% (121 patients) were not eligible for study participation as they were found to be less than 55 years of age.

Of the remaining stroke unit admissions, 173 were clinically too ill to participate, 7 died before they could be assessed, 87 were discharged from the stroke unit before the researcher could screen them, 43 were outside of the 72 hour recruitment window, and 2 were excluded for other reasons such as being a non-resident of this area/ visiting from out of the country and/ or language issues. A further 303 patients were not interested, the patient and/ or carer did not provide consent or the participants initially consented but later changed their mind and withdrew consent refusing to participate. Therefore their details and study data were removed from sample.

This produced a final sample size of 298 patients, producing a recruitment rate of 33%. The graded consent forms allowed participants to choose how long they wanted to stay in the study. All the patients decided to participate for the full length of the study (one year), but a small minority (three participants) withdrew their consent during the follow up period choosing only to allow the use of their inpatient data for the study. Of the 298 participants, 293 had a Caucasian background and less than 2% of the study sample had a non-Caucasian background. The mean age of the sample was 79 years (SD 9.0, range 57–101) which consisted of 128 males and 170 females and this is illustrated in Figure 7.2.

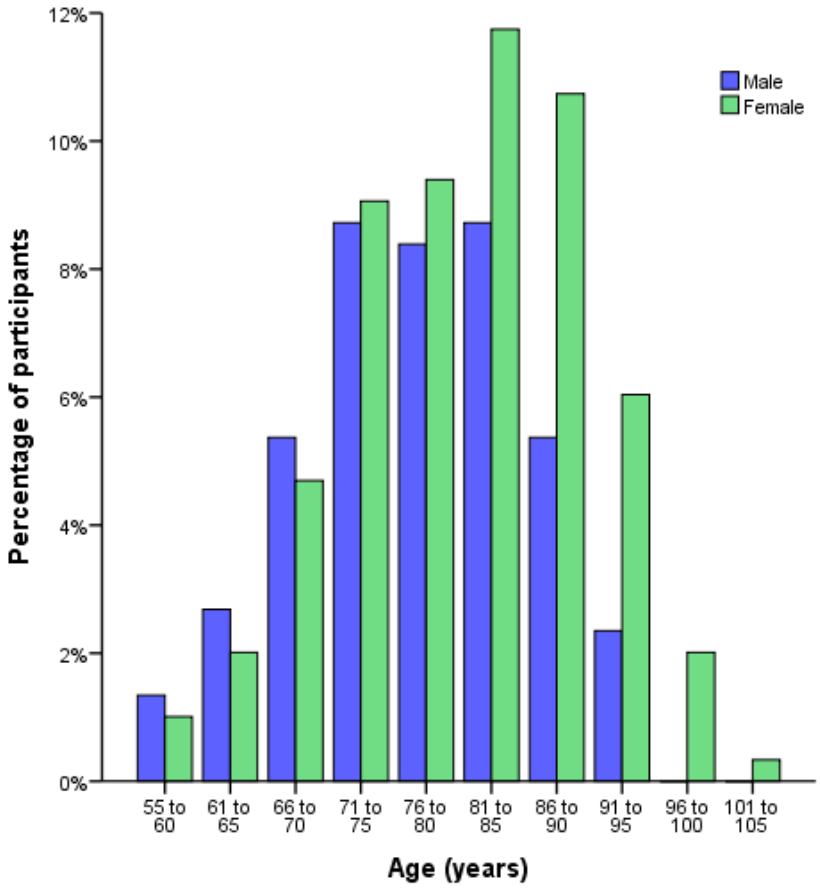


Figure 7.2: The age distribution of the study sample.

For comparative purposes, the excluded patient group had 386 males and 569 females with a mean age of 83 years. There were no significant differences between the excluded patient groups and the selected study sample. All 298 participants were assessed by one researcher at the acute stroke unit at the LGI, with rehabilitation follow up at the SJUH or CAH stroke units.

7.2 The physical clinical factors

In the study sample, 271 patients suffered an infarct which accounted for 91% of the sample and 27 patients (9%) suffered a haemorrhage. 131 (44%) were diagnosed as having a left sided lesion and 167 (56%) were diagnosed as having a right sided lesion. The Bamford Classification scale was used as a clinical descriptor and the distribution of the types of stroke (TACS, PACS, LACS and POCS) are shown in Figure 7.3.

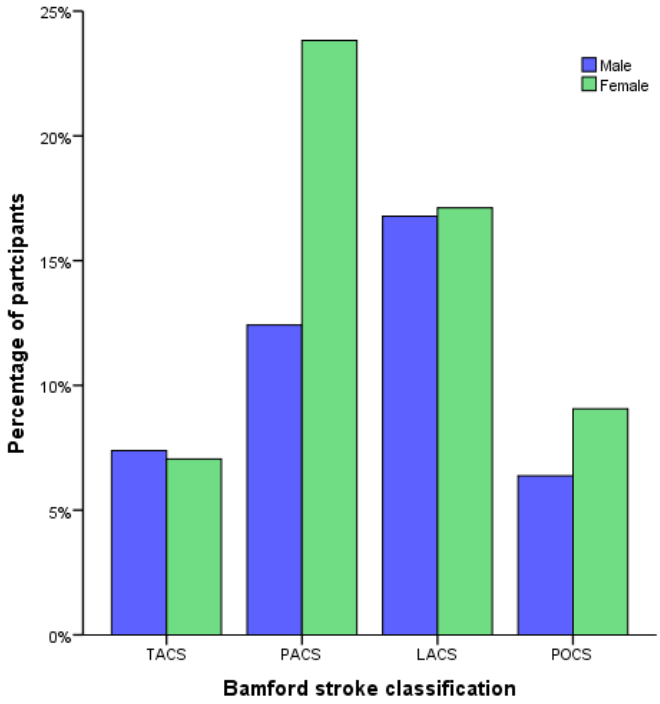


Figure 7.3: The distribution of the Bamford stroke types within the sample.

As Figure 7.3 shows 34 participants (14%) were classed as TACS, 108 (36%) as PACS, 101 (34%) as LACS and 46 (15%) as POCS. All 298 subjects were assessed within 24 hours of a suspected stroke with a CT head to exclude any bleeds and 15% required further MRI or repeat CT scans to assist with the diagnosis. Of the stroke patients 90% were admitted to HASU or the ASU with 24 hours of a suspected stroke, with 8% admitted to the stroke unit within 48 hours and less than 2% were admitted to unit over 48 hours later. Upon admission the patients experienced the following clinical symptoms; 58 (20%) had sensory loss, 55 (19%) had sensory inattention, 172 (58%) had communication difficulties such as dysphasia or dysarthria, 89 (30%) had an unsafe swallow, 167 (56%) had a change in gait and 51 (17%) exhibited evidence of visuospatial disorders.

In addition to the presentation of a stroke, the majority of patients also had existing significant physical illness as derived from the patient's medical history. These were classed as nil conditions, less than 3 clinical conditions as mild illness, 3 to 5 conditions as moderate illness and over 5 clinical conditions as severe illness. According to this grouping, 8 (3%) had nil physical illness, 77 (26%) as mild, 150 (50%) as moderate and 63 (21%) as severe physical illness. A note of the number of medications regularly taken for physical illness was also made at the time of admission. The number of medications for the study sample ranged from 0 to 23 medications with a mean of 7 $\pm$ 4.3 SD (interquartile range 4 to 10, median 7). Only 18 patients (6%) had no regular medications prior to having a stroke, 64 (22%) were

recorded as taking less than 5 medications, 144 (48%) were recorded as taking between 5 to 10 medications and 72 patients (24%) were recorded taking over 10 medications. In the sample 67 patients (22%) were recorded as having a history of a previous stroke prior to their current admission. The study sample had 165 patients (55%) that were found to be smokers (current and past) and 108 (36%) also consumed a moderate amount of alcohol in their regular routine, with only 2 drinking alcohol excessively over the recommended amount. Other physical factors that were listed as confounders were also recorded. The patients that recorded as positive for these factors were as follows; 106 (36%) incontinence, 143 (48%) constipation, 56 (19%) malnutrition, 106 (36%) dehydration, 95 (32%) infection, 31 (10%) hypoxia, 88 (30%) electrolyte imbalance and 12 (4%) recent surgery. On the whole, the data collected for these factors was well recorded and will be discussed later in this chapter.

7.3 The non-clinical and psychosocial factors

The marital status of the sample compromised of; 47 (16%) single, 122 (41%) married, 25 (8%), divorced and 104 (35%) widowed. 151 (51%) were recorded as living alone and 147 (49%) lived with their partner or a family member. Accommodation prior to discharge was classed as either living at home/ in sheltered housing or as an institutional placement in nursing homes, care homes or residential homes. Prior to admission 287 (96%) were recorded as living at home, in sheltered housing or religious accommodation and were mostly independent in their daily living. 11 participants (4%) were admitted from care homes, residential homes or nursing homes. The patient's history of mental health prior to admission was also recorded where 26 patients (9%) patients were diagnosed with pre-existing dementia and 23 patients (8%) with clinical depression.

English was the primary language for 295 participants, with only three participants (1%) recorded as non-English speakers but had a sufficient level of English for the assessments. 184 patients (62%) required some sort of aids such as glasses or hearing aids. 27 patients (9%) were left handed, 205 (69%) were right handed and for 66 patients (22%) this data was not recorded. The education and occupation of the participants were recorded according to the scales described in Chapter five (appendix 21 and 22). With regards to the education in the sample (Figure 7.4), only one participant was recorded as illiterate. 248 (83%) were educated to primary/ secondary school, 38 (13%) attended college, army or completed an apprenticeship and 11 participants (4%) attended university. There was a wide range of occupations across the study sample as shown in Figure 7.5, with only 63 patients (21%) that were recorded as not stated or 'retired'.

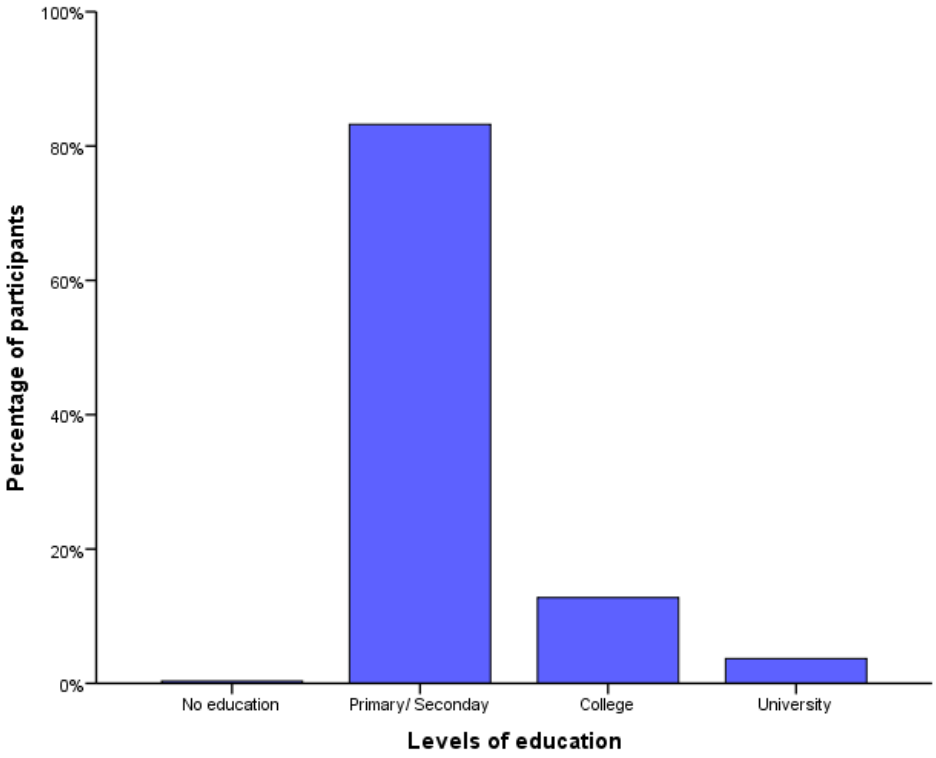


Figure 7.4: The education levels across the sample.

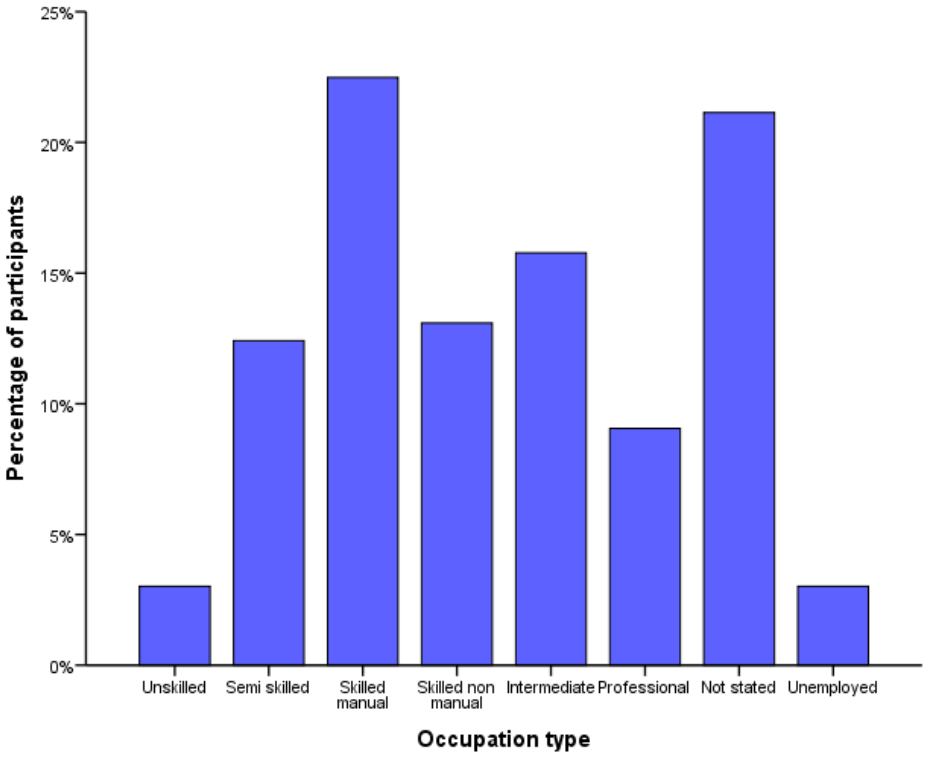


Figure 7.5: The types of occupation across the sample.

7.4 Delirium diagnosis

7.4.1 **Assessing the presence of delirium using the CAM-ICU and DRS-R98**

The CAM-ICU was used to detect the presence of delirium where a positive score is needed for 3 out of the 4 features. The MEWS score was initially used to screen for potential participants. Once enrolled into the study, the GCS or the RASS were used to assess the patient's mental status/ altered level of consciousness as part of the CAM-ICU screening tool. All patients were assessed at the same time point regardless of whether they displayed any symptoms of delirium. 200 patients exhibited no signs of delirium during their stay in hospital. 78 patients tested positive for delirium either during their stay or in the subsequent follow up periods producing an incidence of 26.2%. However there were a further 20 cases that displayed some signs of delirium, despite testing negative for the CAM-ICU, producing a combined total of 98 cases of delirium and cumulative incidence of 32.9%. The delirium diagnosis was made in conjunction with the DRS-R98.

All 298 patients were assessed using the DRS-R98, which had a total score of 39. Categories were created for the DRS-R98 scores which were as follows; 0 to 14 no delirium present, 15 to 23 mild delirium, 24 to 32 moderate delirium and 31 to 39 severe delirium. Patients were assessed at days one and four, weeks two and three and months one and six.

7.4.2 **Assessing the duration of delirium and association with other factors**

For patients that were delirium positive, the duration of delirium was recorded as the cumulative number of delirium positive days. The range of delirium positive days was 1 to 33 days with a mean of 9.5 days $\pm$ 6.9 SD (interquartile range 4 to 13, median 8).

The relationship between delirium diagnosis and the other variables was calculated using the Pearson chi-squared test for categorical variables and the independent samples t-test for continuous variables. The results are shown in Figure 7.6.

Characteristic n ± SD or n (%)	Total n=298	Delirium n=98	No Delirium n=200	P value	OR*	95% CI Lower	 Upper
Patient details							
Age, mean ± SD	79±9.0	83.2±8.1	77.5±8.9	<0.0001	1.08	1.05	1.12
Male	128 (42.9%)	38 (38.8%)	90 (45%)	0.308	0.77	0.47	1.27
Caucasian	293 (98.3%)	96 (97.9%)	197 (98.5%)	0.733	0.73	0.12	4.45
English speaker	295 (98.9%)	96 (97.9%)	199 (99.5%)	0.211	0.24	0.02	2.69
Living at home	287 (96.3%)	92 (93.9%)	195 (97.5%)	0.119	0.39	0.12	1.32
Living alone	151 (50.7%)	55 (56.1%)	96 (48%)	0.188	1.39	0.85	2.25
Marital status							
Single	47 (15.8%)	15 (15.3%)	32 (16%)	0.877	0.95	0.49	1.85
Married	122 (40.9%)	37 (37.8%)	85 (42.5%)	0.434	0.82	0.50	1.35
Divorced	25 (8.4%)	6 (6.1%)	19 (9.5%)	0.323	0.62	0.24	1.61
Widowed	104 (34.9%)	40 (40.8%)	64 (32%)	0.134	1.47	0.89	2.42
Left handedness	27 (9.1%)	8 (8.2%)	19 (9.5%)	0.605	0.69	0.26	1.81
Education							
None[+]	1 (0.3%)	0 (0%)	1 (0.5%)	0.483	-	-	-
School	248 (83.2%)	83 (84.7%)	165 (82.5%)	0.643	1.17	0.61	2.27
College	38 (12.8%)	12 (12.2%)	26 (13%)	0.445	0.72	0.31	1.68
University	11 (3.7%)	3 (3.1%)	8 (4%)	0.686	0.76	0.20	2.92
Occupation							
Unskilled	9 (3%)	5 (5.1%)	4 (2%)	0.142	2.63	0.69	10.04
Semi skilled	37 (12.4%)	13 (13.3%)	24 (12%)	0.756	1.12	0.54	2.31
Skilled manual	67 (22.5%)	15 (15.3%)	52 (26%)	0.038	0.51	0.27	0.97
Skilled non-manual	39 (13.1%)	7 (7.1%)	32 (16%)	0.033	0.40	0.72	0.95
Intermediate	47 (15.8%)	13 (13.3%)	34 (17%)	0.406	0.75	0.37	1.49
Professional	27 (9.1%)	6 (6.1%)	21 (10.5%)	0.216	0.56	0.22	1.43
Unemployed	9 (3%)	3 (3.1%)	6 (3%)	0.977	1.02	0.25	4.17
Not stated/ 'Retired'	63 (21.1%)	36 (36.7%)	27 (13.5%)	<0.0001	3.72	2.09	6.63
Medical history							
Medications	7.3±4.3	7.2±3.8	7.4±4.5	0.790	0.99	0.94	1.05
Physical illness	3.9±2.4	4.2±2.3	3.8±2.4	0.178	1.07	0.97	1.19
Smoker	165 (55.4%)	45 (45.9%)	120 (60%)	0.022	0.57	0.35	0.92
Drinker	108 (36.2%)	27 (27.6%)	81 (40.5%)	0.029	0.56	0.33	0.95
Dementia	26 (8.7%)	18 (18.4%)	8 (4%)	<0.0001	5.40	2.26	12.92
Depression	23 (7.7%)	7 (7.1%)	16 (8%)	0.795	0.89	0.35	2.23
Previous stroke	67 (22.5%)	28 (28.6%)	39 (19.5%)	0.078	1.65	0.94	2.89
Stroke details							
Bamford type							
TACS	43 (14.4%)	21 (21.4%)	22 (11%)	0.016	2.21	1.15	4.25
PACS	108 (36.2%)	41 (41.8%)	67 (33.5%)	0.160	1.43	0.87	2.35
LACS	101 (33.9%)	24 (24.5%)	77 (38.5%)	0.016	0.52	0.30	0.89
POCS	46 (15.4%)	12 (12.2%)	34 (17%)	0.286	0.68	0.34	1.38
Infarct	271 (90.9%)	85 (86.7%)	186 (93%)	0.077	0.49	0.22	1.09
Right lesion	167 (56%)	57 (58.2%)	110 (55%)	0.605	0.88	0.54	1.43
Clinical symptoms							
Sensory inattention	55 (18.5%)	22 (22.4%)	33 (16.5%)	0.214	1.47	0.80	2.68
Sensory loss	58 (19.5%)	18 (18.4%)	40 (20%)	0.738	0.90	0.49	1.67
Communication	172 (57.7%)	65 (66.3%)	107 (53.5%)	0.035	1.71	1.04	2.83
Unsafe swallow	89 (29.9%)	34 (34.7%)	55 (27.5%)	0.202	1.40	0.83	2.35
Gait changes	167 (56%)	57 (58.2%)	110 (55%)	0.605	1.14	0.70	1.85
Visuospatial	51 (17%)	28 (28.6%)	23 (11.5%)	<0.0001	3.08	1.66	5.71
Complications							
Incontinence	106 (35.6%)	55 (56.1%)	51 (25.5%)	<0.0001	3.74	2.24	6.22
Constipation	143 (47.9%)	60 (61.2%)	83 (41.5%)	0.001	2.23	1.36	3.65
Malnutrition	56 (18.8%)	23 (23.5%)	33 (16.5%)	0.148	1.55	0.85	2.82
Dehydration	106 (35.6%)	49 (50%)	57 (28.5%)	<0.0001	2.51	1.52	4.14
Infection	95 (31.9%)	59 (60.2%)	36 (18%)	<0.0001	6.89	4.01	11.85
Hypoxia	31 (10.4%)	12 (12.2%)	19 (9.5%)	0.466	1.33	0.62	2.86
Electrolyte imbalance	88 (29.5%)	46 (46.9%)	42 (21%)	<0.0001	3.33	1.97	5.61
Surgery	12 (4%)	5 (5.1%)	7 (3.5%)	0.509	1.48	0.46	4.80

Figure 7.6: Delirium diagnosis and association with other factors.

* Odds ratio (OR) for the incidence of delirium. [+] Small sample size, analysis not performed.

With regards to patient details, the age of the participant and the occupation subgroups of skilled manual and skilled non-manual were shown to be significantly associated with the delirium diagnosis, as shown in Figure 7.6. The ‘not stated/ retired’ subgroup was also significant, but this was most likely a proxy marker for an increase in age. For medical history smoking, drinking, dementia, the TACS and LACS stroke subtypes and the clinical symptoms of communication and visuospatial disorders showed a significant association with delirium. A significant association was also seen for complications such as incontinence, constipation, dehydration, infection and electrolyte imbalance.

7.4.3 **The combined use of the CAM-ICU and the DRS-R98**

The CAM-ICU and DRS-R98 tools were administered by one researcher and the completion rates for these assessments were 98%. Some patients did not stay in hospital till the allocated time points and so a pre-discharge delirium assessment was done where possible. There were certain assessments that were missed due to the patient discharges or deaths at the weekend, when the researcher was not present. The assessments using the CAM-ICU and DRS-R98 were conducted by the researcher (S. Ahmed) who had been trained in use of the delirium assessments tools. The tools were well tolerated by the patients and the combined use of the CAM-ICU and DRS-R98 produced results that were in agreement which reinforced the diagnosis, as shown in previous studies.

Once experience had been gained, the assessment tools were quick to administer but in a busy stroke unit this may prove difficult. Use of the DRS-R98 requires experience and the staff may not be able to spend as much time assessing patients for delirium as compared to the researcher whose primary aim was to assess delirium occurrence. The time taken to train the staff on the stroke unit may be a point to consider if a delirium screening/ assessment tool was introduced to the stroke care pathway.

7.4.4 **Possible confounders for delirium**

The following confounders were also analysed for possible associations with the delirium diagnosis; incontinence, constipation, malnutrition, dehydration, electrolyte imbalance, infection, hypoxia, recent surgery, smoking and alcohol intake. Analysis of these factors in relation to delirium diagnosis was calculated using binary logistic regression and the results are shown in Figure 7.7.

Characteristic n (%)	Total n=298	Delirium n=98	No Delirium n=200	P value	OR*	95% CI Lower	95% CI Upper
Incontinence	106 (35.6%)	55 (51.9%)	51 (48.1%)	0.256	1.52	0.74	3.11
Constipation	143 (48.0%)	60 (42.0%)	83 (58.0%)	0.139	1.58	0.86	2.90
Malnutrition	56 (18.8%)	23 (41.4%)	33 (58.9%)	0.434	0.74	0.35	1.57
Dehydration	106 (35.6%)	49 (46.2%)	57 (53.8%)	0.922	0.96	0.45	2.06
Infection	95 (31.9%)	59 (62.1%)	36 (37.9%)	<0.0001	4.72	2.38	9.35
Hypoxia	31 (10.4%)	12 (38.7%)	19 (61.3%)	0.148	0.47	0.17	1.31
Electrolyte imbalance	88 (29.5%)	46 (52.3%)	42 (47.7%)	0.014	2.26	1.18	4.32
Surgery	12 (4.0%)	5 (41.7%)	7 (58.3%)	0.382	1.87	0.46	7.62
Smoking	165 (55.4%)	45 (27.35)	120 (72.7%)	0.240	0.70	0.39	1.26
Alcohol	108 (36.2%)	27 (25.0%)	81 (75.0%)	0.353	0.74	0.38	1.41
Dementia	26 (8.7%)	18 (69.2%)	8 (30.8%)	0.009	4.01	1.41	11.43
Depression	23 (7.7%)	7 (30.4%)	16 (69.6%)	0.419	0.62	0.19	1.99
Previous stroke	67 (22.5%)	28 (41.8%)	39 (58.2%)	0.507	1.26	0.64	2.46
Physical illness (mean)	3.9	4.2	3.8	0.183	1.09	0.96	1.24
Medications (mean)	7.3	7.2	7.4	0.247	0.96	0.88	1.03

Figure 7.7: Analysis of factors in relation to delirium diagnosis.

* Odds ratio (OR) for the incidence of delirium. The relationship between the delirium diagnosis and each variable was analysed using a generalised linear model.

Figure 7.7 showed that certain specific patient variables had an association with the participant's delirium diagnosis. The presence of infection, an electrolyte imbalance and the presence of dementia had a significant association with a delirium positive diagnosis.

7.5 Post-admission outcomes

7.5.1 Mortality over one year post-stroke

With regards to mortality, all patients were followed up for one year after their admission to the stroke unit. A total of 15 patients died before the one month stage, 38 deaths were recorded between one to six months and 19 deaths were recorded between six months and the one year stage. The sample had a total of 72 deaths (24.2%) during the twelve month period after their admission to hospital, as shown in Figure 7.8a.

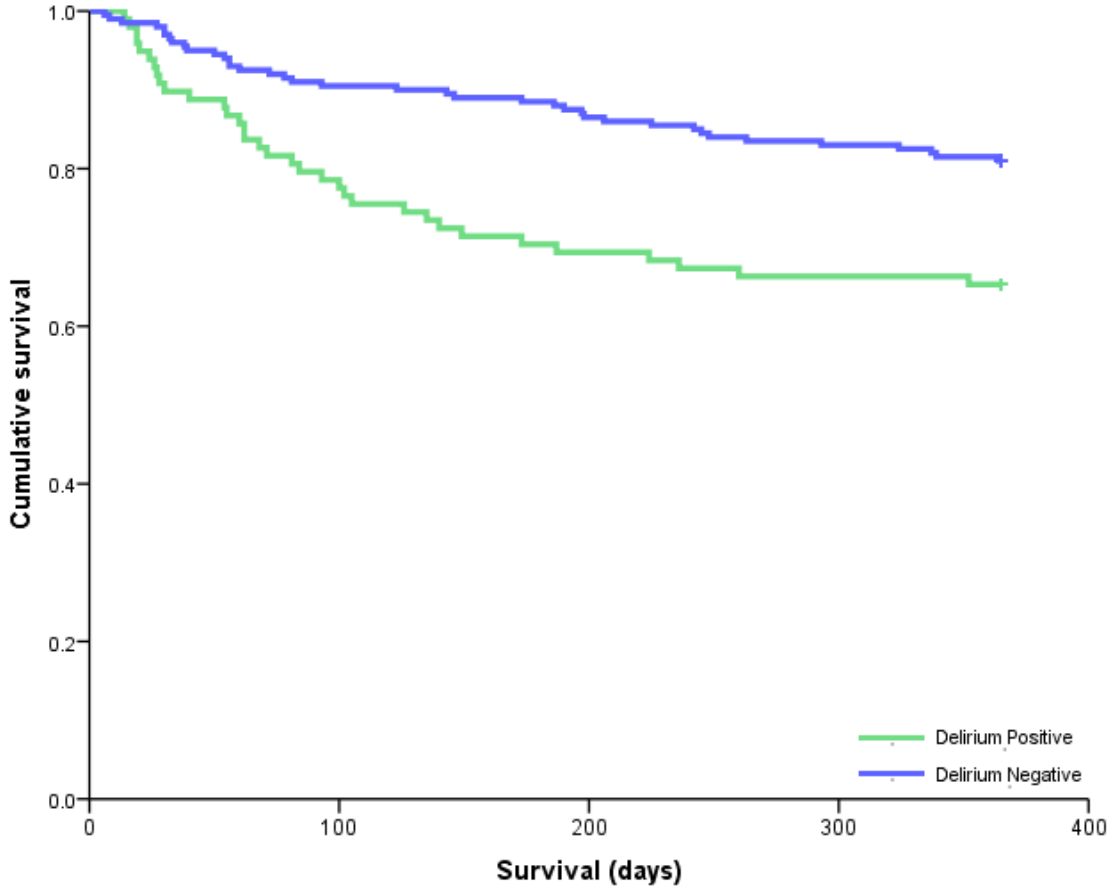
The log rank test demonstrated a significant effect on mortality for the delirium group compared to the non-delirium group (P<0.002). The unadjusted effect of delirium diagnosis

on survival is shown in Figure 7.8b. The group was not split further into dementia subgroups for the delirium diagnosis as it was felt that there were too few numbers for a significant difference.

Cumulative mortality, n (%)	Total n=298	Delirium n=98	No Delirium n=200	P value	OR*	95% CI Lower	95% CI Upper
1 month	15 (5%)	9 (9.2%)	6 (3%)	0.022	3.27	1.13	9.47
6 months	53 (17.8%)	29 (29.6%)	24 (12%)	0.006	2.59	1.30	5.17
12 months	72 (24.2%)	34 (34.7%)	38 (19%)	0.529	0.71	0.25	2.04

Figure 7.8a: Cumulative mortality over a one year period.

* Odds ratio (OR) for the incidence of delirium. All study participants were followed up for one year after discharge from hospital. The study sample had a total of 72 deaths (24.2%) over this period.



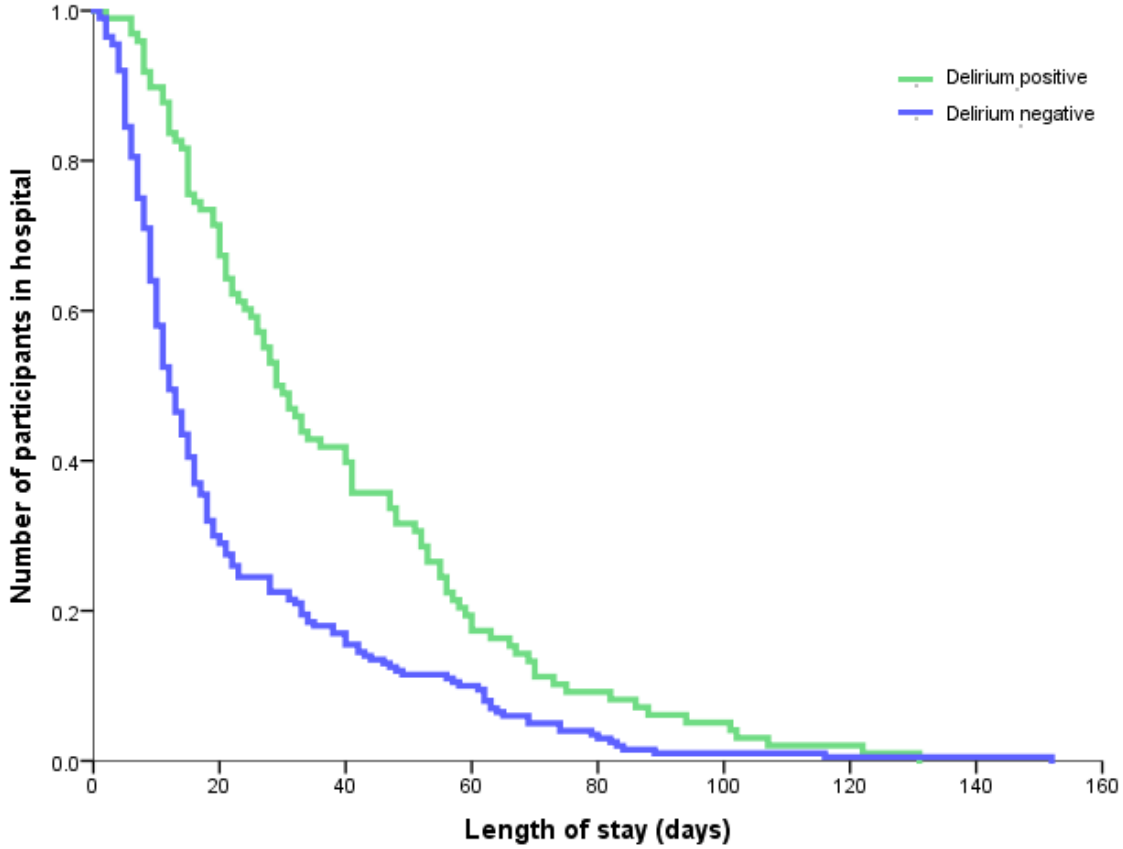
Log rank test P<0.002

Figure 7.8b: Survival in relation to delirium diagnosis.

The unadjusted effect of delirium diagnosis on survival is shown above.

7.5.2 **Length of hospital stay**

The length of stay for the study sample ranged from 1 day to 152 days with mean of 27 days ± 26.0 SD (inter quartile range 9 to 40 days, median 16). The total amount of time spent in hospital included any time spent in A&E, the hyper acute stroke unit, the acute stroke unit, the stroke rehab unit and time spent in any other hospital ward. The delirium group had a mean of 38.5 days ± 27.9 SD compared to the non-delirium group which had a mean of 21.5 days ± 23.0 SD. The difference in length of stay between groups was calculated using the independent samples t-test (P<0.0001). The log rank test demonstrated a significant effect on length of stay for the delirium group compared to the non-delirium group (P<0.0001). Figure 7.9 shows the Kaplan-Meier curve for the unadjusted effect of delirium diagnosis on the length of stay for the study sample.



Log rank test P<0.0001

Figure 7.9: Length of stay in relation to delirium diagnosis.

7.5.3 **Discharge destination**

The discharge destination of the study sample is shown in Figure 7.10. In the study sample, 15 participants died before the one month stage and a cumulative total of 22 participants died during their stay in hospital. Of the remaining patients 222 were discharged home and 54 were discharged to an institutionalised placement such as a nursing home, care home or residential home. The difference in discharge destination between the delirium and non-delirium group was calculated using the Pearson chi-squared test. The presence of delirium had a significant effect on discharge destination (P<0.0001).

Discharge destination, n (%)	**Total** n=298	**Delirium** n=98	**No Delirium** n=200	**P value**	**OR***	**95% CI Lower**	**Upper**
Home	222 (74.5%)	49 (50.0%)	173 (86.5%)	<0.0001	0.16	0.09	0.28
Institutionalisation	54 (18.1%)	36 (36.7%)	18 (9.0%)	<0.0001	5.87	3.11	11.08
Died in hospital	22 (7.4%)	13 (13.3%)	9 (4.5%)	0.007	3.25	1.34	7.88

Figure 7.10: Discharge destination in relation to delirium diagnosis.

* Odds ratio (OR) for the incidence of delirium.

7.6 Outcomes six months post-stroke

7.6.1 **Physical function**

With regards to the assessment of long term outcomes at the six month follow up, three participants declined any further follow up assessments. In addition to this a further 56 participants had passed away, leaving a total of 239 participants at the six month stage. All 298 patients had their pre-stroke function recorded by the nursing staff upon admission to the stroke unit. The nursing staff used the Rankin scale/ Oxford handicap scale with input from the patient's medical notes, family and carers and the patient themselves and also a Barthel score was conducted by nursing staff upon hospital discharge. As part of the study protocol, the NEADL was carried out during the patient's admission to hospital to estimate their pre-stroke function. With a possible total score of 66, the item scores range from 0 indicating that they could not manage this activity at all compared to a max item score of 3 indicating that they were fully independent in that particular activity. The NEADL was administered to 297 participants during their stay in hospital. Only one participant did not

complete the assessment due to a sudden deterioration in their health. For those patients who survived and consented to participate for the full duration of the study, the NEADL was then repeated at the six month stage. The range of NEADL scores at baseline and six months are shown in Figure 7.11.

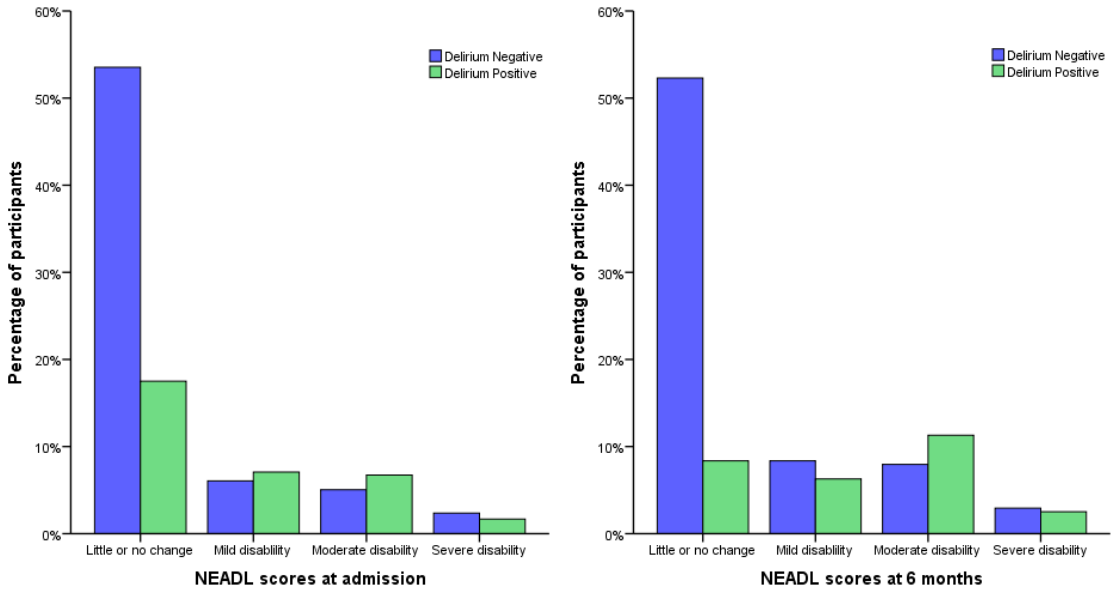


Figure 7.11: Comparison of NEADL scores at admission and at six months.

As there were no predefined categories for the NEADL scores, the following scoring categories were created in order to group patients together for comparison. The scoring categories employed for the NEADL were as follows; a score of 66 to 50 indicates little or no change, 49 to 34 indicates mild disability, 33 to 18 indicates moderate disability and a score of 17 to 0 indicates severe disability.

The median NEADL scores were 63 at admission and 55 at six months. There was a significant difference in NEADL scores between admission and at six month post-stroke (Wilcoxon Signed Ranks Test Z= -10.45, P<0.0001). The changes in the NEADL scores were analysed according to delirium diagnosis, which indicated there was a significant decrease in physical function (Mann Whitney U Test, P<0.0001) associated with delirium.

7.6.2 **Risk of dementia**

All 298 patients had the AD-8 dementia screen administered by the researcher upon admission to the stroke unit. The AD-8 has a total possible maximum score of 8, where an item score of 2 or more indicates a change in certain behaviours over the specified time

period and indicative of possible risk of dementia. The IQCODE was also administered to all carers for their input, where each item is scored as 1/2 to indicate improvement, 3 to indicate no change, 4 to indicate slight deterioration and 5 to indicate significant deterioration, giving a total possible maximum score of 80. The total score is then divided by the number of items (in this case 16) to give the final score. A final score of 4 or 5 was considered indicative of dementia risk. The nursing staff did not used any screening tools for dementia, but a note for pre-existing dementia was made in the patient's medical history as part of the stroke care pathway. Upon admission the median scores for the AD-8 and the IQCODE were 0 and 3 respectively. All AD-8 and IQCODE scores were completed at admission. For those patients who survived and consented to participate for the full duration of the study, the AD-8 and IQCODE were repeated at the six month stage. At the follow up stage, three participants declined any further assessments. A further 56 participants died by the follow up stage, leaving a total of 239 participants that completed the AD-8 and IQCODE. At six months, the median scores for the AD-8 and the IQCODE were 1 and 3 respectively. The range of AD-8 and IQCODE scores at baseline and six months are shown in Figure 7.12a and 7.12b.

There was a significant difference in dementia scores upon admission and at six month post-stroke for both the AD-8 (Wilcoxon Signed Ranks Test $Z= -8.00$, $P<0.0001$) and the IQCODE (Wilcoxon Signed Ranks Test $Z= -7.29$, $P<0.0001$). The changes in the dementia screening scores, both the AD-8 and IQCODE were analysed according to the delirium diagnosis. There was a significant increase in dementia risk for both the AD-8 (Mann Whitney U Test, $P<0.0001$) and the IQCODE (Mann Whitney U Test, $P<0.0001$) associated with delirium.

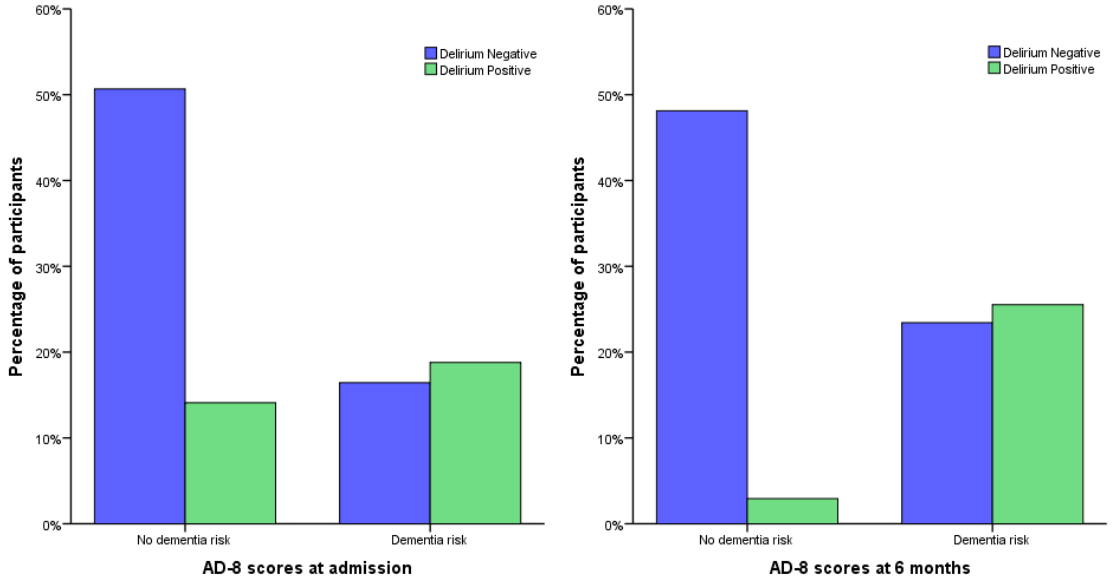


Figure 7.12a: Comparison of AD8 scores at admission and at six months.

The scoring categories for the AD-8 were as follows; a score of 0 or 1 indicates no risk of dementia whereas a score between 2 to 8 indicates risk of dementia.

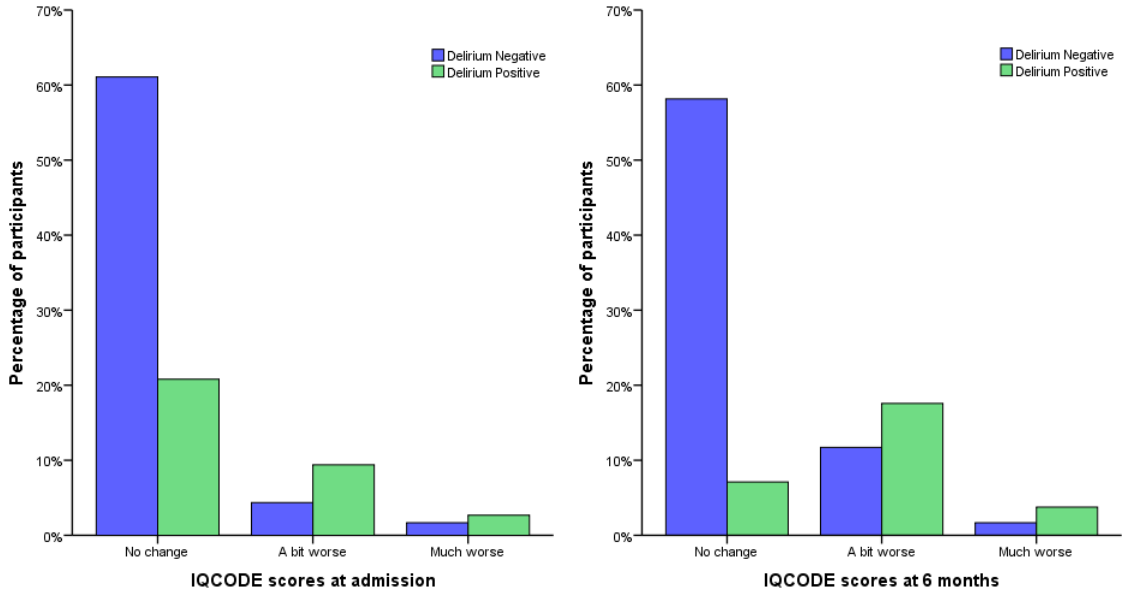


Figure 7.12b: Comparison of IQCODE scores at admission and at six months.

The scoring categories for the IQCODE were as follows; an average score of 1 to 3 indicates no change, an average score of 4 indicates the change is a bit worse and an average score of 5 indicates that the change is much worse.

7.6.3 **Assessment of mood**

As part of the study protocol, the GDS was to be administered to all participants upon admission to the stroke unit. However 19 participants did not complete the GDS due to severe communication difficulties and/ or a sudden deterioration in their health. As a result only 279 participants were able to complete the GDS assessment in full upon admission to hospital. The GDS assessment has a maximum score of 30 which is split into categories of no depression, mild depression and severe depression. The nursing staff did not use any screening tools for depression, but a note of depressive episodes was made in the patient's medical history as part of the stroke care pathway. Those that were thought to be at high risk had a mood screen administered by the nurses and then referred to the psychiatrist/ OT for further assessment using the Wimbledon score.

At the six month stage, three participants declined to participate for the full duration of the study and so the GDS was not repeated. Also a further 56 participants had died by the follow up stage, leaving a total of 239 participants who were able to complete the GDS at six months. There were only 233 participants that had completed the GDS assessment upon admission and at six months. The median GDS scores at both admission and at six months were 4 and the range of GDS scores is shown in Figure 7.13.

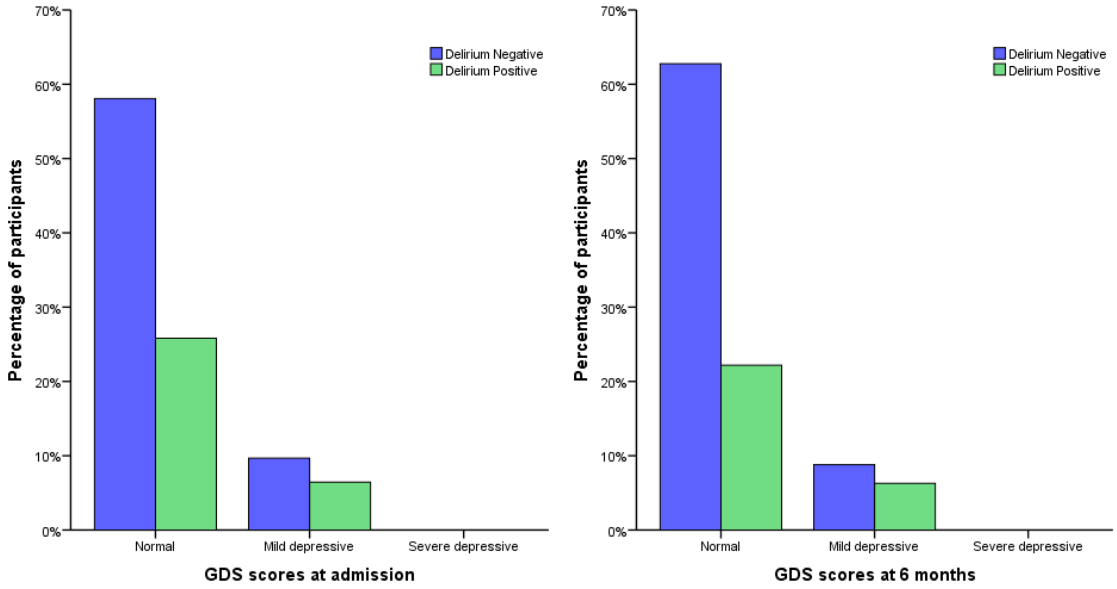


Figure 7.13: Comparison of GDS scores at admission and at six months.

The scoring categories for the GDS were as follows; a score between 0 to 9 indicates no depression, 10 to 19 indicates mild depression and a score between 20 to 30 indicates severe depression.

There was a significant difference in the GDS scores upon admission and at six month post-stroke (Wilcoxon Signed Ranks Test Z= -2.08, P<0.04). The changes in the GDS scores were then analysed according to delirium diagnosis. Although there was a difference in depressive symptoms between admission and at six months in relation to the delirium (Mann Whitney U Test, P<0.09), the results did not reach statistical significance.

7.6.4 **Cognitive impairment**

As part of the study protocol, the ACE-R was chosen to assess cognitive impairment due to its shorter duration compared to other assessment tools. In addition to this, the MMSE was also incorporated into the ACE-R exam which was advantageous. The ACE-R had a maximum total score of 100, testing domains such as attention and orientation, memory, fluency, language and visuospatial abilities. A cut off score of 88 (94% sensitivity, 89% specificity) was used to indicate cognitive impairment. Upon hospital admission, the AMTS with a maximum score of 10 was often administered to assess the patient's orientation to time and place. This was then subsequently followed up by an SMMSE or ACE-R by the occupational therapy staff on the stroke unit, depending on how compliant the patient was, and the results were recorded in the medical notes.

During the recruitment phase however, the occupational therapy team switched to the MoCA due to payment issues with the ACE-R/ MMSE. The MMSE and MoCA are shown to have good concordance so this was not an issue, however subsequently the team later switched back to using the MMSE. For the purposes of this study, the ACE-R was administered to the participants regardless of changes on the stroke unit. It was found that patients, and often those that were found to be showing signs of cognitive impairment, often refused to continue the assessment after starting the ACE-R exam. Further to this many of the patients experienced changes in vision and motor ability after their stroke and so they were not able to adequately answer all the questions on the exam. The changes in the patient's ability post-stroke had been anticipated prior to starting the study and alternative arrangements had been made should the need arise.

Of the 298 patients, only 164 patients completed the ACE-R in full. Since the data relating to ACE-R score was incomplete, no further analysis of this measure was undertaken. It was decided early on in the study that the SMMSE would be used upon admission as an alternative cognitive assessment if the need arose. The TICS had been shown to correlate highly with the MMSE and so it was decided that the TICS could be used as an alternative measure of cognition at the six month stage if required.

7.6.4.1 The SMMSE and the TICS

Of the 298 participants in the study sample, 42 participants did not complete the SMMSE upon admission. The incomplete assessments were due to the following reasons; 15 had severe dysphasia, 18 were not responsive and 9 refused or were unable to complete the assessment. This left a total of 256 participants who completed the SMMSE in full upon admission. The SMMSE has a total maximum score of 30, which is split into categories of normal cognition, mild cognitive impairment, moderate cognitive impairment and severe cognitive impairment.

For the patients that survived and consented to participate for the full duration of the study, the TICS assessment was administered at the six month stage. Of the study population, three participants declined any further assessments at the follow up stage. A further 56 participants had died by the six month stage, leaving a total of 239 participants who were able complete the TICS assessment. Of the total study population, there were only 197 participants that had completed the SMMSE at admission and the TICS at six months. The range of SMMSE and TICS assessment scores are shown in Figure 7.14.

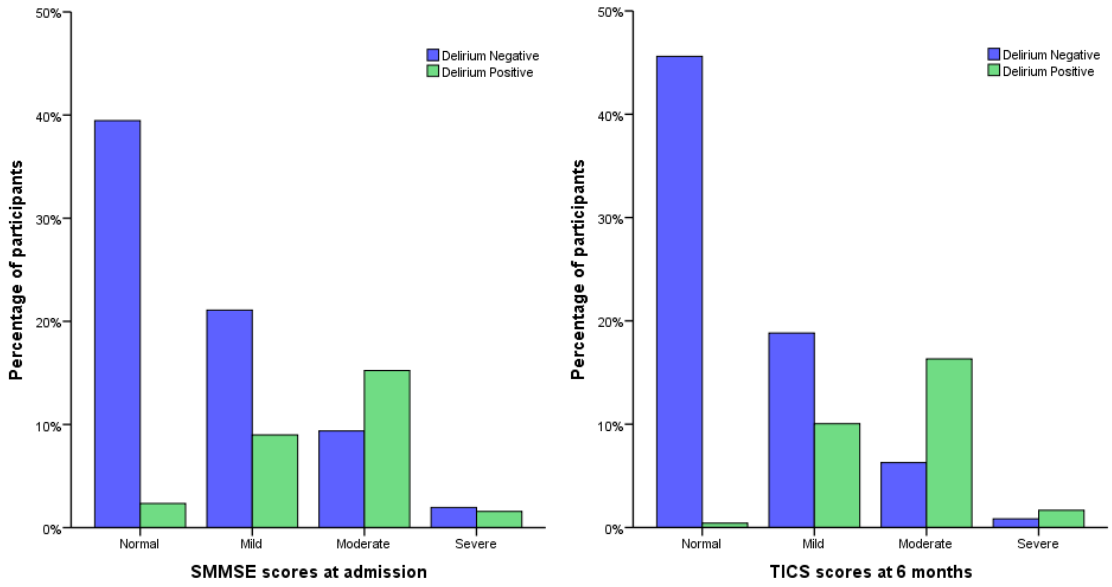


Figure 7.14: Comparison of SMMSE at admission and TICS at six months.

The SMMSE scores were split into the following categories; 27 to 30 indicates normal cognition, 21 to 26 indicates mild cognitive impairment, 11 to 20 indicates moderate cognitive impairment and 0 to 10 indicates severe cognitive impairment. These scoring categories were also the same for the TICS assessment administered at the six month stage.

Although two different exams were used, the TICS had similar scoring categories, had high correlation with the SMMSE and could be administered over the phone as well as face to face. There was a significant difference in cognition scores upon admission and at six months post-stroke (Wilcoxon Signed Ranks Test Z =-3.67, P<0.0001). The changes in the cognitive screening scores were analysed according to delirium diagnosis but did not indicate a change in cognitive impairment (Mann Whitney U Test, P<0.97) associated with the presence of delirium, that was statistically significant.

7.7 Conclusion

The stroke population investigated for this study was based in Leeds, West Yorkshire. Over a cumulative 14 month period, 1,253 new patients were admitted to the stroke units at the Leeds Teaching Hospitals Trust. Of this total, 298 stroke patients were recruited into this study by the researcher, producing a recruitment rate of 33%. These patients were then followed up for a one year period and during the follow up stages, only three participants refused any further assessments. There were a total of 72 deaths over the one year period. The study sample had a total delirium incidence of 32.9% and delirium positive patients were associated with higher mortality rates, a longer stay in hospital and increased requirements for some form of institutional care placements after discharge. The long term outcome measures such as physical function and risk of dementia were comparatively worse in the delirium group than the non-delirium group. Assessment of mood and change in cognitive impairment did not have a strong association with delirium diagnosis, the reasons for which are discussed in Chapter eight.

7.7.1 **Key points**

- Out of the 1,253 admissions, 298 patients were recruited for the stroke sample producing total incidence of delirium of 32.9%.
- Delirium positive patients were associated with a higher mortality rate compared to their non-delirium counterparts.
- Delirium patients were also found to have a longer length of hospital stay and increased need for institutionalisation.

- The study also identified a number of confounding variables that may impact on the presence of delirium. However it should be noted this was exploratory study only.
- Long term outcomes such as poorer physical function and increased risk of dementia were associated with a delirium positive diagnosis.

8 Discussion: Potential flaws

8.1 The systematic review

The systematic review was performed in June 2010 by a comprehensive search of the relevant medical literature databases as described in Chapter three. The search strategy (appendix 1) was developed by the researcher (S. Ahmed) with training and guidance from staff members at the University of Leeds Health Sciences library who specialised in systematic reviews. The search was conducted using the maximum number of medical databases that were relevant to the search topics of ‘delirium’ and ‘acute stroke’ in order to avoid missing any potentially relevant articles. However there is always the possibility that some articles may be missed as they have been not have been covered by the selected search terms or they may have been recently published. Furthermore in order to avoid compromising the sensitivity of the search, a decision was made not to narrow the search by using specific terms such as 'incidence', 'outcomes' and 'confounding variables and/or risk factors'. This produced a broad set of results, which were then analysed by the reviewer.

A possible second systematic review was considered in order to investigate which tools would be best suited to screen for delirium. This second systematic review would specifically focus on the feasibility of the screening tools with the possibility of rating the sensitivity and specificity of the tools currently available. However this was not done due to time restrictions and it was decided that the aims initially selected for the systematic review would be sufficient to inform the research questions and study design. Subsequently a systematic review analysing the suitability of the delirium tools currently available was published in 2013 by another research group[570]. All the abstracts identified by the database searches were reviewed by one reviewer (S. Ahmed) and ideally a second review would have been conducted by a separate independent reviewer. The second reviewer would have independently screened for relevance and fulfilment of the inclusion criteria to determine if the results were in agreement with the original reviewer. However due to limitations in time and resources, this was not possible.

The authors of the selected studies identified by the review were contacted by the reviewer (S. Ahmed) for clarification or additional information not stated in articles. An attempt was also made to obtain suitable translations for those studies not written in the English language. Furthermore the bibliographies of each article were checked to identify other studies that may have been missed by the electronic searches. Grey literature and thesis

materials were excluded from the review and it is possible that inclusion of these materials may have strengthened the search. A final step to strengthen the search would have been to conduct a manual hand search of journals relevant to the topics of delirium and acute stroke. Again due to limited time and resources this was not done, which may make the systematic review prone to publication bias by primarily relying on published journal articles. Subsequently the systematic review search was conducted again for publication in April 2014, which highlighted the journal articles[571-573, 226, 574-579, 243] that had been published since the last search in June 2010. This produced a further six distinct new study populations in addition to the twelve populations previously identified in June 2010. A meta-analysis was also performed for the April 2014 search as there was more data to analyse the findings in this topic area. A summary of the April 2014 search is discussed in Chapter nine (Section 9.4). Given the aforementioned explanations, I believe that this systematic review was adequate for the purposes of this thesis in providing information on which to base the research questions and study design.

8.2 The study sample and setting

As with any research, it is good practice to eliminate bias in the study design where possible and some of these sources of bias were discussed in Chapter five.

8.2.1 **Composition of the sample**

The composition of the study sample was of consecutive stroke patients admitted to the LGI over the age of 55 years. As discussed in Chapter seven, the primary reasons for exclusion were patients that were clinically unwell and therefore unable to complete the required assessments and patients that refused consent to participate in the study. Refusal of consent occurred for a number of reasons such as; patients did not want to be disturbed and wanted to be left alone during their stay in hospital stating ‘it was not for them’, patients that felt it would be too much of a burden considering their recent stroke diagnosis, patients that learned of the voluntary nature of the study and refused as they felt they would not gain any benefit from participating and finally patients that were wary of the research topic and what the results of certain assessments such as the cognitive exams could mean for them in the future. Regarding the last point, it is possible that certain patients that were suffering from delirium or dementia may have refused consent in the belief that they may have been

treated differently once assessed. Therefore by not participating in these assessments they avoided situations in which they may have felt isolated or uncomfortable.

The recruitment rate of 33% for this study may seem low in comparison to other published studies in this area. However, in addition to the comments made above, there are a number of other reasons that may explain this figure. The sample population consisted of very ill stroke patients with multiple co-morbidities who were often too physically ill to participate, some participants has severe communication problems and found it too difficult or tiring to participate, the voluntary nature of the study meant that the study was not given preference amongst the other ongoing research studies on the ward and many of the larger stroke based research studies did not allow for co-recruitment in order to avoid research fatigue in participants, participant recruitment was only conducted at one hospital site (LTHT) and lastly there was only one researcher (S. Ahmed) on the ward to screen, recruit and assess potential participants with very little input from the staff on the stroke unit staff as they were busy with their own day to day duties, which was as expected. Upon consideration of these factors, although the recruitment rate may not be as high as other published studies, it is understandable given the circumstances described.

With regards to previously published studies, the mean age of this study sample (79 years) is in keeping with published studies that were of a similar design. With regards to ethnicity, only 5 people (less than 2% of the study sample) were not Caucasian. The overall admission figures are in keeping with the published data that had a similar stroke services set up and the similar mortality rates are a likely indication that there were no differences in physical health between this study sample and the data of previously published studies.

The age and gender of the included study sample when compared to potential participants that were excluded showed no significant differences. This indicates there was no selection bias present as there was homogeneity between the excluded source population and in the included study population. As no other data were collected for the excluded population, a further analysis determining the homogeneity of the included and excluded populations could not be made.

It is possible that some potential patients may have been unintentionally missed due to reasons such as;

a) **Potential misdiagnosis**. Stroke is a medical emergency that requires immediate attention and with the recent stroke awareness campaigns it seems highly unlikely that a stroke could remain undetected. However it may be possible that certain patients with severe multiple co-morbidities as well as dementia and/or delirium could be missed by

staff as they may not be able to detect a significant change in their behaviour due to pre-existing conditions. Symptoms may also be mistaken for other neurological conditions and delays in CT and/or MRI scans may further delay the correct diagnosis, although these possibilities remain highly unlikely.

b) **The researcher**. Potential participants may have been missed as the researcher was primarily based on the acute stroke unit at the LGI, with regular visits to HASU to screen new patients as they arrived. With specialist stroke units set up at the LGI and the restructuring of the stroke services across both the LGI and SJUH sites, it is hospital policy that once a stroke diagnosis is confirmed, the patient is made a priority and is transferred to the stroke unit as soon as possible for specialist treatment. Therefore the ward registers on the stroke units were monitored on a regular basis to reflect this. It is possible however that a potential participant may have already been an existing inpatient being treated for another condition on another ward, where they remained for the duration of their stay and then subsequently discharged from that ward. It is also possible that the potential participants may have had a stroke after a surgical procedure which may have led to death or a possible transfer to the intensive care unit. As a result such cases may have been missed as they would not have been admitted to the stroke unit.

c) **Physical illness.** Potential participants were excluded if they had severe communication difficulties such as severe dysarthria, dysphasia, deafness or problems with their vision that prevented them from completing the study assessments. In some cases, where consent was obtained, these patients were included in the analysis of the incidence data but excluded in the analysis of the prognostic outcomes for the study as there were no baseline assessment scores for comparison. With regards to presence of delirium, certain cases also had to be excluded as these patients became emotionally distressed, not co-operative and in some cases patients displayed aggressive and threatening behaviours which made it inappropriate to approach them.

There is always a possibility that the delirium incidence in this study may have been underestimated. For example certain episodes of delirium may have been presented themselves in between the assessment timings specified in the study protocol and these episodes could have resolved by the time the researcher made the next repeat assessment. It is also possible that there may have been potential delirium cases in the excluded study population that were not screened and did not participate due to illness severity or refusal of consent. Overall, the admissions figures for the stroke unit in the year 2011 to 2012 were similar to the admissions figures supplied by the research stroke network for the year 2010

to 2011, as discussed in Chapter five. Bearing in mind the multiple co-morbidities associated with the stroke population and the limited resources available to the researcher, the selected study sample seems to be as inclusive as possible, thus suggesting a low recruitment bias.

8.2.2 **The study setting**

The study sample was acquired from only one site at the Leeds Teaching Hospitals Trust (LTHT). Acute stroke admissions were based at the Leeds General Infirmary (LGI) with further stroke rehabilitation services provided at St James University Hospital (SJUH) and Chapel Allerton Hospital (CAH). Although the use of only one study site could possibly affect the generalisability of study findings, the LTHT did offer a specialised stroke service. Currently emphasis is being placed on setting up specialised stroke services across the UK and efforts to raise the awareness of stroke amongst the general public is proving to be effective. The stroke policy at the LTHT is as follows. The Brain Attack Team (BAT) is led by Dr John Bamford and consists of a nurse specialist and a stroke nurse that are based in the A&E department at the LGI. Once the BAT team have assessed the stroke patients, those that are eligible for thrombolysis are typically recruited within the hour. If patients are not eligible for thrombolysis then they are transferred within four hours, to either the HASU or the ASU depending on the severity of their symptoms. If patients are admitted at the weekend or during the night and there is no senior registrar available, then they are seen by the on call SHO and transferred. A CT head scan is usually done with 24 hours of admission to exclude any signs of a haemorrhagic stroke and later a follow up MRI scan may be used to identify the site of the stroke or exclude other causes. As the patient recovers, they are either discharged accordingly or sent to stroke rehabilitation at either SJUH or CAH for further treatment, with follow ups with the community based rehabilitation teams if required after discharge. The setup at the LTHT is similar to many other hospital stroke services.

It is likely that models of care, specific stroke pathways and the management of stroke patients may differ slightly between hospitals. As the study recruitment only took place at one study site, it is difficult to determine what these differences in care provision may have been. With regards to recruitment at the Leeds Trust, there was a clear stroke pathway in place for the treatment and management of stroke patients, both for acute and rehabilitation purposes. As well as having communication with the physiotherapy and occupational therapy departments, the stroke team also had good communication with the neuropsychiatry and old age liaison psychiatry teams as well. This indicates that the staff

was aware of certain issues post-stroke and submitted referral requests as and when they were needed.

Originally two hospital trusts had been listed for study recruitment with the LTHT as the primary site and the BFHT as the secondary site. A number of back up sites had also been selected at Calderdale and Harrogate should they be needed if recruitment fell short of the specified target numbers. However once the study began, there were certain issues with recruitment at the BFHT site. The stroke units at the BFHT had a fewer number of beds which catered to a mix of conditions that included strokes, TIA's and other neurological conditions, whereas the LTHT had a separate neurology ward and a larger number of stroke beds available, as discussed in Chapter five. To add to this, there were a large number of research studies ongoing at the BFHT which meant that in many cases co-recruitment of patients was not possible and the stroke researchers were very cautious not to over burden patients by recruiting them into numerous studies.

Furthermore, the researcher had a better familiarity with the stroke protocol and an established network with the staff and departments at the LTHT where the initial pilot studies and researcher training took place. As there was only one researcher, there was a limit to how much could be done within a certain time period and it would have taken more time to develop this network at the BFHT. There would also have been an associated increase in the travelling time taken to commute back and forth between the two sites, a decrease in resources such as money (for parking) and time that would have been allocated to active recruitment, patient follow ups, admin and data analysis. The same reasoning would have applied to any of the backup sites based at Calderdale, Harrogate and Wakefield. A possible solution would have been to hire a research assistant to conduct some of the assessments but again this would cost in terms of time and money to train them. The introduction of a second assessor for the research could also have led to differences in patient interaction, variation in the screening and assessment protocols and the potential for variation in the results recording procedure, thus decreasing the reliability of the scoring process. However it has also been acknowledged previously in Section 5.5.8 that the use of only one assessor (S. Ahmed) may be a potential source of bias as the researcher would not have been blinded to the participant's diagnosis. It is possible that the presence or absence of certain conditions such as delirium may have influenced the scoring of the assessments and the generalisability of this study. Overall in order to avoid the aforementioned issues, a decision was made to concentrate solely on the primary site at the LTHT, where more time could be spent at the LGI to increase the study progress.

Each hospital serves specific areas and as the entire study sample was acquired from one site, the difference in certain variables could be significant between hospital catchment areas. If two or more study sites had been used, then differences in certain variables such as such as ethnicity or socioeconomic background could have been analysed to see if they had any effect on the results. However of the published studies, 12 of the research groups all recruited from only one site and so the recruitment practices of this study were in keeping with the published literature. The case mix of stroke type, time of assessment, scans and diagnosis, use of medications and the physical illness of the study sample were similar to the previously published data. It is therefore assumed that the results of this study can be generalised to other stroke service settings.

8.3 Recording the physical clinical factors

The data on the confounding variables based on physical clinical factors were well monitored and recorded. The CRF's designed for the study were based on the LTHT stroke proforma so much of the data could be extracted relatively easily from the medical notes. The date and time of scans, stroke type, onset of symptoms, past medical history specifically listing physical illness and recent surgery, number of medications, pre-stroke function, details of the clinical exam and current physical condition of the patients were completed in all the cases when the patient was clerked in. Less than 2% of the sample consisted of inpatient transfers from others wards and so although they did not have a completed stroke proforma, most of the information could be extracted from the medical notes, nursing notes and by accessing the scans and reports on the hospital server.

Where the patient was not a good historian, then alternative sources of information such as the patient's family or the staff at the institution placement were consulted for further information. As part of the admissions procedure, the patient's general practitioner was also contacted to obtain a complete medical history and an up to date list of medications. However it should be noted that in some cases although certain drugs were listed as regular medications, some of the patients admitted to not taking them as regularly or had stopped them altogether without consulting their GP. The reasons for this ranged from the presence of conditions such as dementia where the patient had been confused, to patients knowingly stopping their medications through their own personal choice. An effort was made to record the correct number of medications being taken, but this may not have always been accurate.

Other physical factors that were listed as confounders included; incontinence, constipation, malnutrition, dehydration, electrolyte imbalance, infection and hypoxia. Again these were generally well recorded and could be obtained from the nursing notes and from the hospital results server. Confounders such as malnutrition, incontinence and constipation were routinely monitored and recorded for the majority of patients whereas variables such as dehydration, electrolyte imbalance, infection and hypoxia were monitored and recorded according to the patient's needs. In Chapter six, the recording procedure for the presence of certain factors was categorised as positive if the cumulative time period lasted five days or more. It should be noted that for certain patients their total length of hospital stay was much shorter that the specified five day period. Upon checking the data, it was found that this was only true for less than 6% of the study sample and those that did have a shorter hospital stay often did not suffer from the confounding variables listed. The accurate monitoring and recording of the confounders was important in determining the relationship between the presence of delirium and confounding variables.

8.4 Recording the non-clinical and psychosocial factors

The data on the confounding variables based on non-clinical and psychosocial factors were again well monitored and recorded. Details of the patient's marital status, education, employment and history of mental health including pre-existing dementia and delirium were again routinely recorded in the LTHT stroke proforma. Dementia, depression and anxiety were often classed as a physical illness in the stroke proforma as well as in the mental health section. Details of the patient's education, employment and social support/ background were obtained during the patient interview and recorded for analysis using the scales described in Chapter six (appendix 21 and 22).

Details of the patient's accommodation were recorded in both the stroke proforma and the nursing notes. For analysis the data was divided into two main categories, which consisted of; living alone, with a partner or family or in sheltered housing as category one and living in an institutional placement such as a care home, residential home or nursing home as category two. An effort was made to determine whether certain institutional placements were classed as a nursing home or a residential home by contacting the staff. However this was not always straight forward as many institutional placements now provide patients with both nursing and residential care needs from the same placement site. It is due to this reason that all care homes, residential homes or nursing homes were classed as one category for analysis, a decision that could be criticised as being incorrect. Although the classification of

these confounding variables may not have been considered acceptable, every effort was made to make sure that the data was as accurate as possible.

8.5 Recording the delirium diagnosis

The diagnostic process of identifying delirium within this study population may have had some limitations. For example although the doctors on the ward did provide some diagnostic input, there were no independent evaluations carried out by specialist staff to assess delirium diagnosis. Furthermore a 'gold standard' diagnostic tool was not employed as a reference standard for comparison with the delirium tools chosen for this study. With regards to the detection and diagnosis of delirium, the CAM-ICU was used to screen for delirium whilst the DRS-R98 was used to assess the severity of delirium cases. These tools have been shown to have good sensitivity and specificity for delirium detection, as discussed in Chapter five. However it must be noted that these tools had not been specifically tested for use in the stroke population and prior to study recruitment no suitable tools had been tested and validated for this purpose[449, 450]. From the data and tools available during the design stage of the study, the CAM-ICU was chosen as the most suitable as it had been designed not to rely on verbal communication. When using the CAM-ICU firstly a check is made to determine the patient's response level by gently squeezing their hand. If they respond, then the test can continue but if they are unresponsive it is better try later on to see if there is any change in response levels.

With certain items of the tool, alternative approaches could be used in the screening process according to the patient's abilities. For example in the CAM-ICU feature two to test inattention (appendix 12), if the patient has limited speech then this item can be scored using the hand squeeze. Alternatively if the patient has limited movement post-stroke, then this item can be scored using the picture sets. Care was taken to use assessment aids that were printed in a large size, on buff coloured paper with a non-shiny finish in order to minimise any potential issues with vision. However there were still issues, as the CAM-ICU feature three to test disorganised thinking proved to be the hardest item to assess in non-verbal patients.

There will always be a certain number of patients where a complete assessment may not be possible. Furthermore a certain number of severely ill, non-testable patients may have had delirium but assessing this was difficult. Severely ill patients should be monitored regularly and in some cases during the night as delirium is a fluctuating condition and certain patients

display signs of delirium at night. However this was not possible due to limitations in resources. Furthermore a certain number of participants may not score positively on the CAM-ICU, as it is feasible that the cut off points for a positive diagnosis may have been set too high, making it harder to reach diagnostically. Despite not scoring highly positive on the CAM-ICU, these participants still exhibited signs of delirium and were included in the incidence figures. This is classed as sub-syndromal delirium, which was discussed previously in Chapter one (Section 1.1.2). In this study this was true for 20 patients who exhibited signs of sub-syndromal delirium, accounting for less than 7% of the study sample.

The DRS-R98 was completed for all participants as it relied on the information from the medical notes, staff on the stroke unit and the researcher's own observations. According to the literature, patients with the hypoactive type of delirium have the worst prognosis and are missed in about 75% of cases[27], as discussed in Chapter one. This is often due to similar presentations of hypoactive delirium, dementia and depression. In some cases delirium can be found super imposed on pre-existing dementia[157], making it difficult to make a diagnosis. In addition to this, the literature suggests that people with dementia may be much more susceptible to developing delirium, as previously discussed in Chapter one. Multiple diagnoses do exist in clinical practice but the primary focus of this study was to determine the level of delirium present in the study population. Only one researcher was used to administer the assessment tools which ensured that the assessments were conducted in exactly in the same manner. All four parts of the CAM-ICU were performed on all patients regardless of delirium diagnosis, at the same time points in the study in order to avoid bias. The assessment tools were well tolerated by the patients in this study.

For this study the CAM-ICU was administered by the researcher. However the fact that it is quick and easy to administer and is well tolerated by patients makes the CAM-ICU a good candidate to be incorporated into a possible standardised protocol for delirium detection, for which further research would be required. However the CAM-ICU on its own is not sufficient to provide further detailed information and so it is suggested that the combined use of the DRS-R98 with the CAM-ICU, would be a better use of the diagnostic tools. Although the DRS-R98 does not require much interaction with the patient, it does require the staff to take some time out to complete the assessment by examining the medical notes and nursing notes in more detail. There are many specialities within the medical profession and so not all staff will have been trained to detect subtle changes in psychiatric behaviour. This can be further demonstrated by examining the medical notes where often phrases such as 'remains pleasantly confused' or 'signs of disorientation/ confusion noted' are used to describe episodes of confusion with little indication regarding the onset or duration of the episode or very little or more often no further details or descriptions being recorded in the notes. With

this in mind, the introduction of a delirium screening and assessment tool as part of the admissions procedure would require a certain level of training in delirium detection for all staff. For the purpose of this study, the combined use of the CAM-ICU and DRS-R98 was sufficient for delirium detection in the stroke population and was in keeping with the types of assessment tools used in similar studies.

8.6 Post-admission outcomes

8.6.1 **Mortality over one year**

Of all the outcomes measures, mortality was the least susceptible to bias as it was unaffected by the study design. The date of death was easily derived from medical notes, contacting the patient's general practitioner or searching the hospital database which tracks the location of the patient's case notes, details of their admission to hospital and their survival status.

8.6.2 **Length of stay**

Inclusion of the patient into the study did not affect the clinical care received by the patients and the study did influence the treatment or management of patients in any way. The diagnosis of delirium was often made after consulting the staff who decided what course of action to take and whether any referrals needed to be made. Therefore the length of stay was independent of the study's primary aims. It was noted that the presence of delirium, pre-existing dementia or depression upon admission did increase the length of hospital stay, which in turn also impacted on the patient's possible need for an institutionalised placement in the future.

8.6.3 **Discharge destination**

Again similar to length of stay, the discharge destination of the participants was independent of the study's aims. An assessment of the patient's current state of health is often made with input from the patient's themselves, their family and the medical staff looking after them, in order to determine whether a patient requires an institutionalised care placement. The length

of stay is sometimes negatively affected in some cases, as patients may spend a longer time in hospital whilst waiting for confirmation of their care placement.

8.7 Outcomes six months post-stroke

8.7.1 **Physical function**

A pre-stroke score of physical function was recorded using the Rankin scale/ Oxford handicap scale in the stroke proforma with input from the patient and/ or the patient's carers. This method of retrospective data collection could be susceptible to recall error, especially in cases where the patient may be confused in which case, the input from the carer or staff from the care placements was used instead. The Barthel score was also used by staff upon admission to and discharge from the hospital. However, this assessment has a strong ceiling effect, which was previously discussed in Chapter five. An independent assessment of physical function was made prospectively by the researcher by administering the NEADL upon admission and then repeating the assessment at the six months after the stroke. Although the NEADL was an extra assessment to be administered to the patient, it was found to be well tolerated by the study participants and was completed by all but one participant.

8.7.2 **Risk of dementia**

According to the literature reviewed in Chapter one, patients with the hypoactive type of delirium have the worst prognosis and are missed in about 75% of cases. This is often due to similar the presentations of hypoactive delirium and dementia and in some cases delirium can be found super-imposed on pre-existing dementia, making it difficult to make a diagnosis. The literature also suggests that people with pre-existing dementia are much more susceptible to develop delirium. The nursing staff did not used any screening tools for dementia, but a note for pre-existing dementia was made in the patient's medical history as part of the stroke care pathway. For the purposes of this study, the dementia assessment was made using both the AD8 for patients and IQCODE for the carers. Both assessments were well tolerated and completed by all the participants.

8.7.3 **Assessment of mood**

Although the nursing staff did not use any screening tools for depression, a note of depressive episodes was made in the patient's medical history as part of the stroke proforma. Those that were thought to be at high risk were further assessed using mood screens such as the Wimbledon score[580], Signs of Depression Score (SODS) or Stroke Aphasic Depression Questionnaire Hospital version (SADQH)[581, 582]. During the study if a patient was showing signs of depression, a note of this was made in the nursing notes using phrases such as 'anxiety' or 'low mood' where no further details were given and perhaps further questioning may have been required. However referrals were made by the stroke team for these patients to be seen by clinical neuropsychology or the mental health team. For the purposes of this study, the GDS was administered upon admission to hospital and then repeated at the six month stage.

Only 6% of the study participants did not complete the GDS assessment at baseline as they were either unable due to illness, tiredness or were no longer interested in completing the assessment. This may have been due to length of the assessment and in hindsight the shorter version of the GDS, the GDS-15[583] may have been better tolerated. It is also possible that the nature of questions may have been upsetting for some participants and so they refused to answer any further questions at that time. Rating scales are effectively symptom checklists that are well tolerated, quick to administer and often used for research purposes. These scales can only provide a snapshot of how the participant is feeling at that point in time and not a complete in depth and accurate diagnosis. It is possible that a certain number of cases that scored positively for depression may not have been clinically depressed. Most likely these participants may have been temporarily suffering from an adjustment disorder after being diagnosed with a life changing event such as a stroke[584, 585]. As the patient's rate of recovery improves post-stroke, the depressive symptoms may also be short lived. However there may be true cases of clinical depression and so the study sample may have been a mixture of depression as well as short term depressive episodes related to the stroke.

8.7.4 **Cognitive impairment**

Upon hospital admission, the AMTS which has a maximum score of 10 was often administered by hospital staff to assess the patient's orientation to time and place. Further in depth assessment was then followed up by either an SMMSE or ACE-R depending on how compliant the patient was, and the results were recorded in the medical notes.

The use of the ACE-R was the measure that was the least well tolerated by patients in this study. This was often due to communication difficulties or visual issues that the patients were suffering from after having a stroke and therefore they were not able to complete the exam. On the other hand, a certain number of participants once the assessment had begun decided they no longer wanted to continue. Certain patients found to be showing signs of cognitive impairment, often refused to continue the assessments any further and asked the researcher to come back later as a way of avoiding any further questioning.

In addition to these issues, during study recruitment the occupational therapy team at the LTHT switched from using the ACE-R assessment to the MoCA[536] due to recent copyright and payment issues with the ACE-R/ MMSE[586]. The MMSE and MoCA have been shown to have good concordance[536] so this was not an issue. However, subsequently the team switched back to using the ACE-R/ MMSE after two to three months.

Changes in patient's ability post-stroke had been anticipated during the study design and there was a possibility that some measures such as the ACE-R assessment may not be fully completed during hospital admission for many participants. A measure of cognitive impairment that was independent of the delirium and dementia assessment tools was needed and so a backup assessment had been selected should the need arise. The SMMSE and the TICS assessments were used as alternatives in order to salvage some sort of measure of cognitive impairment for analysis. An issue with the SMMSE is that the test scores can be influenced by the patient's age and education levels, which can cause a variation in the scores[530].

Out of a study population of 298, only 66% (197 participants) completed the cognitive assessments in full both at admission and at the six month stage. This was clearly a smaller group of scores for the SMMSE/ TICS assessment analysis when compared to the other outcome measures analysed and could be a possible explanation for the lack of significant results for this outcome measure. An alternate explanation may also be that due to the significant degree of cognitive impairment post-stroke in the whole study group, any possible significant associations with the delirium diagnosis may be have been masked.

8.8 Conclusion

Efforts were made to minimise the effects of bias in the study during recruitment and data collection. However there were still some potential sources which may or may not have had an impact on the data collected and analysed in the study. This chapter described the

possible sources of bias and error and what was done before, during and after the data collection and analysis to minimise its effect on the results. The next chapter will look at the results in the context of the wider population and whether these results are generalisable to similar study settings and services.

8.8.1 **Key points**

- Taking into consideration the limited time and resources, the results of the systematic review were sufficient for the purposes of this thesis.
- The recording of the data for the physical clinical, non-clinical and psychosocial factors was relatively straight forward and was completed in full for the majority of participants.
- Mortality was the outcome that was least susceptible to bias.
- Measures for physical function, dementia risk and to some extent assessment of mood were generally well tolerated.
- Measures for cognitive impairment were not as well tolerated by study participants and an alternative measure had to be used in order to obtain usable data for this outcome.

9 Discussion: Study findings

9.1 Diagnosis of delirium

This prospective cohort study was the first UK based one year follow up study to investigate delirium incidence in acute stroke. The study employed patient and carer interviews with standardised diagnostic tools to determine the incidence of delirium and its impact on long term outcomes for patients, in the acute stroke population. With a study sample of 298 patients, the delirium incidence of 32.9% was in keeping with the incidence rates found in the published literature of delirium and acute stroke which ranges from 10 to 48%[61, 443-447, 111, 448, 47, 449, 450, 197, 451, 452] and including the newer studies which have been published since this study began[571-573, 226, 574-579, 243]. The meta-analysis performed for the April 2014 search results, gave an average incidence of 23.7%.

The combined use of the CAM-ICU and DRS-R98 was not specifically tested and validated for use in the stroke population when this study started recruitment in July 2011. However the majority of the newly published studies in this area employed similar tools for delirium detection. Upon reviewing the literature, this study found that the use of the CAM-ICU for screening and the DRS-R98 for further diagnosis, proved to be an effective combination to determine delirium incidence in the stroke population. With regards to the use of the CAM-ICU in the stroke population, some adjustments such as the use of assessment aids e.g. visual response/ cue cards, were employed as communication aids in order to assess patients as effectively as possible after a stroke.

Although the CAM-ICU and DRS-R98 have shown good sensitivity and specificity for delirium detection in other non-stroke settings, it must be noted that this study was not a validation study. Therefore no analysis of the tools was made in this regard for use in the stroke population. Since this study began, a systematic review has been published analysing the suitability of the range of delirium tools available for use in stroke[570], concluding that the CAM and the DRS were the most commonly used research tools. The same research group also conducted a survey investigating the delirium screening practices in stroke amongst hospital staff in Scotland[587]. The survey highlighted inconsistencies in delirium screening in the Scottish stroke services and the uncertainties of the staff regarding the most suitable delirium tools for use in stroke. Lees et al, reviewed a number of screening tools in a sample of 111 stroke patients[588]. Their analysis concluded that the 4AT[589] was a suitable choice for delirium and cognitive screening, however it should be noted that the comparisons were

based on the standard MOCA diagnostic threshold and may not be applicable to the stroke population.

Subsequently the CAM-ICU has been validated for use in stroke, exhibiting high sensitivity and specificity with good inter-rater reliability and accuracy[575]. Recommendations were made by the research group to conduct serial screenings for delirium and preferably starting screening much earlier e.g. the day after stroke onset. In addition to this, a new variant of the CAM has been developed by Inouye et al. The CAM-S[590] has strong psychometric properties and can now measure the severity of a delirium episode, in comparison to the previous versions of the CAM that could only be used for delirium screening.

9.2 Admission outcomes

9.2.1 **Mortality**

Although no difference was seen at the twelve month follow up, the mortality rates at the one and six month follow up period were significantly higher in the delirium group compared to the non-delirium group. There was a difference between groups at twelve months (34.7% delirium, 19% non-delirium), but this difference did not reach significance. The only other one year follow up study data for comparison was published in 2006[452], although the total percentage of deaths in this study (72 out of 298 participants, 24.2%) was similar to the study by Sheng et al (34 out of 156 participants, 23.8%). Since then subsequent studies, which have previously been highlighted in Chapter eight, have published data that also follow a similar trend regarding mortality with similar confidence intervals[443, 446-448, 47, 571, 449, 450, 226, 574-577, 452]. This will be discussed further in Section 9.4.

9.2.2 **Length of hospital stay**

Patients with delirium spent a significantly longer period of time in hospital (38.5 days) when compared to their non-delirium counterparts (21.5 days). The presence of delirium had a negative effect on the length of stay. Again, this is in keeping with the published literature in this area and of the research groups[445, 111, 448, 47, 449, 450, 575-577, 452] that recorded length of stay

9.2.3 **Discharge destination**

When compared to the existing living arrangements prior to hospital admission, the delirium positive group of patients were less likely to return to their original accommodation and the presence of delirium increased the likelihood that the patient would require some form of institutional care placement. Furthermore the measures of physical function were linked to the need for future care placements, as patients that scored lower on the ADL scales were highlighted with an increased need for care than previously provided. Despite its strong ceiling effect, a Barthel score was often administered by the hospital staff prior to hospital discharge in order to identify the care needs of the patient. Again this was in keeping with the majority of the published literature[448, 47, 449, 450, 576, 452] which also recorded discharge destination.

9.3 Outcomes six months post-stroke

Despite the number of deaths (72 in total), and the dropouts, and graded participation chosen by three participants (1%), the remaining study sample was sufficiently large to form reliable conclusions. Although there were valid reasons provided for the slightly lower recruitment rates (33%) when compared to other published studies, steps had been taken to reduce any potential bias and there is evidence that the recruited patient group was representative of the larger stroke population.

The confounding factors were not adjusted for when analysing the outcomes between delirium positive and delirium negative groups. The primary hypothesis that delirium patients had an increased risk of mortality was supported by the study data. The secondary hypotheses regarding increased length of stay and an increased need for a future institutionalised care placement again were both supported by the study data. For this study, long term outcomes such as physical function, future risk of dementia, assessment of mood and changes in cognitive impairment were also analysed. This study aimed to provide a comprehensive long term follow up of outcomes at six months. At the time of commencing this study, good quality data on long term outcomes in the published literature were lacking, with only a select few studies providing a comprehensive follow up after discharge such as Henon et al[47], McManus et al[449, 450] and Sheng et al[452].

There are several ways in which the presence of delirium could affect patient outcomes post-stroke. In this study sample, poorer physical function was associated with the presence of delirium. Physical function was also often used as an indicator for the need for future

placement in institutionalised care. The presence of delirium suggests an underlying physical illness which if left untreated can add to existing co-morbidities in the patient. The symptoms of delirium can also interfere with the treatment of stroke, leading to poorer long term outcomes for delirium positive patients.

The risk of dementia did increase with the presence of delirium and this finding was statistically significant for both of the tools used. Although there was a significant difference between scores at baseline and at six months, the presence of cognitive impairment was not significantly higher in the delirium group compared to the non-delirium group. Patients with delirium can display behaviours such as inattention, disorganised thought processes and memory impairment which can interfere with their recovery and rehabilitation. Unfamiliar surroundings and people can also increase levels of confusion and in cases of hyperactive delirium; aggressive or violent behaviours can act as a barrier and prevent staff from aiding the patient's recovery process.

Regarding the assessment of mood, although there was significant difference between scores at baseline and at six months, delirium positive patients were not associated with higher GDS scores. As discussed in Chapter eight, it is possible that some patients may be displaying signs of a short term adjustment disorder after as stroke as opposed to clinical depression. The impact of a stroke coupled with poor physical health and the presence of delirium can cause a lack of motivation which may affect the patient's mental and physical recovery.

With regards to the confounders, a number of variables were taken into account when analysing the differences between the delirium positive and delirium negative groups. With regards to assessing risk factors independently, the study sample may be seen as inadequate due to the number (n = 298). However this part of the study was always regarded as an exploratory study rather than a definitive risk factor study aimed at producing a delirium risk factor predictor model. A number of confounders were found to associated with the presence of delirium and it is possible that certain confounders could combine together to increase the likelihood of certain outcomes such as poor physical function or cognitive impairment. As delirium is an indicator of underlying physical illness, by alleviating and improving certain confounding variables upon admission, there may be a possibility to improve the long term prospective outcomes for patients with delirium.

9.4 Comparisons with the published literature

The systematic review in Chapter three identified a need for a UK based study that recruited a prospective cohort of stroke patients, representative of the population being studied with a long term follow up period and the use of suitable diagnostic instruments. At the time of designing this study, no delirium instruments had been validated for use in the stroke population. This was reflected in the published literature as the majority of research groups used tools such as the DSM criteria, the DRS or the CAM with some studies opting to the use the MMSE. The MMSE as mentioned previously is not an appropriate screening tool for delirium. McManus et al[449, 450], used the CAM to screen for delirium whilst Sheng et al[452] used the DSM, with no groups assessing severity. A systematic review of the published literature concluded that it would be better to use two tools in combination with each other. The addition of DRS-R98 would be used to measure severity whilst CAM-ICU as a screening tool would be better suited for this study as it did not rely on verbal responses and so it could accommodate stroke patients. Both tools had shown good concordance with each other in a general medical setting and as mentioned previously, the CAM-ICU has now been validated for use in stroke[575].

Of the studies included in the systematic review, the majority of the research groups only assessed outcomes up until discharge. With regards to long term outcomes, very few studies provided a comprehensive long term follow up after discharge. These included McManus et al[449, 450] at one month, Henon et al[47] at six months with Sheng et al[452] as the only research group to provide a full one year follow up. For this study although a full twelve month follow up was planned in the initial stages, time restrictions meant that a compromise had to be made in the study design. Therefore a comprehensive assessment of outcomes was made at six months, with only a mortality check being performed at twelve months. Had there been sufficient time, then a full follow up of physical function, mood assessment, dementia risk and cognitive impairment could have been conducted at the one year stage.

The systematic review search conducted in April 2014 highlighted eleven new papers that had been published since the last search conducted in June 2010. A summary of these recently published studies can be found in Figure 9.1 and Figure 9.2. In certain research groups, further analysis had been conducted using the same stroke populations previously identified in the June 2010 search. This was true of the research groups McManus et al[449, 450, 226] and Oldenbeuving et al[577, 578, 197, 579, 243]. As a result the April 2014 search identified six new study populations in addition to the twelve previously identified in June 2010.

Author and country	Study design and setting	Sample (M = male, F = female, Age = mean age)	Recruitment criteria (I = Inclusion, E = Exclusion)	Assessments	Occurrence of delirium	Risk factors
Oldenbeuving, 2011 *(The Netherlands)*	Prospective cohort Stroke unit	630 admitted, 527 recruited 62 delirium *(38M, 24F) Age = 78* 465 non-delirium *(250M, 215F) Age = 71*	I: Consecutive stroke (CI or IH) E: SAH, TIA, <18 years of age (Oldenbeuving, 2008 cohort)	CAM (admission, day 2-4 & 5-7) DRS (daily for delirium) NIHSS (admission) IQCODE (admission)	11.8%	IQCODE> 50, right sided lesion, anterior circulation large vessel strokes, infection and NIHSS score, cortical atrophy
McManus, 2011 *(UK)*	Prospective observational Stroke unit	110 eligible, 82 recruited 23 delirium *(15M, 8F) Age = 75* 59 non-delirium *(36M, 23F) Age = 63*	I: Stroke (CI or IH), delirium assessment within 4 days, E: SAH, GCS score <8, delirium < 24 hrs, English speaker (Follow up for McManus, 2008, 2009 cohort)	CAM (4 days & then weekly) IQCODE (admission)	28%	-
Van Rijsbergen, 2011 *(The Netherlands)*	Retrospective case control Hospital based	527 original cohort, 50 recruited (62 delirium, 465 non-delirium) 22 delirium *(11M, 11F) Age = 75.8* 28 delirium *(18M, 10F) Age = 74.6*	I: cohort 2 year follow up, age, sex and stroke matched E: death, poor health (Sub -study of Oldenbeuving, 2011 cohort)	Delirium assessments already conducted CDR and Rotterdam CAMCOG (upon sub-study recruitment)	11.8%	-
Kostalova, 2012 *(Czech Republic)*	Prospective observational Stroke unit	275 admitted, 197 screened, 119 recruited, 100 assessed 43 delirium *(24M, 19F) Age = 80* 57 non-delirium *(30M, 27F) Age = 73*	I: Stroke (CI or IH), delirium assessment within 24 hrs, E: SAH, head trauma, brain tumour, neurosurgery, comatose, psychosis, non-Czech speaker	DSM-IV (daily in 1st week) CAM-ICU and RASS (daily) NIHSS (admission)	43%	Older, pre-stroke dementia, ICH, lesions> 40cm, anticholinergic meds, TACI strokes and metabolic disorders (RF's for poor CI at follow up)
Melkas, 2011 *(Finland)*	Prospective cohort Hospital based	1622 admitted, 642 eligible, 486 recruited, 263 assessed 50 delirium *(26M, 24F) Age = 72.5* 213 non-delirium *(109M, 104F) Age = 70.4*	I: Stroke (CI only) E: SAH, IH, incomplete assessments	DSM-IV (days 1 to 7) MMSE, ADL, IADL, BI, Blessed functional activity scale (admission)	19%	Pre-stroke cognitive decline, severe stroke and low education

Figure 9.1: The incidence of delirium in stroke populations identified in the April 2014 search.

CI: Cerebral Infarction, IH: Intracerebral Haemorrhage, SAH: Subarachnoid Haemorrhage, TIA: Transient Ischaemic Attack, MMSE: Mini-Mental State Examination, CAM: Confusion Assessment Method, DRS: Delirium Rating Scale, DSM: Diagnostic and Statistical Manual, ADL: Activities of Daily Living, BI: Barthel Index, IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly, GCS: Glasgow Coma Scale, MRS: Modified Rankin Scale

Author and country	Study design and setting	Sample (M = male, F = female, Age = mean age)	Recruitment criteria (I = Inclusion, E = Exclusion)	Assessments	Occurrence of delirium	Risk factors
Mitasova, 2012 *(Czech Republic)*	Prospective observational Stroke unit	331 admitted, 236 screened, 151 recruited, 129 assessed 55 delirium, 79 non-delirium *(72M, 57F) Age = 71.2*	I: Stroke (CI or IH), delirium assessment within 24 hrs E: SAH, head trauma, brain tumour, neurosurgery, comatose, psychosis, non-Czech speaker	CAM-ICU, DSM-IV (daily) NIHSS, SOFA, Blessed dementia rating scale and Mississippi aphasia screen test (admission) BI (week 1 and 6 months)	42.6%	-
Miu, 2013 *(China)*	Prospective cohort Stroke unit	314 recruited 86 delirium, Age = 78.8 228 non-delirium, Age = 70.7	I: Stroke (CI or IH) E: TIA, stroke due to cerebral venous thrombosis, severe trauma, neurosurgery, age <50 years, GCS <5	CAM (daily day 1 to 5) Charlson Comorbidity Index (CCI), NIHSS, IQCODE (admission) MRS and BI (admission and 6 months)	27.4%	Stroke aetiology/location, medical complications, pre-existing cognitive impairment, visual neglect and dysphagia
Oldenbeuving, 2013 *(The Netherlands)*	Prospective cohort Stroke unit	527 original cohort, (62 delirium, 465 non-delirium) 353 recruited	I: Existing cohort, patients with genomic DNA isolation data E: death, poor health (Sub -study of Oldenbeuving, 2011 cohort)	Delirium assessments already conducted	11.8%	-
Kara, 2013 *(Turkey)*	Prospective cohort Hospital based	150 recruited 42 delirium *(30M, 12F) Age = 68* 108 non-delirium *(75M, 33F) Age = 61.2*	I: Stroke (any type) E: Comatose, severe aphasia	DSM-IV, DRS (daily 5 day) NIHSS, IQCODE (admission)	28%	Ischaemic heart disease, anticholinergic meds, haemorrhagic, TACI and cardioembolic strokes
Kutlubaev, 2013 *(Russia)*	Prospective cohort Neurovascular unit	271 admitted, 96 recruited 22 delirium (8M, 14F) Age = 74 74 non-delirium (42M, 32F) Age = 66	I: Stroke (CI or IH), delirium assessment within 3 days E: SAH, TIA, comatose, history of psychiatric illness	DSM-IV (within 3 days) NIHSS, MRS (admission)	22.9%	Old age, severe stroke, chronic cerebral changes, fever, catheterisation and positive snout reflex
Oldenbeuving, 2013 *(The Netherlands)*	Prospective cohort Hospital based	527 original cohort, (62 delirium, 465 non-delirium) 273 validation set, 15% delirium (131M, 142F) Age = 72	I: Consecutive stroke (CI or IH) E: SAH, TIA, <18 years of age (Sub -study of Oldenbeuving, 2011 cohort)	Delirium assessments already conducted	11.8%	-

Figure 9.1: The incidence of delirium in stroke populations identified in the April 2014 search – continued.

CI: Cerebral Infarction, IH: Intracerebral Haemorrhage, SAH: Subarachnoid Haemorrhage, TIA: Transient Ischaemic Attack, MMSE: Mini-Mental State Examination, CAM: Confusion Assessment Method, DRS: Delirium Rating Scale, DSM: Diagnostic and Statistical Manual, ADL: Activities of Daily Living, BI: Barthel Index, IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly, GCS: Glasgow Coma Scale, MRS: Modified Rankin Scale

Author	Occurrence	Outcomes	Confounding variables	Quality of study
Oldenbeuving, 2011 *(The Netherlands)*	11.8% delirium	Lower BI scores and unfavourable outcomes (death or low BI) at 1 month Longer hospital stays (23.7 days Vs 13.9 days) High inpatient mortality (19.4% Vs 6.5%)	Age, NIHSS score, TACI and PACI strokes, right sided lesion, high IQCODE, cortical atrophy, infection and metabolic disorders associated with delirium.	High
McManus, 2011 *(UK)*	28% delirium	Inpatient mortality (30.4% Vs 1.7%) 1 year mortality (25% Vs 7.4%) 2 year mortality (8.3% Vs 10.2%)	Age and delirium significantly associated with inpatient mortality. Age and pre-stroke cognitive decline significant for 1 year mortality and only cognitive decline for 2 year mortality.	High
Van Rijsbergen, 2011 *(The Netherlands)*	11.8% delirium	Delirium is an independent predictor of dementia onset 2 years post stroke Delirium patients have 5 to 7 fold increased risk of dementia	CDR: delirium, metabolic disorders, infection, cerebral atrophy, and white matter changes associated with dementia and delirium and cerebral atrophy were independent predictors. CAMCOG: Delirium, females and lower education associated with dementia and delirium and female independent predictors.	Medium
Kostalova, 2012 *(Czech Republic)*	43% delirium	Delirium duration 5 days (range 1-28) Risk prediction model produced	Older, pre-stroke dementia, chronic alcoholism, elevated GGT, thrombocytopenia associated. Hyponatremia, high creatinine and high bilirubin more frequent in delirium. ICH, NIHHS >10, lesion >40cm, TACI strokes, SOFA score and metabolic disorders.	High
Melkas, 2011 *(Finland)*	19% delirium	Delirium increases onset of post-stroke dementia at 3 months Shorter survival (6.1 years Vs 9.1 years)	Low education, severe stroke and pre-stroke cognitive decline associated with delirium. Age, post stroke dementia and stroke severity associated with poor survival.	High

Figure 9.2: The outcomes of post-stroke delirium studies identified in the April 2014 search.

Author	Occurrence	Outcomes	Confounding variables	Quality of study
Mitasova, 2012 *(Czech Republic)*	42.6% delirium	BI lower as inpatient and at 6 months Delirium duration 4 days (range 1-28) Longer stay (18 days Vs 12 days) median High 6 month mortality (23.6% Vs 14.9%) Validation of CAM-ICU for use in stroke	-	High
Miu, 2013 *(China)*	27.4% delirium	Poorer functional mobility and physical performance at discharge, 6 months and 12 months post-stroke Longer stay (45 days Vs 22.1 days) High institutionalisation (62.3% Vs 11.2%) High inpatient mortality (18.8% Vs 2.2%) High 1 year mortality (30.2% Vs 7.4%) 1 year survival (281.65 days Vs 348.7 days)	Age, NIHSS, urinary retention, chest infection, previous cognitive impairment, TACI and POCI strokes as predictors for delirium. Age, CCI, large area of infarct, dysphagia, visual neglect, fever, urinary tract infection, chest infection and pre-existing cognitive decline associated with nursing home placement at 1 year. Age, CCI, dysphagia and chest infection independent predictors for mortality at 1 year.	High
Oldenbeuving, 2013 *(The Netherlands)*	11.8% delirium	No association between APOEe4 allele and occurrence of post-stroke delirium No difference in duration of delirium	No association with any of the variables tested.	Medium
Kara, 2013 *(Turkey)*	28% delirium	Low BI scores High inpatient mortality (71.4% Vs 28.6%)	NIHSS, pre-stroke cognitive decline, high IQCODE scores, advanced leukoaraiosis, high CHIPS score, ECG (high amplitude diffuse slow disorder), metabolic and infectious disorders all associated with delirium.	High
Kutlubaev, 2013 *(Russia)*	22.9% delirium	Lower MRS scores Chronic brain changes and stroke complications risk factors for delirium	Old age, severe stroke, cerebral changes, fever, catheterisation, positive snout reflex likely to develop delirium. Severity of posterior leukoaraiosis independent predictor of delirium onset.	High
Oldenbeuving, 2013 *(The Netherlands)*	11.8% delirium	Risk prediction model produced to predict delirium in 1st week of admission based on age, stroke severity/ subtype and infection	-	High

Figure 9.2: The outcomes of post-stroke delirium studies identified in the April 2014 search – continued.

From the newer literature published, Kostalova et al[572] focused on producing a risk prediction model and therefore did not record any follow up outcomes. Kara et al[571] and Kutlabaev et al[573] only analysed outcomes during the participant's stay in hospital and upon discharge. The groups Oldenbeuving et al[577], recorded follow up outcomes till one month, Melkas et al[574], investigated outcomes till three months and Mitasova et al[575], analysed outcomes till six months post-stroke. McManus et al[226], provided further analysis for mortality one to two years after a stroke using their existing cohort. Miu et al[576], was the only new research group to provide a full one year comprehensive follow up. Almost all the new studies provided data on risk factors, outcome predictors and/ or confounding variables. The only exception to this were the studies by Mitasova et al[575], which was primarily a validation study and Oldenbeuving et al[578], (a sub-study of a previous paper) which focused on producing a delirium risk prediction model.

A meta-analysis was also performed to analyse mortality, institutionalisation and length of stay, the results of which are shown in Figure 9.3. It should be noted that certain research groups did not provide complete data for certain outcomes and/ or did not quantify sub-group sizes. As a result the data for these studies could not be included in the analysis. In order to make comparisons with the published literature, the data for this study (marked as Ahmed 2014) was also included in the analysis. The funnel plots and the results of the original meta-analysis performed on only the published literature have also been included (appendix 23).

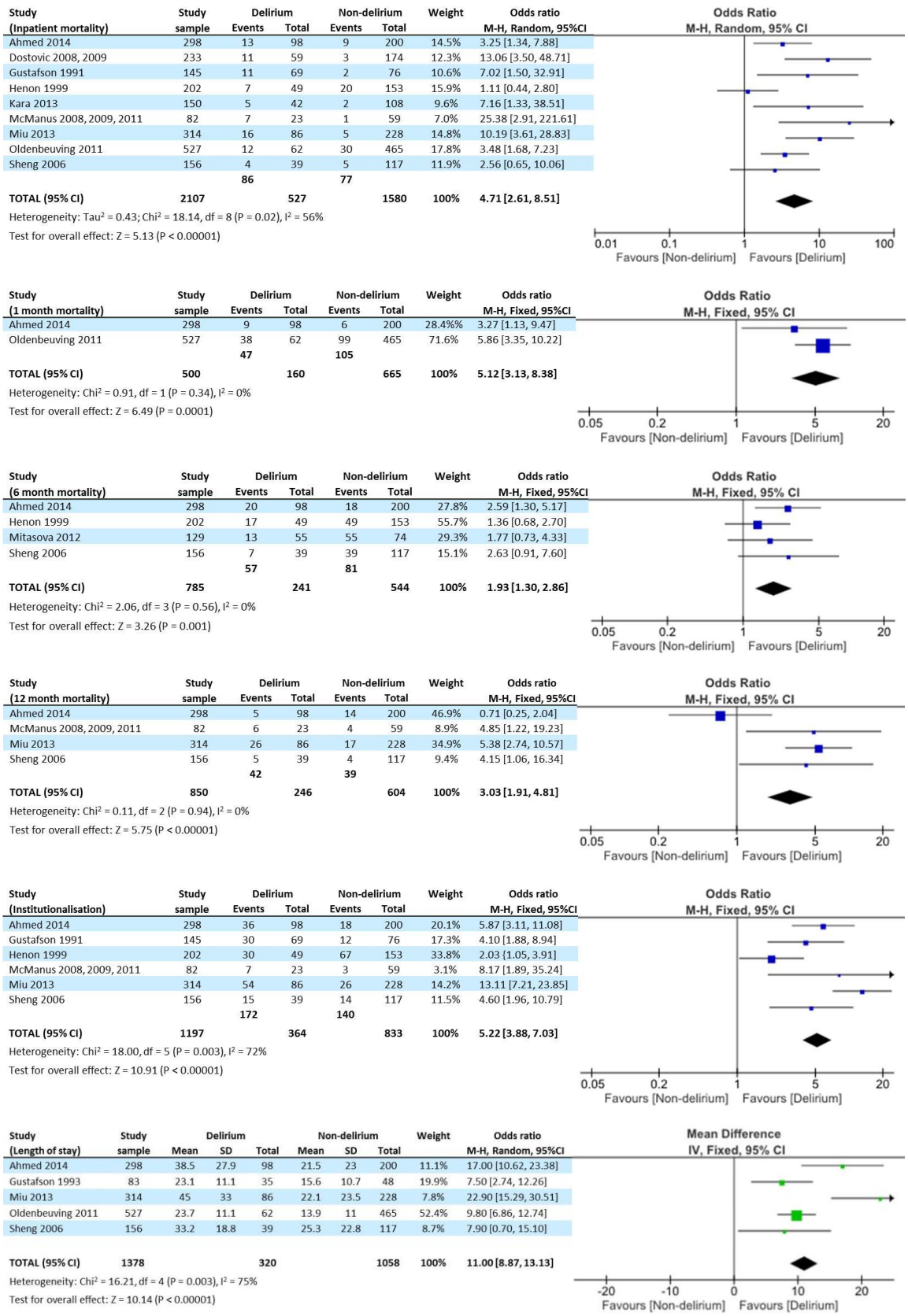


Figure 9.3: Results of the meta-analysis performed for the April 2014 search.

To allow comparisons with the published literature identified by the systematic review, the data for this study has also been included in the comparison and is marked as Ahmed 2014.

With regards to the composition of the sample, the mean age of previously published literature ranged from 55 to 79 years, with 74 years as the median age. This study had a mean age of 79 years which was in keeping with the published literature and representative of the elderly stroke population being studied. Age was a key factor in the representation of the sample as presentation of physical illness in the elderly is significantly different to that of younger adults. There are also implications regarding quality of life as the elderly population unavoidably have an increased incidence and prevalence of illness. Less strict exclusion policies were also used in this study with only age (55+ years), stroke diagnosis and sufficient health to participate as the main points upon which study recruitment was made. To conclude, every effort was made to conduct a successful long term follow up study that investigated the incidence of delirium in stroke using appropriate diagnostic tools suited to the participant's needs, with a study sample that was representative of the stroke population.

9.5 Implications for future research and clinical practice

9.5.1 **Areas of further research for delirium and stroke**

The incidence of delirium in stroke in the published literature ranges from 10 to 48% with the April 2014 meta-analysis producing an average incidence of 23.7%. There were, and still are, a number of obstacles ranging from; ethical considerations, capacity, unsuitable assessment tools and lack of studies, instrument suitability to variations in age, gender and stroke type for sample cohorts and the wide variation in exclusion criteria set by research groups. With regards to the confounders data analysed in this study, the results of this group of variables could be used as a pilot study to power a larger risk factor study with the end point of possibly generating a predictive delirium risk factor model such as the model by Inouye et al[54]. Since this study began other research groups such as Carrasco et al[63], have also produced delirium predictive models for use in the elderly, whilst groups such as Kostalova et al[591, 572], and Oldenbeuving et al,[578] have focused on producing a predictive model specifically for post-stroke delirium.

With regards to suitable assessment tools, a recent systematic review[570] by Carin-Levy et al, was published listing the various delirium tools that are currently available and analysing their strengths and weaknesses for use in the stroke population. The review also collated information on incidence rates and outcome predictors as well, helping to consolidate the slowly growing body of literature being published on post-stroke delirium. Recently the CAM-ICU was validated for use in stroke by the research group Mitasova et al[575]. The research

group tested the delirium instrument in a stroke setting and found that it had good inter-rater reliability, sensitivity, specificity and accuracy. The adoption of a validated stroke specific detection tool for delirium by research groups will help to standardise the reporting of post-stroke delirium incidence, thus allowing better cross comparisons between future studies. Issues such as cohort homogeneity, possibly produced by unnecessary strict exclusion criteria[251, 252] are still an issue, but these may improve as better standardised incidence and outcome studies are published. The increased levels of mortality and morbidity associated with post-stroke delirium[228, 226, 574, 592] should be considered when calculating sample sizes so that the analysis and results of future studies are adequately powered.

Some studies have shown that admission from an institutionalised care placement seems to be a significant delirium risk factor[232]. In some cases it was suggested that delirium may be present upon admission rather than after admission, possibly in the form of delirium superimposed on dementia[158]. Incidence studies based in community settings could help to clarify this situation[81, 593]. If incidence rates were found to be significantly high in care settings, then it may worth considering conducting a trial evaluating preventative delirium measures in the community. It may also be beneficial to collaborate with GP's for data collection and relay any information on delirium diagnosis back to the community so that they can be continued to be monitored once discharged from hospital. Another area of delirium research that has been ignored in larger cohort studies is the psychological aspect of delirium both at admission and follow up. As discussed in Chapter two, stroke survivors often suffer from adjustment reaction disorders, emotional changes and depression after a stroke[585, 594, 218]. The after effects of stroke coupled with episodes of delirium could result in a significantly poorer prognosis for patients. Delirium symptoms often overlap with signs of dementia and depression[145]. This can make a differential diagnosis challenging as evidenced by the numerous single case reports examining these occurrences. It would be beneficial to assess and follow up the occurrence of depression as well as dementia post-stroke[595] and delirium on a larger scale and to further explore the implications of whether the patient's psychological status may have a potential effect on these outcomes.

9.5.2 **Delirium as an outcome measure for future studies**

In research studies outcome measures such as mortality, functional ability and cognitive impairment are just some of the measures that are commonly used[410, 406]. They are used as markers to measure a patient's progress or deterioration and there are number of well validated assessments tools that facilitate this process. It may be worth considering

implementing delirium as an outcome measure[430, 596] that would be routinely used in research studies, specifically in the area of stroke. For example the incidence of delirium is routinely analysed in many hip fracture studies and a similar study design could be implemented for stroke research. Delirium is caused by an underlying physical illness and a significant number of these conditions are reversible. For example, avoiding malnutrition and dehydration[597], treating conditions such as incontinence and constipation efficiently[59] and quicker mobilisation strategies for patients post-stroke[363, 373] could all help improve the patient's level of health. These conditions are common after stroke and are also contributing factors for delirium onset. Therefore by promoting better quality care in medical settings and treating such conditions more efficiently would also mean a decrease in the occurrence of post-stroke delirium. The lower delirium rates in stroke units could be seen as providing better care for patients. In effect measurement of delirium occurrence would no longer be the objective of future research studies but instead delirium would be seen as a marker of better good quality care in studies. In order to implement this, the use of a stroke validated delirium tool such as the CAM-ICU[575], would need to be adopted and employed in stroke units as part of the standard admissions pathway.

9.5.3 **Detection and treatment of delirium in stroke**

This study has shown that delirium is commonly present within the acute stroke population and can have an adverse effect on several patient outcomes. Delirium is regarded as an indicator for an underlying physical illness and by not identifying and treating the cause might result in poor prognosis for the patient, as evidenced by the published literature. Therefore it is assumed that the increased physical illness in patients can increase the occurrence of delirium. With regards to post-stroke complications, conditions such as pneumonia (due to an unsafe swallow and immobility) or pulmonary embolism (due to immobility) are common and have also found to be predictors of delirium[598]. Pneumonia and pulmonary embolism are given greater emphasis in stroke and have national programmes highlighting the need for efficient management of such conditions[270, 271]. It may be considered that the incidence of post-stroke delirium may have a higher incidence in comparison to other conditions such as pulmonary embolism and so it could be worthwhile implementing similar national programmes for delirium. However a further risk factor study would be required to explore these factors and investigate this topic in further detail.

With published incidence rates ranging from 10 to 48%, as well poor outcomes, it is clear that delirium has the potential to increase the workload of hospital staff if left untreated. This

would also lead to an increase in referrals to psychiatry and the mental health team, increasing their workload. Although a number of clinicians are aware of what delirium is, the majority of staff are still unaware and not educated in detecting the signs of delirium[169, 599]. This leads to many cases remaining undetected, mistaken or misdiagnosed. Even in places when detection is common, little action may be taken due to lack of staff understanding and awareness of how to treat a case of delirium[587]. As a result delirium is a common occurrence in many of the referrals sent to psychiatry services and approximately 10% of referred patients exhibited signs of delirium[600].

Psychiatric input may involve assessing the patient's cognition, making a differential diagnosis where dementia or depression may be present, identifying the symptoms and their cause, treatment and how best to manage the patient[600, 32]. Good communication is necessary between the various teams involved in the care of patient as each have their own area of expertise. Many reviews have indicated the need for the better systematic prevention and management of delirium by identifying key risk factors and how best to minimise them to avoid hindering patient progress[187]. There are a number trials evaluating prevention intervention measures in care homes'[81, 593], across various hospitals settings[131] (as described in Chapter one), to improve communication with the patient's families/ carers[179] and to increase the awareness of clinical staff[425].

The need to implement these measures alongside decreasing conflicting definitions, standardising terminology[601] and better screening procedures in clinical practice is evident[83]. Future research contributions to the pathophysiology of delirium[602, 109] to identify/ develop treatments as well as the development of risk prediction models[63, 54, 591, 572, 578] will help to improve the detection and management of delirium in stroke. With regards to training, the published literature shows that improvements in geriatric medicine translate to better outcomes for the elderly population and the routine use of tools such as the Comprehensive Geriatric Assessment (CGA) can improve patient outcomes[140, 603]. As both delirium and stroke have been strongly associated with an increase in age, introducing the routine use of an assessment such as the CGA may be beneficial. The assessment, when administered upon admission to the stroke unit, could help to highlight key issues earlier on facilitating the efficient and effective management of the patient. Suggestions have also been made for improvements in the geriatric medicine training provided for junior doctors[604] and a recent study by Jenkin et al,[605] showed a small increase in delirium knowledge and awareness associated with training in geriatric medicine.

9.5.4 **Development of a standardised delirium protocol in stroke**

As discussed previously lack of staff education and awareness, misdiagnosis and the use of inappropriate tools have all contributed to low rates of delirium detection on the ward[425]. It has been suggested that earlier involvement of psychiatry service would be beneficial in cases of delirium[32]; however this would be time consuming for the referral service and not feasible in the long term. An alternative solution would be to introduce a routine screening protocol as part of the admissions process. Research suggests that in some situations the staff are informed on the importance of delirium but are using incorrect tools to identify potential cases[587]. Therefore it is assumed that the routine use of the correct diagnostic tool may increase detection rates and as a result improve the clinical management of the syndrome as staff awareness and familiarity increases. It should be noted that the sensitivity of tools such as the CAM-ICU when used in a clinical setting, may differ from that of a research environment. With regards to clinical implementation the research group Mitasova et al[575], make a good point in that the use of a tool such as the CAM-ICU would require calibration with ongoing monitoring and compliance checks. This would need to be done in order to ensure that delirium screening procedures were efficient and of good quality.

Leentjens et al[606] conducted a survey of delirium guidelines across Europe and found there was a lack of evidence based guidelines for the management of delirium. Suggestions were made for the development of globally consistent guidelines which would help improve clinical and research practice. With regards to delirium in stroke, the NICE guidelines for stroke (CG68)[270] and for delirium (CG103)[132] are currently valid and do not require any further changes to be made in relation to post-stroke delirium. The existing delirium risk factor guidance and prevention methods from NICE are still applicable to the stroke population as they are for any other patient population. The presentation of delirium remains the same in most patient groups as delirium symptoms are clinically dominant, although there is overlap with the stroke symptoms. Therefore the issue does not lie with the existing guidelines. It is not guidelines alone that change the management of delirium, but more so the organisational and educational changes that are needed[607]. Further research is needed to determine whether education could have a preventative effect on delirium occurrence and whether this increased awareness could be transformed into increased rates of delirium detection. Trials evaluating delirium educational programs as demonstrated in other clinical settings[425, 131] could also be conducted in stroke units to determine their effectiveness, in order to implement educational and organisational changes to create better practices in delirium management.

The introduction of stroke units nationally have been found to improve patient outcomes as well as being cost effective[365, 495, 361, 366, 360, 367, 362]. Many stroke services have been restructured in order to offer more specialised care to stroke patients efficiently and effectively. The various teams such as physiotherapy, occupational therapy and old age liaison psychiatry all have their own areas of expertise and participate in the weekly multidisciplinary team meetings on the unit. The incidence rates of delirium in the stroke population are significant and cannot be ignored and it would make clinical sense to incorporate a regular delirium education and awareness program for the clinical staff, in addition to the existing care packages offered on the ward. Cases of delirium may require different disciplines to gain a detailed insight into the causes, but at the same time general medical/ stroke unit staff also need to be aware of what signs to pay attention to. This may include elements of delirium detection, simple screening assessments for cognitive impairment and behavioural changes such as depression as well as avoiding the use of specific drugs that may worsen a delirium episode.

In the early stages of a delirium education and awareness program, the clinical staff would need to be trained in detecting cases of delirium, and once competent this training could then be delivered to other staff members. Training would have to be repeated on a regular basis as new staff members join the stroke unit. It is possible that the initial basic training and education on delirium could be provided by the psychiatry services. This would be equally beneficial to the clinical staff as well as the psychiatrically trained staff who then have more time and resources to tend to more complex cases that require their attention.

In the long term training the clinical staff, specifically the nurses on the stroke unit, would be beneficial as it is these staff members that regularly interact with patients and are able to build up a rapport with them. By observing the baseline interactions of the patients, any subsequent subtle changes in the patient's behaviour, mental status and routine could be identified much more efficiently. These cases could be treated whilst the patients remain on the stroke units thus avoiding the need for transfers or interactions with new people that may possibly increase confusion and disorientation. For more complex cases where a differential diagnosis may be required, the patients could be referred to the psychiatry services for more in-depth analysis and treatment.

In order to produce a delirium screening protocol the assessment tool needs to be quick and easy to administer in a busy clinical setting such as the stroke unit. Shorter assessment tools are more likely to appeal to staff as they would be less time consuming, work intensive and the staff would be more likely to adhere to the protocol in their day to day duties. In this study, the CAM-ICU was a quick and easy screening tool to administer and was very well

tolerated by patients, although the tool may require some training and experience for reliable use. It has also recently been validated for use in the stroke population with good results[575]. The DRS-R98 could then be used to provide further details if a patient tested positive for delirium. Although the DRS-R98 was initially introduced for research purposes, it is now being using by clinical staff such as experienced psychiatrists to detect delirium. In order to use the DRS-R98, staff would need to be trained in its use or perhaps a simplified version of the DRS-R98 could be developed for use by non-psychiatrically trained staff.

The combined use of the CAM-ICU as a one sheet assessment would hopefully be appealing, with a separate DRS-R98 sheet for the additional details if the patient does test positive. This short assessment tool could easily be incorporated into the existing stroke proforma currently being used at the LTHT, although stroke proformas may vary between different hospitals. A delirium protocol would need development, testing and subsequent calibration checks, but it is possible to implement a standardised screening practice for post-stroke delirium at some point in the near future. Putting the aforementioned steps into practice could help to initiate a more efficient and effective management method to help treat the underlying causes of delirium and regular screening could make a significant improvement in post-stroke delirium detection rates.

9.6 Conclusion

Taking into account all the information presented, the results of this study are generalisable to similar stroke services. However it is fair to conclude that further data on delirium and acute stroke are needed. Aside from the incidence data, more prospective cohort studies employing similar delirium diagnostic tools validated for use in the stroke population are required. Studies need to be well designed, with particular being paid attention towards possible confounders, composition and size of samples and statistical analysis methods employed. There is still a need for studies with a comprehensive long term follow up that have regular repeated measurements in order to assess the outcomes as accurately as possible. Specific outcomes of interest include; mortality, length of hospital stay, discharge destination, physical function, assessment of mood, risk of dementia and cognitive impairment. Once these data have been generated, it would provide the basis upon which a standardised delirium protocol could be implemented as previously described in this chapter. Until then, staff on stroke units can be made aware of the signs of delirium and taught environmental measures on how best to limit disruption to the patient's recovery post-stroke and delirium, with more complex cases being referred to the mental health team.

9.6.1 **Key points**

- For this study the incidence of delirium in the acute stroke population was recorded as 32.9% and delirium was shown to have a significant effect on mortality figures.
- Other outcomes that were negatively affected by delirium included; length of stay, discharge destination, physical function and risk of dementia.
- More study data are required with a comprehensive follow up and repeat assessment of outcomes measures after discharge.
- The collection of such data may eventually enable the introduction of a standardised delirium screening protocol for use in stroke units.

Conclusion of the thesis

The summarised key points of the thesis are as follows:

a) The findings of this study calculate the cumulative incidence of delirium to be at 32.9% suggesting that there is a significant delirium burden in the acute stroke population.

b) Delirium has a significant association with long term mortality after a stroke.

c) Early delirium in the immediate post-stroke onset period has an effect on adverse outcomes such as increased length of hospital stay and institutionalisation.

d) Persistent delirium after one month post-stroke has an effect on physical function and risk of dementia for up to six months after suffering a stroke.

e) Staff on stroke units may benefit from education about delirium, how to detect it and how best to manage delirium in stroke patients. The effectiveness of such a programme would require further research.

f) Consideration should also be given to the development of a standardised screening protocol for delirium on the stroke unit that could help to improve detection rates.

g) Delirium is a sufficiently frequent complication in acute stroke to warrant the development of a prevention intervention. This would require further research.

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Appendices

Appendix 1: Sample literature search strategy for systematic review

A list of the databases and search criteria used for the systematic review.

Databases searched include; AMED, BIOSIS, Biological Sciences, CINAHL, Cochrane, CSA neurosciences, EMBASE, Global Health, MEDLINE, PsychINFO, TRIP, Web of Science/ Knowledge.

1. exp Delirium/
2. deliri*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
3. confus*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
4. hallucinat*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
5. disorient*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
6. hysteri*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
7. "acute confusional state".mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp Stroke/
10. (acute adj2 stroke).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
11. "cerebral infarction".mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
12. "cerebrovascular event".mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
13. "cerebrovascular accident".mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
14. "cerebrovascular incident".mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
15. "ischaemic stroke".mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
16. "cerebral haemorrhage".mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
17. "cerebral hemorrhage".mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
18. "haemorrhagic stroke".mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
19. "hemorrhagic stroke".mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
20. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 8 and 20
22. limit 21 to english language

Appendix 2: Data extraction form/ quality scoring sheet

Study Title: **Author:**		**Quality score**
Location		
Study design		
Number of participants		
Mean age		
Inclusion/exclusion criteria		
Incidence		
Delirium tool		
Assessment periods		
Outcome measures		
Assessment tools used		
Duration of follow up		
Confounding variables		
Risk factors identified		

Appendix 3: Patient information sheet

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INFORMATION SHEET FOR PATIENTS

DELIRIUM AND ACUTE STROKE

We would like to ask you to take part in a research project. This information sheet is to explain about the research project and how you would be involved if you decided to take part. It is important for you to understand why the research is being carried out. Please read this information sheet carefully and discuss it with your family and friends and/ or general practitioner. If you would like some more information or if you have any comments or questions about the study, please feel free to ask me or anyone else involved in the study. Please take your time to decide whether you wish to be involved in the project or not.

What is the study about?

Sudden changes in ill health may result in acute confusion. These episodes of confusion are known as delirium and often occur in the older population. Delirium affects 5 to 15% of people in general medical or surgical wards and in 20 to 30% of patients in intensive care units.

Some studies suggest delirium can delay and even limit recovery in stroke patients resulting in longer hospital stays. Detection of delirium is difficult and it is particularly challenging in patients suffering from stroke. The symptoms of stroke can mask certain features of delirium and make it difficult to determine if these changes are due to stroke or due to an episode of delirium.

The aim of this study is to firstly identify the occurrence of delirium in stroke patients. We also aim to find better assessment methods, assess patient outcomes after discharge and identify any variables that may increase the risk of delirium occurring.

Why have I been chosen?

We are investigating the occurrence of confusion in people who have recently had a stroke. A member of the ward staff believes you might be a suitable person to take part in this study.

Do I have to take part?

No. It is entirely up to you whether you wish to participate in this study or not. Even if you do agree, you can withdraw at any time without giving any reason. Your participation is this study is requested to help better understand delirium and assess patient outcomes after hospital discharge. We will also be trying to identify potential variables that may increase the risk of delirium occurring.

What will happen to me if I take part?

Following your agreement to take part in the study, a researcher will make a record of all your tests and examinations since your admission to the hospital. A detailed history of past and current illnesses will be taken as well as a note of any medications you may have been prescribed. A researcher will assess you by asking you and the people looking after you some questions to see if you might have developed delirium. If delirium is detected, then this information will be shared with the ward team looking after you.

For the duration of your stay in hospital, the researcher will continue to monitor your medical notes and carry out delirium assessments at regular intervals during your stay. Once discharged from hospital, the researcher will follow up your progress by assessing how you are managing after your stroke and if you need any help. These follow up assessments will be done at 6 and 12 months and can be done by home visits, telephone interviews or postal questionnaires.

Are there any possible risks to me if I decide to take part in this study?

No. We will only be asking you some questions to assess your recovery progress. We will not be prescribing any medications and will only be making notes of any medications prescribed to you by your own doctor and hospital consultant.

What will happen to my answers and the data collected during participation?

Everything you say and all data collected during your participation in the study will be kept confidential and will be analysed anonymously as part of the study.

What will happen to the results of this research project?

Once the study is completed and the results are analysed, a summary of the study findings will be sent to you. The results of the study will be published, but individual participant results will not be identifiable in the report.

Who is organising and funding this research project?

This research project is funded by the University of Leeds.

Will you inform my GP?

We will request permission from you to do so. If a clinically relevant abnormality is detected, then we will write to the GP with your permission.

What if something goes wrong?

If you are not happy with the response you receive, or for any reason do not wish to raise your concern directly with the study team, you are free to contact the head of Research and Development at the University of Leeds. The details are:

Ms Clare Skinner
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Office – 0113 343 4897
Email – governance-ethics@leeds.ac.uk

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this strategy, the normal National Health Service complaints mechanisms should be available to you.

Whom do I contact for information or advice?

The name of the person who is running the study in your area is **Miss Saima Ahmed** (contact details listed below).

Thank you for considering participation in this study.

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Appendix 4: Carer information sheet

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INFORMATION SHEET FOR CARERS

DELIRIUM AND ACUTE STROKE

We would like to inform you that ..... is eligible to take part in our research study. This information sheet is to explain how he/ she will be involved in the project and to let you know why the research is being carried out. Please read this information sheet carefully and discuss it with the patient. If you would like some more information or if you have any comments or questions about the study, please feel free to ask me or anyone else involved in the study.

What is the study about?

Sudden changes in ill health may result in acute confusion. These episodes of confusion are known as delirium and often occur in the older population. Delirium affects 5 to 15% of people in general medical or surgical wards and in 20 to 30% of patients in intensive care units.

Some studies suggest delirium can delay and even limit recovery in stroke patients resulting in longer hospital stays. Detection of delirium is difficult and it is particularly challenging in patients suffering from stroke. The symptoms of stroke can mask certain features of delirium and make it difficult to determine if these changes are due to stroke or due to an episode of delirium.

The aim of this study is to firstly identify the occurrence of delirium in stroke patients. We also aim to find better assessment methods, assess patient outcomes after discharge and identify any variables that may increase the risk of delirium occurring.

Why has this patient been chosen?

This patient has recently had a stroke, making them eligible to take part in our study. We believe that people who have had a stroke are at a higher risk of developing delirium.

Does this patient have to take part?

No. It is entirely up to you and the patient whether or not to participate in this study. Even if you both agree, you can withdraw at any time without giving any reason. Furthermore their participation is the study will not affect any care that they may be receiving and refusal to take

part in these additional tests will not have an adverse effect in their current or future care. His/her co-operation will be invaluable for us to help others suffering from similar symptoms both now and in the future.

What will happen to the patient if they decide to take part?

Following both patient consent and your agreement to take part in the study, a researcher will make a record of all the tests and examinations since the patient's admission to the hospital. A detailed history of their past and current illnesses will be taken as well as a note of any medications they may have been prescribed. A researcher will assess the patient by asking them some questions to see if the patient might have developed delirium. If delirium is detected, then this information will be shared with the ward team looking after the patient.

For the duration of the patient's stay in hospital, the researcher will continue to monitor their medical notes and carry out delirium assessments at regular intervals during their stay. Once discharged from hospital, the researcher will follow up the patient's progress by assessing how they are managing after their stroke and if they need any help. These follow up assessments will be done at 6 and 12 months and can be done by home visits, telephone interviews or postal questionnaires where appropriate.

Are there any possible risks to the patient if they decide to take part in this study?

No. We will only be asking the patient some questions to assess their recovery progress. We will not be prescribing any medications and will only be making notes of any medications prescribed to the patient by their own doctor and hospital consultant.

What will be expected of me as the patient's carer, in this study?

In addition to assessing the patient, we may also briefly interview you to gain further information about the patient. The researcher may ask you questions about the patient's state of health prior to them having a stroke and whether you have noticed any changes in their behaviour or health, over a certain period of time. The answers that you provide will be kept confidential and analysed anonymously as part of the study.

As the patient's carer, if the patient has made any advance decisions about participating in research then please let us know. We will keep you fully informed during the study, but if you have any concerns or feel that the patient should be withdrawn from the study then please let us know.

What will happen to the answers and the data collected during participation?

Everything you and the patient say and all data collected during participation in the study will be kept confidential and will be analysed anonymously as part of the study.

What will happen to the results of this research project?

Once the study is completed and the results are analysed, a summary of the study findings will be sent to you if you wish. The results of the study will be published, but individual participant results will not be identifiable in the report.

Who is organising and funding this research project?

This research project is funded by the University of Leeds.

Will you inform the patient's GP?

We will request permission from the patient and/ or their consultee (i.e. someone appointed to speak on the patient's behalf) to do so. If a clinically relevant abnormality is detected, then we will write to the GP with the patient's permission.

What if something goes wrong?

If you are not happy with the response you receive, or for any reason do not wish to raise your concern directly with the study team, you are free to contact the head of Research and Development at the University of Leeds. The details are:

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Miss Saima Ahmed
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Appendix 5: Consultee information sheet

UNIVERSITY OF LEEDS

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Professor John Young
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BD9 6RJ

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John.Young@bradfordhospitals.nhs.uk

INFORMATION SHEET FOR CONSULTEES

DELIRIUM AND ACUTE STROKE

We would like to inform you that ..... is eligible to take part in our research study. This information sheet is to explain how he/ she could be involved in the project and to let you know why the research is being carried out. Please read this information sheet carefully and discuss it with the patient. If you would like some more information or if you have any comments or questions about the study, please feel free to ask me or anyone else involved in the study.

What is the study about?

Sudden changes in ill health may result in acute confusion. These episodes of confusion are known as delirium and often occur in the older population. Delirium affects 5 to 15% of people in general medical or surgical wards and in 20 to 30% of patients in intensive care units.

Some studies suggest delirium can delay and even limit recovery in stroke patients resulting in longer hospital stays. Detection of delirium is difficult and it is particularly challenging in patients suffering from stroke. The symptoms of stroke can mask certain features of delirium and make it difficult to determine if these changes are due to stroke or due to an episode of delirium.

The aim of this study is to firstly identify the occurrence of delirium in stroke patients. We also aim to find better assessment methods, assess patient outcomes after discharge and identify any variables that may increase the risk of delirium occurring.

Why has this patient been chosen?

This patient has recently had a stroke, making them eligible to take part in our study. We believe that people who have had a stroke are at a higher risk of developing delirium.

What will be expected of me in my role as a consultee, in this study?

We feel that this patient is unable to decide for himself/ herself whether to participate in this study. To help decide whether the patient should be involved in this study, we would like to ask your opinion whether or not they would want to be involved. We would ask you to consider what

you know of their wishes and feelings and consider their best interests. Please let us know of any advance decision they may have made about participating in research.

If you feel that the patient would have no objection to participating in this study, then we will ask to read and sign the consultee declaration form. We will keep you fully informed during the study so you can let us know if you have any concerns or feel that the patient should be withdrawn from the study. If you are unsure about taking on the role of consultee, then you may seek independent advice. We will understand if you do not want to take on this responsibility.

Does this patient have to take part?

No. It is entirely up to you and the patient whether or not to participate in this study. Even if you both agree, you can withdraw at any time without giving any reason. Furthermore their participation is the study will not affect any care that they may be receiving and refusal to take part in these additional tests will not have an adverse effect in their current or future care. His/ her co-operation will be invaluable for us to help others suffering from similar symptoms both now and in the future.

What will happen to the patient if they decide to take part?

Following both patient consent and your agreement to take part in the study, a researcher will make a record of all the tests and examinations since the patient's admission to the hospital. A detailed history of their past and current illnesses will be taken as well as a note of any medications they may have been prescribed. A researcher will assess the patient by asking them and the people looking after them some questions to see if the patient might have developed delirium. If delirium is detected, then this information will be shared with the ward team looking after the patient.

For the duration of the patient's stay in hospital, the researcher will continue to monitor their medical notes and carry out delirium assessments at regular intervals during their stay. Once discharged from hospital, the researcher will follow up the patient's progress by assessing how they are managing after their stroke and if they need any help. These follow up assessments will be done at 6 and 12 months and can be done by home visits, telephone interviews or postal questionnaires where appropriate.

Are there any possible risks to the patient if they decide to take part in this study?

No. We will only be asking the patient some questions to assess their recovery progress. We will not be prescribing any medications and will only be making notes of any medications prescribed to the patient by their own doctor and hospital consultant.

What will happen to the answers and the data collected during participation?

Everything the patient says and all data collected during participation in the study will be kept confidential and will be analysed anonymously as part of the study.

What will happen to the results of this research project?

Once the study is completed and the results are analysed, a summary of the study findings will be sent to you if you wish. The results of the study will be published, but individual participant results will not be identifiable in the report.

Who is organising and funding this research project?

This research project is funded by the University of Leeds.

Will you inform the patient's GP?

We will request permission from you and the patient to do so. If a clinically relevant abnormality is detected, then we will write to the GP with the patient's permission.

What if something goes wrong?

If you are not happy with the response you receive, or for any reason do not wish to raise your concern directly with the study team, you are free to contact the head of Research and Development at the University of Leeds. The details are:

Ms Clare Skinner
Research Manager
Faculty of Medicine and Health
Level 10, Room 10.110
Worsley Building
University of Leeds
Leeds
LS2 9LN
Office – 0113 343 4897
Email – governance-ethics@leeds.ac.uk

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this strategy, the normal National Health Service complaints mechanisms should be available to you.

Whom do I contact for information or advice?

The name of the person who is running the study in your area is **Miss Saima Ahmed** (contact details listed below).

Thank you for considering participation in this study.

Miss Saima Ahmed
Room G.02, Charles Thackrah Building
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Appendix 6: General practitioner information sheet

UNIVERSITY OF LEEDS

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INFORMATION SHEET FOR GP

DELIRIUM AND ACUTE STROKE

We would like to inform you that one of the participants in our research study; ..... is under your care. This information sheet is to explain how he/ she will be involved in the project and to let you know why the research is being carried out. Please read this information sheet carefully and ask me or anyone else involved in the study if you would like some more information or have any comments.

What is the study about?

Sudden changes in ill health may result in acute confusion. These episodes of confusion are known as delirium and often occur in the older population. Delirium affects 5 to 15% of people in general medical or surgical wards and in 20 to 30% of patients in intensive care units.

Some studies suggest delirium can delay and even limit recovery in stroke patients resulting in longer hospital stays. Detection of delirium is difficult and it is particularly challenging in patients suffering from stroke. The symptoms of stroke can mask certain features of delirium and make it difficult to determine if these changes are due to stroke or due to an episode of delirium.

The aim of this study is to firstly identify the occurrence of delirium in stroke patients. We also aim to find better assessment methods, assess patient outcomes after discharge and identify any variables that may increase the risk of delirium occurring.

Why has my patient been chosen?

This patient has recently had a stroke, making them eligible to take part in our study. We believe that people who have had a stroke are at a higher risk of developing delirium post stroke.

Does my patient have to take part?

No. It is entirely up to the patient whether he/ she participates in the study or not and he/ she can withdraw at any time without giving any reason. Furthermore their participation is the study will not affect any care that they may be receiving and refusal to take part in these additional tests

will not have an adverse effect in their current or future care. His/ her co-operation will be invaluable to help us better understand other individuals that may suffer from similar symptoms in the future.

What will happen to my patient if they decide to take part?

Following the patient's agreement to take part, a trained and experienced researcher will ask each participant some questions to establish a diagnosis of the presence of delirium using recognised criteria. At regular intervals during their stay in hospital, assessments for delirium, functional ability and other variables will be carried out. Once discharged, the researcher will follow up the patient's progress by home visits, telephone interviews or postal questionnaires where appropriate, at 6 and 12 months. No medication will be prescribed by the researchers and no interference with the hospital consultant's care plan. All data will be analysed anonymously.

What will happen to the answers given by my patient?

Everything they say will be kept confidential and analysed anonymously as part of the study.

Whom do I contact if I have any questions or comments, or require further information?

The name of the person who is running the study in your area is **Miss Saima Ahmed** (contact details listed below).

Thank you for taking the time to read this information sheet.

Miss Saima Ahmed
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Appendix 7: Patient consent forms

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UNIVERSITY OF LEEDS

CONSENT FORM FOR PATIENTS

DELIRIUM AND ACUTE STROKE

I ..... confirm that:	Please initial box
1. I confirm that I have read and understood the patient information sheet.	☐
2. I have received enough information about the study.	☐
3. I understand the reason for the research and what will happen if I take part.	☐
4. I have had an opportunity to ask questions and I am satisfied with the answers.	☐
5. I understand I am free to withdraw from the research at anytime.	☐
6. I would like to express my wish to continue/ not continue future participation in this study, even if I lose the ability to consent again.	☐
7. I understand and agree that my current consultant and general practitioner will be informed of my participation in the study.	☐
8. I understand and agree to the researchers contacting my general practitioner and having access to my medical notes for this study.	☐
9. I agree to participate in this study: - During my stay in hospital - Up to one month - Up to six months - Up to twelve months (full duration)	☐ ☐ ☐ ☐
10. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the University of Leeds, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐

	PARTICIPANT	RESEARCHER
Name	.....	.....
Signed	.....	.....
Date	.....	.....

Note: Once completed; one copy to patient, one copy to be kept in medical notes and one copy for researcher site file.

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UNIVERSITY OF LEEDS

CONSENT FORM FOR PATIENTS

DELIRIUM AND ACUTE STROKE

Whilst you were unwell, we felt that you were unable to say whether or not you should participate in this study and so we asked your consultee (i.e. someone appointed to speak on your behalf) for their advice. Now that your health has improved, we would like to ask whether you would be happy to continue participating in this study.

I ..... confirm that:	**Please initial box**
1. I confirm that I have read and understood the patient information sheet.	☐
2. I have received enough information about the study.	☐
3. I understand the reason for the research and what will happen if I take part.	☐
4. I have had an opportunity to ask questions and I am satisfied with the answers.	☐
5. I understand I am free to withdraw from the research at anytime.	☐
6. I would like to express my wish to continue/ not continue future participation in this study, even if I lose the ability to consent again.	☐
7. I understand and agree that my current consultant and general practitioner will be informed of my participation in the study.	☐
8. I understand and agree to the researchers contacting my general practitioner and having access to my medical notes for this study.	☐
9. I agree to participate in this study:	
- During my stay in hospital	☐
- Up to one month	☐
- Up to six months	☐
- Up to twelve months (full duration)	☐
10. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the University of Leeds, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐

	PARTICIPANT	**RESEARCHER**
Name	.....	.....
Signed	.....	.....
Date	.....	.....

Note: Once completed; one copy to patient, one copy to be kept in medical notes and one copy for researcher site file.

Appendix 8: Carer consent form

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UNIVERSITY OF LEEDS

CONSENT FORM FOR CARERS

DELIRIUM AND ACUTE STROKE

I ..... confirm that: **Please initial box**

1. I have read and understood the carer information sheet. ☐
2. I have received enough information about the study and I am happy to participate in this study. ☐
3. I understand the reason for the research and what will happen to the patient if they decide to take part. ☐
4. I have had an opportunity to ask questions and I am satisfied with the answers I have received. ☐
5. I understand that the patient is free to withdraw from the research at anytime. ☐
6. I understand that the researcher may wish to interview me, as the patient's carer, to obtain further information about the patient. ☐
7. I understand the patient's expressed wish regarding study participation in the future, even if the patient loses the ability to consent again to this study. ☐
8. I understand that the patient's current consultant and general practitioner will be informed of their participation in the study. ☐
9. I understand that the researchers will contact the patient's general practitioner and will have access to their medical notes for this study. ☐
10. I understand that relevant sections of the patient's medical notes and data collected during the study, may be looked at by individuals from the University of Leeds, from regulatory authorities or from the NHS Trust, where it is relevant for participation in this research. I give permission for these individuals to have access to those records. ☐

	CARER	RESEARCHER
Name	.....	.....
Signed	.....	.....
Date	.....	.....

Note: Once completed; one copy to carer, one copy to be kept in medical notes and one copy for researcher site file.

Appendix 9: Consultee declaration form

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UNIVERSITY OF LEEDS

DECLARATION FORM FOR CONSULTEES

DELIRIUM AND ACUTE STROKE

I ..... confirm that: **Please initial box**

1. I have read and understood the consultee information sheet. ☐
2. I have received enough information about the study and I believe that the patient would be happy to take part in this study. ☐
3. I understand the reason for the research and what will happen to the patient if they decide to take part. ☐
4. I have had an opportunity to ask questions and I am satisfied with the answers I have received. ☐
5. I understand that the patient is free to withdraw from the research at anytime. ☐
6. I understand what is required of me, in my role as the patient's consultee. ☐
7. I understand the patient's expressed wish regarding study participation in the future, even if the patient loses the ability to consent again to this study. ☐
8. I understand that the patient's current consultant and general practitioner will be informed of their participation in the study. ☐
9. I understand that the researchers will contact the patient's general practitioner and will have access to their medical notes for this study. ☐
10. I understand that relevant sections of the patient's medical notes and data collected during the study, may be looked at by individuals from the University of Leeds, from regulatory authorities or from the NHS Trust, where it is relevant for participation in this research. I give permission for these individuals to have access to those records. ☐

	CONSULTEE	RESEARCHER
Name	.....	.....
Signed	.....	.....
Date	.....	.....

Note: Once completed; one copy to carer, one copy to be kept in medical notes and one copy for researcher site file.

Appendix 10: Exclusion case report form

EXCLUSION DETAILS

Gender ☐ Male ☐ Female

Date of Birth _____ Age _____

Ethnicity

☐ White
☐ Mixed – White and Black African
☐ Mixed – White and Asian
☐ Other Mixed Background
☐ Asian – Indian
☐ Asian – Pakistani
☐ Asian – Bangladeshi
☐ Other Asian Background
☐ Black – Caribbean
☐ Black – African
☐ Other Black Background
☐ Chinese
☐ Other (please state) _____
☐ Not stated

Reasons for exclusion:

☐	Patient died	Cause of death
☐	Severely ill	MEWS assessment
☐	Translator unavailable	Language spoken
☐	Incapacity	MCA assessment outcome
☐	Refused consent	Patient refused/ consultee unavailable
☐	Other	Please give further details

Other additional notes:

Appendix 11a: Clinical assessment: Bamford stroke classification

CURRENT STROKE DETAILS (continued)

Clinical classification of stroke symptoms (Bamford classification)

☐ **Total anterior circulation stroke (TACS)** A significantly poorer prognosis A combinations of: - weakness/ numbness of at least 2 out of face, arm and leg - homonymous visual field defect - dysphasia, dyscalculia or visuospatial disorder	☐ **Partial anterior circulation stroke (PACS)** 2 out of 3 criteria from TACS i.e. - isolated dysphasia, dyscalculia or field defect or limb weakness - weakness of one limb only
☐ **Lacunar stroke (LACS)** - Pure motor weakness of face, arm and/ or leg - Pure sensory deficit of face, arm and/ or leg - Sensorimotor – combinations of above - No cortical signs or symptoms - Ataxic hemiparesis i.e. weakness or clumsiness	☐ **Posterior circulation stroke (POCS)** - Brainstem or cerebellar symptoms/ signs - Ipsilateral cranial nerve palsy with contralateral motor or sensory signs - Bilateral motor/ sensory symptoms - Isolated hemianopia

Pathological classification of stroke:

☐ Ischemic (I) ☐ Haemorrhagic (H) ☐ Syndrome (S) indeterminate prior to imaging

Weakness:

☐ Right side	☐ Mono (one limb)	☐ Paresis (weak, incomplete paralysis)
☐ Left side	☐ Para (both legs)	☐ Plegia (severe, complete paralysis)
☐ Global	☐ Hemi (arm & leg one side)	☐ Not applicable
☐ No weakness	☐ Tetra (all limbs affected)	

Brain scan results:

Appendix 11b: Clinical assessment: MEWS and GCS scores

CLINICAL EXAMINATIONS (continued)

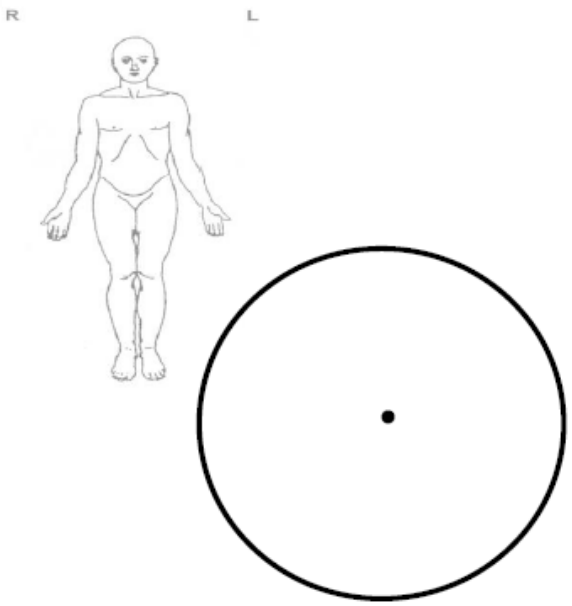
Sensory testing:

Is there any sensory loss?

☐ Yes (state on diagram) ☐ No

Is there sensory inattention?

☐ Yes (left or right) ☐ No



Communication difficulties:

☐ None ☐ Dysphasia
☐ Mild ☐ Dysarthria
☐ Moderate ☐ Untestable
☐ Severe ☐ Mute

Swallowing:

Can the patient swallow safely?

☐ Yes ☐ No

Gait:

☐ Normal ☐ Ataxic
☐ Hemiparetic ☐ Unable to stand
☐ Other _____

Visuospatial disorders:

Is there evidence of visuospatial dysfunction?

(e.g. neglect or sensory inattention)

☐ Yes ☐ No

Please draw in the numbers on the clock face

Glasgow coma scale (GCS):

Eye response (E)
1 none
2 to pain
3 to verbal command
4 spontaneously

☐ Total

Verbal response (V)
1 none
2 incomprehensible sounds
3 inappropriate words
4 confused response
5 clear, orientated response

Motor response (M)
1 None
2 extensions to pain
3 flexion to pain
4 withdrawal from pain
5 localising pain
6 obeying commands

MEWS Score:	3	2	1	0	1	2	3
Systolic BP	<70	71-80	81-100	101-199	---	>200	---
Heart rate (BPM)	---	<40	41-50	51-100	101-110	111-129	>130
Respiratory rate (RPM)	---	<9	---	9-14	15-20	21-29	>30
Temperature (^{0}C)	---	<35	---	35.0-38.4	---	>38.5	---
AVPU	---	---	---	A	V	P	U

Appendix 12: Confusion Assessment Method for Intensive Care Unit (CAM-ICU)

CONFUSION ASSESSMENT METHOD – INTENSIVE CARE UNIT (CAM – ICU)

Feature 1: Acute onset or fluctuating course Positive if you answer 'yes' to either 1A or 1B.	**Positive**	**Negative**
1A: Is the patient different that his/ her baseline mental status? OR **1B:** Has the patient had any fluctuations in mental status in the past 24 hours as evidenced by fluctuation on a sedation scale (e.g. RASS), GCS or previous delirium assessment?	Yes	No
Feature 2: Inattention Positive if either score for 2A or 2B is less than 8. Attempt the ASE letters first. If patient is able to perform this test and the score is clear record this score and move to feature 3. If patient is unable to perform this test or the score is unclear, then perform the ASE pictures. IF you perform both tests, use the ASE pictures' results to score the feature.	**Positive**	**Negative**
2A: ASE Letters: record score (enter NT for not tested) **Directions:** Say to the patient, *"I am going to read you a series of 10 letters, whenever to hear the letter 'A', indicate by squeezing my hand."* Read letter from the following letter list in a normal tone **S A V E A H A A R T** Scoring: Errors are counted when the patient fails to squeeze on the letter 'A' and when the patient squeezes on any letter other than 'A'.	Score (out of 10): _____	
2B: ASE Pictures: record score (enter NT for not tested) Directions are included on the picture packets.	Score (out of 10): _____	
Feature 3: Disorganised thinking Positive if the combine score is less than 4	**Positive**	**Negative**
3A: Yes/ No questions (Use either set A or set B, alternate on consecutive days if necessary): **Set A** 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? **Set B** 1. Will a leaf float on water? 2. Are there elephants in the sea? 3. Do two pounds weigh more than one pound? 4. Can you use a hammer to cut wood? Score _____ (Patient earns 1 point for each correct answer out of 4) **3B: Command** Say to the patient "Hold up this many fingers" (examiner hols up two fingers in front of patient) "Now do the same thing with the other hand" (not repeating the number of fingers) * If patent is unable to move both arms, for the second part of the command ask patient "add one more finger) Score _____ (patient earns 1 point if able to successfully complete the entire command)	**Combined score of (3A +3B): _____ (out of 5)**	
Feature 4: Altered level of consciousness Positive if the actual RASS score is anything other than "0" (zero)	**Positive**	**Negative**
If RASS IS -4 or -5, then stop and reassess the patient at a later time. **If RASS is above -4 (-3 to +4), then continue with delirium assessment.**		
Overall CAM-ICU (Features 1 and 2 and either feature 3 or 4):	**Positive**	**Negative**

Appendix 13: Delirium Rating Scale - Revised 98 (DRS-R98)

DELIRIUM RATING SCALE – REVISED 98 (DRS – R98)

Severity	Item Score				Optional Information
Sleep-wake cycle	0	1	2	3	Naps Nocturnal disturbance only Day-night reversal
Perceptual disturbances	0	1	2	3	Sensory type of illusion or hallucination: auditory visual olfactory tactile Format of illusion or hallucination: simple complex
Delusions	0	1	2	3	Type of delusion: persecutory Nature: poorly formed systemised
Lability of affect	0	1	2	3	Type: angry anxious dysphoric elated irritable
Language	0	1	2	3	Check here if intubated, mute etc.
Thought process	0	1	2	3	Check here if intubated, mute etc.
Motor agitation	0	1	2	3	Check here if restrained *Type of restraints:*
Motor retardation	0	1	2	3	Check here if restrained *Type of restraints:*
Orientation	0	1	2	3	Date: Place: Person:
Attention	0	1	2	3	
Short-term memory	0	1	2	3	Record # of trials for registration of items: Check here if category cueing helped:
Long-term memory	0	1	2	3	Check here if category cueing helped:
Visuospatial ability	0	1	2	3	Check here if unable to use hands:
Diagnostic Item	**Item Score**				**Optional Information**
Temporal onset of symptoms	0	1	2	3	Check here if symptoms appeared on a background of other psychopathology
Fluctuation of symptom severity	0	1	2		Check here if symptoms only appear during the night
Physical disorder	0	1	2		

SCORE: 0 = None 1 = Mild 2 = Moderate 3 = Severe

SEVERITY SCORE ____ **TOTAL SCORE** ____

Appendix 14: Nottingham Extended Activities of Daily Living (NEADL)

NOTTINGHAM EXTENDED ACTIVITIES OF DAILY LIVING (NEADL)

In the last few weeks, did you...	Score
MOBILITY	
1. Walk around outside?	
2. Climb stairs?	
3. Get in and out of a car?	
4. Walk over uneven ground?	
5. Cross roads?	
6. Travel on public transport?	
IN THE KITCHEN	
7. Manage to feed yourself?	
8. Manage to make yourself a hot drink?	
9. Take hot drinks from one room to another?	
10. Do the washing up?	
11. Make yourself a hot snack?	
DOMESTIC TASKS	
12. Manage your own money when out?	
13. Wash small items of clothing?	
14. Do your own housework?	
15. Do your own shopping?	
16. Do a full clothes wash?	
LEISURE ACTIVITIES	
17. Read newspapers or books?	
18. Use the telephone?	
19. Write letters?	
20. Go out socially?	
21. Manage your own garden?	
22. Drive a car?	
TOTAL	

SCORE: **0** = Not at all **1** = With help **2** = Alone but with difficulty **3** = Alone with ease

Appendix 15: Geriatric Depression Scale (GDS)

GERIATRIC DEPRESSION SCALE (GDS)

Choose the best answer for how you felt the past week:

	Yes	No
1. Are you basically satisfied with your life?		1
2. Have you dropped many of your activities and interests?	1	
3. Do you feel that your life is empty?	1	
4. Do you often get bored?	1	
5. Are you hopeful about the future?		1
6. Are you bothered by thoughts you can't get out of your head?	1	
7. Are you in good spirits most of the time?		1
8. Are you afraid that something bad is going to happen to you?	1	
9. Do you feel happy most of the time?		1
10. Do you often feel helpless?	1	
11. Do you often get restless or fidgety?	1	
12. Do you prefer to stay at home, rather than going out and doing new things?	1	
13. Do you frequently worry about the future?	1	
14. Do you feel you have more problems with memory than most?	1	
15. Do you think it is wonderful to be alive now?		1
16. Do you often feel downhearted and blue?	1	
17. Do you feel pretty worthless the way you are now?	1	
18. Do you worry a lot about the past?	1	
19. Do you find life every exciting?		1
20. Is it hard for you to get started on new projects?	1	
21. Do you feel full of energy?		1
22. Do you feel that your situation is hopeless?	1	
23. Do you think that most people are better off than you are?	1	
24. Do you frequently get upset over little things?	1	
25. Do you frequently feel like crying?	1	
26. Do you have trouble concentrating?	1	
27. Do you enjoy getting up in the morning?		1
28. Do you prefer to avoid social gatherings?	1	
29. Is it easy for you to make decisions?		1
30. Is your mind as clear as it used to be?		1
TOTAL		

SCORE: 1 for Yes on questions; 2-4,6,8,10-14,16-18,20,22-26,28
1 for No on questions; 1,5,7,9,15,19,21,27,29,30

Appendix 16: Addenbrooke's Cognitive Exam - Revised (ACE-R)

ADDENBROKES COGNITIVE EXAM – REVISED (ACE – R)

ORIENTATION *(Score 1 mark for each correct answer)*
What day / date / month / year / season — 0 – 5 ☐

(Score 1 mark for each correct answer)
Which building / floor / town / county / country — 0 – 5 ☐

REGISTRATION *(Score on first trial only. Repeat 3 times if necessary)*
Repeat the words 'lemon', 'key', 'ball' — 0 – 3 ☐
No. of trials ____

ATTENTION & CONCENTRATION *(Score 1 mark for each correct answer)*
Take 7 away from 100 and repeat for five subtractions — 0 – 5 ☐
i.e. 93, 86, 79, 72, 65

Spell **WORLD** for me? Spell it backwards? — Score for best task

ATTENTION & ORIENTATION

MEMORY – RECALL *(Score 1 mark for each correct answer)*
What were three words I asked to repeat and remember? — 0 – 3 ☐

MEMORY – ANTEROGRADE MEMORY *(Score only on the third trial)*
Repeat this name & address three times and remember it — 0 – 7 ☐

	1st trial	2nd trial	3rd trial
Harry Barnes 73 Orchard Close Kingsbridge Devon			

0 – 4 ☐

MEMORY – RETROGRADE MEMORY
Name of current prime minister
Name of the woman prime minister
Name of USA president
Name of USA president assassinated in 1960's

MEMORY

LANGUAGE – REPETITION *(Score 2 if all correct, 1 if 3 & 0 if 2 or less)*
Repeat '**hippopotamus**', '**eccentricity**', '**unintelligible**', '**statistician**' — 0 – 2 ☐

Repeat '**Above, beyond & below**' — 0 – 1 ☐

Repeat '**No ifs, ands or buts**' — 0 – 1 ☐

LANGUAGE – NAMING
Name the pictures shown — 0 – 2 ☐

Point to picture associated with monarchy — 0 – 10 ☐
Point to picture which is a marsupial
Point to picture that is found in the Antarctic — 0 – 4 ☐
Point to picture that has a nautical connection

Read the following words: *(Score 1 only if all correct)* — 0 – 1 ☐
sew **pint** **soot** **dough** **height**

LANUAGE

ADDENBROKES COGNITIVE EXAM – REVISED (ACE – R) (continued)

VISUOSPATIAL

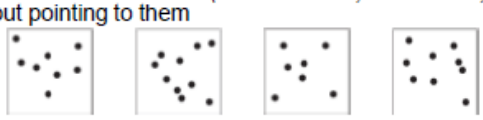
Overlapping pentagons: copy

Wire cube:: copy

Clock: draw a clock face with numbers and hands at ten past five.

(Score circle = 1, numbers = 2, hands = 2 if all correct)

Count the dots without pointing to them



0 – 1 ☐
0 – 2 ☐
0 – 5 ☐
0 – 4 ☐

FLUENCY

VERBAL FLUENCY – LETTER 'P' AND ANIMALS

I'm going to give you a letter of the alphabet. Generate as many words beginning with this letter, excluding the names of people or places. You have one minute & the letter is P.

> 17 =7
14 -17= 6
11-13= 5
8-10= 4
6 -7= 3
4-5=2
2-3=1
<2 = 0

Now can you name as many animals as possible, beginning with any letter?

> 21 =7
17-21= 6
14-16= 5
11-13= 4
9-10= 3
7-8=2
5-6=1
<5 = 0

Letter P
0 – 7 ☐

Animals
0 – 7 ☐

LANGUAGE

LANGUAGE – COMPREHENSION

Follow this instruction

Close your eyes

3 stage command:
'Take the paper in your right hand. Fold the paper in half. Put the paper on the floor.'

LANGUAGE – WRITING

(Score 1 if sentence has subject and verb)

Make up a sentence and write it in the space below.

0 – 1 ☐
0 – 3 ☐
0 – 1 ☐

VISU

PERCEPTUAL ABILITIES

Identify the following letters

0 – 4 ☐

MEMORY

RECALL

What do you remember of the address we were repeating at the beginning?

Harry Barnes 73 Orchard Close Kingsbridge Devon

0 – 7 ☐

RECOGNITION

To be done if subject failed to recall one or more items. If all items recalled, score 5.

Jerry Barnes	Harry Barnes	Harry Bradford	Recalled
73	73	76	Recalled
Orchard Place	Oak Close	Orchard Close	Recalled
Oakhampton	Kingsbridge	Dartington	Recalled
Devon	Dorset	Somerset	Recalled

0 – 5 ☐

SCORE

General scores			Subscores		
	MMSE	/30		Attention & Orientation	/18
	ACE-R	/100		Memory	/26
				Fluency	/14
				Language	/26
				Visuospatial	/16

Appendix 17: Ascertain Dementia (AD-8)

ASCERTAIN DEMENTIA (AD – 8)

Remember, "Yes, a change" indicates that there has been a change in the last several years caused by cognitive (thinking and memory) problems.

	Score
1. Problems with judgement (e.g. problems with thinking, decision making, bad financial decisions)	
2. Less interest in hobbies/ activities	
3. Repeats the same things over and over (questions, stories or statements)	
4. Trouble learning how to use a tool appliance, or gadget (e.g. VCR, PC, microwave, remote control)	
5. Forgets correct month or year	
6. Trouble handling complicated financial affairs (e.g. balancing checkbook, income taxes, paying bills)	
7. Trouble remembering appointments	
8. Daily problems with thinking and/ or memory	
TOTAL SCORE	

SCORE:
Yes - A change = 1
No - No change = 0
N/A - Don't know = void

Combined with 'Word List Recall' task:

Read list of 10 high-frequency, high-imagery words at a constant rate of 1 word every 2 seconds.
Original words: **Butter, Arm, Corner, Letter, Queen, Ticket, Grass, Stone, Book, Stick**
New Words: **Cat, Apple, Window, Table, Penny, Wheel, Clock, Scarf, Basket, Water**

Task	Score
Word List Recall Memory The word list is read to the subject 3 times, each time in a randomised order. *(Give one point for each correctly recalled word)*	1st trial 2nd trial 3rd trial
Delayed Word List Memory No additional cues given. Subject must spontaneously recall as many of the 10 words. *(Give one point for each correct word recalled)*	1st trial 2nd trial 3rd trial
Delayed Recognition Word Read 10 original words and 10 new words. Subject asked to identify new words. *(Give one point for each correctly recognised 'old' & 'new' word)*	1st trial 2nd trial 3rd trial
TOTAL SCORE	

Appendix 18: Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)

INFORMANT QUESTIONNAIRE ON COGNITIVE DECLINE IN THE ELDERLY (IQCODE)

Compared with 10 years ago, how is this person at:

	Score
1. Remembering things about family and friends e.g. occupations, birthdays, addresses	
2. Remembering things that have happened recently	
3. Recalling conversations a few days later	
4. Remembering his/her address and telephone number	
5. Remembering what day and month it is	
6. Remembering where things are usually kept	
7. Remembering where to find things which have been put in a different place from usual	
8. Knowing how to work familiar machines around the house	
9. Learning to use a new gadget or machine around the house	
10. Learning new things in general	
11. Following a story in a book or on TV	
12. Making decisions on everyday matters	
13. Handling money for shopping	
14. Handling financial matters e.g. the pension, dealing with the bank	
15. Handling other everyday arithmetic problems e.g. knowing how much food to buy, knowing how long between visits from family or friends	
16. Using his/her intelligence to understand what's going on and to reason things through	
TOTAL SCORE	

SCORE:
1 = much improved
2 = a bit improved
3 = not much change
4 = a bit worse
5 = much worse

Appendix 19: The Standardised Mini Mental State Exam (SMMSE)

STANDARDISED MINI MENTAL STATE EXAMINATION (SMMSE)

SMMSE TEST SCORE	SCORE
(Score 1 mark for each correct answer)	
1. What Year / Season / Month / Date / Day	/ 5
2. What Country / Province / City / Building / Floor	/ 5
3. Repeat the words 'ball', 'car', 'man'	/ 3
4. Spell **WORLD** for me? Spell it backwards?	/ 5
5. What were three words I asked to repeat and remember?	/ 3
6. Show wristwatch. Ask: What is this called?	/ 1
7. Show pencil. Ask: What is this called?	/ 1
8. Repeat '**No ifs, ands or buts**'	/ 1
9. Follow this instruction: **Close your eyes**	/ 1
10. Make up a sentence and write it in the space below.	/ 1
11. Overlapping pentagons: copy 	/ 1
12. 3 stage command: **'Take the paper in your right hand. Fold the paper in half. Put the paper on the floor.'**	/ 3
TOTAL	

ABBREVIATED MENTAL TEST SCORE (AMTS)

ABBREVIATED MENTAL TEST SCORE	SCORE
1. Age	
2. Time (to the nearest hour)	
3. Address for recall at end of test – this should be repeated by the patient to ensure it has been heard correctly: 42 West Street	
4. Year	
5. Name of hospital	
6. Recognition of two persons (doctor, nurse etc)	
7. Date of birth	
8. Year of first world war	
9. Name of present monarch	
10. Count backwards 20 – 1	
TOTAL	

Appendix 20: The Telephone Interview for Cognitive Status (TICS)

TELEPHONE INTERVIEW FOR COGNITIVE STATUS (TICS)

(1) Explain exam to the subject or patient's carer. (2) Get address (3) Be sure that distractions are minimal (e.g. No TV or radio on, remove pens and pencils from reach). (4) Be sure sources of orientation (e.g. Newspapers, calendars) are not in subject's view. (5) Carers may offer reassurance, but not assistance. (6) Single repetitions permitted, except for items 5 and 8.

	Score
1. 'Please tell me your full name?'	
2. 'What is today's date?'	
3. 'Where are you right now?'	
4. 'Count backwards from 20 to 1.'	
5. 'I'm going to read you a list of words & try to remember them . When I am done, tell me as many words as you can, in any order. Ready? The words are: cabin, pipe, elephant, chest, silk, theatre, watch, whip, pillow, giant. Now tell me all the words you can remember.'	
6. 'One hundred minus 7 equals what?' 'And 7 from that?' etc	
7. 'What do people usually use to cut paper?' 'How many things are there in a dozen?' 'What do you call the prickly green plant that lives in the desert?' 'What animal does wool come from?'	
8. Say this: 'No ifs, ands or buts' Say this: 'Methodist episcopal'	
9. 'Who is the President of the United States right now?' 'Who is the Vice-President?'	
10. 'With your finger, tap 5 times on the part of the phone you speak into.'	
11. 'I'm going to give you a word and I want you to give me its opposite. For example, the opposite of hot is cold. What is the opposite of 'west'? What is the opposite of 'generous'?	
TOTAL SCORE	

SCORE:
1 = much improved
2 = a bit improved
3 = not much change
4 = a bit worse
5 = much worse

Appendix 21: Scale used to classify levels of education

The following scales were used to classify the participant's level of education.

Classifying levels of education

1	No education
2	Primary school
3	College/ further training/ apprenticeship
4	University

Appendix 22: Scale used to classify levels of employment

The following scale was used to classify the participant's main occupation prior to retirement.

Classifying types of profession

1	Unskilled manual i.e. *labourer, cleaner*
2	Semi-skilled manual i.e. *farm work, postman*
3	Skilled manual i.e. *electrician, bus driver*
4	Skilled non-manual i.e. *policeman, salesman*
5	Intermediate i.e. *teacher, farmer*
6	Professional/managerial i.e. *accountant, doctor*

Appendix 23: Analysis of the published literature in April 2014

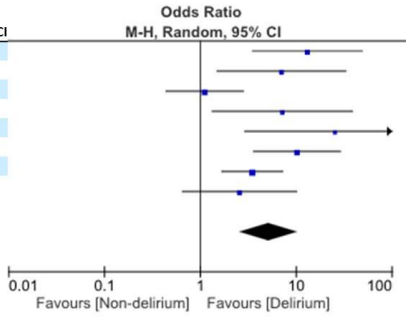
Forest plots of the April 2014 meta-analysis.

Inpatient mortality

Study	Study sample	Delirium Events	Delirium Total	Non-delirium Events	Non-delirium Total	Weight	Odds ratio M-H, Random, 95%CI
Dostovic 2008, 2009	233	11	59	3	174	12.3%	13.06 [3.50, 48.71]
Gustafson 1991	145	11	69	2	76	10.6%	7.02 [1.50, 32.91]
Henon 1999	202	7	49	20	153	15.9%	1.11 [0.44, 2.80]
Kara 2013	150	5	42	2	108	9.6%	7.16 [1.33, 38.51]
McManus 2008, 2009, 2011	82	7	23	1	59	7.0%	25.38 [2.91, 221.61]
Miu 2013	314	16	86	5	228	14.8%	10.19 [3.61, 28.83]
Oldenbeuving 2011	527	12	62	30	465	17.8%	3.48 [1.68, 7.23]
Sheng 2006	156	4	39	5	117	11.9%	2.56 [0.65, 10.06]
		73		68			
TOTAL (95% CI)	**1809**		**429**		**1380**	**100%**	**5.13 [2.56, 10.28]**

Heterogeneity: Tau² = 0.57; Chi² = 17.83, df = 7 (P = 0.01), I² = 61%

Test for overall effect: Z = 4.61 (P < 0.00001)

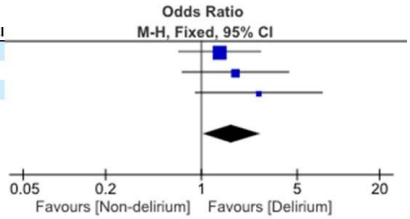


6 month mortality

Study	Study sample	Delirium Events	Delirium Total	Non-delirium Events	Non-delirium Total	Weight	Odds ratio M-H, Fixed, 95%CI
Henon 1999	202	17	49	49	153	55.7%	1.36 [0.68, 2.70]
Mitasova 2012	129	13	55	55	74	29.3%	1.77 [0.73, 4.33]
Sheng 2006	156	7	39	39	117	15.1%	2.63 [0.91, 7.60]
		37		63			
TOTAL (95% CI)	487		143		344	100%	1.67 [1.03, 2.71]

Heterogeneity: Chi² = 1.06, df = 2 (P = 0.59), I² = 0%

Test for overall effect: Z = 2.08 (P = 0.04)

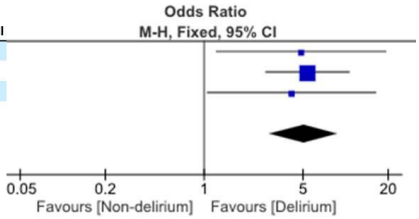


12 month mortality

Study	Study sample	Delirium Events	Delirium Total	Non-delirium Events	Non-delirium Total	Weight	Odds ratio M-H, Fixed, 95%CI
McManus 2008, 2009, 2011	82	6	23	4	59	16.8%	4.85 [1.22, 19.23]
Miu 2013	314	26	86	17	228	65.6%	5.38 [2.74, 10.57]
Sheng 2006	156	5	39	4	117	17.6%	4.15 [1.06, 16.34]
		37		25			
TOTAL (95% CI)	**552**		**148**		**404**	**100%**	**5.07 [2.92, 8.83]**

Heterogeneity: Chi² = 0.11, df = 2 (P = 0.94), I² = 0%

Test for overall effect: Z = 5.75 (P < 0.00001)

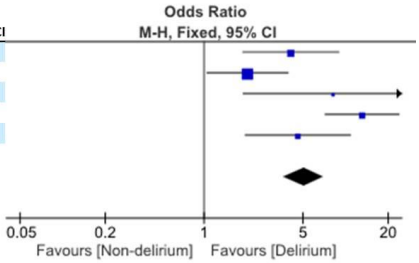


Institutionalisation

Study	Study sample	Delirium Events	Delirium Total	Non-delirium Events	Non-delirium Total	Weight	Odds ratio M-H, Fixed, 95%CI
Gustafson 1991	145	30	69	12	76	21.6%	4.10 [1.88, 8.94]
Henon 1999	202	30	49	67	153	42.2%	2.03 [1.05, 3.91]
McManus 2008, 2009, 2011	82	7	23	3	59	3.9%	8.17 [1.89, 35.24]
Miu 2013	314	54	86	26	228	17.8%	13.11 [7.21, 23.85]
Sheng 2006	156	15	39	14	117	14.4%	4.60 [1.96, 10.79]
		136		122			
TOTAL (95% CI)	**899**		**266**		**633**	**100%**	**5.06 [3.61, 7.07]**

Heterogeneity: Chi² = 17.91, df = 4 (P = 0.001), I² = 78%

Test for overall effect: Z = 9.46 (P < 0.00001)

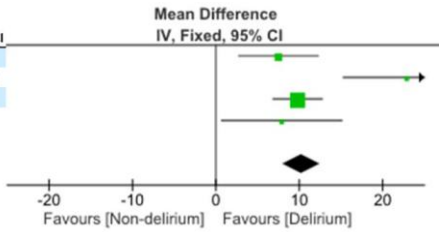


Length of stay

Study	Study sample	Delirium Mean	Delirium SD	Delirium Total	Non-delirium Mean	Non-delirium SD	Non-delirium Total	Weight	Odds ratio M-H, Random, 95%CI
Gustafson 1993	83	23.1	11.1	35	15.6	10.7	48	22.4%	7.50 [2.74, 12.26]
Miu 2013	314	45	33	86	22.1	23.5	228	8.8%	22.90 [15.29, 30.51]
Oldenbeuving 2011	527	23.7	11.1	62	13.9	11	465	59.0%	9.80 [6.86, 12.74]
Sheng 2006	156	33.2	18.8	39	25.3	22.8	117	9.8%	7.90 [0.70, 15.10]
TOTAL (95% CI)	**1080**			**222**			**858**	**100%**	**10.25 [7.99, 12.50]**

Heterogeneity: Chi² = 12.39, df = 3 (P = 0.006), I² = 76%

Test for overall effect: Z = 8.90 (P < 0.00001)



Funnel plots of the April 2014 meta-analysis.