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Recovery after stroke

Assessment and treatment; with focus on motor function

Thesis for the degree of philosophiae doctor

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Norwegian University of
Science and Technology
Faculty of Medicine
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Funksjonell bedring etter hjerneslag

Undersøkelse og behandling med fokus på motorisk funksjon

Hjerneslag er en av våre største og alvorligste folkesykdommer og antall personer som får hjerneslag vil øke i de kommende år. Dette vil få store konsekvenser for personene som rammes, deres familie, helsevesenet og samfunnet. Lammelser er det vanligste utfallet etter hjerneslag og problemer med å bevege seg fører gjerne til redusert livskvalitet. Som en følge av dette blir det lagt stor vekt på fysioterapi og motorisk trening ved rehabilitering av pasienter med akutt hjerneslag.

Det overordnede formålet med denne avhandlingen var å øke kunnskapen om motorisk bedring etter hjerneslag ved å evaluere effekten av to ulike behandlingsformer sammenlignet med den standard behandling som i dag gis til disse pasientene. Det var også et mål å undersøke hva som skjer med hjernens aktivering hos pasienter med akutt hjerneslag som behandles i en vitenskaplig basert slagenhet.

En randomisert og kontroller studie ble gjennomført for å evaluere effekten av tidlig støttet utskriving for pasienter bosatt i Malvik, Melhus og Klæbu kommune som var innlagt ved Slagenheten ved St. Olavs Hospital. Sekstito pasienter ble inkludert og randomisert enten til utskriving med oppfølging av et koordinerende tverrfaglig team eller til standard rehabilitering. Resultatene viste ingen betydningsfulle forskjeller mellom gruppene med hensyn til selvhjulpenhet, balanse eller ganghastighet, men en forbigående mindre sosial isolasjon i gruppen som fikk oppfølging av det tverrfaglige teamet. I studien fant man også en sterk sammenheng mellom alvorlige lammelser i benet ved innleggelse og redusert balanse ett år senere.

En annen randomisert og kontrollert studie ble gjennomført for å evaluere effekten og gjennomførbarheten av trening med begrenset bruk av frisk side for pasienter med subakutt og kronisk hjerneslag. Tretti pasienter ble inkludert og randomisert enten til ti dager intensiv trening av den affiserte hånden kombinert med en vott på den friske hånden, eller til en kontrollgruppe som fikk standard rehabilitering. Alle pasientene tolererte den intensive treningen. Behandlingsgruppen oppnådde en større bedring i den affiserte armen sammenlignet med kontrollgruppen umiddelbart etter at

behandlingen var avsluttet. Seks måneder senere var det imidlertid ingen forskjell mellom gruppene lenger.

Til slutt ble det gjennomført en studie for å undersøke hvilke endringer som skjer i hjernen etter hjerneslag hos pasienter som behandles med tidlig mobilisering i en vitenskaplig basert slagenhet. Tolv pasienter med hjerneinfarkt ble inkludert og undersøkt med funksjonell magnetresonanstomografi (MRI) og funksjonelle tester 4 – 7 dager etter symptomdebut og 3 måneder senere. Alle pasientene, unntatt en, hadde fullstendig bedring av den affiserte armen i henhold til våre kriterier. Resultatene viste at hjernens aktivering allerede i tidlig fase var i ferd med å gjenopprette sin normale funksjon selv om pasientene fortsatt hadde lammelser på dette tidspunktet. Videre viste resultatene at de områdene i hjernen som ble aktivert tilsvarer områder som aktiveres under motorisk læring. Til slutt viste resultatene at pasientene tok i bruk tilleggsområder i den friske hjernehalvdelen for å gjenvinne god håndfunksjon.

Forskningsarbeidet har vist at det er usikkert om utskriving med oppfølging av et koordinerende tverrfaglig team har noen betydningsfull effekt for pasienter som bor i Malvik, Melhus og Klæbu kommune. Videre har arbeidet vist at trening med begrenset bruk av frisk side fører til bedre funksjon i den affiserte armen på kort sikt men er sannsynligvis ikke bedre enn standard rehabilitering på lang sikt. Til slutt har dette arbeidet vist at pasienter som behandles i en slagenhet aktiverer områder i hjernen som har med motorisk læring å gjøre ved gjenopptrening av håndfunksjon. Dette indikerer at man i fremtiden sannsynligvis bør legge vekt på treningsmetoder som stimulerer denne type omorganisering i hjernen.

Navn kandidat: Torunn Askim
Institutt: Institutt for samfunnsmedisin (ISM)
Veiledere: Bent Indredavik (hovedveileder), Siv Mørkved og Asta Håberg (bi-veiledere)
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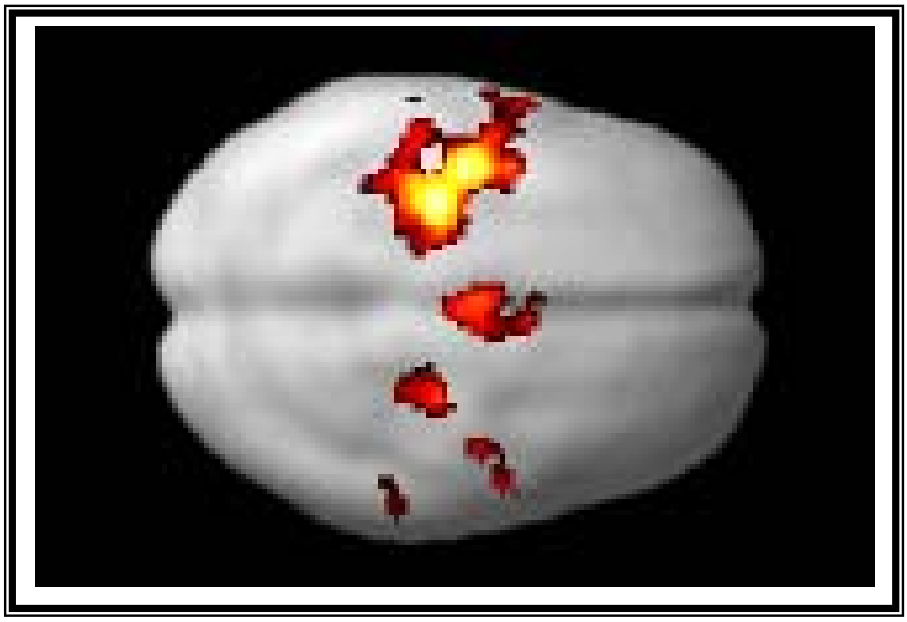
To my Grandmother Kristine,

who suffered from severe stroke at the age of 70, but recovered with the help of her daily exercises, and who returned to her normal life including her daily walks, working in the garden and cycling to the grocery store. Her vitality inspired me until she died, 21 years later.



The art of brain activation after acute ischaemic stroke.

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Summary

The incidence of stroke has not changed significantly in recent decades. However, the actual number of strokes is likely to increase as a consequence of the increasing number of elderly people, creating a significant burden on the health care system, the patients and their families. Pareses are the most common impairment reported after stroke. Motor impairments are associated with reduced self-perceived health, and consequently rehabilitation after stroke has a strong emphasis on physiotherapy and motor training. However, more knowledge about motor recovery and effects of therapy is needed for further improvement of rehabilitation processes and of outcome for the large number of stroke victims.

The overall aim of this thesis was to increase the knowledge about motor recovery after stroke by evaluating the effect of two different rehabilitation programmes compared to standard rehabilitation regimes and by investigating changes in brain activity in patients treated in terms of the recommended guidelines in the acute phase and during follow-up.

A randomised controlled trial was performed to evaluate the effect of an early supported discharge (ESD) service for patients with acute stroke living in a rural community. Sixty-two eligible patients were included and randomised to either an ESD service or to standard follow-up. The trial revealed no significant benefit on the Modified Rankin Scale, Barthel Index, Berg Balance Scale or walking speed, but significantly less isolation in the ESD group at the six-week follow-up. However, analysis of all cases with all assessments available showed a non-significant trend toward greater improvement in balance in the ESD group from one week to six weeks follow-up. The trial identified a strong association between initial severe leg paresis, but not with initial moderate leg paresis, and reduced balance one year after the stroke. There was also a strong association between initial inability to walk and reduced balance one year after the stroke.

Another randomised controlled trial was performed to evaluate the efficacy and feasibility of Constraint-Induced Movement Therapy (CIMT) organised as group therapy for patients with subacute and chronic stroke. Thirty eligible patients were included and randomised to a CIMT group receiving ten days of intensive motor training of the affected arm or to a control group receiving standard rehabilitation. The CIMT group showed a statistically significant greater

improvement in motor function of the affected arm at the post-treatment assessment. However, this difference did not persist at six months' follow-up. There were no differences between the groups at any time in relation to the amount of use of the affected arm or to independence in activities of daily living.

Finally, a longitudinal follow-up study was performed to investigate the changes in brain activation patterns from the acute to the chronic phases and their relationship to motor learning after stroke. Twelve eligible patients with acute ischaemic stroke were included and assessed with functional magnetic resonance imaging (fMRI) and clinical tests within one week after stroke and three months later. All patients, except one, had complete recovery of the affected arm according to our criteria. Increased activation in cerebellum, striatum, angular gyrus and insula was revealed in the acute phase compared to the chronic phase. The chronic phase demonstrated a restoration of the lateralised primary motor network, in addition to increased bilateral somatosensory association areas and contralesional secondary somatosensory areas (SII). The activation patterns are not identical but comparable to a motor learning process.

In conclusion, this thesis shows that the ESD service did not significantly influence death or dependency, balance or walking speed for patients living in a rural community. However, it may lead to less isolation and a transient improvement in self-perceived health. The thesis also demonstrates that CIMT organised as group therapy is feasible and efficient in the short term but may not be superior to standard rehabilitation in the long term. Finally, the thesis has revealed that the motor network changes associated with successful motor recovery are comparable to changes observed in motor learning studies in healthy subjects, and also indicating the importance of bi- and contralesional brain activation for successful motor recovery after stroke.

Acknowledgements

This project began with the implementation of the ESD trial in a rural setting, which was supported by the Norwegian Department of Health. During the four years spent preparing this thesis, the work has been funded partly by the Fund for Postgraduate Training in Physiotherapy (80%) and partly by the Clinical Services Department at St. Olavs Hospital, Trondheim University Hospital (20%). A final three months of funding was given by the Department of Public Health and General Practice, in the Faculty of Medicine at the Norwegian University of Science and Technology. In addition to the valuable financial support, I have received a lot of personal support during the years this project has taken, and many people should be acknowledged.

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Thanks to occupational therapist Heidi Hammer and to nurse Anita Elvenes, my helpful colleagues in the mobile stroke team. Thanks also to my co-worker Gun Ekeberg, and to all the primary health care providers in the municipality of Malvik, Melhus and Klæbu who cooperated with us so willingly.

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Finally, and most of all, I am grateful to my husband Lars who has lived with this thesis for so long and so intensely, especially during the past autumn, but still has encouraged me to finish it, and to my dear and loving children, Johanne, Håvard and Ingvild, who have always reminded me about the really important things in life.

List of papers

I Askim T, Rohweder G, Lydersen S, Indredavik B. Evaluation of an extended stroke unit service with early supported discharge for patients living in a rural community. A randomized controlled trial. Clinical Rehabilitation 2004;18:238-248

II Askim T, Mørkved S, Indredavik B. Does an extended stroke unit service with early supported discharge have any effect on balance or walking speed? J Rehabil Med 2006;38:368-374

III Dahl AE, Askim T, Stock R, Langørgen E, Lydersen S, Indredavik B. Short and long term outcome of Constraint-Induced Movement Therapy after stroke. A randomised controlled feasibility trial. Clinical Rehabilitation 2007 (in press).

IV Askim T, Indredavik B, Vangberg T, Håberg A. Motor network changes associated with successful motor skill relearning after acute ischemic stroke. A longitudinal functional MRI study. Neurorehabilitation & Neural Repair 2007 (submitted).

Abbreviations

ADL	Activities of daily living
BI	Barthel Index
BOLD	Blood-oxygen-level-dependent
CIMT	Constraint-Induced Movement Therapy
EEG	Electroencephalography
ESD	Early supported discharge
FAST	Face Arm Speech Test
fMRI	Functional magnetic resonance imaging
ICF	International Classification of Functioning, Disability and Handicap
IPL	Inferior parietal lobule
LACI	Lacunar infarction
LI	Laterality index
MEG	Magnetoencephalography
MI	Primary motor cortex
MII	Secondary motor cortex
MISI	Primary sensorimotor cortex
MNI space	A coordinate system for identification of the anatomical structures of the brain
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NHPT	Nine Hole Peg Test
PACI	Partial anterior circulation infarction
PET	Positron emission tomography
POCI	Posterior circulation infarction
ROI	Regions of interest
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
SSS	Scandinavian Stroke Scale
TACI	Total anterior circulation infarction
UL-MAS	Upper limb items on the Motor Assessment Scale
WHO	World Health Organization

1 Introduction

1.1 The burden of stroke

Stroke is the third most frequent cause of death, after heart disease and cancer, and a major cause of disability for those who survive (Statistisk sentralbyrå, 2003; Bonita et al., 1997). Stroke mortality is a function of the incidence (new cases per year) and case fatality (proportion of those who die). It varies widely in different regions of the world and depends on factors such as local environmental, cultural, socioeconomic and genetic variables (de Freitas GR et al., 2005). A population-based stroke study in Innherred in Norway in 1994-96 reported an annual incidence of first-ever stroke to be 3.1 per 1000 in persons aged 15 years and older. The proportion of first-ever stroke and recurrent stroke is respectively 75% and 25% (Ellekjaer et al., 1997). Adjusted to the Norwegian population we would expect 11 000 first-ever strokes and 3500 recurrent strokes to occur every year for the next years (Ellekjaer & Selmer, 2007). In the WHO MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) project, the incidence of first-ever and recurrent stroke in Northern Sweden did not change significantly from 1985 to 1998, but the 28-day case-fatality declined from 20% to 11% over the 14-year period (Stegmayr & Asplund, 2003). There are no studies concerning incidence and case fatality trends in Norway. The overall 30-day case fatality was reported to be 19% for first-ever strokes in the Innherred study (Ellekjaer et al., 1997; Ellekjaer & Selmer, 2007).

The Swedish data indicates that the changes in mortality can be principally attributed to change in case fatality rather than change in incidence (Stegmayr & Asplund, 2003; Sarti et al., 2003). Plausible explanations for the reduction in case fatality include better stroke care, a decline in stroke severity, and newer methods for diagnosing stroke (CT and MRI) allowing detection of milder stroke cases (de Freitas GR et al., 2005; Sarti et al., 2003). The risk of stroke increases with age, and due to the increased birth rate after the Second World War, the number of persons above the age of 65 is expected to increase by approximately 50% between now and 2030, with a corresponding increase in the total numbers of stroke (Waaler, 1999). This implies that the burden of stroke will continue to grow, affecting increasing numbers of individuals, and their families, and increasing the cost to the economy. The mean cost

associated with each new stroke in Norway, from onset to death, is estimated at NOK 600 000 (Fjaertoft & Indredavik, 2007).

In conclusion, the expected increase in number of strokes, and the decrease in stroke mortality, will continue to place a significant burden on the health care system, the stroke patients and their families in the foreseeable future.

1.2 Definition of stroke

Stroke is defined as rapidly developed clinical signs of focal (or global[1]) disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death), with no apparent cause other than a vascular origin: it includes patients presenting clinical signs and symptoms suggestive of subarachnoid haemorrhage, intracerebral haemorrhage or cerebral ischaemic necrosis. It does not include transient cerebral ischaemia or stroke events in cases of blood disease (e.g. leukemia, polycythaemia vera), brain tumour or brain metastases (The WHO MONICA Project, 2007).

The focal signs are: unilateral or bilateral motor impairment (including dyscoordination), unilateral or bilateral sensory impairment, aphasis/dysphasis (non-fluent speech), hemianopia (half-sided impairment of visual fields), diplopia, forced gaze (conjugate deviation), dysphagia of acute onset, apraxia of acute onset, ataxia of acute onset and perception deficit of acute onset (The WHO MONICA Project, 2007).

Early stroke detection is possible by using the Face Arm Speech Test (FAST). FAST was developed in 1998 as a stroke identification instrument, and evaluates the presence or absence of face palsy, asymmetric arm weakness, and speech abnormalities (Harbison et al., 2003; Goldstein & Simel, 2005). Eighty-two percent of all stroke patients have one or more of these three symptoms (unpublished data from the Stroke Unit, St. Olavs Hospital, Trondheim).

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[1]Global: this applies to patients with subarachnoid haemorrhage or deep coma but excluding coma of systemic vascular origin such as shock, Stokes-Adams syndrome or hypertensive encephalopathy.

Focusing on these three findings improves diagnostic accuracy and reliability (Goldstein & Simel, 2005).

1.3 Types of stroke

Stroke includes cerebral infarction, intracerebral haemorrhages and subarachnoidal haemorrhages. The infarctions make up 85% of the cases, the intracerebral haemorrhages 12% and the subarachnoidal haemorrhages 3% of the cases admitted to hospital (Ellekjaer et al., 1997). The following two sections will focus on the infarctions, as they make up the majority of strokes.

1.4 Classification of ischaemic stroke

The infarctions can be classified into lacunar infarctions (LACI), total anterior circulation infarctions (TACI), partial anterior circulation infarctions (PACI) and posterior circulation infarctions (POCI), according to the Oxfordshire clinical classification (Bamford et al., 1991). The LACI presents with pure motor stroke, pure sensory stroke, sensorimotor stroke, or ataxic hemiparesis. The symptoms in TACI are a combination of new higher cerebral dysfunction, homonymous visual field defect, and ipsilateral motor and/or sensory deficits of at least two areas of the face, arm, and leg. The PACI is defined as the presence of two of the three components of the TACI syndrome, with higher cerebral dysfunction alone, or with a motor/sensory deficit more restricted than those classified as LACI. The POCI presents with any of the following: ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit, bilateral motor and/or sensory deficit, disorder of conjugate eye movement, cerebellar dysfunction without ipsilateral long track deficit, or isolated homonymous visual field defect (Bamford et al., 1991). This clinical classification has also shown to be a reasonably valid way of predicting the site and size of cerebral infarctions (Wardlaw et al., 1996).

1.5 The mechanism of ischaemic stroke

Cerebral infarction is the neurological evidence of critical reduction of cerebral blood flow in a circumscribed part of the brain, resulting from the sudden or gradually progressing occlusion of a brain artery (Hossmann, 2006). The infarction core is characterised by cell injury and necrosis surrounded by a region with functionally silent but structurally intact cells called the penumbra. The penumbra is a region of constrained blood supply in which energy

metabolism is preserved, and it will regain its function if the blood flow and oxygenation improve in time (Astrup et al., 1981).

1.6 The purpose of this thesis

A basic understanding of the processes of recovery after stroke and the evidence for motor training and follow-up services are still undetermined. The purpose of the investigation presented in this thesis was to increase the knowledge about this topic. Two randomised controlled trials and one longitudinal follow-up study were carried out to achieve this goal. In the first randomised trial we wanted to evaluate the effect of a multidisciplinary rehabilitation programme. In the second trial we wanted to evaluate the effect of an intensive mass-practice programme. In the third study we wanted to study the changes in brain activation patterns that occur with motor recovery in a selected group of patients with acute ischaemic stroke, treated in a stroke unit with early mobilisation and early supported discharge service. The background for this work will be presented in the next section.

2 Background

2.1 Evidence-based stroke treatment

Evidence-based medicine is the continuous, explicit and careful use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research (Sackett et al., 2007). The Cochrane Collaboration is an international non-profit and independent organisation, dedicated to making up-to-date, accurate information about health care readily available worldwide (Cochrane Collaboration, 2007). In a Cochrane search, 80 reviews with 'stroke' in the record title were identified, indicating that there might be a considerable amount of evidence about different stroke treatments. One of these reviews, 'Organised inpatient (stroke unit) care for stroke patients' (Stroke Unit Trialists' Collaboration, 2002), provides evidence of the benefit of stroke unit treatment. Another review, 'Services for reducing duration of hospital care for acute stroke patients' (Early Supported Discharge Trialists, 2007), shows growing evidence for early supported discharge.

2.1.1 Stroke unit treatment

Several randomised controlled trials have been performed in different countries and clinical settings to assess the effectiveness of stroke unit care for hospitalised stroke patients. The results of these studies show that stroke unit care reduces death and dependency in the short and long term (Stroke Unit Trialists' Collaboration, 2002). The complex interventions that were used experimentally on small selected groups of patients included in the randomised trials are also shown to be applicable and effective for all acute stroke patients admitted to stroke units (Candelise et al., 2007; Asplund et al., 2003).

There are different kinds of stroke units, focusing on different aspects of acute stroke treatment. They can be most commonly classified as stroke ward, mixed rehabilitation ward or mobile stroke team. Stroke wards include: a) acute stroke units, which are an intensive model of care with continuous monitoring and high nursing staff levels; b) rehabilitation stroke units which accept patients after a delay of around 7 days or more, and which focus on

rehabilitation; and c) comprehensive stroke units, a combined acute and rehabilitation ward, which accept patients acutely but also provide rehabilitation for several weeks if necessary. A mixed rehabilitation ward is likely to be staffed by a multidisciplinary team including specialist nurses, in a ward providing a generic rehabilitation service, but not exclusively caring for stroke patients. A mobile stroke team is a multidisciplinary team providing care in a variety of settings (Stroke Unit Trialists' Collaboration, 2002). The literature indicates that stroke units with a strong focus on physical therapy and rehabilitation are the most beneficial (Langhorne & Pollock, 2002; Indredavik, 2007).

The Stroke Unit at St. Olavs Hospital is defined as a comprehensive stroke unit. It was established in association with a well conducted randomised controlled trial (Indredavik, 1999), which demonstrated that effective stroke unit treatment increases the proportion of patients able to live at home, improves functional outcome, reduces the needs for institutional care and reduces early mortality compared to stroke patients treated in a general ward (Indredavik et al., 1991). These beneficial effects also persist in the long term (Indredavik et al., 1997; Indredavik et al., 1999a).

This stroke unit is now established as one of the normal range of specialist facilities at St. Olavs Hospital, and it can be regarded as an evidence-based ward. The important features of the care on this ward include diagnostic evaluation and systematic observation during the first 72 hours, acute medical treatment to reduce the brain damage, early mobilisation, preventing complications, initiating secondary prevention, early and regular evaluation of the potential for rehabilitation, early initiation of rehabilitation and patient-specific planning for further rehabilitation after discharge. Of all these factors, early mobilisation seems to be the most important, followed by stabilisation of the diastolic blood pressure (Indredavik et al., 1999b).

2.1.2 Early supported discharge for stroke patients

The provision of acute treatment in a stroke unit is the recommended “gold standard” for all patients suffering from acute stroke (Norges forskningsråd, 1995; Aboderin & Venables, 1996). However, there has been a lack of rigorous evidence about the best treatment after discharge from hospital. A clinical trial was designed by Indredavik and Fjærtoft with the objective of determining the most effective way of organising post-acute stroke care, so as to improve outcomes without increasing the use of health resources (Fjærtoft, 2005).

In this clinical randomised controlled trial, 320 patients were randomly allocated either to a standard service, or to an early supported discharge (ESD) service. The results demonstrated significantly improved functional outcome and shorter institutional stay for patients in the ESD group compared to those in the standard group (Indredavik et al., 2000; Fjaertoft et al., 2003). A meta-analysis including 11 ESD trials shows an overall reduction in death and dependency for patients in the ESD groups. The hospital stay was eight days shorter for patients assigned to ESD services compared to those assigned to conventional care. However, all the reviewed trials were conducted in urban settings, and the effectiveness and appropriateness of ESD service in rural communities should also be tested (Langhorne et al., 2005; Early Supported Discharge Trialists, 2007).

The successful ESD trial in Trondheim inspired us to replicate the trial for patients living in some of the more rural municipalities surrounding the city. Although the patients from this area received equivalent treatment within the stroke unit, the hospital was a longer distance from their homes, which made it more challenging to interact with both relatives and the primary health care service. We wanted to adapt the main points of the ESD service in Trondheim and to investigate whether this service was effective and beneficial for patients living in the municipalities of Malvik, Melhus and Klæbu. A clinical randomised trial was designed to evaluate the effect of an ESD service in a rural setting and the results are presented in *Paper I* and *Paper II* of this thesis.

2.2 Predicting functional outcome

The quest to identify those factors which can help predict functional recovery after stroke has been the subject of extensive research. It has been argued that certain sub-groups of the stroke population may benefit more than others from specific rehabilitation services. In order to achieve the most efficient use of such services, it is important to identify predictors that discriminate between stroke patients with good and poor recovery potential. Several prognostic factors such as age, gender, previous stroke, time from onset of stroke to hospital admission, severity of paralysis, ischaemic lesion volume, balance and functional admission score, have been identified.

Age is assumed to be an important predictor of stroke recovery, with younger patients having better outcomes (Jongbloed, 1986; Kwakkel et al., 1996; Jorgensen et al., 1999; Nakayama et al., 1994; van de Port et al., 2006). However, age does not influence the neurological aspects, suggesting a poorer compensatory ability in elderly stroke patients (Nakayama et al., 1994). Outcomes do not seem to differ between men and women (Counsell & Dennis, 2001). The influence of previous stroke is somewhat conflicting, showing both no influence (Counsell & Dennis, 2001) and an association with poorer outcome (Kwakkel et al., 1996; Woldag et al., 2006). On the other hand, prolonged time from onset of symptoms to hospitalisation would appear to be a valid predictor of recovery of function associated with poorer outcome (Kwakkel et al., 1996; van de Port et al., 2006). Initial neurological impairment assessed by means of the Scandinavian Stroke Scale score predicts the incidence of death and dependency in patients with mild ischaemic stroke (Christensen et al., 2005). The evidence for an association between initial leg paresis and functional outcome is also conflicting, showing both a strong association between leg paresis and the ability to regain independent walking (Wandel et al., 2000; Olsen, 1990; Jorgensen et al., 1995a), and no association between initial leg paresis and increased risk of falling when the results were adjusted for depressive symptoms (Jorgensen et al., 2002). However, the overall degree of impairment and weakness in the acute stage appears to influence functional outcome (Counsell & Dennis, 2001). Furthermore, the Barthel Index was the single predictor of walking ability in a multivariate model (Wandel et al., 2000). Finally, initial trunk control (Kwakkel et al., 1996; Franchignoni et al., 1997; Duarte et al., 2002; Hsieh et al., 2002), and change in standing balance (Kollen et al., 2005) are described as significant predictors, influencing the functional outcome after stroke. Many of these factors are probably interrelated.

Ischaemic lesion volume is also considered to be an important predictor of post-stroke functional outcome, but the role of brain imaging data is not consistent. Magnetic resonance diffusion weighted imaging included in a three-item prediction model was validated showing good sensitivity and specificity (Baird et al., 2001). However, that particular study may be criticised for selection bias, as it included a highly selected group of stroke patients. Methodological shortcomings of most studies, such as different neuro-imaging methods, different timing of imaging and different outcome assessment, confound the prognostic value of magnetic resonance imaging (MRI) in predicting stroke outcome (Schiemanck et al., 2006).

The conflicting results in the association between leg paresis and functional outcome might be contingent on the different ways of categorising the extent of leg paresis. With reference to this issue, we wanted to assess the association between different degrees of initial leg paresis as determined by the leg item on the Scandinavian Stroke Scale and balance one year after the stroke. Different balance measures also have an impact on assessment of functional outcome. The movement item on the Scandinavian Stroke Scale may be used as a simple measure of functional balance, and we wanted to assess whether different degrees of initial movement ability according to this item were associated with balance one year after the stroke. The results of these analyses are presented in *Paper II*.

2.3 Motor training after stroke

Motor impairments are the most commonly reported impairments after acute stroke, with upper limb motor deficits present in 77% and lower limb motor deficits present in 72% of patients one week after onset of first-ever stroke (Lawrence et al., 2001). Reduced balance is another common motor impairment, and about 50% of those admitted to further rehabilitation were not able to stand without support one month after onset of stroke (Benaim et al., 1999). However, spasticity would appear to be a less common problem, as it was present in only 19% of the patients investigated three months after stroke (Sommerfeld et al., 2004).

Motor impairments are associated with reduced self-perceived health (Suenkeler et al., 2002; Sturm et al., 2004) and consequently, rehabilitation after stroke has a strong emphasis on physiotherapy and motor training.

2.3.1 Different physiotherapy approaches

A range of physiotherapy approaches based on different ideas about motor recovery following stroke have been implemented (Pollock et al., 2007). In the 1950s and 1960s neurofacilitation approaches based on available neurophysiological knowledge were developed, including the Bobath approach (Davies, 1999), which became the most commonly used method. In the 1980s the potential importance of neurophysiology and motor learning was highlighted (Schmidt, 1991) and the motor learning, or relearning, approach (Carr & Shepherd, 1987) was proposed. The Bobath approach has emphasised the importance of facilitating movement and

of tactile stimulation (hands on) (Davies, 1999), while the Motor Relearning Programme emphasises active patient involvement with focus on goal setting, and task-specific practice to improve function after stroke (Carr & Shepherd, 1987). Within the Motor Relearning Programme approach, the actions to be learned are practiced in an appropriate context, with exercises directed specifically at the muscles required for the performance of the action, working through the range at which they must generate force. Furthermore, the patients practise movement tasks with the therapist as a coach who encourages the performance by instruction, manual guidance, demonstration or verbal feedback. Instructions are given in such a way as to present a clear goal and to reduce uncertainty. Manual guidance may be used in the early phase to give the patient an idea about what to do. The action to be executed can be demonstrated either alive or on videotape, and verbal feedback is given to provide information about achievement of the goal and how the movement was performed (Carr & Shepherd, 1998). Shumway-Coock & Woollacott (2001) describe the Motor Relearning Programme as a task-oriented approach based on newer theories of motor control, also referred to as a system approach (Woollacott & Shumway-Cook, 1990).

However, anecdotal evidence and the results of questionnaire-based studies suggest that it is difficult to distinguish between the practical implementation of the two approaches (van Vliet et al., 2001). This is confirmed in the recent review by Pollock et al (2007), who recommends that further research should focus on investigating clearly defined and described techniques and task-specific interventions regardless of their historical or philosophical origin, in order to develop an evidence-based physiotherapy (Pollock et al., 2007).

2.3.2 Task-specific treatment

Dean and Shepherd (Dean & Shepherd, 1997) performed the first randomised placebo-controlled trial to test the effect of task-specific postural training. They trained chronic stroke patients to increase their upper limb radius while seated and to increase the contribution of the affected lower leg to support balance. At the end of a two-week programme, subjects were able to reach faster and further, to increase the load on the affected foot, and to increase activation of affected lower limb leg muscles compared with the control group. This study provides strong evidence of the efficacy of task-specific motor training in improving the ability to balance during seated reaching activities after stroke (Perennou & Bronstein, 2005).

A more recent randomised controlled trial evaluated the effect of a 3-month structured, supervised, home-based exercise programme which included task-specific balance training in combination with exercises to improve range of motion, strength and endurance. The results demonstrated improved recovery in patients treated with the home-based programme compared to those treated with usual care (Duncan et al., 2003).

Treadmill training is frequently used to improve endurance in both healthy people and in particular patient groups. Treadmill training is also described as a task-specific method to improve gait function after stroke. For this purpose two different forms of treadmill training exist: body-weight-supported treadmill training (BWSTT) and unsupported treadmill training. Wood-Dauphinee & Kwakkel (Wood-Dauphinee & Kwakkel, 2005) have investigated the impact of BWSTT that ranges from no support to 40 % support in five randomised controlled trials involving 266 stroke patients. The analysis showed significantly better (29 %) gait endurance for the BWSTT group, despite great variability in the intensity of the different studies. No significant differences according to gait speed, balance or walking ability were detected (Wood-Dauphinee & Kwakkel, 2005). In contrast, another meta-analysis showed that BWSTT tended to produce a non-significant trend toward higher walking speed compared to other interventions, among stroke patients who could walk independently at the start of treatment (Moseley et al., 2005). There is no evidence that treadmill training without body-weight-support has an additional effect on walking compared to conventional gait training programmes on the floor (Wood-Dauphinee & Kwakkel, 2005; Moseley et al., 2005).

The benefit of task-specific training to improve muscle strength in the affected arm or leg has also been evaluated in some randomised clinical trials (Winstein et al., 2004; Yang et al., 2006), showing less impairment and greater isometric strength in the affected arm (Winstein et al., 2004), increased strength in the affected leg, and improved functional outcome (Yang et al., 2006). The intensity of the task-specific intervention varied from 30 minutes progressive resistance strength training for the lower extremity per week for four weeks (Yang et al., 2006), to task-specific functional training of the upper extremity (e.g. pointing or grasping) of at least 20 hours within six weeks (Winstein et al., 2004).

Although it would appear that task-specific training is effective in enhancing recovery after stroke, there is still no consensus about the appropriate amount or intensity of this training. So

it is relevant to ask whether people who receive “more intensive” as opposed to “less intensive” rehabilitation in all phases achieve better and faster motor and functional recovery.

2.3.3 More intensive therapy versus less intensive therapy

Intensive training may refer to increased work rate and/or increased amount of training. It would appear that the literature in this field most commonly uses the term “intensive training” to describe an increased amount of training, and that will be how the term is used in this thesis.

Two systematic reviews suggest that early implementation of intensive stroke rehabilitation is associated with enhanced and faster improvement of the functional recovery after stroke (Kwakkel et al., 1997; Langhorne et al., 1996). A more recent meta-analysis supports the hypothesis that augmented exercise therapy has a small but favourable effect on ADL (Kwakkel et al., 2004). The intensive rehabilitation group received at least 16 hours more exercise therapy within the first six months after stroke than the control group. It should be noted that the content of therapy differed between the studies examined, and that this may have influenced the results.

Based on this evidence, it would appear that more intensive training is better than less intensive training. However, the observation of physical activity between 8 am and 5 pm in seven acute stroke units in Melbourne, Australia, revealed that the patients spent only 12,8 % of day time walking or in transfer activities (Bernhardt et al., 2004), suggesting a potential for increasing the amount of training during the initial hospital stay after acute stroke. However, it should also be acknowledged that intensive therapy is not feasible for every patient or clinical setting because of the individual’s inability to tolerate the extra therapy sessions (Kwakkel et al., 2004).

2.3.4 Constraint-Induced Movement Therapy

Constraint-Induced Movement Therapy (CIMT) is a new and well described therapy which combines intensive task-specific training with shaping (i.e. gradual adaptation of the tasks to increasingly complex movements as function improves, see section 4.3.2.) and restriction of the unaffected limb (Taub et al., 1999a; Sirtori et al., 2003). The theoretical framework of

CIMT is based on the learned non-use phenomenon. This phenomenon was revealed through the observations of monkeys after experimentally induced upper limb deafferentation, leading to reduced use of the affected arm. However, the monkey could be encouraged to use the deafferented extremity by restricting movement of the intact limb (Taub & Uswatte, 2003). Taub and Uswatte (Taub & Uswatte, 2003) suggest in their synthesis of research on CIMT that this non-use is a learning phenomenon. Three possible processes can explain the learned non-use: 1) punishment for using the affected limb (e.g. uncoordination and falling or loss of food objects), 2) positive reinforcement for using the intact limb and 3) reduced cortical representation of the affected limb. Based on this, Taube and Uswatte assume that the inability to use the affected limb after stroke may also be explained by the learned non-use phenomena, and they propose a family of techniques which may overcome the learned non-use (Taub et al., 1999b; Taub & Uswatte, 2003).

CIMT is mainly applied to stroke patients in the subacute or chronic phase, and several studies have revealed positive effects of this treatment compared to other treatments in the short term (Sterr et al., 2002; Taub et al., 1993; Taub et al., 2006; van der Lee et al., 1999; Wittenberg et al., 2003; Wolf et al., 2006). The most recent study by Wolf et al (2006) has shown the most convincing effect. In this trial, the short-term effect persisted at one year follow-up with significantly better motor function, greater amount of use and better quality of movement of the affected arm, as well as better self-perceived hand function. This study is the first multisite randomised controlled trial to demonstrate the efficacy of a rehabilitative intervention. It therefore moves neuro-rehabilitative care into the area of evidence-based medicine (Luft & Hanley, 2006). However, the criteria for inclusion in the CIMT studies cited have been strict, and only 6 % of the stroke population fulfilled the criteria for inclusion in the EXCITE trial (Wolf et al., 2006). In order to make the intervention more feasible for a greater proportion of the stroke population, modified versions of CIMT have also been evaluated (Page et al., 2005; Page et al., 2004; Dromerick et al., 2000). Page et al (2005) found that individualised, half-hour therapy sessions, three times per week for 10 weeks, combined with five hours of restraint on the unaffected arm every weekday, improved arm function significantly in a group of acute stroke patients, compared to traditional rehabilitation (Page et al., 2005). Modified CIMT may be a feasible and effective treatment for improving function and use of the more affected arm in chronic stroke patients as well (Page et al., 2004; Dromerick et al., 2000).

So far, the majority of CIMT trials have been conducted in the US and only two from Europe have been published (Sterr et al., 2002; van der Lee et al., 1999). Given this, we wanted to assess the efficacy and feasibility of 6 hours' daily CIMT organised as group therapy in the Norwegian health care system. This trial is reported in *Paper III*.

2.4 Motor recovery after stroke

In most stroke patients, recovery follows an exponential progression, with a fast initial improvement during the first six weeks and a slower recovery for the next six weeks (Jorgensen et al., 1995c). Animal studies have shown that the cerebral cortex undergoes significant functional plasticity for weeks to months following injury (Nudo & Milliken, 1996). Spared regions adjacent to the infarction and far removed from the infarction undergo functional alterations that are modified by behavioural experience (Nudo, 2007).

It has also been shown in an animal model that rehabilitation initiated five days after focal ischaemia was much more effective than waiting for one month before beginning rehabilitation (Biernaskie et al., 2004). This study demonstrates significant interaction between rehabilitation and spontaneous recovery processes early after stroke. The mechanisms of this recovery process may be listed in three general changes within the sensorimotor network: restitution, substitution, and compensation (Dobkin & Carmichael, 2005). Restitution is relatively independent of external variables such as physical and cognitive stimulation. Restitution includes reduction of edema, absorption of blood, restoration of ionic currents, and restoration of axonal transport (Dobkin & Carmichael, 2005), and also reperfusion due to vessel recanalisation (Butefisch et al., 2006). Substitution depends on external stimuli such as practice with the affected hemiparetic arm or leg during rehabilitation. Substitution includes the functional adaptations of diminished, but partially restored, neural networks that compensate for components lost or disrupted by the injury. Substitution may add a cost to the mental or physical energy needed to carry out a relearned motor skill (Dobkin & Carmichael, 2005). This may contribute to explaining some of the fatigue experienced by a significant proportion of the stroke population (De Groot et al., 2003). Compensation aims to improve the mismatch between a patient's impaired skills and the demands of the patient or the environment (Dobkin & Carmichael, 2005).

2.4.1 Brain plasticity

A range of imaging techniques have been applied to visualise patterns of altered brain activation following stroke, and to characterise changes in activity patterns with recovery and rehabilitation. Electroencephalography (EEG) records electrical activity from electrodes at the scalp, while magnetoencephalography (MEG) records the magnetic changes associated with the changing electrical fields. These approaches offer the advantage of recording signals that are closely related to the underlying neuronal activity, and thus have high temporal resolution; however, their spatial resolution is limited. In contrast, techniques such as functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) record signals related to the metabolic or hemodynamic consequences of such electrical activity (Johansen-Berg, 2007). A methodological challenge is the heterogeneity and absence of blood-oxygen-level-dependent (BOLD) signals measured in fMRI observed in some studies in patients with vascular disease (Binkofski & Seitz, 2004; Krainik et al., 2005; Rossini et al., 2004). Still, PET and fMRI offer significant advantages in term of spatial resolution, with fMRI as the superior, allowing for fine-grained localisation of the remapping that may occur after stroke (Johansen-Berg, 2007).

Several fMRI studies have been undertaken in the past decade to study the role of brain plasticity in the recovery after stroke. Both cross-sectional and longitudinal study designs have been used, but the longitudinal design would appear to be more appropriate to study the evolution of the activity pattern as recovery takes place (Calautti & Baron, 2003). The reported patterns of change are variable, but some consistencies have now emerged. These may be classified into three major patterns of change: 1) local remapping within the primary motor cortex, 2) increased activity in non-primary sensorimotor areas, and 3) increased activity in the undamaged hemisphere (Johansen-Berg, 2007).

The local remapping implies a ventral or posterior shift in the location of primary sensorimotor (MISI) cortex activation (Pineiro et al., 2001; Calautti et al., 2003; Cramer & Crafton, 2006). There are recent suggestions that smaller infarction volumes are associated with more ventral and larger infarction volumes with more posterior activation foci. On the other hand, better behavioural outcome would appear to be associated with greater posterior activation, and poorer outcome with a more ventral activity (Cramer & Crafton, 2006). Increased recruitment of non-primary motor areas, such as inferior parietal cortex, cingulate

cortex and pre-motor cortex has been reported (Tombari et al., 2004; Nelles et al., 1999; Loubinoux et al., 2003). It is suggested that this pattern represents adaptive plasticity, in which undamaged areas of cortex take over the function of the damaged regions. It is proposed that this pattern will never result in complete recovery (Calautti & Baron, 2003; Johansen-Berg, 2007). A number of studies have reported increased activity of the unaffected sensorimotor cortex following stroke (Cao et al., 1998; Cramer et al., 1997; Gerloff et al., 2006; Thiel et al., 2007; Schaechter & Perdue, 2008), suggesting a significant role for the non-stroke hemisphere in mediating recovery. Although the majority of corticospinal outputs are crossed, approximately 30% of them remain uncrossed. It is suggested that these fibres bring signals from the undamaged hemisphere to the affected side of the body (Iwamura et al., 2001).

2.4.2 Motor learning and recovery

Motor learning is defined as a set of processes associated with practice that lead to relatively permanent change in performance capability (Schmidt, 1991). Studies in healthy humans have demonstrated that incremental acquisition of motor skills follows two distinct stages: first, an early, fast learning stage in which considerable improvement in performance can be seen within a single training session, and secondly, a later, slow stage in which further gains can be observed across several sessions (and even weeks) of practice (Doyon et al., 2003). It is proposed in an animal model that motor skill acquisition, or motor learning, is a prerequisite for task-related changes in the activation maps of primary motor cortex (Plautz et al., 2000), and consequently it is suggested that motor learning is required for both substitution, i.e. when undamaged brain regions are recruited to generate commands to the same muscles as were used before the injury (true recovery), and compensation, i.e. the use of alternative muscles to accomplish the task goal (Krakauer, 2006). Several brain structures, including the striatum, cerebellum, and motor cortical regions of the prefrontal lobe, are considered to be critical for acquisition of motor skilled behaviour, and it is suggested that the acquisition of motor skills reproduces changes in the cortico-striatal and cortico-cerebellar systems over the course of motor skill learning in healthy subjects (Doyon et al., 2003).

Previous longitudinal brain imaging studies after stroke have mainly focused on the neural correlates to motor recovery, but not on whether these changes share features with brain plasticity in healthy subjects over the course of motor skill learning. The task-oriented

approaches, particularly the Motor Relearning Programme, are based on motor learning principles assuming that recovery after stroke i.e. relearning of lost motor skills, are comparable to motor learning in healthy subjects (Carr et al., 1987). Whether brain activation corresponding to motor recovery following stroke can be explained by motor learning mechanisms is still undetermined. In the last paper of this thesis, we wanted to study the motor network changes in patients admitted to a comprehensive stroke unit, treated with early mobilisation and physiotherapy according to a task-oriented approach, within the framework of motor learning.

3 Aims of the thesis

The overall aim of this thesis was to increase the knowledge about recovery, particularly motor recovery, after stroke, by evaluating the effect of one multidisciplinary rehabilitation programme and one intensive mass-practice programme compared to standard treatment programmes, and to investigate changes in brain activation over the course of motor recovery after stroke.

The specific aims are:

- To evaluate the effect of an ESD service coordinated by a multidisciplinary mobile stroke team for patient with acute stroke living in a rural community *(Paper I and Paper II)*.

- To assess the association between initial leg paresis and initial movement ability and balance one year after stroke *(Paper II)*.

- To evaluate the effect and feasibility of Constraint-Induced Movement Therapy for patients with subacute and chronic stroke admitted to an in-patient rehabilitation clinic *(Paper III)*.

- To assess the early motor network changes in a group of stroke patients treated in a comprehensive stroke unit, and to investigate its relationship to motor learning *(Paper IV)*.

4 Material and Methods

This thesis includes two randomised controlled trials: one early supported discharge trial (ESD trial) and one constraint-induced movement therapy trial (CIMT trial), as well as a longitudinal functional MRI study (fMRI study). They are presented in four papers (*Paper I-IV*). An integrated stroke service provided as a framework for this project (Figure 1).

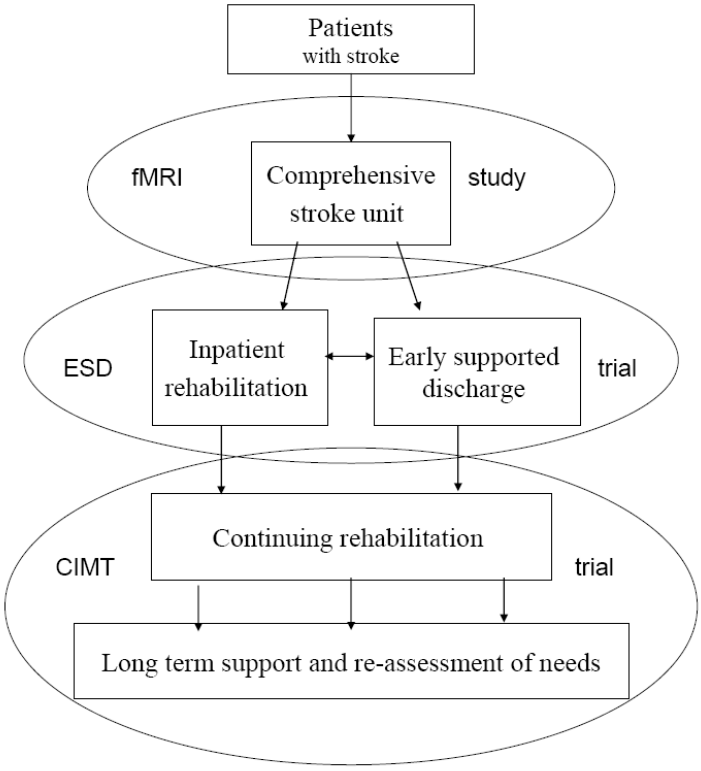

Figure 1. A model for the studies implemented in this thesis (The illustration is adapted with permission from the Early Supported Discharge Trialists)

4.1 Study participants

Three different samples, including acute, subacute and chronic stroke patients, were studied. Patients admitted to the stroke unit at St. Olavs Hospital were screened for inclusion in the ESD trial and the fMRI study, while patients within the area of the Central Norway Regional Health Authority were screened for inclusion in the CIMT trial. The inclusion criteria are described in Table 1, and the baseline characteristics of the included patients are listed in Table 2.

Table 1. Inclusion criteria for patients screened for inclusion into *Paper I-IV*

Study population	N	Eligibility criteria	Paper
Patients with the diagnosis of acute stroke, admitted to the Stroke Unit at St. Olavs Hospital, living in the municipality of Malvik, Melhus or Klæbu	62	1) Scandinavian Stroke Scale (SSS) score greater than 2 points and less than 58 points. 2) Living at home before the stroke. 3) Inclusion within 72 hours after admission to the stroke unit and seven days after onset of symptoms. 4) Able and willing to provide informed consent	I, II
Patients with the diagnosis of subacute and chronic stroke living within the area of Central Norway Regional Health Authority	30	1) Age: 18 - 80 years 2) More than two weeks from onset of stroke 3) Weakness or reduced dexterity of the affected hand 4) More than 20˚ active wrist extension and 10˚ active finger extension 5) More than 20 points on Mini Mental State Examination (MMSE) 6) Less than 13 points on Montgomery and Aasberg Depression Rating Scale 7) Less than 2 cm deviation from the midline on line bisection 8) No other neurological diseases 9) More than 6 months' life expectancy 10) Sufficient endurance to participate, evaluated by clinical assessment 11) Able and willing to provide informed consent	III
Patients with the diagnosis of acute stroke, admitted to the Stroke Unit at St. Olavs Hospital, living in the municipality of Trondheim, Malvik, Melhus or Klæbu	12	1) First-ever stroke 2) Age: 50 - 75 years 3) No other diseases in the central nervous system 4) Modified Rankin Scale score less than 3 points before the stroke 5) Hand item or arm item on SSS more than 0 points and less than 6 points 6) Six points on the consciousness item on SSS 7) Inclusion 4 to 7 days after onset of symptoms 8) More than 20 points on MMSE 9) Can tolerate MRI scanning 10) No contraindication to MRI scanning 11) Able and willing to provide informed consent	IV

Table 2. Baseline characteristics for patients included in *Paper I-IV*

Study	**ESD trial**		**CIMT trial**		**fMRI study**
Paper	*Paper I, II*		*Paper III*		*Paper IV*
Design	Randomised controlled trial		Randomised controlled trial		Longitudinal follow-up
Group allocation	TG	CG	TG	CG	
N	31	31	18	12	12
Age (years), mean (SD)	77 (7)	76 (9)	62 (8)	60 (12)	67 (5)
Gender, number (%) male	16 (52)	17 (55)	16 (89)	7 (58)	8 (67)
Medical history, number (%)					
Transient ischaemic attack	6 (19)	2 (7)	0 (0)	2 (17)	1 (1)
Stroke	2 (7)	1 (3)	1 (6)	2 (17)	0 (0)
Myocardial infarction	5 (16)	7 (23)	3 (17)	2 (17)	1 (1)
Atrial fibrillation	3 (10)	8 (26)	2 (11)	0 (0)	1 (1)
Hypertension	3 (10)	10 (32)	8 (44)	5 (42)	4 (33)
Diabetes	1 (3)	5 (16)	4 (22)	3 (25)	2 (17)

TG, treatment group; CG, control group

4.2 Study intervention applied in the ESD trial (Paper I and II)

4.2.1 The standard stroke unit service

The patients in the standard service group were offered the well documented treatment for stroke patients in the Stroke Unit at St. Olavs Hospital (Indredavik et al., 1991; Indredavik et al., 1997; Indredavik et al., 1998; Indredavik et al., 1999a). This treatment is defined as the stroke unit treatment of choice according to evidence-based recommendations. After discharge from the hospital, further rehabilitation was delivered by the primary health care system in the municipalities of Malvik, Melhus and Klæbu. However, the primary health care system was organised differently in each of these three municipalities. Melhus was the only municipality with a community-based in-patient rehabilitation clinic. In addition, the number of occupational and physical therapists varied widely. Traditionally, patients were discharged to further in-patient rehabilitation in a nursing home or back to their homes.

The standard stroke unit service is described as an ordinary stroke unit service (OSUS) in *Paper I* and *Paper II*.

4.2.2 The early supported discharge service

The early supported discharge (ESD) service was developed during a previous trial for patients living in the city of Trondheim (Indredavik et al., 2000; Fjaertoft et al., 2003; Fjaertoft et al., 2004). It comprised the standard stroke unit service combined with a home-based programme of follow-up care coordinated by a multidisciplinary hospital outreach stroke team which offers early supported discharge.

The multidisciplinary team was based within the stroke unit and comprised a nurse, a physiotherapist, an occupational therapist and the consultant availability of a physician. The team was specially trained to organise and coordinate the follow-up in cooperation with the primary health care system and to offer support during the first four weeks after discharge from the stroke unit. An important feature of this cooperation was the transfer of expertise about the diagnosis of stroke and stroke treatment to the primary health care system. In principle, the same primary healthcare system was available to patients in both groups, but the multidisciplinary team was only available to the ESD group.

The locality covered by the three participant municipalities may be described as a rural community with a dispersed settlement pattern, indicating that the patient's home is likely to be a long distance away from the community centre and the hospital. As soon as a patient was randomised to the ESD service, the team was contacted, and one of the three team members started collecting information about the patient's previous and present functioning, disabilities and contextual factors. At the same time the primary healthcare system was informed about the patient. For those patients living within 45 minutes driving distance from the hospital, where direct discharge to home was likely to occur, a home visit was usually made as soon as the medical condition of the patient allowed this. The aim of the visit was to assess the home environment, to define the goals of further rehabilitation and to make a plan for follow-up together with the family and the primary healthcare providers. For those patients living more than 45 minutes from the hospital, we asked the primary healthcare providers to make this visit. The need for further rehabilitation was subsequently defined over the telephone. The team member then established a service and support system for the patient, allowing them to return home as soon as possible and to continue the necessary training and rehabilitation at home, in a day clinic or both. On the day of discharge, a meeting was organised with the patient and his/her family, the physician and the mobile stroke team member. The aim of the

meeting was to jointly define the plans for further follow-up care. The definite day of discharge was decided in collaboration with the team member, the patient and their family.

For patients with extensive deficits after a stroke who needed help and support 24 hours a day, plans for further in-patient follow-up in a rehabilitation clinic were made.

During the first four weeks after discharge the multidisciplinary team acted as a safety net for the patient, and kept in contact both by telephone and by at least one other home visit to ensure the appropriate level of follow-up care. This period of close follow-up by the mobile team terminated with an outpatient consultation for those patients living within 45 minutes driving distance from the hospital. A consultation was conducted in the patient's home for patients living farther from the hospital. The physician responsible for the patient's treatment during the acute hospital stay, the team member, the patient, and if possible, the family participated in this visit.

When a group of patients was identified within the same community, the patients and their families were invited to a local meeting. The aim of this meeting was to give general information about acute and chronic issues of stroke care, as well as to give the patients an opportunity to share their experiences.

The ESD service is described as an extended stroke unit service with early supported discharge (ESUS) in *Paper I* and *Paper II*.

4.3 Study intervention applied in the CIMT trial (Paper III)

4.3.1 Standard rehabilitation

The patients in the control group received standard rehabilitation which was defined as community-based follow-up treatment according to each patient's needs, involving both upper and lower extremity training. When long-term rehabilitation was necessary, in-patient rehabilitation was given, including both physiotherapy and occupational therapy. Patients were otherwise, or after in-patient rehabilitation, followed up by the primary health care system, including physiotherapy mainly provided over two sessions per week.

The standard rehabilitation is described as traditional rehabilitation in *Paper III*.

4.3.2 Constraint-Induced Movement Therapy

The patients in the intervention group received Constraint-Induced Movement Therapy (CIMT) at a level close to that described by Taub et al (Taub et al., 2006). Although the original CIMT is described as a one-to-one therapy, we wanted to organise it as group therapy, with up to four patients in each group, led by a physiotherapist, with an occupational therapist, and assisted by a nurse when needed. The three key principles of CIMT are described below:

1) Forced use of the affected arm

The patients were expected to restrain the unaffected arm by wearing a mitten during most of their waking hours. The occupational therapist designed and made a mitten with no fingers and a firm plastic material at the volar side. To make the mitten more comfortable the dorsal side was made of light material (Figure 2). The mitten was one size, and fitted both the right and the left hand. It could easily be removed during activities dealing with water, warm drinks, at the toilet, and for safety reasons such as walking with a cane. The removal of the mitten was registered in a log.

2) Shaping movements

The next principle is training through the use of shaping movements of the affected arm. Shaping implies gradual adaptation of the tasks to increasingly complex movements as function improves, and is described in detail in the supplementary Appendix I, available online at http://stroke.ahajournals.org (Taub et al., 2006). Every patient formulated five goals related to ADL or to leisure activities, before the training started. After assessing the motor function and functional ability, the therapists designed an individual activity plan adjusted to the patients' abilities and goals. Significant tasks were chosen from a collection of about 150 functional tasks within ten domains. The domains were: personal care, kitchen and household, games, handicrafts, gardening, office work, shopping, sports, strength and mobility.

Figure 2. The mitten on the less affected hand

The tasks included both functional tasks such as laying the table, and more specific training in the components of the functional tasks. The activities ranged from simple to complex tasks and were individually adjusted with regard to number of repetitions, tempo, resistance, range of motion, and weight.

3) Mass practice

The third principle was massing the practice of both shaping movements 6 hours per day and restraining the unaffected arm during 90% of waking hours. A schedule for a two-week period was prepared, and every day started with preparing and eating breakfast at eight o'clock. This was followed by exercises of the affected hand within the different domains until the afternoon. The participants had short breaks when they moved from one domain of activity to another after approximately half an hour. The therapists encouraged and motivated the patients to maintain a high intensity of activity during the exercises, and the nursing staff encouraged and motivated the patients to keep the mitten on during the rest of the waking hours.

4.4 Study intervention applied in the fMRI study (Paper IV)

The fMRI study had no specific study intervention, but all patients were treated in a comprehensive stroke unit at St. Olavs Hospital (Indredavik et al., 1991) with emphasis on

mobilisation within the first 24 hours after onset of symptoms and physiotherapy according to a task-oriented approach (Indredavik et al., 1999b). Further follow-up care was coordinated by a multidisciplinary team for the first four weeks after discharge (Indredavik et al., 2000; Askim et al., 2004). Hence, all patients received the recommended "gold standard" of stroke treatment.

4.5 Outcome measures (Paper I-IV)

A battery of appropriate generic and specific outcome measures is used in this thesis. Generic measurements are developed for use in a general, apparently healthy, population and may be used to compare the level of disability within different groups of patients (e.g., Barthel Index, walking speed). The specific measures are designed for a population with a specific disease, with items specific to the problems of the client population (e.g. Stroke Impact Scale, Motor Assessment Scale). Generic measures tend to be less sensitive to change compared to the specific measures (Finch et al., 2002).

4.5.1 A conceptual framework

Several measurement paradigms are helpful in organising outcomes with respect to the various health effects experienced by clients and the short- and long-term effects of therapy. The World Health Organisation's (WHO) International Classification of Functioning, Disability and Health (ICF) is one of the most relevant to the evaluation of physical rehabilitation (Finch et al., 2002).

ICF is a multipurpose classification designed to provide a scientific basis for understanding and studying health and health-related states, outcomes and determinants, and to establish a common language for describing health and health-related states in order to improve communication between different users (World Health Organization, 2001). ICF has two parts: (1) *functioning and disability*, and (2) *contextual factors.* Functioning and disability consist of the components: (a) *body functions and structures*, and (b) *activities and participation*. Contextual factors consist of the components: (c) *environmental factors*, and (d) *personal factors* (World Health Organization, 2001). In order to visualise the current understanding of the interaction of various components, a model of Functioning and

Disability is presented in Figure 3 (World Health Organization, 2001).

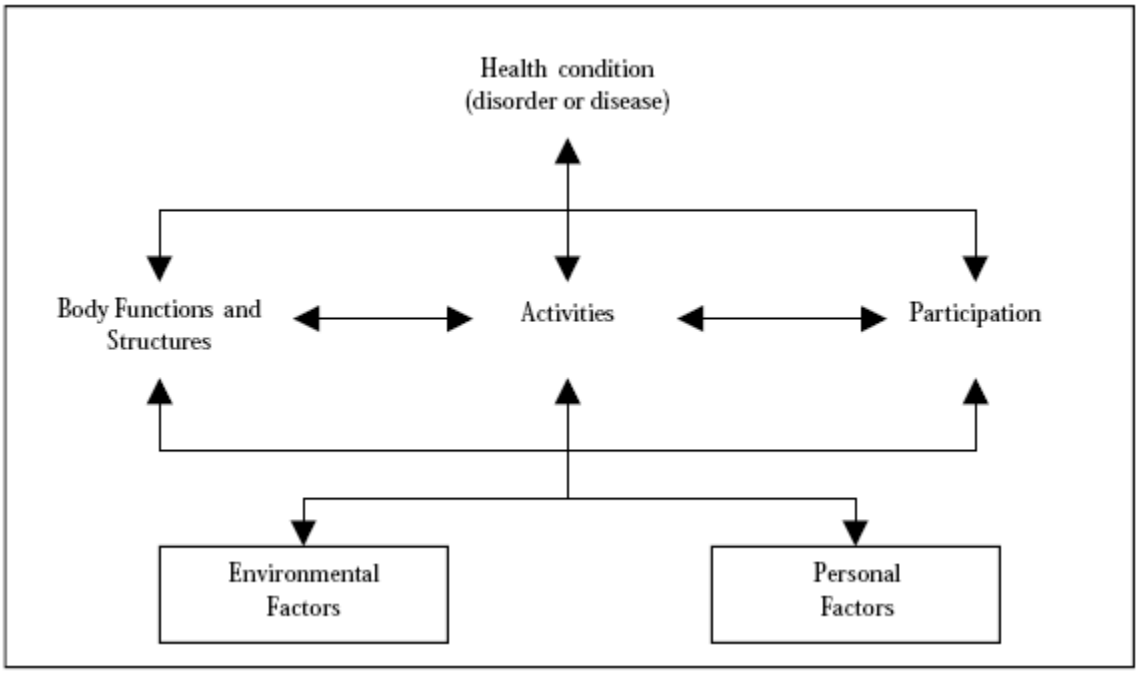

Figure 3. Interaction between the components of ICF (http://www.who.int/classifications/icf/site/intros/ICF-Eng-Intro.pdf)

Outcomes may be measured at any of these levels:

1. Body Function and Structure (impairment): problems in body function or structure as a significant deviation or loss.
2. Activities: the execution of a task or action by an individual.
3. Participation: the involvement in a life situation.

Body Function and Structure and Activities and Participation are all affected by environmental and personal factors (referred to as contextual factors within the ICF).

The outcomes measured in this thesis are listed in Table 3 in terms of the above-mentioned levels.

4.5.2 Reliability and validity

Several aspects of reliability and validity should be considered when choosing an appropriate measurement. Internal consistency, test-retest reliability and inter-rater reliability are three types of reliability. Internal consistency is applicable when multi-item measures are

summarised into a single score (Finch et al., 2002). Test-retest reliability, based on parallel assessments of clients on different occasions and inter-rater reliability, based on parallel assessments by different raters, will be considered for the measures reported in Table 3.

Face validity, content validity, criterion validity and construct validity are considered when the degree of validity of a measurement is evaluated. *Face validity* considers whether a measure appears to measure what it is intended to measure. *Content validity* exists to the extent that a measure is composed of a comprehensive sample of items that completely assess the domain of interest. *Criterion validity* examines the extent to which a measure provides results that are consistent with a gold standard. Typically, criterion validity is divided into concurrent validity and predictive validity. In the absence of a gold standard, the construct validity has to be considered. *Construct validity* involves forming theories about the attribute of interest and then assessing the extent to which the measure under investigation provides results that are consistent with the theories (Finch et al., 2002). Available and appropriate aspects of validity will be reported for the measurements used in this thesis in Table 3.

Table 3. Outcome measures used in this thesis

Measurement	Purpose	Test parameters	Reliability	Validity estimates	Paper
Body structure (impairments)					
Structures of the nervous system					
Functional MRI (fMRI)	To assess neuronal activity indirectly, through the blood-oxygen-level – dependent (BOLD) signal	- Number of activated voxels. - Intensity of activated voxels.	Test-retest reliability: Reliability coefficient (R) = 0.62 for the representation of hand movements in precentral gyrus, R=0.47 in postcentral gyrus, R=0.36 in SMA and R=0.03 in paracentral lobule for a hand motor task conducted by healthy subjects on three different days (Havel et al., 2006). Median ICC = 0.76 in different motor ROIs measured with one day interval in five healthy males (Friedman et al., 2007). Inter-rater reliability: Not assessed	Criterion validity: Early and high activation of ipsilesional primary sensorimotor cortex and insula predicts good recovery after stroke (Loubinoux et al., 2007). Construct validity: High adherence to known somatotopic arrangement in healthy subjects (Stoeckel et al., 2007) Age- and disease- related changes in the neurovascular coupling may cause the absence of BOLD signal (Pineiro et al., 2002; Rossini et al., 2004; Krainik et al., 2005; D'Esposito et al., 2003)	IV
Neurological scales					
Scandinavian Stroke Scale (SSS)	To assess neurological impairments after stroke.	Summary score (0-58) of 9 focal symptoms.	Test-retest reliability: Not assessed Inter-rater reliability: Weighted kappa (κ_w) for the nine items ranges from 0.688 to 0.912. Pearson's correlation coeffesient (r) = 0.963 between long term scores of two observes (Lindenstrøm et al., 1991)	Content validity: The content validity seems obvious but it is not referred to in the literature. Criterion validity: Predicts death and dependence in patients with mild ischaemic stroke (Christensen et al., 2005). Predicts discharge displacement and functional disability at discharge in all stroke patients (Jorgensen et al., 1995b).	I, II, IV

Table 3. Continued

Measurement	Purpose	Test parameters	Reliability	Validity estimates	Paper
Cognitive scales					
Mini Mental State Examination (MMSE)	Screening of cognitive function.	Summary score (0-30) of 20 cognitive tasks	Test-retest reliability: *r* =0.887 with one day interval in a group of patients with depressive symptoms. *r*=0.988 with 28 days interval in a group of patients with mixed diagnosis (Folstein et al., 1975). Inter-rater reliability: *r*=0.827 between two testers (Folstein et al., 1975).	Criterion validity: MMSE at baseline is somewhat predictive of functional improvement (Salter et al., 2005a). Construct validity: Discriminates between stroke patients and controls with significant lower MMSE score in stroke patients (Salter et al., 2005a).	III, IV
Activities					
Activities of daily living					
Barthel Index (BI)	To assess functional independence in personal care and mobility	Summary score (0-100) of 10 functional tasks. The dichotomised scale with BI≥95 defined as favourable outcome is used in Paper I.	Test-retest reliability: Weighted kappa (κ_w) = 0.98 with two weeks interval for subjects with stroke of varying severity (Wolfe et al., 1991). Inter-rater reliability: κ_w = 0.96 between different raters rating subjects with stroke of varying severity (Wolfe et al., 1991).	Content validity: BI was the only scale among three ADL scales that included all 11 of the most commonly used variables (Finch et al., 2002). Criterion validity: BI has been used as a gold standard for the criterion validation of other measurements but has not been validated this way (Finch et al., 2002). Initial BI after stroke predicts level of activity (Salter et al., 2005b). Construct validity: High correlation with walking speed, Berg Balance Scale and the Rankin Scale (Salter et al., 2005b)	I, II, IV

Table 3. Continued

Measurement	Purpose	Test parameters	Reliability	Validity estimates	Paper
Functional Independent Measure (FIM)	To assess degree of dependence in performance of basic daily living activity.	Summary score (18-126) of eighteen items (13 motor, 5 cognition), rated on a 1-7 scale.	Test-retest reliability: *r*=0.90 in a group of patients undergoing neurorehabilitation (Finch et al., 2002; Kidd et al., 1995). Inter-rater reliability: Intraclass correlation coefficient (ICC)=0.96 in a group of stroke patients (Segal & Schall, 1994).	Content validity: There is consensus about the appropriateness of the items (Finch et al., 2002). Criterion validity: Predicted minutes of assistance, supervision, and the need for either type of assistance in a group of patients with traumatic brain injury (Corrigan et al., 1997). High correlation between BI and FIM motor sub scale (Hsueh et al., 2002). Construct validity: The FIM discriminates between patients on the basis of age, comorbidity and discharge destination (Dodds et al., 1993).	III
The Modified Rankin Scale (mRS)	To assess the overall independence in stroke patients.	Degree of independence rated on a 0 – 6 scale. The dichotomised scale with mRS≤2 defined as favourable outcome is used in Paper I.	Test-retest reliability: κ_w=0.95 with two weeks interval for subjects with stroke of varying severity (Wolfe et al., 1991) Inter-rater reliability: κ_w=0.90 between different raters rating subjects with stroke of varying severity (van Swieten et al., 1988).	Construct validity: There is a relationship between mRS and Barthel Index at different stages after stroke (Banks & Marotta, 2007). There are evidence for the association between mRS and type of ischaemic stroke and acute neurological impairment (Banks & Marotta, 2007). Not sensitive to small changes, especially the dichotomised scale (Wade, 1992)	I, II, IV

Table 3. Continued

Measurement	Purpose	Test parameters	Reliability	Validity estimates	Paper
Balance					
Berg Balance Scale (BBS)	To assess balance in everyday motor activities.	Summary score (0-56) of 14 motor tasks, rated on a 0-4 scale	Test-retest reliability: ICC=0.99 in a group of chronic stroke patients (Berg et al., 1995). Inter-rater reliability: ICC=0.99 in a group of elderly people with impaired balance (Berg et al., 1992). ICC=0.98 in a group of chronic stroke patients (Berg et al., 1995).	Content validity: Content was developed in three phases, each including a different panel of clients and professional (Berg et al., 1989). Criterion validity: A score less than 45 indicates that an individual may be at greater risk of falling (Berg et al., 1992). 53% sensitivity to detect fallers among elderly people (Bogle Thorbahn & Newton, 1996). Subjects with BBS score of 36 and below are at extremely high risk of falling (Shumway-Cook et al., 1997) Construct validity: High correlation between BBS and BI mobility subscale and between BBS and Fugl-Meyer, balance subscale during the first twelve weeks after stroke (Berg et al., 1992). Discriminates among persons using different kinds of walking aids (Berg et al., 1992).	II

Table 3. Continued

Measurement	Purpose	Test parameters	Reliability	Validity estimates	Paper
Mobility and motor function					
Walking speed	To assess aspect of normal and pathological gait.	Time to walk 5 metres at maximum pace (m/s)	Test-retest reliability: *r*=0.91 for maximum speed in a group of healthy volunteers (Bohannon, 1997). *r*=0.93 and ICC (2.1)=0.92 for comfortable walking speed with one-day interval in a stroke population (Evans et al., 1997). Inter-rater reliability: ICC=0.998 for fast walking speed in persons with traumatic brain injury (van Loo et al., 2003)	Criterion validity: Gait speed has been used as the gold standard to validate numerous outcome measures in different patient populations (Finch et al., 2002). Construct validity: Maximum walking speed correlates with muscle strength in the lower extremity (Bohannon, 1997).	II
Dynamometer (Jamar)	To assess transversal grip strength	The mean of three trials of maximal force (kg/lb).	Test-retest reliability: ICC (2.1) =0.85 in a group of asymptomatic persons (Coldham et al., 2006). ICC=0.91 over three sessions with one week interval in a group of chronic stroke patients (affected hand) (Boissy et al., 1999). Inter-rater reliability: ICC=0.96 in a group of patients with trauma disorders (MacDermid et al., 1994).	Criterion validity: Failure to recover measurable grip strength before 24 days was associated with absence of useful arm function at three months (Heller et al., 1987). Construct validity: Improvement in grip strength is associated with recovery of more complex tasks in stroke patients (Sunderland et al., 1989).	IV
Pinchmeter (Jamar)	To assess key grip strength	The mean of three trials of maximal force (kg).	Test-retest reliability: Not assessed Inter-rater reliability: ICC=0.97 in a group of patients with trauma disorders (MacDermid et al., 1994).	Not available	IV

Table 3. Continued

Measurement	Purpose	Test parameters	Reliability	Validity estimates	Paper
Upper limb Motor Assessment Scale subscale (UL-MAS)	To assess the motor function of the upper extremity after stroke	Summary score (0-18) of the upper limb items (item 6, 7 and 8) of the total Motor Assessment Scale (MAS) (Carr et al., 1985). Each item is rated on a 0-6 scale.	Test-retest reliability: *r*=0.98 in MAS (Carr et al., 1985). Inter-rater reliability: *r*=0.98 – 1.00 for the upper limb items (Poole & Whitney, 1988). ICC (2.1)=0.93 – 1.00 for item 6, 7, and 8 on the Norwegian version of MAS (Kjendahl et al., 2005).	Content validity: The items and scoring options are based on the observation and progress of a large number of stroke patients (Carr et al., 1985). Construct validity: All three items are measuring the same construct and the sum score of the UL-MAS can be interpreted as a total score for upper limb function (Lannin, 2004). Item 6,7 and 8 on MAS correlates very well with Fugl-Meyer Assessment upper extremity portion (r=0.93) (Malouin et al., 1994).	IV
Nine Hole Peg Test (NHPT)	To assess manual dexterity	Time to place 9 pegs within 120 seconds (s). The mean of two trials is used as a test parameter.	Test-retest reliability: *r*=0.459 for the right hand and *r*=0.442 for the left hand of one trial in healthy adults (Oxford et al., 2003). Spearman rho correlation=0.68 – 0.90 with two weeks interval in a group of chronic stroke patients (Heller et al., 1987). Inter-rater reliability: *r*=0.984 for the dominant hand and *r*=0.993 for the non-dominant hand in healthy adults (Oxford et al., 2003). Spearman rho correlation=0.83 – 0.99 in chronic stroke patients (Heller et al., 1987).	Construct validity: Measures recovery of arm function after stroke. Is most sensitive to change at the middle and upper range of recovery (Heller et al., 1987; Parker et al., 1986).	IV

Table 3. Continued

Measurement	Purpose	Test parameters	Reliability	Validity estimates	Paper
Wolf motor function test (WMFT)	To assess upper extremity motor function	Performance time (pt): mean time to perform 15 motor tasks (seconds) Functional ability (fa): mean score of 15 motor tasks, rated on a 1-6 scale	Test-retest reliability: *r*=0.90 in a group of chronic stroke patients on WMFT (pt). *r*=0.95 in a group of chronic stroke patients on WMFT (fa) (Morris et al., 2001). Inter-rater reliability: ICC (2.1) = 0.97 in patients with chronic stroke on WMFT (pt). ICC (2.1) = 0.88 in patients with chronic stroke on WMFT (fa) (Morris et al., 2001).	Construct validity: Can differentiate the more affected extremity from either extremity of individuals without impairment (Wolf et al., 2001). High correlation between WMFT (pt) and FMA and between WMFT (fa) and FMA in a group of patients with subacute stroke (Ang & Man, 2006). WMFT (pt) classified 86.7% of original grouped cases into the correct groupings (Ang & Man, 2006).	III
Instrumental Activities of Daily Living					
Motor activity log (MAL) - 30 item version	To measure enhanced quality and quantity of participation of the affected arm in activities of daily living after CIMT.	Mean score of quality of movement (qom) or mean score of amount of use (aou) of 30 functional items, rated on a 0-5 scale	Test-retest reliability: ICC (3.1) ranging from 0.40 to 0.76 in 28 of the 30 items on MAL (qom), and ICC (3.1) ranging from 0.44 to 0.68 in 28 of the 30 items on MAL (aou) in a group of chronic stroke patients (Uswatte et al., 2006). Inter-rater reliability: Not assessed	Construct validity: High correlation between MAL (qom) and SIS hand function scale, and between MAL (aou) and SIS hand function scale. High correlation between MAL (qom) and accelerometry. Medium correlation between MAL (aou) and accelerometry (*r*=0.47) (Uswatte et al., 2006). Sensitivity to change was not confirmed by Action Research Arm Test (van der Lee et al., 2004).	III

Table 3. Continued

Measurement	Purpose	Test parameters	Reliability	Validity estimates	Paper
Participation					
Nottingham Health Profile (NHP)	To assess subjective health status	38 statements grouped within six dimensions, each ranging from 0-100, with a high score indicating poor health status. Global score: The percentage of statements answered with yes, subtracted from 100. A high score indicates high health status.	Test-retest reliability: Correlation range from r=0.75 to r=0.88 among patients with vascular diseases (Salter et al., 2005c). Inter-rater reliability: Not applicable	Content validity: It contains items with some degree of correlation with pain and physical rating (Finch et al., 2002). Construct validity: Does not discriminate between healthy controls and a group of chronic stroke patients (Visser et al., 1995). The emotional reaction subscale correlated highly (Spearman's p = 0.71) with scores on the General Health Questionnaire, used to detect important mood disturbance in a group of stroke patients (Finch et al., 2002; Ebrahim et al., 1986).	I

Table 3. Continued

Measurement	Purpose	Test parameters	Reliability	Validity estimates	Paper
Stroke Impact Scale (SIS), Version 2.0	To assess subjective health status in stroke patients	64 items assessing eight domains. Each item is rated on a five point scale (1-5). Aggregated scores within each domain, ranging from 0 to 100, are generated with an algorithm.	Test-retest reliability: ICCs of the eight domains are in the range of 0.7 to 0.92, except for emotion (0.57) (Duncan et al., 1999). Inter-rater reliability: Not available	Content validity: Was established through its development from focus groups that included stroke survivors, caregivers, and health care professionals who were experts in stroke (Finch et al., 2002). Construct validity: Sensitivity to change was adequate in persons with moderate stroke but not in minor stroke from 3 months to 6 months post stroke (Duncan et al., 1999). High correlation between SIS domain of ADL and BI, and between SIS domain of hand function and Fugl-Meyer upper extremity subscale (Duncan et al., 1999).	III
Family					
Caregiver Strain Index (CSI)	To detect strain in the carer of stroke patients	Summary score (13-26) of a 13 item index.	Test-retest: Not assessed Inter-rater: Not assessed	Content validity: Adult children were interviewed to identify the most common stressors in caring for an elderly parent (Robinson, 1983). Criterion validity: A positive response to seven or more items on the index would indicate a greater level of stress (Robinson, 1983). Construct Validity: A significant relationship between CSI scores and caregivers not having received assistance with their own feelings and problems (Robinson, 1983).	I

4.6 Sample size estimation (Paper I - IV)

No power calculations were performed in any of the present studies. According to the ESD trial, we knew from the Trondheim study that a sample size of 320 patients was needed with a 15 % rate of success on the Modified Rankin Scale, using a significance level of 0.05 and power of 80 % (Fjærtoft, 2005). It was unrealistic to include this number of patients from our study population, so we included as many patients as possible within the time limits of the trial, with the intention of undertaking a methodologically robust study which could also be included in meta-analyses. With a view to the CIMT trial, we knew from other trials that the number of eligible patients would be low. In addition, no minimal clinically important difference for our primary outcome measure, the Wolf Motor Function Test, has been reported. Based on this we decided to design a trial with high internal validity and to include as many patients as possible within the time limit of the trial, with the intention of assessing both the effect and the feasibility of this intervention. In *Paper IV* we based our sample size estimation on the number of patients usually included in fMRI studies in order to perform a random effect study. However, economic resources and the availability of eligible patients also influenced the number included.

4.7 Study design for the ESD trial (Paper I and II)

The ESD trial was a clinical randomised trial. The flow of patients through the trial is illustrated in Figure 4.

4.7.1 Randomisation

Patients fulfilling the inclusion criteria were included, and were block randomised in blocks of four, six or eight patients, to either a standard service or the newly devised ESD service. The order of the blocks was randomly chosen. Sealed opaque envelopes were used for randomisation and the procedure was carried out by an external office.

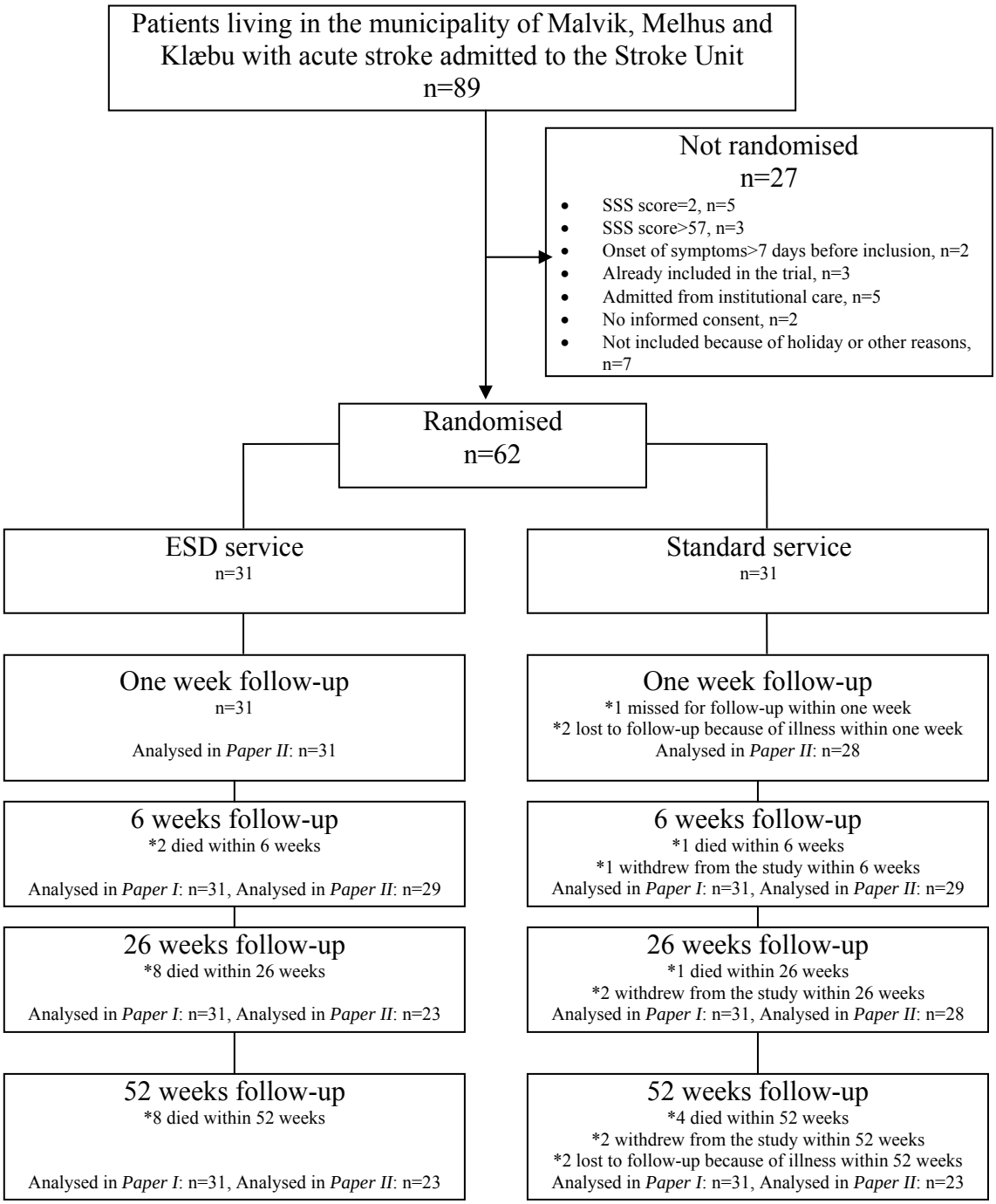

Figure 4. Study design and the flow of patients through the ESD trial

4.7.2 Blinding

An independent and blinded assessor specially trained in the use of all the outcome measures performed the assessments in the patients' home. However, the patients were not blinded to the allocated treatment and therefore this was a single blinded trial.

4.8 Study design for the CIMT trial (Paper III)

The CIMT trial was a clinical randomised trial with pre- and post-treatment assessment, and six moths follow-up. The flow of patients through the trial is illustrated in Figure 5.

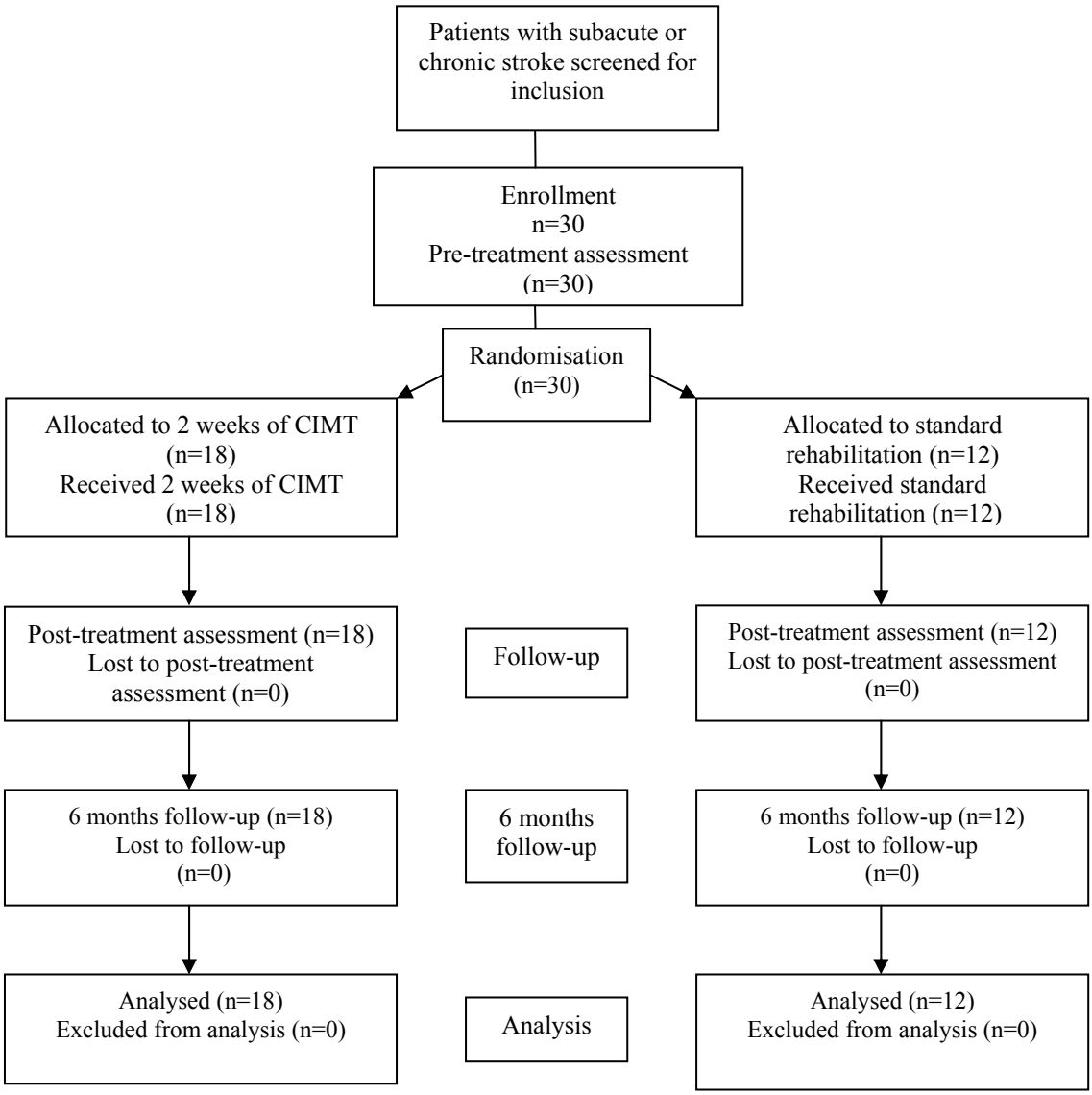

Figure 5. Study design and the flow of patients through the CIMT trial

4.8.1 Randomisation

Patients fulfilling the inclusion criteria were included and block-randomised into a CIMT group or a control group receiving standard rehabilitation, according to a 3:2 ratio. This ratio

was chosen to assess the feasibility of CIMT for as many patients as possible. Sealed opaque envelopes were used for randomisation and the procedure was carried out by an external office.

4.8.2 Blinding

Two independent assessors, blinded to treatment assignment, performed all the assessments in a test laboratory at the hospital. The patients were not blinded to the allocated treatment, and consequently this was a single blinded trial.

4.9 Study design for the fMRI study (Paper IV)

The fMRI study was a longitudinal study with baseline assessment and three months follow-up. The flow of patients through the study is illustrated in Figure 6.

Initial Scandinavian Stroke Scale score, Oxfordshire classification (Bamford et al., 1991) and co-morbidity were recorded at inclusion. Motor function and disability were scored using a range of outcome measures (see Table 3) in the acute phase, four to seven days after stroke onset, and in the chronic phase, three months later. Functional MRI scanning was performed at the same time points.

The motor task applied during the fMRI scanning was thumb-index finger opposition at self-paced maximal rate (SP task) performed with the affected hand. Before imaging, the task was explained and subsequently performed by the patient to ensure full compliance. Patients' arms were positioned with both forearms resting on their abdomen. An experienced observer registered finger movement frequency and assessed the degree of associated arm and mirror movements during fMRI. The motor task was visually cued on a screen at the bore opening. Each task was performed alternating between 29 seconds rest, i.e. fixation, and 29 seconds activation, i.e. SP task, with a total of five baseline and four activity epochs.

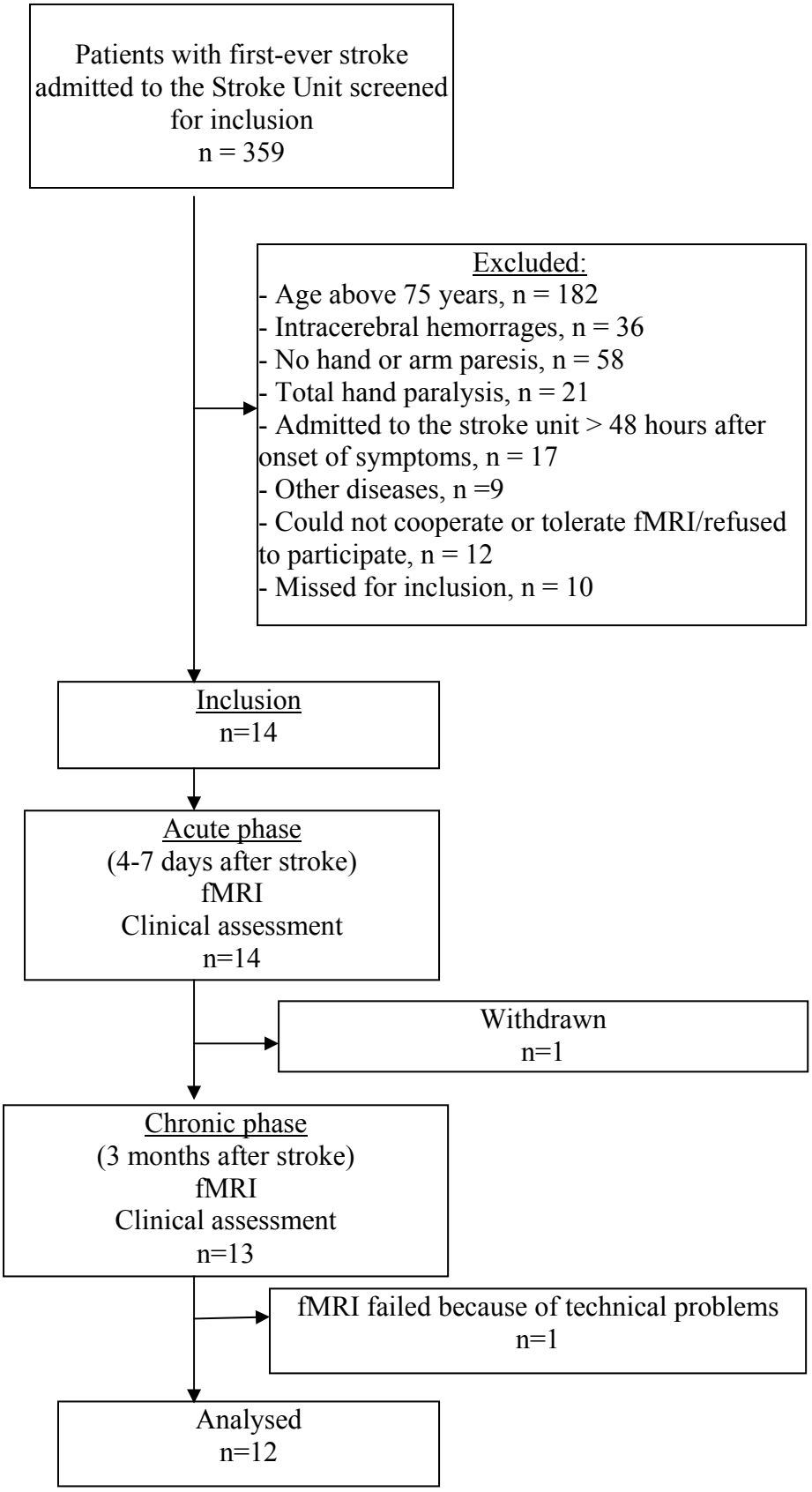

Figure 6. Study design and the flow of patients through the fMRI study

4.10 Analysis

A *p*-value < 0.05 was considered significant in all analysis. Analysis of all clinical data has been carried out in SPSS 13.0 (SPSS inc, USA), while image data was analysed using statistical parametric mapping 5 (SPM5, Wellcome Department of Imaging Neuroscience, http://www.fil.ion.ucl.ac.uk/spm/) running on MatLab 6.5.1 (The Mathworks Inc., USA). Different statistical approaches have been used in the different papers and will be described in the following sections.

4.10.1 Baseline assessments

At baseline, the distribution of gender, medical history, living conditions, diagnosis, side affected and home community were compared with the Chi-square test or Fisher's Exact Test when appropriate. The differences in severity of stroke according to Scandinavian Stroke Scale, Barthel Index, Modified Rankin Scale scores and months since stroke were analysed with the Mann-Whitney U-test. The difference in age was analysed with the *t*-test for independent samples.

4.10.2 Follow-up assessments

Intention to treat analysis

Intention to treat analysis is a strategy for the analysis of randomised controlled trials which compares patients in the groups in which they were originally randomly assigned. This is generally interpreted as including all patients, regardless of whether they actually satisfied the entry criteria, the treatment actually received, and subsequent withdrawal or deviation from the protocol (Hollis & Campbell, 1999). However, there is no precise answer as to how one should impute missing data from patients who drop out or die during the trial. Sophisticated imputation methods are merely devices for facilitating the final analysis. They are no substitute for the real data (Fayers & Machin, 2000). Intention to treat analysis was used in all analysis on the Modified Rankin Scale and Barthel Index (*Paper I*), and Wolf Motor Function Test, Motor Activity Log, Functional Independent Measure and Stroke Impact Scale (*Paper III*). Missing data from Modified Rankin Scale and Barthel Index were gathered by using all

available information including baseline assessment and information from readmission to the hospital. There were no dropouts or missing data in the CIMT trial.

Per protocol analysis

Per protocol analysis is the opposite alternative to intention to treat analysis, where only those who satisfy the entry criteria of the trial and who subsequently adhere to the protocol are analysed. However, clinical effectiveness may be overestimated by such analysis, which may yield systematic errors in the data (May et al., 1981). Per protocol analysis was performed on the Nottingham Health Profile, Caregiver Strain Index and average Barthel Index score in *Paper I*, and Berg Balance Scale and fast walking speed in *Paper II*.

Analysing group differences

Differences between the groups in the proportion of patients independent and deceased were compared by the Fisher's Exact Test. The Nottingham Health Profile, Caregiver Strain Index, Berg Balance Scale, average Barthel Index score and length of stay, were compared by the Mann-Whitney U-test. The fast walking speed was compared using student *t*-test for independent samples.

In small randomised controlled trials there is an increased risk for imbalance between the groups at baseline. This was the case in *Paper I, Paper II* and *Paper III*. Different statistical approaches are available to adjust for these differences (Vickers & Altman, 2001).

***Paper I*:** Multiple logistic regression was used to obtain a more precise estimate of the dichotomised Modified Rankin Scale score (primary outcome) adjusting for potential confounders such as stroke severity measured by Scandinavian Stroke Scale score, age and living conditions (Kleinbaum 2002). Age was dichotomised at the median, Scandinavian Stroke Scale was entered in the model as a continuous variable, and living condition was categorised as living alone or not.

***Paper II*:** The Berg Balance scale did not fulfil the assumption of normal distribution by inspection of Quantile-Quantile plots, and consequently no parametric tests could be used. In this case we chose to compare the change score to adjust for the initial imbalance. The Mann-Whitney U-test was used to analyse the difference in change. A similar approach was chosen

for walking speed; however, due to normal distribution, the student *t*-test for independent samples was chosen as the statistical method.

***Paper III*:** Normal distribution assumptions were checked by visual inspection of Quantile-Quantile plots for all outcome measures in *Paper III*. Wolf Motor Function Test, performance time, had a skewed distribution and a logarithmic transformation was performed. In the statistical tests the transformed scale was used as a test parameter, but in the summary statistics, the log transformed scale was transformed back to its original scale to aid in interpretation. Differences between groups were analysed with analysis of covariance (ANCOVA) with the baseline score of the dependent variable as a covariate (Vickers & Altman, 2001). In a second-level analysis it was adjusted for age, gender, time from onset of stroke and dominant side affected (Pocock et al., 2002).

Analysing change within groups

Changes within groups were calculated by subtracting the follow-up score from the baseline score. The change score were analysed by Wilcoxon Signed Rank Test for Berg Balance Scale *(Paper II)*, Scandinavian Stroke Scale, Barthel Index, Modified Rankin Scale and Motor Assessment Scale *(Paper IV)* or paired *t*-test for walking speed *(Paper II)*, self-paced tapping rate, log transformed Nine Hole Peg Test, transversal grip strength and key grip strength *(Paper IV).*

Analysing association of function

Multiple logistic regression was used to analyse the association between initial leg paresis and initial movement ability as independent variables, and the dichotomised Berg Balance Scale score 52 weeks after stroke as the dependent variable, allowing adjustments for potential confounders such as age, gender, treatment group and number of days from onset of symptoms to hospital admission

Analysing functional MRI data

Functional MRI data was analysed using Statistical Parametric Mapping 5 (SPM5) running on MATLAB 6.5.1. A region of interest (ROI) consisting of the entire pre- and post-central gyri including primary motor cortex (MI), secondary motor cortex (MII), primary somatosensory cortex (SI), somatosensory association cortex, secondary somatosensory cortex (SII), plus the entire cerebellum, bilateral thalami, caudate nuclei, putamen and globus pallidi,

supplementary motor area (SMA), rostral inferior parietal lobe (IPL) and insula was drawn in MNI space using the software MRIcro.

Images for patients with right-sided infarctions were flipped. Group activation maps for acute and chronic phases were determined with a one-sample *t*-test using false discovery rate (FDR) set to FDR<0.05 (Genovese et al., 2002). Cluster size was 15 voxels. A paired *t*-test was used to test for differences between the acute and chronic phases, and in a covariate analysis regions positively co-varying with changes in the functional motor score between acute and chronic phases were assessed. Due to the small number of patients and the specific hypothesis, a more lenient statistical threshold ($p<0.01$, uncorrected) was applied in these analysis.

Based on the number of activated voxels in the different ipsilesional (I) and contralesional (C) cortical ROIs defined from the fMRI images, a Lateralisation Index (LI) was calculated according to the equation: (I-C)/(C+I) for the cerebral and (C-I)/(C+I) for the cerebellar hemisphere. The LI was calculated for MISI, MIISII, IPL, insula and cerebellum. The index ranges from 1 to -1. LI=1 means all activated voxels in the ipsilesional cerebral and contralesional cerebellar hemisphere, while LI=-1 means all activated voxels in the contralesional cerebral and ipsilesional cerebellar hemisphere.

All analyses of image data were performed by co-workers at the Department of Circulation and Medical Imaging. The analyses are described in detail in *Paper IV*.

5 Synopsis

5.1 Paper I

Evaluation of an extended stroke unit service with early supported discharge for patients living in a rural community. A randomised controlled trial

An extended stroke unit service with ESD was beneficial for patients living in the city of Trondheim. The aim of the present trial was to evaluate the effect of an equivalent ESD service for patients living in a rural community. A randomised controlled trial was designed to compare a newly constructed ESD service with the standard and well documented service. Sixty-two eligible patients with acute stroke living in the municipalities of Malvik, Melhus and Klæbu were included in the trial. Thirty-one patients were allocated to the standard service, and thirty-one patients were allocated to the ESD service with further rehabilitation co-ordinated by a multidisciplinary mobile team in close cooperation with the primary health care system. The results showed that 12 patients (39%) in the ESD group versus 16 patients (52%) in the standard service group were independent according to the Modified Rankin Scale 52 weeks after onset of stroke (p=0.444). The odds ratio for independence (ESD service versus standard service) was 0.33 (95% confidence interval; 0.088 – 1.234). According to the Nottingham Health Profile, the ESD service group showed a significant lower score (better outcome) on the social isolation item compared to the standard service group (p=0.045). Otherwise there were no significantly differences according to the Nottingham Health Profile, Barthel Index, Caregiver Strain Index, length of stay or mortality. An ESD service for patients living in the rural community seems to have no influence on death or dependency but might indicate a trend towards less social isolation. However, the sample size was too small to yield any definite conclusion.

5.2 Paper II

Does an extended stroke unit service with early supported discharge have any effect on balance or walking speed?

Our ESD trial did not show any beneficial effect according to the primary outcome measure. However, it cannot be precluded that the intervention might demonstrate beneficial effects according to a more sensitive outcome scale. The early discharge with focus on rehabilitation

in the patient's home might have an impact on functional balance. The aim of *Paper II* was to use secondary data from the ESD trial to evaluate whether the ESD service had any effect on balance or walking speed. An additional aim was to explore the association between initial leg paresis, initial movement ability and balance one year after stroke. Per protocol analysis was performed, identifying different numbers of patients in each group at baseline and follow-up. The results showed no significant differences between the groups according to Berg Balance Scale or fast walking speed despite a significant faster walking speed (p=0.043) in the standard service group at one week post stroke. Only those cases with all assessments available were analysed for change within the groups. This results showed a significant improvement on the Berg Balance Scale from one week to six weeks follow-up (p=0.013) and a significant improvement in fast walking speed from one week to six weeks follow-up (p=0.022), from one week to twenty-six weeks follow-up (0.044) and from one week to fifty-two weeks follow-up (p=0.028) in the ESD group. There was no significant improvement in the standard service group at the same time point. However, when the change scores were compared there was only a trend (p=0.065) in favour of better balance in the ESD group from one week to six weeks follow-up. All patients with initial severe leg paresis suffered from poor balance one year after the stroke, but there was no association between moderate paresis and poor balance at the same time. The odds ratio (95 % confidence interval (CI)) for poor balance was 42.1 (3.5 – 513.9) among patients with no initial walking ability and 4.6 (0.8 – 26.5) among patients walking with support. An ESD service for patients living in the rural community seems to have no influence on balance or walking speed. However, the non-significant trend toward greater change on the Berg Balance Scale from one week to six weeks follow-up in the ESD group indicates a possible effect on balance for early rehabilitation in the patients' home. The study revealed a strong association between initial severe leg paresis, but not between initial moderate leg paresis, and poor balance one year after the stroke. There was also a strong association between initial inability to walk and poor balance, while the odds ratio for poor balance among patients who initially walked with support was weaker.

5.3 Paper III

Short and long term outcome of Constraint-Induced Movement Therapy after stroke. A randomised controlled feasibility trial

Constraint-Induced Movement Therapy (CIMT) belongs to a group of therapies that aims to permanently increase the amount of use and quality of movement of a paretic upper extremity following stroke. The majority of CIMT trials have been conducted in the US, and few have been published from Europe. The primary aim of this trial was to assess the effect of CIMT compared to standard rehabilitation, in the short and long term, considering arm motor function, independence in ADL and self-perceived health in patients after stroke. A secondary aim was to assess the feasibility of CIMT, organised as group therapy in the Norwegian healthcare system. A randomised controlled trial was designed to compare ten days of CIMT organised at an in-patient rehabilitation clinic with standard rehabilitation. Thirty patients with unilateral hand impairment after stroke were included. Eighteen patients were allocated to six hours of arm therapy for 10 consecutive weekdays while using a restraining mitten on the unaffected hand for 90 % of their waking hours, and twelve patients were allocated to standard rehabilitation. The results showed a statistically significant shorter performance time (4.76 seconds versus 7.61 seconds, p=0.030) and greater functional ability (3.85 versus 3.47, p=0.037) according to the Wolf Motor Function Test (primary outcome) in the CIMT group compared to the control group at post-treatment assessment. There was a non-significant trend toward greater amount of use (2.47 versus 1.97, p=0.097) and better quality of movement (2.45 versus 2.12, p=0.105) in the CIMT group according to the Motor Activity Log. No such differences were seen on the Functional Independent Measure. At 6 months follow-up the CIMT group maintained their improvement, but as the control group also improved during the follow-up period, there were no significant differences between the groups on any measurements. From the present trial we can conclude that CIMT seems to be an effective method to improve motor function in the short term, and it was feasible to organise CIMT as group therapy for this selected group of patients. However, no long-term effect was found and it is still unclear to what extent the functional improvement after CIMT is ultimately beneficial for activities of daily living.

5.4 Paper IV

Motor network changes associated with successful motor skill relearning in patients with acute stroke. A longitudinal functional MRI study

In most stroke patients, recovery follows an exponential progression, with a fast initial improvement in the first six weeks, and a slower recovery for the next six weeks. Many

functional MRI studies have been undertaken in the past decade to study the role of brain plasticity in the recovery after stroke. The aim of the present study was to assess the early motor network changes in a group of stroke patients treated in a comprehensive stroke unit with ESD and further follow-up coordinated by a multidisciplinary team using a task-oriented approach, and to investigate its relationship to motor learning. Twelve patients with the diagnosis of first-ever stroke, who were admitted to the Stroke Unit at St. Olavs Hospital and fulfilled the inclusion criteria, were assessed with functional MRI and clinical tests within one week after stroke and three months later. The results showed significant improvement in terms of all functional outcome measures (SSS, BI, mRS, UL-MAS, NHPT, transversal grip strength, and key grip strength). All patients except one had complete recovery of the affected arm/hand as measured by UL-MAS. Increased activation in secondary sensorimotor areas (ipsilesional angular gyrus and insula, bilateral putamen and contralesional cerebellum) was revealed in the acute phase compared to the chronic phase. The chronic phase demonstrated higher activation in the ipsilesional hand motor area (MISI), corresponding to restored laterality of the primary motor network, in addition to increased bilateral activity in the somatosensory association area plus increased contralesional activity in the secondary somatosensory area (SII). The contralesional SII activation correlated positively with improvement in dexterity as measured by UL-MAS and NHPT, and transversal grip strength, as well. The observed changes in activation pattern from the acute to the chronic phases are comparable to changes described in motor learning studies, while the recruitment of bilateral somatosensory association areas and contralesional SII is considered to represent cortical plasticity involved in successful relearning of motor skills after stroke.

6 Discussion

6.1 The main result of the thesis

This thesis has revealed that the ESD service did not significantly influence death or dependency, balance or walking speed for patients living in a rural community. However, it may lead to less isolation and a transient improvement in self-percieved health. The thesis has also revealed that CIMT organised as group therapy is feasible and efficient in the short term but may not be superior to standard rehabilitation in the long term. Finally, the thesis has shown that the motor network changes associated with successful motor recovery are comparable to changes described in motor skill learning in healthy subjects. These changes involve restoration of the lateralised primary motor network in addition to increased recruitment of bilateral somatosensory association areas and increased contralesional SII activation.

6.2 Comparing the ESD trial with other studies

Nine randomised trials evaluating an ESD service for stroke patients were published before our trial. Of these, two trials had no multidisciplinary team (Suwanwela et al., 2002; Ronning & Guldvog, 1998) while seven trials evaluated an ESD service organised by a multidisciplinary team (Rudd et al., 1997; Rodgers et al., 1997; Widen et al., 1998; Bautz-Holtert et al., 2002; Anderson et al., 2000; Mayo et al., 2000; Indredavik et al., 2000). A recent update identified a new ESD trial with a multidisciplinary team (Donnelly et al., 2004). Our trial will be discussed in the light of the eight trials with comparable interventions listed in Table 4.

Table 4. Trials which have compared the effect of early supported discharge for acute stroke patients versus conventional care. Odds ratio (OR) and 95% confidence interval (CI) for death and dependency at end of follow-up (Early Supported Discharge Trialists, 2007; Langhorne & Holmqvist, 2007).

Study	Treatment n/N	Control n/N	OR (95% CI)
Adelaide (Anderson et al., 2000)	13/42	16/44	0.78 (0.32 – 1.92)
Belfast (Donnelly et al., 2004)	29/59	32/54	0.66 (0.32 – 1.40)
London (Rudd et al., 1997)	105/167	109/164	0.85 (0.54 – 1.34)
Montreal (Mayo et al., 2000)	17/58	24/56	0.55 (0.25 – 1.20)
Newcastle (Rodgers et al., 1997)	22/46	28/46	0.59 (0.26 – 1.35)
Oslo (Bautz-Holtert et al., 2002)	16/42	17/40	0.83 (0.34 – 2.01)
Stockholm (Widen et al., 1998)	9/42	12/41	0.66 (0.24 – 1.79)
Trondheim 2000 (Indredavik et al., 2000)	64/160	81/160	0.65 (0.42 – 1.01)
Trondheim 2004 (Askim et al., 2004)	19/31	15/31	1.69 (0.62 – 4.63)

6.2.1 Setting

Our multidisciplinary team was based within the stroke unit and included a nurse, a physiotherapist, an occupational therapist and the consulting service of a physician. This is in accordance with the trials from Oslo (Bautz-Holtert et al., 2002), Stockholm (Widen et al., 1998), and Trondheim (Indredavik et al., 2000). The five remaining trials had community-based inreach teams (contacted patients prior to discharge) well-informed about the local services (Rudd et al., 1997; Rodgers et al., 1997; Anderson et al., 2000; Mayo et al., 2000; Donnelly et al., 2004). Langhorne et al (2005) have shown that trials with hospital outreach teams have better outcomes than trials with community inreach teams. The hospital-based setting is in our view an important factor for a successful ESD service, although this is not demonstrated in our trial. Within this setting, it is possible for the team to start collecting information about the patient immediately after admission to the stroke unit, and to establish close cooperation between the patient, the family, and the staff during the hospital stay. The team also made plans for the discharge and further follow-up in close cooperation with the primary health care system during the in-patient period.

All of the comparable trials, except our ESD trial, have so far been conducted within urban centres. Three municipalities neighbouring the city of Trondheim are defined in this trial as the rural setting. However, it may be disputed whether this area is rural or not. The population density was about 31 inhabitants per square kilometres within our rural area, indicating a disperse settlement compared to 446 inhabitants per square kilometres within the city of

Trondheim. However, some of the areas within the municipality of Malvik, Melhus and Klæbu had a settlement pattern more resembling a suburb of Trondheim.

In conclusion, our hospital-based multidisciplinary team is comparable to that in three other ESD trials, while our trial is so far the only trial within a rural setting. This makes it somewhat difficult to compare our results with other trials and may also explain why our results differ from those of the other trials. This will be further discussed in section 6.2.4.

6.2.2 Study patients

Our inclusion criteria targeted all patients with acute stroke who were conscious at inclusion and who were independent before the stroke. Based on these criteria, we included 70 % of those patients admitted to the stroke unit from the municipalities of Malvik, Melhus and Klæbu. The mean age was 77 years in the treatment group and 76 years in the control group, while the median Barthel Index at baseline was 55/100 in both groups. The typical population included in other ESD trials had a median Barthel Index at randomisation of 70/100, while the mean or median age in these trials ranged from 68 to 78 years (Langhorne et al., 2005). Our unselected group of patients is more disabled compared to this typical population, and also compared to patients included in the Trondheim trial (Indredavik et al., 2000). Subgroup analysis has shown that patients with initially moderate disability (Barthel Index of 50 - 100) appear to benefit best from ESD services (Langhorne et al., 2005), indicating that the most severely disabled patients may not have the capability to utilise the coordinated ESD service.

In conclusion, our patients were more disabled than patients in other comparable ESD trials, which may also partly explain why our ESD trial not replicated the benefits of this treatment demonstrated in most other studies.

6.2.3 Study intervention

Three different subtypes of ESD interventions are described (Early Supported Discharge Trialists, 2007): (1) ESD team co-ordination and delivery, which implies a co-ordinated multidisciplinary ESD team that co-ordinates and provides post-discharge care; (2) ESD team co-ordination, which implies a co-ordinated multidisciplinary ESD team which co-ordinates and supervises discharge and immediate post-discharge care, but then hands over the

responsibility to other services; and (3) no ESD team, which implies that post-discharge services are not provided by a co-ordinated multidisciplinary ESD team. Our study intervention is described as ESD team co-ordination in line with the trials from Trondheim and Oslo (Langhorne & Holmqvist, 2007).

The aim of *Paper I* was to evaluate the effect of the ESD service, tested out in the Trondheim trial, for patients living in a rural community. Due to the distance between the hospital and the three rural municipalities some minor changes in the features of the extended service were made. However, the study interventions are still comparable.

The multidisciplinary team is regarded as a significant component of the ESD service, as most of the evidence of benefit of ESD services comes from trials implementing specialist multidisciplinary team which work is coordinated through regular meetings (Langhorne et al., 2005). ESD trials with no ESD team have shown a non-significant trend toward increased death and dependency (Langhorne & Holmqvist, 2007). This result supports the importance of the ESD team coordination.

Another important component of the ESD service may be the emphasis on early and intensive task-oriented exercise therapy in the patients' home coordinated by the team member, but conducted by the primary health care providers. This is in contrast to most other trials in which the ESD team also delivered the post-discharge care (Anderson et al., 2000; Rudd et al., 1997; Mayo et al., 2000; Rodgers et al., 1997; Widen et al., 1998; Donnelly et al., 2004). Whether the early training in the patients' home is delivered by the team member or the primary health care provider may not be the main issue. Both alternatives might be beneficial, depending on how the local services are organised. However, it may be important that the training is given at a particular level according to the patients' individual needs.

In conclusion, our study intervention is comparable to other ESD trials with team coordination. However, there is no evidence for this alternative being superior to ESD team coordination and delivery.

6.2.4 Results

The primary outcome of *Paper I* was the dichotomised Modified Rankin Scale (mRS ≤ 2) showing a non-significant trend toward better outcome in the control group. This is in contrast to all other comparable ESD trials. The latest ESD meta-analysis (Figure 7), including both published and unpublished individual data, showed reduced death and dependency for patients receiving ESD after stroke (Langhorne & Holmqvist, 2007). Among these trials the Trondheim trial is the most convincing, showing a significantly higher proportion of independent patients in the ESD group at six months follow-up (Indredavik et al., 2000) and one year after the stroke (Fjaertoft et al., 2003). There may be several reasons why our trial did not replicate this result. Firstly, collapsing the data into the dichotomised Modified Rankin Scale generally lowers statistical power and reduces the chance of finding a significant treatment effect because information from many subjects is ignored. For example, patients responding to treatment with an improvement from 4 to 3 points are ignored in an analysis on the dichotomised scale (Bath et al., 2007). This reduces the chance of detecting significant differences especially in trials with small sample sizes. The rural setting implies a small number of inhabitants and consequently difficulties in including sufficient numbers of patients to comply with sample size estimates. However, it is still important to perform small trials with high internal validity which can be included in Cochrane Reviews or other meta-analysis. The methodological robustness of the present trial is confirmed by the inclusion of the trial in the latest ESD meta-analysis by Langhorne & Holmquist (2007). Secondly, our trial is so far the only ESD trial conducted for patients living in a rural community. The different organisation of the primary health care system, and the variation in the numbers of physiotherapists and occupational therapists in the urban centres and rural communities, may also account for the lack of benefit of our ESD service. Small communities are characterised by people knowing each other, and the people working in the primary health care system often know their patients and relatives. This may lead to closer relationship and a better coordinated standard service. Consequently, the difference between the ESD service and the standard service may not be as significant in the rural community as in urban centres. Thirdly, the small sample size may give rise to an uneven distribution of confounding factors at baseline. In addition, an adverse event in one of the groups will have greater impact on the results where there is a small sample size. The analysis on Berg Balance Scale in *Paper II* revealed a non-significant trend toward initial better balance in the control group. This finding supports the theory about an uneven distribution at baseline.

One may question whether ESD encourages dependency, but this appears unlikely because the equivalent ESD service was very beneficial for patients living in the city of Trondheim (Indredavik et al., 2000).

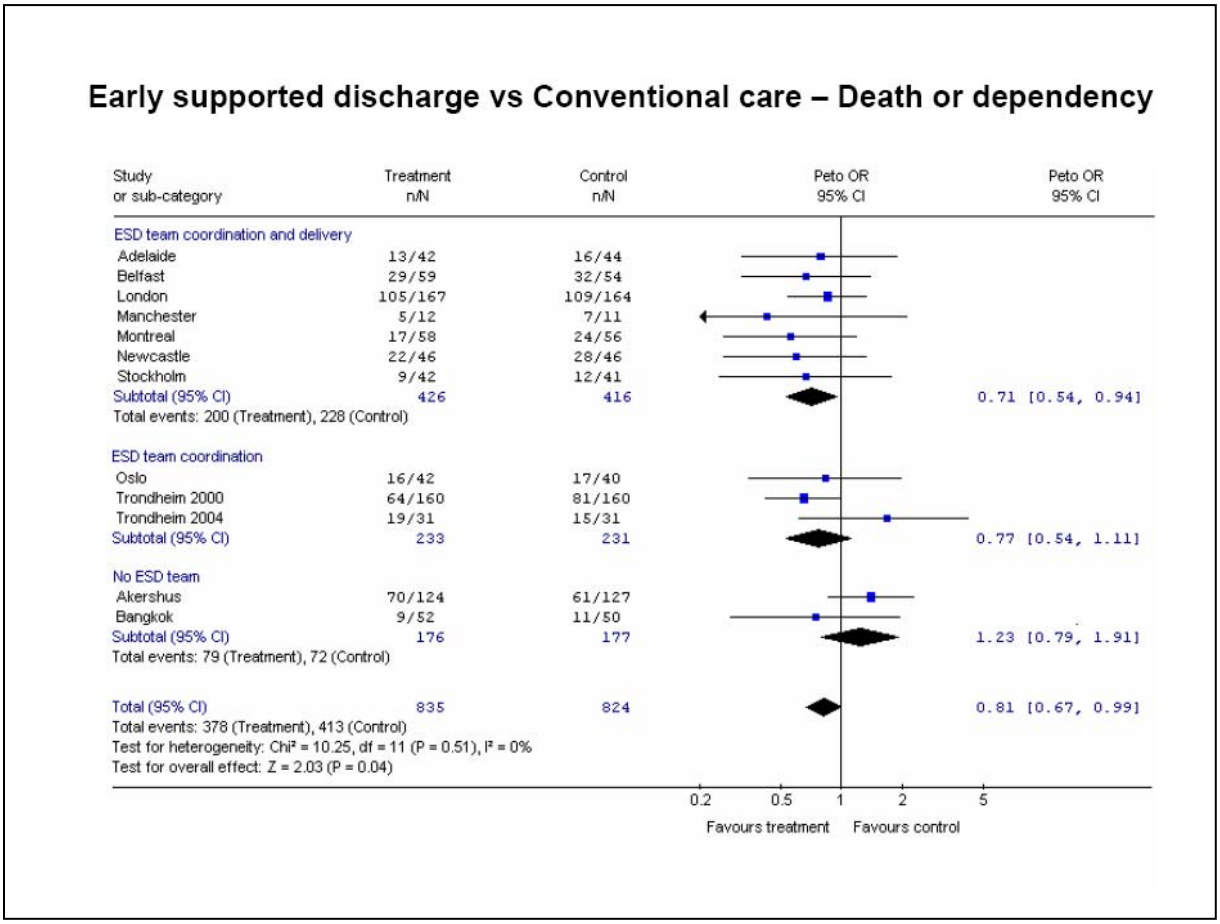

Figure 7. Latest update of meta-analysis on ESD trials (Langhorne & Holmqvist, 2007) (Printed with permission from the Early Supported Discharge Trialists)

The results on the Modified Rankin Scale were confirmed by the Barthel Index. Self-perceived health as measured by the Nottingham Health Profile revealed no significant differences between the groups at any time except less social isolation in the ESD group at 26 weeks follow-up. Improved self-perceived physical health was reported in the Montreal trial (Mayo et al., 2000), and improved global subjective health in the Trondheim trial (Fjaertoft et al., 2004), but no improved self-perceived health was found in any of the other comparable trials (Anderson et al., 2000; Rudd et al., 1997; Rodgers et al., 1997; Bautz-Holtert et al., 2002; Donnelly et al., 2004; Widen et al., 1998).

The Caregiver Strain Index was used to detect whether the ESD increases the burden on the caregivers. Four other trials have evaluated this aspect and found no increased burden, in line with the present trial (Donnelly et al., 2004; Rudd et al., 1997; Rodgers et al., 1997; Fjaertoft et al., 2004). However, one trial found significantly lower mental health among caregivers in the ESD group (Anderson et al., 2000). This last result implies that the impact of ESD on the caregivers' health and well-being should be further investigated.

The ESD service has been shown to be a cost-saving treatment with less use of in-patient rehabilitation (Anderson et al., 2002). Our trial showed a non-significant reduction of seven in-patient days in the ESD group, which emphasises the potential cost-saving advantage of this treatment.

This is to our knowledge the first ESD trial reporting results on the Berg Balance Scale. The ordinal Berg Balance Scale has good responsiveness (Mao et al., 2002). To discover a clinical significant change on six Berg Balance Scale points in patients with moderate to mild stroke, power calculations, using a significance level on 0.05 and 90 % power, have revealed a sample size of 30 patients in each group. This is not so far from the number of patients analysed in *Paper II*, which strengthens the validity of these results. The between group analysis showed no significant differences at six, 26 or 52 weeks post stroke. However, the Berg Balance Scale showed a non-significant trend toward better outcome in the control group at one week follow-up. This difference could not be ascribed to the effect of the ESD service, as the intervention had not yet started at this time. To adjust for these differences, the change within each group on all cases completing all assessments during the one year follow-up period was assessed and compared. The results showed an almost significant ($p=0.065$) greater improvement on the Berg Balance Scale from one to six weeks follow-up in the ESD group compared to the control group, indicating greater gains on balance for patients receiving ESD service. This result should be interpreted with caution, as the control group was closer to the ceiling effect on the Berg Balance Scale than the ESD group, and the low number of remaining participants implies that the groups may not be fully comparable at that stage.

The walking speed did not show equally greater improvement in the ESD group, indicating that functional training in the patients' home might facilitate functional balance as measured with the Berg Balance Scale but not fast walking speed. However, we have no detailed

records of the home-training programme, and it is possible that the treatment was not as intensive and task-specific as intended. Three other trials have also reported no differences between the groups according to walking speed (Rudd et al., 1997; Widen et al., 1998; Donnelly et al., 2004). Further research should emphasise task-specific exercise therapy with a higher intensity in addition to an ESD service to enhance further improvement on both balance and walking speed.

The second aim of *Paper II* was to assess the association between initial leg paresis and balance one year after the stroke and to assess the association between initial movement ability and balance at one year follow-up. All four cases with initial severe leg paresis suffered from poor balance after one year, but there was no association between initial moderate paresis and balance. Those with no initial walking ability had a significantly increased risk of poor balance, while those walking with support showed a non-significant trend ($p=0.085$) toward poor balance at one year follow-up. As far as we know, no other studies have assessed an equivalent association. Balance is an important component of walking, and poor balance is a major cause of falls (Lord SR et al., 2001). A number of other studies have assessed the significance of leg paresis in predicting falls or walking function after stroke (Wandel et al., 2000; Olsen, 1990; Jorgensen et al., 1995a; Jorgensen et al., 2002; Kollen et al., 2005). The results from these studies are conflicting, showing both a strong association between initial severe leg paresis and poor recovery of walking function (Jorgensen et al., 1995a; Wandel et al., 2000), and no association between initial leg paresis and the risk of falling when the results were adjusted for depression (Jorgensen et al., 2002), and finally that improvement in standing balance control is more important than improvement in leg strength to achieve improvement in walking ability (Kollen et al., 2005). Our results indicate a strong association between initial severe leg paresis and poor balance, in line with two other studies (Jorgensen et al., 1995a; Wandel et al., 2000). The lack of significant association between initial moderate leg paresis and balance implies that moderate leg paresis is of minor importance for balance and walking ability after stroke, which is in line with Kollen et al. (2005). However, the significance of initial movement ability on balance one year after stroke is confirmed by a number of studies claiming the importance of trunk control for functional outcome after stroke (Franchignoni et al., 1997; Duarte et al., 2002; Hsieh et al., 2002).

In conclusion, the main result of our ESD trial deviates from other comparable ESD trials; however, some of the secondary outcome measures show a slight trend toward greater improvement in the ESD group in line with the other trials. This deviating result is mainly explained by low statistical power due to the small sample size and more disabled patients in our trial. The rural setting may also partly explain this deviating result.

6.3 Internal validity of the ESD trial

Internal validity implies that the differences observed between groups of patients allocated to different interventions may, apart from random error, be attributed to the treatment under investigation. The internal validity is threatened by four categories of bias: selection bias, performance bias, detection bias and attrition bias (Juni et al., 2001).

6.3.1 Selection bias

The main reason for using randomisation is to prevent selection bias by creating groups that are comparable for any known or unknown potentially confounding factors (Altman & Bland, 1999). The randomisation procedure in the present trial was carefully planned before the study started. Sealed opaque envelopes were used for randomisation and the procedure was carried out by an external office. This procedure was established practice at the time of study planning, with a view to avoid selection bias, although a computer-generated randomisation would have been preferable today.

There are several prognostic baseline variables that can be potential confounders in stroke trials. Some of the most important are age, gender, stroke subtype, living condition and neurological impairment (Kapral et al., 2005; Nakayama et al., 1994; Patel et al., 2000; Christensen et al., 2005; Jorgensen et al., 1999); however, gender is documented both to be a predictor (Kapral et al., 2005) and not to be a predictor (Jorgensen et al., 1999) of recovery after stroke.

Although none of these variables was significantly different at baseline in our trial, we cannot exclude the possibility that some of them may bias the result after all. Accordingly, we chose to adjust our primary outcome for age, living condition and neurological impairment, assessed

by the Scandinavian Stroke Scale, in a multiple logistic regression model. Only age and neurological impairment remained significant and were included in the final model.

6.3.2 Performance bias

Performance bias occurs if additional treatment interventions are provided preferentially to one group (Juni et al., 2001). All patients randomised to the ESD group and all patients randomised to the control group were treated according to the protocol, i.e. ESD coordination or standard follow-up care, respectively; however, a carry-over effect from the ESD group to the standard group cannot be excluded.

The primary health care system upgraded their skills associated with stroke treatment through regular meetings with the mobile stroke team before and during the trial. A methodological challenge was that the same primary health care system provided services for both groups, while the follow-up care was coordinated by the multidisciplinary mobile stroke team only in the ESD group. This design increases the risk of a carry-over effect from the patients in the ESD group to patients in the control group. Hence, the difference between the ESD coordination and the standard service may not be significant any longer. The increased risk of performance bias in small communities with few staff in the primary health care system might be avoided by randomising different municipalities to different treatments. However, this design also has several methodological challenges.

6.3.3 Detection bias

Detection bias arises if the knowledge of patient assignment influences the assessment of outcome. This is avoided by the blinding of those assessing the outcome (Juni et al., 2001). The assessor in the present trial was blinded to patient assignment. It was impossible to blind the patients to their assignment and we cannot exclude the possibility that some of the patients revealed their assignment to the assessor. This might theoretically have influenced some of the results. However, this is not very likely according to the performance-based outcome measures, though it may have affected the self-reported outcome measures. Outcome measures used in this trial, assessed for reliability, are documented to have good test-retest and inter-rater reliability, which also is a prerequisite for avoiding detection bias.

The primary outcome in *Paper I* was the dichotomised Modified Rankin Scale. In addition, the dichotomised Barthel Index (BI≥95) and mean Barthel Index were used as secondary outcomes to measure independence in activities of daily living. These are the most widely used outcome measures in previous stroke trials (Duncan et al., 2000; Stroke Unit Trialists' Collaboration, 2002; Early Supported Discharge Trialists, 2007). However, both scales are claimed to be insensitive to small changes (Bath et al., 2007). The advantage is their robustness, minimising the chance of detection bias.

The Berg Balance Scale and timed walking speed are both performance-based measurements with minimal risk of detection bias.

The Nottingham Health Profile was one of the first measures to emphasise the subjective aspects of health assessment. The Nottingham Health Profile is short and easy to complete, and the wording is simple and easily understood (Fayers & Machin, 2000). However, each item is a negatively loaded statement, to which the patients are supposed to answer yes or no. Hence, the scale is focused on disability rather than ability, which may increase the risk of reporting poor self-perceived health. However, this problem will probably be equal for participants in both groups and consequently will not affect the detection bias. In recent years many generic and disease-specific outcome measures of self-perceived health have been developed. For stroke patients the Stroke Impact Scale is regarded as a reliable and valid measure (Duncan et al., 1999), but the responsiveness is not convincing (Salter et al., 2005c). Consequently, the generic Medical Outcome Study Short Form 36 (SF-36) is today the most frequently applied measure of self-perceived health in stroke trials (Salter et al., 2007).

The carers of stroke patients experience significant strain (Robinson, 1983). In the present trial the Caregiver Strain Index was used to assess this aspect during follow-up. Although the patient allocation was known to the carers, is it unlikely that this knowledge would influence their response according to this measurement.

6.3.4 Attrition bias

Deviation from the protocol and loss to follow-up often lead to the exclusion of patients after they have been allocated to treatment groups, which may introduce attrition bias (Juni et al., 2001). No patients were excluded after they had been allocated to the treatment groups. An

intention to treat analysis was performed according to the primary outcome measure in *Paper I*, which excludes the possibility for attrition bias. There was a 26 % death or dropout incidence during the 52 weeks follow-up. Eight patients died in the ESD group, and in the control group four patients died, two patients suffered from severe illness and two patients withdrew from the study. If the most severely disabled patients in the control group withdrew from the study, this could lead to a higher functional level among those remaining in the per protocol analysis, which may in turn introduce attrition bias. However, this bias goes in disfavour to the ESD group.

In conclusion, the small sample size may have increased the risk of selection bias in our ESD trial. However, the possibility of performance bias and attrition bias may have influenced the results in disfavour of the ESD service. Finally, there is no evidence for detection bias in this trial. Despite these possible biases, our ESD trial is judged to have high internal validity.

6.4 External validity of the ESD trial

External validity of a trial is the extent to which results of the trial provide a correct basis for generalisation to other circumstances. The external validity comprises several dimensions. It is related to the applicability of the results of a study to other "populations, settings, treatment variables and measurement variables" (Juni et al., 2001). If intervention trials are judged as internally valid the external validity should be high. According to the small sample size in the present trial the external validity may be difficult to interpret.

The median proportion of patients eligible for the ESD service in previous ESD trials was 41%, indicating that this service is favourable for a selected group of stroke patients (Langhorne et al., 2005). However, our inclusion criteria were broad, including an unselected population (70 %) from three municipalities surrounding the city of Trondheim. The Stroke Unit had 14 available hospital beds during this trial. Patients who were admitted to other wards at the hospital when the Stroke Unit was full were not considered for inclusion in the trial. The exclusion of patients due to lack of beds could hardly have any impact on the external validity. The Trondheim trial with comparable inclusion criteria included 68% of their target population (Indredavik et al., 2000). This trial was judged to have good external validity (Fjaertoft et al., 2005).

The setting for this trial was a dedicated stroke unit in cooperation with the primary health care system in three rural municipalities. The organisation of the primary health care system may be different in rural communities and urban centres, and consequently our results may not be applicable to other settings.

The present trial is judged to have high internal validity. However, this is the first ESD trial conducted within a rural setting, and the small sample size makes it difficult to generalise the results, hence the trial has low external validity. Final conclusions about the effect of an ESD service for patients living in a rural community cannot be drawn before a number of ESD trials or a multisite trial is conducted within this setting.

6.5 Comparing the CIMT trial with other studies

To our knowledge seven randomised controlled trials evaluating the effect of six hours' daily CIMT have been published before our trial (Sterr et al., 2002; Suputtitada et al., 2004; Taub et al., 1993; Taub et al., 2006; van der Lee et al., 1999; Wittenberg et al., 2003; Wolf et al., 2006). Our results will be discussed in the light of these seven trials summarised in Table 5. Different outcome measures are used in these trials. In Table 5 the results on Wolf Motor Function Test and Motor Activity Log are preferably reported if used. In two trials Action Research Arm test is reported instead.

Table 5. Randomised controlled trials evaluating the effect of 10 days of CIMT compared to different control treatments

First author of study	n/N*	Participants	CIMT-treatment	Control-treatment	Post-treatment assessment	Follow-up assessment
Dahl et al. 2007 Trondheim, Norway	18/30	Subacute and chronic stroke: Ranging from 1 to 92 months from stroke Mean age†: 62/60 years.	6 hours of daily training by using a shaping procedure of the affected arm and constraint on the less affected arm for 90% of waking hours. Treated in groups of 3-4 patients at an in-patient clinic.	Standard care ranging from no treatment to various occupational and physical therapy treatments in the home, and outpatient hospital visits.	WMFT: Significant shorter performance time and greater functional ability in the CIMT group. MAL: No significant differences between the groups.	Six months: WMFT: No significant differences MAL: No significant differences
Sterr et al. 2002 Germany	7/15	Chronic stroke: Ranging from 1 to 17 years from stroke. Mean age†: 49/68 years.	6 hours of daily training by using a shaping procedure and constraint on the unaffected arm 90% of waking hours. No information about setting.	3 hours of daily training of the affected arm by using a shaping procedure and constraint on the less affected arm 90% of waking hour.	WMFT: No significant differences in performance time between the groups. MAL: Significant greater amount of use and quality of movement in the CIMT group.	Four weeks: WMFT: No significant differences between the groups MAL: The significant differences persisted.
Suputtitada et al. 2004 Thailand	33/69	Chronic stroke: Ranging from 1 to 10 years from stroke. Mean age†: 60/58 years.	6 hours of daily training. No information about shaping procedure. Healthy hand was covered by a glove for avoiding using it. Patients were encouraged to use their affected arm at home. Treated in groups of 3-4 at an outpatient clinic.	6 hours of daily bimanual upper extremity training according to Neuro-Developmental Treatment. No constraint on less affected arm. Treated in groups of 3-4 in an outpatient clinic.	ARA: No significant differences between the groups on the total ARA score.	No follow-up assessment.

Table 5. Continued

First author of study	n/N	Participants	CIMT-treatment	Control-treatment	Post-treatment assessment	Follow-up assessment
Taub et al. 2006 Alabama	21/41	Chronic stroke: mean 3.6/5.3 years from stroke. Mean age†: 54/50 years.	6 hours of daily training using a shaping procedure. An additional hour of interpolated rest on each weekday. Constraint on the less effected arm for 90 % of waking hours. No information about setting.	6 hours per day with a general fitness programme.	WMFT: Significant lower performance time in the CIMT group. No significant differences in functional ability. MAL: Significant better quality of movement in the CIMT group.	Four weeks: WMFT: Not assessed. MAL: Significant better quality of movement in the CIMT group.
Taub et al. 1993 Alabama	4/9	Chronic stroke: Ranging from 1.2 to 18 years from stroke. Mean age†: 65/63 years.	6 hours of daily training using a shaping procedure. An additional hour of interpolated rest on each weekday. Constraint on the less effected arm for 90 % of waking hours. Outpatient treatment at a rehabilitation clinic.	Focused attention on the more affected extremity.	WMFT: Significant lower performance time and greater functional ability in the CIMT group. MAL: Significant greater amount of use in the CIMT group.	Four weeks and two years: MAL: Significant greater amount of use in the CIMT group.
Van der Lee et al. 1999 The Netherlands	33/66	Chronic stroke: median 3.1 years from stroke. Mean age†: 60/64 years.	6 hours of daily training, training functional activities. Constraint on the less effected arm during training and at home. Treated in groups of four at an outpatient clinic.	6 hours of daily bimanual upper extremity training according to Neuro-Developmental Treatment. No constrain on the less affected arm. Treated in groups of four at an outpatient clinic.	ARA: Significantly higher score in the CIMT group. MAL: Significant greater amount of use in the CIMT group. No significant differences between the groups in quality of movement.	Twelve months: ARA: Significant higher score in the CIMT group MAL: No significant greater amount of use or quality of movement.

Table 5. Continued

First author of study	n/N	Participants	CIMT-treatment	Control-treatment	Post-treatment assessment	Follow-up assessment
Wittenberg et al. 2003 Alabama	9/16	Chronic stroke: Ranging form 12 to 86 months post stroke. Mean age†: 65/63 years.	6 hours of daily training by a shaping procedure. Constraint on the less affected arm. No information about the amount of the restraint. One or two patients were treated together at an in-patient clinic.	3 hours of daily bimanual training, including, 1 hour with passive therapy (stretching and heath) at an in-patient setting	WMFT: No significant differences in functional ability. MAL: Significantly greater amount of use in the CIMT group.	No follow-up assessment.
Wolf et al. 2006 Atlanta	106/ 222	Chronic stroke: Ranging from 3 to 9 months post stroke. Mean age†: 61/63 years.	6 hours of daily standard task-specific training by a shaping procedure. Constraint on less affected arm for 90% of waking hours. Individual training at an outpatient clinic.	Usual care ranging from no treatment to various occupational and physical therapy treatments in the home, day treatment programmes, or outpatient hospital visits	WMFT: Significant shorter performance time and better functional ability in the CIMT group. MAL: Significant greater amount of use and better quality of movement in the CIMT group.	Twelve months: WMFT: Significant shorter performance time in the CIMT group. No significant difference in functional ability. MAL: Significant greater amount of use and better quality of movement in the CIMT group.

*Number of patients randomised to the CIMT group/total number of patients included; †mean age in the CIMT group/mean age in the control group; WMFT, Wolf Motor Function Test; MAL, Motor Activity Log; ARA, Action Research Arm test

6.5.1 Setting

Two of the previous trials were conducted in Europe (Sterr et al., 2002; van der Lee et al., 1999), one in Asia (Suputtitada et al., 2004) and four in the US (Taub et al., 1993; Taub et al., 2006; Wittenberg et al., 2003; Wolf et al., 2006). There are significant differences between the health care system in the US and Norway. This can make comparison between studies difficult, but as the intervention is clearly defined it should still be possible to compare the results. The majority of the trials have accomplished the supervised treatment at an outpatient clinic, with the patients living in their homes, and only one other trial carried out the intervention in an in-patient setting (Wittenberg et al., 2003), comparable to our trial. The in-patient setting was chosen because patients were recruited from the entire Central Norway Regional Health Authority, many living a long way from the hospital. An outpatient setting would probably have emphasised more functional training during the afternoon with the patients living in their own homes. However, the in-patient setting had the advantage of encouraging the patients to wear their mitten during the afternoon.

CIMT is conducted as both individual therapy and as group therapy. Our patients were treated in groups with up to four patients in line with two other trials (Suputtitada et al., 2004; van der Lee et al., 1999). The groups were well staffed with a physiotherapist, an occupational therapist and a nurse when needed. This staffing is near to individual therapy and is comparable to an individual therapy setting. Based on this we will maintain that our setting is comparable to the setting of other CIMT trials.

6.5.2 Study patients

The present trial targeted patients with unilateral impairment of the upper extremity after stroke. Our patients had to demonstrate at least 20˚ of active wrist extension and 10˚ of active finger extension and weakness or reduced dexterity of the affected hand evaluated by clinical assessment. The latter is in contrast to most of the other trials using a maximum score (2.5 or 2.7 points) on the Motor Activity Log (Wolf et al., 2006; Taub et al., 2006; Wittenberg et al., 2003) or Action Research Arm test less than 51 points (maximum 57) (van der Lee et al., 1999; Suputtitada et al., 2004). Initial Motor Activity Log, amount of use, score in our CIMT group was ranging from 0.33 – 4.13 indicating that some of our patients had merely minor impairments in the affected arm and hand and consequently only minor potential to improve.

Our upper age limit was 80. Although this criterion was only used by two other studies (van der Lee et al., 1999; Suputtitada et al., 2004) the mean age in our trial, 62 years in the CIMT group and 60 years in the control group, was close to the other CIMT trials listed in Table 5. However, this is a fairly young sample compared to the mean age of the total stroke population, which is 77.7 years for women and 75.3 years for men (Ellekjaer et al., 1997). Six hours of daily CIMT is probably not suitable for the oldest patients, as comorbidity increases with age (Wyller, 2007) which may reduce the ability to conduct intensive training.

In the present trial we wanted to include both subacute and chronic patients, ranging from one month to eight years after stroke. This is in contrast to all other comparable trials listed in Table 5 including only patients with chronic stroke, except the EXCITE trial, including patients three to nine months after the stroke (Wolf et al., 2006).

Patients with severe aphasia, neglect, and cognitive impairments are generally excluded from CIMT trials and different measures are used for screening of these impairments. According to the Mini-Mental State Examination a cut-off between 23/24 (Wolf et al., 2006; Taub et al., 2006), 21/22 (van der Lee et al., 1999), or 20/21 (Sterr et al., 2002) was used in previous trials. In addition different kind of aphasia tests are used (Sterr et al., 2002; van der Lee et al., 1999; Taub et al., 1993). In our CIMT trial we chose a cut-off between 20/21 on the Mini-Mental State Examination. We had no aphasia test; however, based on clinical experience, we considered that patients with severe aphasia would be excluded according to the chosen cut-off on the Mini-Mental State Examination while patients with minor aphasia were allowed to be included. Patients with neglect were excluded if they deviated more than 2 cm from the centre in line bisection. Twelve points or less on Montgomery and Aasberg Depression Rating Scale was another exclusion criterion.

In conclusion, it would appear that our patients are comparable in age to most other CIMT trials but that they might have reached a higher functional level before inclusion. This higher initial functional level may make it more difficult to achieve further significant improvement. However, no other trials have included patients as early as we did. Despite these minor deviations, our patients are comparable to patients studied in other CIMT trials.

6.5.3 The study intervention

Although CIMT is a well described technique there are some differences in the application of some of the components of the treatment. Firstly, it seems like the shaping procedure is conducted in an even more systematic way in the trials by Taub et al (Taub et al., 2006; Taub et al., 1993) than in the present trial, especially with regard to rigorous recording of increased speed, weight and complexity of task performance. Secondly, the restraint on the less affected arm is achieved in different ways. A resting hand splint and arm sling ensemble was applied in five trials (Sterr et al., 2002; van der Lee et al., 1999; Wittenberg et al., 2003; Taub et al., 2006; Taub et al., 1993) while a glove or mitten was applied in two trials (Suputtitada et al., 2004; Wolf et al., 2006). In the present trial we chose to apply a mitten because it was easy for the patient to remove for safety and hygienic reasons. The disadvantage was that the patients could to some extent use the less affected arm to support the more affected arm when struggling with a task. However, these minor differences in performance of the intervention are not expected to have any noteworthy impact on the results.

Our control group received standard rehabilitation, ranging from no treatment to a variety of occupational and physical therapy in the home or outpatient hospital visits. This was equivalent to the control treatment provided by Wolf et al (2006). The control treatment in the other trials varied widely in terms of both content and intensity. This great variability in control treatments may explain some of the variation in the results of these studies.

In conclusion, our CIMT treatment is comparable to the treatment applied in all other comparable studies. However, it seems like the EXCITE trial by Wolf et al (2006) is the most comparable trial in terms of the control treatment applied.

6.5.4 Results

The significantly shorter performance time and better functional ability according to our primary outcome measure, Wolf Motor Function Test, in the CIMT group compared to the control group at post treatment assessment is confirmed by the EXCITE trial (Wolf et al., 2006). However, the difference did not persist at 6 months follow-up, which is in contrast to Wolf et al (2006) who found significant differences between the groups in performance time but not in functional ability at all follow-up assessments (4 months, 8 months and 12 months).

Our control group showed a significant improvement from baseline to 6 months follow-up. The inclusion of patients with subacute stroke may explain some of this improvement. An additional explanation is the amount of standard rehabilitation given to the control group. The mean (SD) time with physiotherapy and occupational therapy given to the control group during the intervention period was 1.7 (1.3) and 0.8 (1.5) hours per week respectively. Both groups were free to continue with standard rehabilitation after the intervention period. The low dose of standard rehabilitation given over a longer period may have caused some of the improvement for the patients in the control group. This somewhat unexpected improvement in the control group is also seen in the EXCITE trial including 222 patients (Wolf et al., 2006). The low sample size and increased risk of Type II error, i.e. failing to reject the null hypothesis when the alternative hypothesis is true (Rosner B, 2000), is another possible explanation for no long-term effect revealed in the present trial.

Four trials, with varying degrees of intensive arm training applied in the control group, showed conflicting results according to post treatment and follow-up assessment on the laboratory measurements (Sterr et al., 2002; Suputtitada et al., 2004; Wittenberg et al., 2003; van der Lee et al., 1999). Sterr et al (2002) applied three hours of CIMT in the control group, while Wittenberg et al (2003) applied three hours of bimanual upper extremity training. The trials found a significant improvement in both groups, but no differences between the groups according to the Wolf Motor Function Test. This indicates that less intensive training may also be beneficial. Van der Lee et al (1999) and Suputtitada et al (2004) applied six hours of bimanual training in the control group, the former showing a significantly greater improvement in the CIMT group, which persisted at one year follow-up while the latter revealed no short-term effects according to the total Action Research Arm score. These somewhat conflicting results may be explained by the correction for baseline differences in the former and not in the latter trial and the result suggests that the force used is a significant part of CIMT.

The primary aim of CIMT is to increase the use of the more affected arm in activities of daily living and the Motor Activity Log is presumed to measure the attainment of this goal. The Motor Activity Log is a self-reported measure which demands good cognitive skills. This measurement has so far yielded the most convincing results with significant greater amount of use of the affected arm in the CIMT group compared to the control group in previous trials (Sterr et al., 2002; Taub et al., 2006; Taub et al., 1993; van der Lee et al., 1999; Wittenberg et

al., 2003; Wolf et al., 2006). This is in contrast to the present trial, showing only a trend in favour of the CIMT group according to the Motor Activity Log on both the amount of use scale and the quality of movement scale. Our blinded tester was cautious, trying not to influence the patients to exaggerate their scores when completing this form. This may have led to underestimation of the actual improvement of the amount of use of the affected arm in our patients. Another possible explanation is that the amount of use of the affected arm was overestimated in other comparable studies. Although the reliability of 28 out of 30 items on the Motor Activity Log is verified by Uswatte et al (2006), we experienced that patients wanted to give socially desired answers, and the tester had to be extremely aware of this problem. It is a challenge to find appropriate ADL measurements for this intervention, because traditional measurements such as the Functional Independent Measure and Barthel Index do not register increased participation of the more affected arm. However, goal achievement is an clinically important outcome and the use of Goal Attainment Scaling (Hurn et al., 2006) should be tested in future CIMT studies.

The Stroke Impact Scale was chosen to measure self-perceived health at 6 months follow-up, but the analysis did not reveal any differences between the groups in any domain within this scale. This result supports the lack of long-term effect found in the present trial. This is in contrast to the EXCITE trial, which showed a significant difference between the two groups according to self-perceived hand function at both four and twelve months follow-up (Wolf et al., 2006). No other previous studies have reported on self-perceived health, although it is an important aspect of recovery after stroke, and further studies should incorporate the evaluation of this aspect.

In conclusion, our CIMT trial is comparable to most other CIMT trials according to setting, study patients and the CIMT programme, supporting the validity of our results. However, our control treatment is only comparable to the control treatment applied in the EXCITE trial, and the lack of long-term effect may be explained by the small sample size in our trial. The significant improvement in our control group at six months follow-up and the results from other CIMT trials indicates that less intensive training over a longer time period may also be beneficial and should be tested in future studies to find the optimal amount and duration of this treatment.

6.6. Internal validity of the CIMT trial

6.6.1 Selection bias

The randomisation procedure in the present trial was equivalent to the procedure used in the ESD trial, and has probably not introduced any selection bias. However, we knew from the planning of the trial that our sample size would be relatively small with increased risk of uneven distribution of prognostic baseline variables, i.e. time from onset of stroke.

Patients in the subacute phase after stroke have an exponential recovery curve compared to patients in the chronic phase (Jorgensen et al., 1995b). As our patients ranged from one month to eight years after onset of symptoms, an uneven distribution of this variable may bias the results. The baseline variables showed no significant differences between the groups, but some imbalance was observed. The analysis of covariance (ANCOVA) is the preferable statistical method in this situation (Vickers & Altman, 2001). Months since stroke was used as a covariate in these analysis but revealed no significant changes, indicating that the variable is equally distributed or does not have any major impact on the outcome. However, further studies should include a more homogenous group of patients according to time from onset. There are too few eligible patients with acute stroke admitted to any single hospital in our country. A multi-site trial will therefore be necessary to include sufficient subacute patients within a reasonable time limit, in further CIMT studies conducted within the Norwegian health care system.

Other potential prognostic variables include age, gender and side affected. All of these variables were entered, one by one, as covariates in a second-level analysis. However, none of them influenced the outcome.

The randomisation to a CIMT group or a control group was according to the ratio 3:2 respectively. This ratio was chosen because we needed as many patients as possible in the CIMT group to assess feasibility. In addition, not much statistical power is lost by moderate deviations from equal groups (1:1 randomisation ratio). For example, if the effect size is 1.2, (mean difference divided by standard deviation), a 0.05 level two-sample *t*-test has power 88.7% or 87.5% with 15:15 or 18:12 allocation, respectively.

6.6.2 Performance bias

All patients randomised to the CIMT group were treated according to the CIMT intervention, and all the patients randomised to the control group received standard rehabilitation. However, some of the patients in the control group were in-patients at the rehabilitation clinic where the CIMT intervention took place during the trial. Although CIMT patients and control patients were admitted to different wards, we cannot preclude that some control patients have been inspired to increase their amount of individual training, which also was confirmed by the staff at the rehabilitation clinic. However, this bias goes in disfavour to the CIMT group and may explain some of the improvement in the control group.

As both groups were free to continue standard rehabilitation after the intervention period it is reasonable to anticipate that this treatment is equally distributed between the two groups.

6.6.3 Detection bias

The person who performed all the assessments in the present trial was blinded to patient assignment. It was impossible to blind the patients to their assignment, and therefore this was a single blinded trial.

Our primary outcome, Wolf Motor Function Test, is one of the most commonly used measurements in previous CIMT trials (Sterr et al., 2002; Taub et al., 2006; Taub et al., 1993; Wittenberg et al., 2003; Wolf et al., 2006). The test is recorded on video tape and the performance time and functional ability is rated from the video recordings. The reliability and validity of the instrument is stated in Table 3. To ascertain the reliability in the present trial two blinded assessors rated the video tapes. Tasks with discrepancy in the rating were discussed by the two raters before they came to agreement. This procedure should minimise the chance of detection bias.

CIMT is meant to result in enhanced quantity and quality of participation of the affected arm in activities of daily living and the Motor Activity Log was developed to measure this improvement (Taub et al., 1993). The Motor Activity Log is a structured interview to assess the use of the paretic arm and hand during given activities of daily living. The reliability is stated by Uswatte et al (2006). However, it is not recommended to use the measurement as a

primary outcome because the improvement during an intervention period was only weakly correlated to improvement with a performance based measurement (Action Research Arm test) and the longitudinal construct validity is supposed to be weak (van der Lee et al., 2004). In our trial the Motor Activity Log was used as a secondary measurement and it did not confirm the improvement revealed by the Wolf Motor Function Test.

6.6.4 Attrition bias

No patients were excluded from the trial after being allocated to the treatment groups, and no patients died or dropped out during follow-up. This excludes the possibility for any attrition bias in this trial.

In conclusion, the small sample size may have increased the risk of selection bias in our CIMT trial. The possibility of performance bias may have influenced the results in disfavour of the CIMT group. However, there is no evidence for detection bias or attrition bias in this trial, and our CIMT trial is judged to have high internal validity.

6.7 External validity of the CIMT trial

The proportion of eligible patients has been estimated by Taub et al (1993) to be approximately 20% to 25% of the stroke population (Taub et al., 1993), which may be a very optimistic estimate. So far, the EXCITE trial is the only CIMT trial reporting the number of patients screened for inclusion and the proportion of patients included in the trial. In this trial only 6% of the patients screened for inclusion were eligible (Wolf et al., 2006). The inclusion and exclusion criteria in the present trial were very similar to those applied in the EXICITE trial, and consequently a highly selected group of stroke patients was included. It follows that one should be careful to apply the results of this trial to other stroke subgroups.

The setting of the present trial was an in-patient rehabilitation clinic. The use of the constraint on the unaffected arm during 90 % of waking hours may be different for the in-patient compared to the outpatient setting. The in-patients have the advantage of the presence of staff to encourage the use of the mitten in demanding activities of daily living, and the outpatients having the advantage of practicing in more realistic environments in their homes. However,

we will argue that the advantages or disadvantages of an in-patient setting are not a major problem to the external validity and our CIMT treatment can probably be applied to an outpatient setting as well.

The improved short-term effect of CIMT compared to standard treatment shown in our CIMT trial is verified by the EXCITE trial. Based on this and the high internal validity of the present trial, the results could be applied to a highly selected group of stroke patients. However, the small sample size implies that the results should be interpreted with caution.

Finally, CIMT is a resource demanding technique, and the cost-effectiveness of the treatment should therefore be a focus in future research.

6.8 Comparing the fMRI study with other studies

In a literature search on PubMed reviewing only English-language papers, we identified 14 comparable longitudinal studies, assessing the change in brain activation after stroke using fMRI or PET (Nelles et al., 1999; Marshall et al., 2000; Calautti et al., 2001; Calautti et al., 2003; Small et al., 2002; Feydy et al., 2002; Ward et al., 2003; Jang et al., 2003; Loubinoux et al., 2003; Loubinoux et al., 2007; Tombari et al., 2004; Carey et al., 2005; Jaillard et al., 2005; Thiel et al., 2007). These studies vary widely according to location of ischaemic lesion, time since stroke, and age of the patients included in the respective studies. They also vary with regard to the applied task paradigms, clinical outcome measures and outcome of image analysis, such as laterality indices, coordinates of activated maxima, displacement of coordinates, volume of activated voxels, and so on. However, our fMRI study will be discussed within this variable framework.

6.8.1 Study patients

The age of the patients included in the present study ranged from 62 to 75 (mean; 67), while the age of patients included in the other comparable studies ranged from 29 to 75, showing that our patients are in the upper limit of this range. Four studies included patients with mixed infarctions (cortical and sub-cortical) in both hemispheres (Small et al., 2002; Feydy et al., 2002; Ward et al., 2003; Jang et al., 2003; Carey et al., 2005) comparable to our patients. One

study included only cortical infarctions in the right hemisphere (Jaillard et al., 2005), while the nine remaining studies included sub-cortical infarctions in both hemispheres (Nelles et al., 1999; Marshall et al., 2000; Calautti et al., 2001; Calautti et al., 2003; Loubinoux et al., 2003; Loubinoux et al., 2007; Tombari et al., 2004; Thiel et al., 2007). The initial functional level assessed on the Barthel Index in our study ranged from 55 to 100 points. The functional level in the other comparable studies was assessed with a variety of outcome measures, which makes a direct comparison difficult. However, five studies have used the Barthel Index, showing an initial functional level ranging from 35 points to 100 points in four of the studies (Calautti et al., 2001; Ward et al., 2003; Loubinoux et al., 2003; Thiel et al., 2007), which is relatively similar to the functional level in our patients, while one study reported an initial functional level ranging from 15 points to 100 points (Tombari et al., 2004).

Although there is significant variability in the patient characteristics in our study and in previously published longitudinal fMRI studies it can be said in summary that patients included in the present study are fairly comparable to patients included in other fMRI studies in terms of their age, functional level, and location of infarctions. However, patients who are eligible for fMRI studies make up a small and highly selected group of patients, who are younger and less disabled than the general stroke population.

6.8.2 Study intervention

All our patients received evidence-based stroke unit treatment with emphasis on early mobilisation and task-oriented physiotherapy (Indredavik et al., 1991). In addition, early supported discharge coordinated by a multidisciplinary team was given during the further follow-up care (Indredavik et al., 2000; Fjaertoft et al., 2003). The treatment given to the stroke patients included in the other comparable studies is not well described. We suggest the high quality treatment given to our patients may be a distinctive characteristic compared to other fMRI studies.

6.8.3 Results

The main result of the present study was a statistically significant improvement in functional recovery according to all the applied functional outcome measures, despite fairly similar activation maps in the acute and chronic phases. However, in a comparison of the two phases,

three mechanisms were identified as central to successful recovery. These are (1) changes in activation patterns from the acute to the chronic phases comparable to that described in motor learning studies, (2) re-establishment of activation within the primarily lateralised motor network, and (3) recruitment of bilateral somatosensory association areas and contralesional secondary somatosensory cortex (SII).

Laterality indices increased significantly in primary sensorimotor cortex (MISI) and cerebellum from the acute to the chronic phases. This finding is confirmed by previous studies reporting increasingly higher laterality index as recovery takes place (Feydy et al., 2002; Marshall et al., 2000). However, when taking all hemispheric cortical ROIs into account, the laterality index was not significantly different in the two phases. This finding suggests the reemergence of the lateralised MISI and cerebellar activation combined with extensive bilateral somatosensory association and contralesional SII recruitment. These regions are also more active in the chronic compared to the acute phase. Increased activation of contralesional SII has so far been reported to be associated with good recovery of motor function after stroke in one other longitudinal neuroimaging study (Thiel et al., 2007). Two recent cross sectional studies also emphasise the importance of bilateral and contralesional recources for successful recovery after stroke (Gerloff et al., 2006; Schaechter & Perdue, 2008). SII in particular, but also somatosensory association areas, have neurons with bilateral receptive fields, connected through transcallosal projections and possibly via thalamic fibres (Iwamura et al., 2001). These regions project massively to both primary and secondary motor areas, and give rise to sub-cortical and corticospinal projections. It is hypothesised that in patients who have made good recovery after hemiparetic stroke, the ipsilesional MI may rely more heavily on the contralesional MI to control spatiotemporal aspects of affected hand movement (Schaechter & Perdue, 2008). Increased activity in contralesional MI was only associated with good recovery of key grip strength in the present study. However, our results indicate that functional recovery after stroke appears to be linked to plasticity in somatosensory structures in the contralesional hemisphere.

The increased bilateral activation of the thalami from the acute to the chronic phases suggests that this sub-cortical pathway is of major importance for integration of sensory input and motor action in successful motor recovery. Furthermore, afferents from contralesional somatosensory regions may directly or indirectly influence movement via ipsilateral

corticospinal projections, but the importance of this system is undetermined (Jankowska & Edgley, 2006).

By using a range of outcome measures, each reflecting a different aspect of recovery, a more comprehensive understanding of recovery is possible (Duncan et al., 2000). The results from the covariate analysis in the present study strengthen the importance of contralesional somatosensory association areas and SII activation in regaining the ability to perform more complex motor tasks demanding the coordinate activity and dexterity of the entire hand as demonstrated by the positive correlation between UL-MAS and NHPT. Transversal grip strength was also associated with increased contralesional SII activation in addition to increased ipsilesional primary somatosensory activation. The key-grip strength test (KGS), on the other hand, correlated with bilateral hand MI activation with ipsilesional dominance. MI is the only region projecting directly to the motor neurons, and the present result points to preservation of the ipsilesional MI as the major contributor to force in this group of patients with good recovery. Other studies analysing the association with functional recovery have used a variety of different functional outcome measures (Nelles et al., 1999; Calautti et al., 2001; Ward et al., 2003; Loubinoux et al., 2003) and summary scores (Feydy et al., 2002; Small et al., 2002) which makes comparison difficult.

Although, Krakauer (2006) has proposed that motor learning mechanisms is operative during spontaneous recovery and interact with rehabilitative training, no other longitudinal studies have, to our knowledge, investigated motor network changes after stroke in relation to motor learning. Our results will in the next paragraph be discussed in the light of these processes.

In the acute phase compared to the chronic phase, ipsilesional angular gyrus and insula and bilateral putamen/globus pallidi plus contralesional cerebellum were significantly more activated. In the chronic phase compared to the acute phase, there was increased activation of ipsilesional hand region of MISI, bilateral somatosensory association cortex, contralesional SII plus contralesional cerebellum and bilateral thalami. These activation patterns are comparable to neuroimaging studies of neuronal network changes during the course of motor skill learning (Doyon et al., 2003). In the early learning stage there is extended bilateral cerebellar and striatal activation that declines with practice to be replaced by a predominantly sensorimotor cortex network with varying contributions from striatum and/or cerebellum depending on experimental set-up (Doyon et al., 2003; Flament et al., 1996). The increased

cerebellar activation in the early phase of motor skill learning is considered to reflect unconscious monitoring and correction of task performance (Imamizu et al., 2000; Flament et al., 1996). This was also found in the present study. In addition there was evidence for greater conscious awareness of task performance indicated by the increased activation of ipsilesional angular gyrus (Farrer et al., 2008) in the acute phase.

In conclusion, the present study demonstrates that patients with spared ipsilesional MISI treated with a task-oriented approach have brain activation changes comparable to changes observed in motor skill learning. This result supports the postulation about motor learning mechanisms being operative during spontaneous stroke recovery, and that these interact with rehabilitative training (Krakauer, 2006). The increased contribution of bilateral somatosensory association and contralesional SII associated with successful motor recovery emphasises the significance of bi- and contralesional resources in recovery after stroke (Thiel et al., 2007; Gerloff et al., 2006; Schaechter & Perdue, 2008).

6.9 Internal validity of the fMRI study

6.9.1 Detection bias

The person who performed the analysis of the images was blinded to the functional outcome of the patients reducing the risk of detection bias.

Our study was based on the assumption that the baseline activation and the haemodynamic response are the same in both the acute and chronic phases. However, the validity of the relationship between motor performance, the neuronal activation and BOLD response is discussed. Kranik et al (2005) found a heterogeneity in the cerebrovascular reactivity and suggested that this heterogeneity could be a methodological issue in functional imaging studies using task-related BOLD signal in poststroke patients (Krainik et al., 2005). Binkofski and Seitz (2004) found a presence of perilesional activation during motor performance in the subacute stage after the stroke and the transient lack of this activation during the early chronic stage despite the clinical improvement of function in the affected hand. The BOLD response reoccurred in the chronic stage (Binkofski & Seitz, 2004). Based on this we cannot exclude

the possibility that some of the changes or lack of changes from the acute to the chronic phases are caused by these methodological uncertainties.

The choice of movement paradigm used in fMRI studies is also discussed. It is observed that cerebral activation covariates with movement rate in healthy subjects. Increased tapping rate results in increased BOLD signal intensity as well as the volume of activation in the contralateral primary motor cortex (Khushu et al., 2001). However, this linear relationship does not apply to all motor areas (i.e. cerebellum) during the finger tapping (Riecker et al., 2003). A comparison of brain activation in patients requires that they all perform an equivalent motor task, but it is almost impossible to ask a group of stroke patients with different functional levels to perform a task in an identical manner and to do it exactly the same way in both the acute and chronic phases. As patients recover, and function improves, the task will be performed in a more skilled manner and the task is not the same any longer. Our SP task was chosen to ensure that all patients spent about the same effort to conduct the task. In addition we chose to use movement rate as a regressor in some of the analysis, to normalise for the difference in movement rate between subjects and to adjust for the change in movement rate within each subject from the acute to the chronic phases. This analysis showed only minor deviation from the analysis without movement rate as a regressor.

In conclusion, BOLD fMRI is considered to have good internal validity in healthy subjects (Stoeckel et al., 2007). However, there are some concerns about the internal validity for patients with cerebrovascular diseases.

6.10 External validity of the fMRI study

Only 4% of the stroke patients screened for inclusion were eligible to participate. Although no stroke type was actively excluded, the strict inclusion criteria resulted in a highly selected sample. None of the patients had language or other cognitive deficits, because they had to understand the experimental instructions. Furthermore, all patients had to regain the ability to actively move their affected fingers within four days post-stroke. In addition, the BOLD response might be weaker in old age (D'Esposito et al., 2003) and we decided to exclude those patients older than 75 years of age. As a result, our sample consisted of a highly selected

group of stroke patients, comprising fairly young patients with small infarction not encompassing the motor cortex.

A variety of different motor-task paradigms are used in the comparable fMRI studies, most of them at a fixed rate. Our simple SP task does not measure motor skill relearning directly but indirectly through the association to motor recovery and relearning of motor skills, assessed with our outcome measures. In future studies different functional tasks should be tested out in fMRI studies to get a more direct measure of the learning process.

In addition to the concerns about the internal validity, the small and highly selected sample size implies that our results should be interpreted with caution. Hence, the external validity is weak and the study should mainly be regarded as hypothesis-generating work which may enhance our understanding of underlying mechanisms in recovery from stroke, and help to suggest directions for further research in this field. The question of whether task-oriented training based on motor learning principles facilitates brain activation patterns comparable to changes in motor learning studies should be tested in a larger study. The significance of bilateral somatosensory association area and contralesional SII activation for successful motor recovery should also be further investigated.

7 Conclusions

- An ESD service for stroke patients living in a rural community did not appear to have beneficial effect on death or dependency, balance or walking speed in the short or long term, but might give a transient reduction in social isolation. However, when analysing all patients who completed all assessments the results revealed a non-significant trend toward greater improvement on the Berg Balance Scale in the ESD group, indicating a possible beneficial effect on balance from early rehabilitation in the patient's home.

- A strong association was identified between initial severe leg paresis, but not with initial moderate leg paresis, and reduced balance one year after the stroke. There was also a strong association between initial inability to walk and reduced balance one year after the stroke.

- CIMT conducted as group therapy was feasible, and it improved motor function in the affected arm in the short term for a selected group of patients after stroke. It is unclear whether CIMT is superior to standard rehabilitation in the long term as no long-term effect was revealed.

- Functional MRI analysis of a highly selected group of stroke patients treated with task-oriented training revealed motor network changes comparable to changes described in motor skill learning studies.

- The recruitment of bilateral somatosensory association areas and contralesional secondary somatosensory area seems to be of significance for successful motor skill relearning after stroke.

8 Suggestions for future research

- There is a challenge for future research in stroke rehabilitation to develop treatment protocols that can be applied in multi-site trials. A multi-site design should be applied for studies of both ESD services for patients living in rural communities and for studies of CIMT. Although one multi-site CIMT trial has already been conducted in the US, it would be desirable for this trial to be replicated within a European setting.

- It appears that both task-specific and intensive treatment is beneficial after stroke. Future research should focus on detecting the appropriate intensity and amount of training to achieve the highest possible functional level. Cost-effectiveness analysis should be performed within this setting.

- Future research should also focus on deriving more understanding about significant changes within the motor network associated with successful improvement of motor skills, and on investigating how different interventions, such as CIMT, affect brain plasticity.

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Erratum

Paper II

Introduction, second sentence;
”…, and a programme of functional exercises in the patient’s home or in an outpatient clinic, to improve both balance and walking speed after stroke (6-8).”

Should be replaced by;
” …., and a programme of functional exercises conducted in the patient’s home or in an outpatient clinic, improved both balance and walking speed after stroke (6-8).”

Paper I

Paper I is not included due to copyright.

Paper II

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DOES AN EXTENDED STROKE UNIT SERVICE WITH EARLY SUPPORTED DISCHARGE HAVE ANY EFFECT ON BALANCE OR WALKING SPEED?

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Objective: **To evaluate the effect of an extended stroke unit service with early supported discharge on balance and walking speed, and to explore the association between initial leg paresis, initial movement ability and balance one year after stroke.**
Design: **A randomized controlled trial comparing early supported discharge with ordinary stroke unit service.**
Patients: **A total of 62 eligible patients after stroke.**
Methods: **The outcome measures were Berg Balance Scale and walking speed at 1, 6, 26 and 52 weeks after stroke.**
Results: **We found no significant differences between the 2 groups during follow-up. There was a significant improvement on Berg Balance Scale ($p = 0.013$) and walking speed ($p = 0.022$) in the early supported discharge group, but not in the ordinary service group, from 1 to 6 weeks' follow-up. All patients with initial severe leg paresis suffered from poor balance one year after the stroke. The odds ratio for poor balance was 42.1 (95% confidence interval; 3.5–513.9) among patients with no initial walking ability.**
Conclusion: **These results do not conclusively indicate that early supported discharge has an effect on balance. A strong association was found between initial severe leg paresis, initial inability to walk and poor balance after one year.**

Key words: Stroke, posture, gait, rehabilitation.

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INTRODUCTION

Effective stroke unit care with early mobilization improves functional outcome after stroke (1, 2), however, increased risk of falling is a major problem among patients after stroke (3), and impaired balance is one of the main reasons for falling (4). It is beneficial to provide further intensive exercise therapy in the subacute and chronic phase (5), and a programme of functional exercises in the patient's home or in an outpatient clinic, to improve both balance and walking speed after stroke (6–8).

Patients after stroke conventionally undergo a substantial part of their rehabilitation in hospital or rehabilitation clinics. A new kind of service has been developed during the last decade that offers patients early supported discharge (ESD), namely early discharge from hospital with rehabilitation at home. This service seems to reduce long-term dependency (9).

ESD is a composite intervention and comparing the results among various studies is difficult because ESD is conducted in different ways. Early discharge coordinated by a multidisciplinary team seems to be an important factor and the early exercise therapy in the patient's home is another factor that could be beneficial. This early exercise therapy in the patient's home could be defined as task-specific because it consists of functional tasks conducted in a functional setting. Task-specific training is recommended in further research to improve balance and functional outcome after a stroke (10, 11). Previous ESD trials have shown good functional outcome after stroke (9, 12, 13). Improved balance and walking speed may contribute to this result. However, it is still unknown whether ESD is beneficial to balance or walking speed.

Early prediction of functional outcome is another important topic in stroke management, and there is growing interest in conducting longitudinal studies to study the relationship between impairments and disability (3, 14, 15). Kollen et al. (15) claim that initial standing balance is more important than improvement in leg strength to achieve improvement in walking ability, while Jørgensen et al. (14) found a strong relationship between leg paresis and walking function. However, more knowledge about the relationship between specific body functions, such as initial leg paresis or movement ability, and activities, such as improvement in balance during mobility, would be useful in selecting optimal treatment strategies after stroke.

Two ESD trials have been conducted at the Stroke Unit at the University Hospital of Trondheim. The first trial showed reduced death and dependency for patients living in the city of Trondheim (12, 16) and the second trial showed no beneficial effect on functional outcome for patients living in a rural community (17). This study is based upon secondary outcomes from the trial evaluating early supported discharge for patients living in a rural community (17).

The aims of this study were to evaluate the effect of an extended stroke unit service (extended service) with ESD on balance and

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walking speed and to explore initial factors associated with balance one year after treatment in an acute stroke unit.

SUBJECTS AND METHODS

Subjects

Patients from 3 municipalities surrounding the city of Trondheim, who had been admitted to the Stroke Unit at Trondheim University Hospital, were screened for inclusion in the trial. Inclusion criteria were: diagnosis of an acute stroke according to the World Health Organization definition of stroke (18); Scandinavian Stroke Scale (SSS) (19) score greater than 2 points and less than 58 points; living at home before the stroke; inclusion within 72 hours after admission to the stroke unit and within 7 days after the onset of symptoms; able and willing to provide informed consent.

Research design

In the present study a randomized controlled design was used. Patients fulfilling the inclusion criteria were included and block randomized in blocks of 4, 6 or 8 patients, to either an ordinary stroke unit service (ordinary service) or the newly constructed extended service. The order of the blocks was randomly chosen. Sealed opaque envelopes were used for randomization and the procedure was carried out by an external office.

During the acute phase (the first 1–2 weeks) both groups received well-documented stroke unit care with focus on early mobilization combined with a standardized medical programme (20). The follow-up care for the ordinary service group is combined with further inpatient rehabilitation when more long-term rehabilitation is necessary or a follow-up programme organized by the primary healthcare system.

The extended service consisted of stroke unit treatment combined with a home-based programme of follow-up care co-ordinated by a mobile stroke team that offers early supported discharge and works in close co-operation with the primary healthcare system during the first 4 weeks after discharge. In contrast to the ordinary service, the intervention placed emphasis on early and intensive task-specific exercise therapy in the patients' home.

An independent and blinded assessor specially trained in the use of all the outcome measures performed all the assessments.

The Regional Committee on Medical Research Ethics approved the study protocol.

Evaluation

Baseline characteristics were recorded before randomization. All patients were followed-up at 1, 6, 26 and 52 weeks after onset of stroke.

The Berg Balance Scale (BBS) maximum score of 56 was used to measure balance (21, 22). On the multiple regression analysis BBS was dichotomized into good balance (BBS ≥ 45) versus poor balance and increased risk of falling (BBS <45) (22).

Walking speed was clocked across a 5 m length. The distance was walked twice at maximal walking speed. The means of the 2 trials were used as a test parameter representing the fast speed condition.

Motor function of the leg and the movement ability was assessed by use of the subscores from the SSS (19). The original leg score is graded in 5 categories: paralysis (0 point); can move, but not against gravity (2 points); raises leg with flexion in knee (4 points); raises leg straight but with reduced strength (5 points); and raises leg with normal strength (6 points). This item was categorized into 3 categories; severe paresis (0–2 points); moderate paresis (4–5 points) and no paresis (6 points). The originally movement score is also graded in 5 categories; confined to one's bed or wheelchair (0 point); sits without support (3 points); walks with support (6 points); walks with walking aid (9 points); walks 5 m without walking aid or support (12 points). This item was categorized into the following 3 categories; no walking ability (0–3 points), walks with support (6–9 points) and independent walking ability (12 points).

Statistical analysis

Baseline characteristics were compared using Mann-Whitney U test (ordinal data), t-test for independent samples (ratio data), or χ^2 tests (nominal data). Outcomes between the 2 groups at 1 week, 6 weeks, 26 weeks and 52 weeks' follow-up were compared using Mann-Whitney U test (ordinal data) and t-test for independent samples (ratio data).

Change within groups analysis were performed on those patients who had completed all assessments from 1 to 6 weeks, 1 to 26 weeks and 1 to 52 weeks by using Wilcoxon signed rank test on BBS and paired t-test on walking speed.

Differences in change between groups were analysed by Mann-Whitney U test on the BBS and by Student's t-test on walking speed. The change was calculated as the difference between the 6 week test minus the 1 week test, the 26 week test minus the 1 week test and the 52 week test minus the 1 week test.

Multiple logistic regression was used to analyse the association between initial leg paresis and initial movement ability as independent variables, and the dichotomized BBS score 52 weeks after stroke as the dependent variable, allowing adjustments for potential confounders such as age, sex, treatment group and number of days from onset of symptoms to hospital admission (23).

All the analysis was performed in the statistical programme of SPSS 13.0 for Windows and a p-value less than 0.05 was considered significant.

RESULTS

Figure 1 shows the flow of patients through the study and the reasons for exclusion and drop-out according to BBS. In all, 89 patients were screened for inclusion between 1 June 1999 and 15 June 2001. A total of 62 patients were included in the study and 31 patients were randomly allocated to the extended service group and 31 to the ordinary service group. In the ordinary service group there were 2 partial drops out at 1 week follow-up. At 6 weeks' follow-up, 1 of the patients who were lost to follow-up because of illness withdrew from the study and another patient died.

There were no significant differences between the 2 groups for any of the baseline characteristics (Table I).

Table II shows a significant difference in fast walking speed ($p = 0.043$) and a trend toward better BBS score ($p = 0.144$) in the ordinary stroke unit service group at 1 week follow-up. There were no significant differences in BBS score or walking speed between the 2 groups at any other time during follow-up.

Changes within the extended service group (Table III) showed a significant increase in the BBS score from 1 to 6 weeks ($p = 0.013$) and an almost significant increase in BBS score from 1 to 26 weeks ($p = 0.051$). In addition, there was a significant increase in walking speed from 1 to 6 weeks ($p = 0.022$), from 1 to 26 weeks ($p = 0.044$) and from 1 to 52 weeks ($p = 0.028$). There were no significant changes on BBS or walking speed at any time in the ordinary service group.

The differences in change between the 2 groups showed a trend toward greater improvement in the extended service group compared with the ordinary service group from 1 week follow-up to 6 weeks' follow-up ($p = 0.065$) and from 1 week follow-up to 26 weeks' follow-up ($p = 0.142$) on the BBS, but no differences in change between the 2 groups on fast walking speed.

Visual analysis of Figs. 2 and 3 show an initial improvement and a later decline on both BBS and fast walking speed.

In our study 36.9% of patients with no leg paresis, 48.4% of patients with moderate paresis and 100% of patients with severe

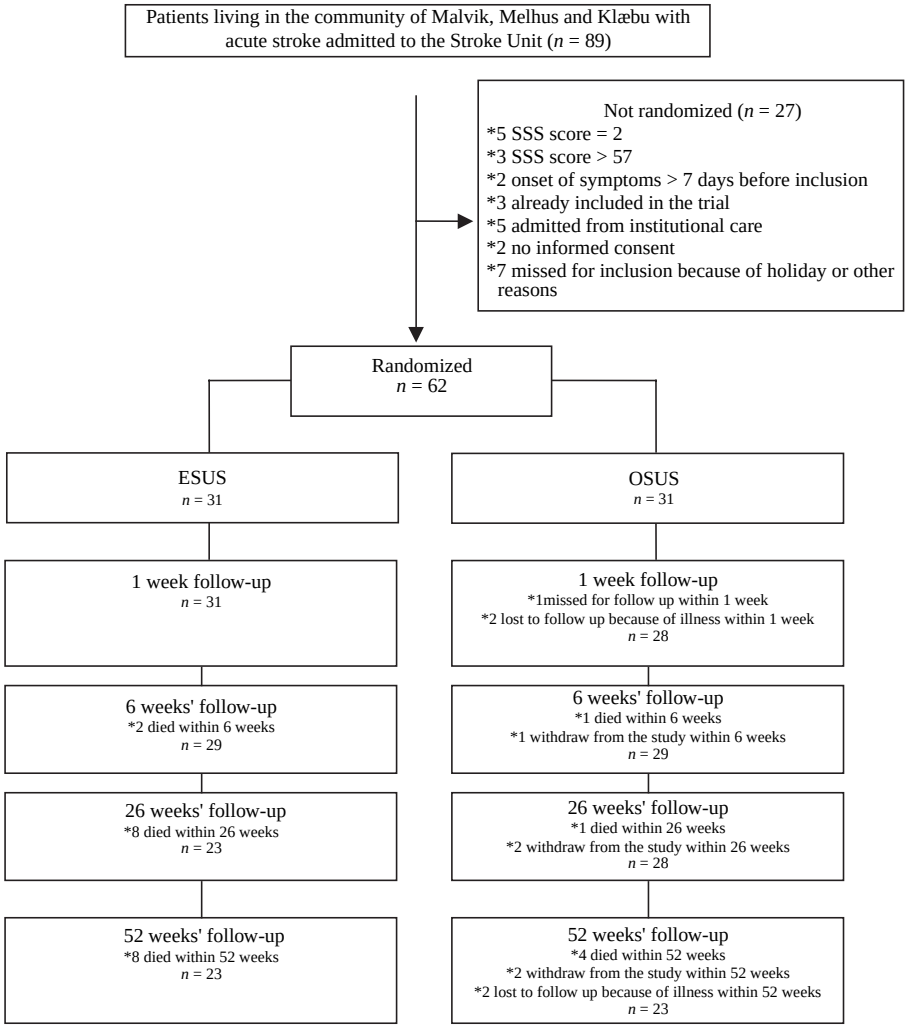

Fig. 1. Flow chart of patients randomized and followed-up with Berg Balance Scale. ESUS = extended stroke unit service; OSUS = ordinary stroke unit service; SSS = Scandinavian Stroke Scale.

leg paresis showed poor balance after one year. According to the movement item, 20.0% of patients with initial independent walking ability, 66.7% of patients able to walk with support and 90.9% of patients with no walking ability showed poor balance. Table IV shows the calculated odds ratio (OR) for poor balance among patients with initial leg paresis and reduced movement ability. Adjustment for potential confounders did not materially change the results, although the OR for poor balance became less significant among patients with initial leg paresis and more significant among stroke patients with reduced initial walking ability.

DISCUSSION

This study shows no significant differences between the extended service group and the ordinary service group on BBS or walking speed at any phase in the treatment. However, the extended service group had a greater improvement on both BBS and fast walking speed than the ordinary service group. The study also shows a strong association between initial severe leg paresis, initial inability to walk and poor balance.

The strength of this study is the randomized controlled design with a blinded assessor. In addition the study population is an unselected population. As shown in Fig. 1 70% of the patients admitted to the stroke unit met the criteria for inclusion in the trial. All the included patients received evidence-based stroke unit treatment according to the "gold standard" (20) and any improvement would have been in addition to the effect of this acute treatment.

There were few inhabitants in the 3 rural municipalities, and consequently a low number of people suffering from stroke. This was the principally reason for the small sample size. The small sample size and the low statistical power according to the primary outcome is the most important weakness of the present study (17). This leads to an increased risk of uneven distribution of potential confounders.

There is no data on BBS or walking speed at baseline, though at 1 week follow-up there was a significantly faster walking

Table I. *Baseline characteristics of patients allocated to extended stroke unit service (ESUS) and ordinary stroke unit service (OSUS)*

	ESUS ($n=31$)	OSUS ($n=31$)
Age (years), mean/median	76.9/77.0	76.3/76.0
Sex, number (%) male	16 (51.6)	17 (54.8)
Living alone number (%)	11(35.5)	15 (48.4)
Diagnosis number (%)		
Non-embolic infarction	18 (58.1)	20 (64.5)
Embolic infarction	5 (16.1)	8 (25.8)
Haemorrhage	7 (22.6)	3 (9.7)
Transient ischemic attack	1 (3.2)	0 (0.0)
Medical history, number (%)		
Transient ischemic attack	6 (19.4)	2 (6.5)
Stroke	2 (6.5)	1 (3.2)
Myocardial infarction	5 (16.1)	7 (22.6)
Atrial fibrillation	3 (9.7)	8 (25.8)
Hypertension	3 (9.7)	10 (32.3)
Diabetes	1 (3.2)	5 (16.1)
Functional state		
Scandinavian Stroke Scale, mean/median	45.4/46.0	41.5/46.0
Barthel Index, mean/median	57.7/55.0	54.0/55.0
Rankin Scale, mean/median	3.7/4.0	3.5/4.0

speed and a trend toward higher BBS score in the ordinary service group. The intervention cannot explain this difference because the patients were still in the stroke unit at this time and the main intervention started at discharge from the stroke unit. The small sample size and a not completely successful randomization have to account for this difference. In addition 3 patients were lost to follow-up in the ordinary service group at 1 week follow-up and may have caused additional uneven distribution. We assume that our analysis comparing groups at 6, 26 and 52 weeks may have been influenced by the initial difference between the 2 groups.

The BBS is measuring balance according to 14 functional tasks. Most of the tasks measure balance during sitting or standing position, and it will be a ceiling effect for patients with very mild stroke and only minor reduction in balance. However, walking speed will not suffer from this ceiling effect as the mean fast walking speed among patients in both groups were much slower than the usual fast walking speed among people at their age (24).

The cut-off on BBS between 44 and 45 points with an increased risk of falling for those with a BBS less than 45 points has been well documented (22), although Harries et al. (25) recommend clinicians to be cautious when using BBS to determine fall risk among patients with chronic stroke. The categorization of the leg and movement items on SSS is done in different ways in the literature. Jorgensen et al. (3) chose to dichotomize the leg item, while Jorgensen et al. (14) kept all 5 categories. There is a wide range of paresis, from total paralysis to a small reduction in strength. It is not likely that moderate paresis would be the same predictor as severe paresis and the categorization into 3 categories; no paresis, moderate paresis, and severe paresis appears to be clinically meaningful. Our results indicate different associations for these categories with severe leg paresis compared with those with moderate leg paresis.

Table II. *Differences between groups on Berg Balance Scale and fast walking speed assessed at 16, 26 and 52 weeks after stroke*

	ESUS	OSUS	p-value
1 week post-stroke			
Berg Balance Scale	($n=31$)	($n=28$)	
Mean (SD)	28.6 (21.4)	35.4 (21.4)	
Median (IQR)[1]	32.0 (4.0–50.0)	43.5 (18.5–54.8)	0.144
Fast walking speed (m/s)	($n=22$)	($n=22$)	
Mean (SD)[2]	0.78 (0.36)	1.03 (0.43)	0.043
6 weeks' post-stroke			
Berg Balance Scale	($n=29$)	($n=29$)	
Mean (SD)	33.9 (21.6)	35.4 (21.1)	
Median (IQR)[1]	46.0 (8.0–51.5)	42.0 (17.5–54.5)	0.464
Fast walking speed (m/s)	($n=21$)	($n=24$)	
Mean (SD)[2]	0.91 (0.31)	1.06 (0.46)	0.217
26 weeks' post-stroke			
Berg Balance Scale	($n=23$)	($n=28$)	
Mean (SD)	35.7 (20.6)	36.3 (20.2)	
Median (IQR)[1]	44.0 (19.0–53.0)	43.5 (23.0–55.0)	0.842
Fast walking speed (m/s)	($n=18$)	($n=22$)	
Mean (SD)[2]	1.02 (0.41)	1.15 (0.53)	0.406
52 weeks' post-stroke			
Berg Balance Scale	($n=23$)	($n=23$)	
Mean (SD)	33.1 (22.1)	36.0 (22.1)	
Median (IQR)[1]	43.0 (6.0–53.0)	45.0 (13.0–56.0)	0.440
Fast walking speed (m/s)	($n=15$)	($n=18$)	
Mean (SD)[2]	0.97 (0.41)	1.22 (0.48)	0.130

ESUS = extended stroke unit service; OSUS = ordinary stroke unit service; IQR = inter quartile range; SD = standard deviation; [1] Mann-Whitney U test; [2] Student's t-test.

Table III. *Changes within groups during follow-up on those patients who completed all assessments on Berg Balance Scale (BBS) and fast walking speed*

	ESUS			OSUS		
	n	Median (IQR)	Change within group *p*-value[1]	*n*	Median (IQR)	Change within group *p*-value[1]
BBS						
1 week	23	38.0 (9–51)		23	50.0 (20–55)	
6 weeks	23	47.0 (9–53)	0.013	23	53.0 (15–56)	0.815
26 weeks	23	44.0 (19–53)	0.051	23	48.0 (23–56)	0.897
52 weeks	23	43.0 (6–53)	0.824	23	45.0 (13–56)	0.505
	n	Mean (SD)	Change within group *p*-value[2]	*n*	Mean (SD)	Change within group *p*-value[2]
Fast walking speed (m/s)						
1 week	14	0.89 (0.35)		17	1.15 (0.39)	
6 weeks	14	1.05 (0.26)	0.022	17	1.21 (0.42)	0.287
26 weeks	14	1.11 (0.42)	0.044	17	1.28 (0.51)	0.122
52 weeks	14	1.02 (0.38)	0.028	17	1.23 (0.50)	0.243

ESUS = extended stroke unit service; OSUS = ordinary stroke unit service; IQR = inter quartile range; SD = standard deviation; [1]Wilcoxon signed rank test; [2]Paired *t*-test; Change within group is change from 1 to 6 weeks, from 1 to 26 weeks and from 1 to 52 weeks.

Although ESD trials seems to be beneficial for long-term dependency (9), it is still unknown which factors are the most efficient. In this study we focus on the early exercise therapy in the patient's home. Regarding dependency we suggest that the functional level can improve both by improvements in body function and by adjustment of the facilities. Improvement in balance measured by the BBS is most likely dependent on improvement within the body systems.

To our knowledge this is the first ESD trial reporting results on the BBS, while 3 other studies have reported walking speed (26–29), The results from those studies support our finding showing no difference in walking speed between the extended service and the ordinary service group. There could be at least 4 reasons for this result. In the first place both groups received stroke unit treatment which improves functional outcome (1, 2, 20) and makes it challenging to achieve further improvement. Secondly, we have not registered the content in detail and cannot be sure if the exercises were as task-specific and functional as intended, even though they were conducted in the patients' homes. Thirdly, the intensity of the exercise therapy may have been too low to give any additional effect. The fourth and last reason could be the additional emphasis on home safety intervention which may result in less challenge to the balance system and less improvement in balance and walking speed.

When each time point is analysed separately, the measurements will be from different subjects. It is of primary interest to analyse how subjects respond over time. The analysis of change within the 2 groups on those patients who are available through the whole study shows a significant improvement on BBS from 1 to 6 weeks' follow-up and from 1 to 26 weeks' follow-up in the extended service group. It also shows an improvement on fast

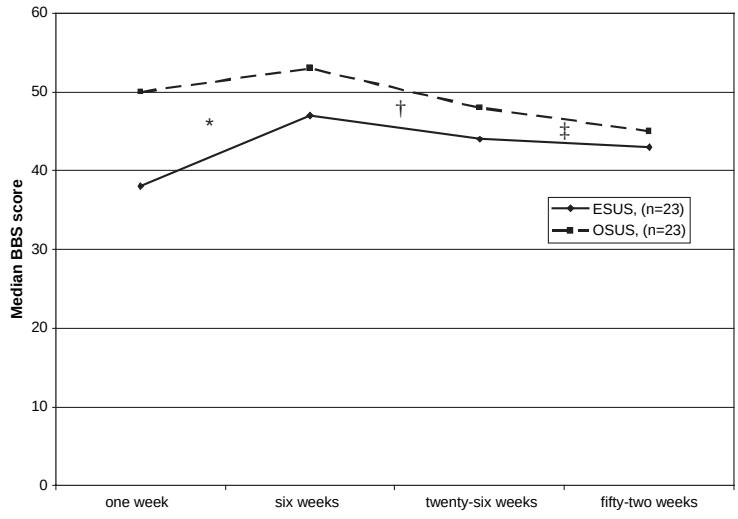

Fig. 2. How patients who have completed all assessments on Berg Balance Scale (BBS) respond over time. *Difference in change between groups from 1 week follow-up to 6 weeks' follow-up ($p = 0.065$). †Difference in change between groups from 1 week follow-up to 26 weeks' follow-up ($p = 0.142$). ‡Difference in change between groups from 1 week follow-up to 52 weeks' follow-up ($p = 0.400$). ESUS = extended stroke unit service; OSUS = ordinary stroke unit service.

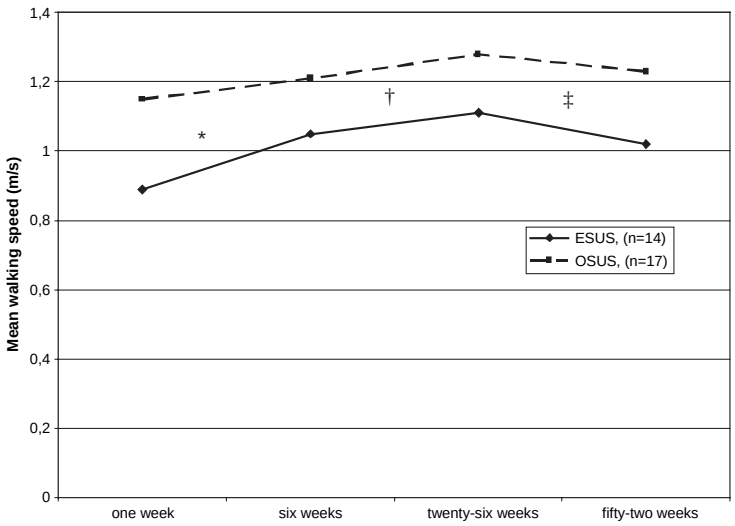

Fig. 3. How patients who have completed all assessments on fast walking speed respond over time. *Difference in change between groups from 1 week follow-up to 6 weeks' follow-up ($p = 0.224$). †Difference in change between groups from 1 week follow-up to 26 weeks' follow-up ($p = 0.494$). ‡Difference in change between groups from 1 week follow-up to 52 weeks' follow-up ($p = 0.557$). ESUS = extended stroke unit service; OSUS = ordinary stroke unit service.

walking speed from 1 to 6 weeks' follow-up, from 1 to 26 weeks' follow-up and from 1 to 52 weeks' follow-up. There were no similar improvements in the ordinary service group. One possible reason for no significant improvement from 1 to 6 weeks' follow-up in the ordinary service group may be due to the fact that this group was already close to the ceiling effect on BBS at 1 week follow-up.

When analysing the differences in change between the 2 groups from 1 week follow-up to each time point we found an almost significant greater improvement ($p = 0.065$) in the extended service group compared with the ordinary service group the first 6 weeks after the stroke and a trend toward greater improvement from 1 to 26 weeks ($p = 0.142$). This improvement might indicate that the extended service group is safer during transfer situations and consequently has reduced risk of falling, although these differences were not confirmed by the fast walking speed, and the trend toward greater improvement on BBS in the extended service group may also be due to the ceiling effect on BBS in the ordinary service group. However, it is difficult to make a final conclusion about the clinical relevance of this result because of the number of subjects is too small.

The visual analysis of Figs. 2 and 3 also shows an initial improvement and further decline in both balance and fast walking speed. This initial improvement and long-term decline in functional outcome and balance is confirmed by Langhammer & Stanghelle (30) in their study comparing Bobath treatment with a motor relearning programme.

Although the OR for poor balance could not be calculated for those with initial severe leg paresis, we will propose there is a strong association between those 2 variables. This result is in contrast to another study which found no association between leg paresis and falling when the results were adjusted for depression (3). One possible reason for this is the different ways of categorizing the leg item and the adjustment of different confounders. The Copenhagen Stroke Study has documented a strong relationship between initial leg paresis and recovery of walking function (14). Balance is an important component of walking function and this study supports our findings showing an association between initial severe leg paresis and poor balance.

Table IV. *Odds ratio (OR) and 95% confidence interval (CI) for poor balance one year after stroke associated with measures of initial leg paresis and initial movement ability*

Variable	Stroke patients (*n*)	Cases with BBS <45 (*n*)	OR (95% CI)[a]	*p*-value[a]
SSS leg score				
No paresis	11	4	1.0	
Moderate paresis	31	15	1.5 (0.3–7.3)	0.581
Severe paresis	4	4	nc	
SSS movement score				
Independent walking ability	15	3	1.0	
Walks with support	20	10	4.6 (0.8–26.5)	0.085
No walking ability	11	10	42.1 (3.5–513.9)	0.003

[a]OR adjusted for age, sex, treatment group and number of days from onset of symptoms to hospital admission; nc = not calculated because there were no cases with good balance; SSS = Scandinavian Stroke Scale; BBS = Berg Balance Scale.

The ability to move depends on trunk control and the strong association between early inability to move and poor balance after one year is confirmed by other studies that identify trunk control as en early predictor of functional outcome after stroke (31–33).

The results of this study of ESD with early rehabilitation in the patient's home does not conclusively indicate that ESD has an effect on balance. In addition, a strong association was found between initial severe leg paresis, initial inability to walk and poor balance after one year.

Further research should emphasize task-specific exercise therapy with a higher intensity in addition to ESD to enhance further improvement on balance and walking speed in order to facilitate an active life for the stroke patients.

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Paper III

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13. Terje Terjesen: FRACTURE HEALING AN STRESS-PROTECTION AFTER METAL PLATE FIXATION AND EXTERNAL FIXATION.
14. Carsten Saunte: CLUSTER HEADACHE SYNDROME.
15. Inggard Lereim: TRAFFIC ACCIDENTS AND THEIR CONSEQUENCES.
16. Bjørn Magne Eggen: STUDIES IN CYTOTOXICITY IN HUMAN ADHERENT MONONUCLEAR BLOOD CELLS.
17. Trond Haug: FACTORS REGULATING BEHAVIORAL EFFECTS OG DRUGS.

1985
18. Sven Erik Gisvold: RESUSCITATION AFTER COMPLETE GLOBAL BRAIN ISCHEMIA.
19. Terje Espevik: THE CYTOSKELETON OF HUMAN MONOCYTES.
20. Lars Bevanger: STUDIES OF THE Ibc (c) PROTEIN ANTIGENS OF GROUP B STREPTOCOCCI.
21. Ole-Jan Iversen: RETROVIRUS-LIKE PARTICLES IN THE PATHOGENESIS OF PSORIASIS.
22. Lasse Eriksen: EVALUATION AND TREATMENT OF ALCOHOL DEPENDENT BEHAVIOUR.
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1986
24. Dagfinn Berntzen: ANALYSIS AND MANAGEMENT OF EXPERIMENTAL AND CLINICAL PAIN.
25. Odd Arnold Kildahl-Andersen: PRODUCTION AND CHARACTERIZATION OF MONOCYTE-DERIVED CYTOTOXIN AND ITS ROLE IN MONOCYTE-MEDIATED CYTOTOXICITY.
26. Ola Dale: VOLATILE ANAESTHETICS.

1987
27. Per Martin Kleveland: STUDIES ON GASTRIN.
28. Audun N. Øksendal: THE CALCIUM PARADOX AND THE HEART.
29. Vilhjalmur R. Finsen: HIP FRACTURES

1988
30. Rigmor Austgulen: TUMOR NECROSIS FACTOR: A MONOCYTE-DERIVED REGULATOR OF CELLULAR GROWTH.
31. Tom-Harald Edna: HEAD INJURIES ADMITTED TO HOSPITAL.
32. Joseph D. Borsi: NEW ASPECTS OF THE CLINICAL PHARMACOKINETICS OF METHOTREXATE.

33. Olav F. M. Sellevold: GLUCOCORTICOIDS IN MYOCARDIAL PROTECTION.
34. Terje Skjærpe: NONINVASIVE QUANTITATION OF GLOBAL PARAMETERS ON LEFT VENTRICULAR FUNCTION: THE SYSTOLIC PULMONARY ARTERY PRESSURE AND CARDIAC OUTPUT.
35. Eyvind Rødahl: STUDIES OF IMMUNE COMPLEXES AND RETROVIRUS-LIKE ANTIGENS IN PATIENTS WITH ANKYLOSING SPONDYLITIS.
36. Ketil Thorstensen: STUDIES ON THE MECHANISMS OF CELLULAR UPTAKE OF IRON FROM TRANSFERRIN.
37. Anna Midelfart: STUDIES OF THE MECHANISMS OF ION AND FLUID TRANSPORT IN THE BOVINE CORNEA.
38. Eirik Helseth: GROWTH AND PLASMINOGEN ACTIVATOR ACTIVITY OF HUMAN GLIOMAS AND BRAIN METASTASES - WITH SPECIAL REFERENCE TO TRANSFORMING GROWTH FACTOR BETA AND THE EPIDERMAL GROWTH FACTOR RECEPTOR.
39. Petter C. Borchgrevink: MAGNESIUM AND THE ISCHEMIC HEART.
40. Kjell-Arne Rein: THE EFFECT OF EXTRACORPOREAL CIRCULATION ON SUBCUTANEOUS TRANSCAPILLARY FLUID BALANCE.
41. Arne Kristian Sandvik: RAT GASTRIC HISTAMINE.
42. Carl Bredo Dahl: ANIMAL MODELS IN PSYCHIATRY.

1989

43. Torbjørn A. Fredriksen: CERVICOGENIC HEADACHE.
44. Rolf A. Walstad: CEFTAZIDIME.
45. Rolf Salvesen: THE PUPIL IN CLUSTER HEADACHE.
46. Nils Petter Jørgensen: DRUG EXPOSURE IN EARLY PREGNANCY.
47. Johan C. Ræder: PREMEDICATION AND GENERAL ANAESTHESIA IN OUTPATIENT GYNECOLOGICAL SURGERY.
48. M. R. Shalaby: IMMUNOREGULATORY PROPERTIES OF TNF-α AND THE RELATED CYTOKINES.
49. Anders Waage: THE COMPLEX PATTERN OF CYTOKINES IN SEPTIC SHOCK.
50. Bjarne Christian Eriksen: ELECTROSTIMULATION OF THE PELVIC FLOOR IN FEMALE URINARY INCONTINENCE.
51. Tore B. Halvorsen: PROGNOSTIC FACTORS IN COLORECTAL CANCER.

1990

52. Asbjørn Nordby: CELLULAR TOXICITY OF ROENTGEN CONTRAST MEDIA.
53. Kåre E. Tvedt: X-RAY MICROANALYSIS OF BIOLOGICAL MATERIAL.
54. Tore C. Stiles: COGNITIVE VULNERABILITY FACTORS IN THE DEVELOPMENT AND MAINTENANCE OF DEPRESSION.
55. Eva Hofsli: TUMOR NECROSIS FACTOR AND MULTIDRUG RESISTANCE.
56. Helge S. Haarstad: TROPHIC EFFECTS OF CHOLECYSTOKININ AND SECRETIN ON THE RAT PANCREAS.
57. Lars Engebretsen: TREATMENT OF ACUTE ANTERIOR CRUCIATE LIGAMENT INJURIES.
58. Tarjei Rygnestad: DELIBERATE SELF-POISONING IN TRONDHEIM.
59. Arne Z. Henriksen: STUDIES ON CONSERVED ANTIGENIC DOMAINS ON MAJOR OUTER MEMBRANE PROTEINS FROM ENTEROBACTERIA.
60. Steinar Westin: UNEMPLOYMENT AND HEALTH: Medical and social consequences of a factory closure in a ten-year controlled follow-up study.
61. Ylva Sahlin: INJURY REGISTRATION, a tool for accident preventive work.
62. Helge Bjørnstad Pettersen: BIOSYNTHESIS OF COMPLEMENT BY HUMAN ALVEOLAR MACROPHAGES WITH SPECIAL REFERENCE TO SARCOIDOSIS.
63. Berit Schei: TRAPPED IN PAINFUL LOVE.
64. Lars J. Vatten: PROSPECTIVE STUDIES OF THE RISK OF BREAST CANCER IN A COHORT OF NORWEGIAN WOMAN.

1991

65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.
66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.

68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

1992

74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

1993

82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
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91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

1994

92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

1995

104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
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107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
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109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

1996

110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANSER.
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117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

1998

132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
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136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.

139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

1999

141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.

168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM

198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
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