NIPH
Norwegian Institute of Public Health

REPORT

2019

HEALTH TECHNOLOGY ASSESSMENT:

Prehospital CT for early diagnosis and treatment of suspected acute stroke or severe head injury

Published by The Norwegian Institute of Public Health
Division of Health Services
Title Prehospital CT for early diagnosis and treatment of suspected acute stroke or severe head injury. A health technology assessment.
Norwegian title Prehospital CT for tidlig diagnostikk og behandling ved mistanke om hjerneslag eller alvorlige hodeskader. En metodevurdering.
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ISBN 978-82-8406-005-7
Project number ID2016_009
Type of publication Health technology assessment
No of pages 93 (138 including appendices)
Client Bestillerforum RHF
Subject Heading (MeSH) Stroke; Craniocerebral Trauma; Tomography Scanners, X-Ray Computed; Tomography, X-Ray Computed; Ambulances; Mobile Health Units; Time-to-Treatment; Triage; Systematic Review; Technology Assessment, Biomedical
Citation Ormstad SS, Lund UH, Chudasama KK, Frønsdal KB, Hov MR, Ormberg I, Hafstad E, Stoinska-Schneider A, Robberstad B, Lauvrak V, Juvet LK. Prehospital CT for early diagnosis and treatment of suspected acute stroke or severe head injury. A health technology assessment. Rapport – 2019. Oslo: Folkehelseinstituttet, 2019.

Table of contents

Key messages

In Norway, approximately 12,000 persons experience acute stroke each year. Time is a crucial factor in the management of stroke, so rapid admission to a hospital for a computed tomography (CT) scan is recommended.

A mobile stroke unit (MSU), an ambulance equipped with a CT scanner, helps bring the hospital to the patient. Research evidence indicates that, compared with conventional care of acute stroke, MSU care probably leads to:

- reduced time from patient's first contact with the emergency dispatch center to thrombolysis (treatment with a clot dissolving agent)
- increased number of patients who receive thrombolysis

MSU care may also lead to:

- reduced time from patient's first contact with the emergency dispatch center to CT imaging
- better functionality at 3 months after stroke.

Our cost- and threshold analysis found that:
One MSU is estimated to cost approximately 6.4 million Norwegian kroner annually. The health gain measured in quality-adjusted life-years (QALYs) was 0.3 per patient receiving thrombolysis through MSU care compared with conventional care. We performed an analysis quantifying the severity criterion by calculating absolute shortfall for patients with acute ischemic stroke who receive conventional care. The results show an absolute shortfall of 5.5 QALYs. We found that the expected cost per QALY is approximately 385,000 Norwegian kroner or lower if one MSU successfully reaches at least 35-40% (145-171) of thrombolysis patients per year.

Title:
Prehospital CT for early diagnosis and treatment of suspected acute stroke or severe head injury. A health technology assessment.

Type of publication:
Health technology assessment (HTA)
Health technology assessment (HTA) is a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the development of safe, effective health policies that are patient focused and that seek to achieve best value.

Doesn't answer everything:
We did not address ethical, legal or social aspects related to prehospital CT

Who is responsible for this publication?
The Norwegian Institute of Public Health completed this HTA, which was commissioned by Bestillerforum RHF.

When were the literature searches conducted?
December 2017, December 2018

Peer review:
Professor Jan Malm, Umeå University
Associate Professor Eline Aas, University of Oslo

Executive summary

Background

Stroke is the second leading mortality cause in most Western countries, and a major cause of adult disability. In Norway, approximately 12,000 persons experience acute stroke each year. In 2017, 8,789 cases of acute stroke were recorded in the Norwegian Stroke Registry (covering 86% of acute stroke patients). Head injuries also constitute a large group of patients arriving at the emergency ward, and are the leading cause of death in persons under the age of 44 years. Those considered to have severe injury require urgent admission to a neurosurgical department.

In acute stroke and severe head injuries, it is crucial that the patient is diagnosed and treated as soon as possible ("time is brain"). If acute stroke or severe head injury is suspected, rapid admission to a hospital to undertake a computed tomography (CT) scan is recommended. In stroke caused by blood clots (ischemic stroke or cerebral infarction), thrombolytic treatment should be given as soon as possible, at most within 4.5 hours after the onset of symptoms. In hemorrhagic stroke (bleeding), on the other hand, thrombolytic treatment is contra-indicated as it may cause life-threatening complications. Thus it is crucial to determine as soon as possible the cause of the stroke in order to provide appropriate treatment. In head injuries, CT imaging allows the identification of those patients who require urgent admission to a neurosurgical department.

Prehospital CT, either performed in a mobile stroke unit (ambulance equipped with a CT scanner) or in "a CT scanner station" located outside hospital, is a novel approach that brings the hospital closer to the patient. It seeks to shorten the time to diagnosis and treatment, as well as to determine which treatment facility the patient should be directed to.

Objective

The aim of this health technology assessment (HTA) is to compare the clinical effectiveness and safety of prehospital CT for early diagnosis and potential prehospital treatment of suspected acute stroke or severe head injury with current practice of diagnosis and treatment carried out after arrival in the hospital. Furthermore, it seeks to shed light on organizational and health economic consequences related to the implementation of prehospital CT in Norway.

Method

Clinical effectiveness and safety

In absence of eligible systematic reviews and HTAs, we conducted systematic searches for primary studies in a selection of relevant databases and trials registries. We limited the searches to publication year 2010 to present, but no restrictions to study type were applied. Two reviewers independently screened identified references, selected full-text publications that met predefined inclusion criteria, and critically appraised the included studies. Data extraction was performed by one reviewer, and checked by a second reviewer. For four outcomes, we were able to synthesize the findings by means of meta-analyses. For other outcomes, results were presented in tables and text. We assessed the certainty of the evidence for the main clinical outcomes using the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation). In GRADE, the certainty of the evidence is expressed either as high, moderate, low, or very low, depending on the level of confidence we have in the effect estimates.

Health economic evaluation

We conducted a cost- and threshold analysis, which attempts to elucidate mean incremental cost-effectiveness ratios (ICERs) at different values for proportions of ischemic stroke patients receiving thrombolysis through mobile stroke unit (MSU) care compared to conventional care (use of standard ambulance). This method makes it possible to identify a threshold value for the proportion that is required for the MSU to achieve an ICER of a predefined level. We also calculated absolute shortfall for patients with acute ischemic stroke receiving conventional care in order to classify severity for the relevant patient population. Further, we performed a one-way sensitivity analysis to investigate the impact of the MSU cost parameter. We modified an existing probabilistic Markov decision analytic model for ischemic stroke patients, developed as a part of an HTA on mechanical thrombectomy conducted by the Norwegian Institute of Public Health in 2016. The analyses do not evaluate consequences of introducing MSUs in non-metropolitan parts of Norway, and they do not account for patients with other indications who might benefit from MSU care.

Results

Clinical effectiveness and safety

Searches for primary studies resulted in a total of 2,628 unique records. Of these, 8 publications, representing 4 studies, were considered eligible for inclusion. The studies comprised two randomized controlled trials (RCTs) and one observational registry study from Germany, and a dosimetry (measurements of radiation exposure) study from the U.S. In all of these studies, the intervention consisted of an MSU for stroke.

MSU care reduced the time from alarm to imaging and from alarm to thrombolysis. Based on the study findings, the difference between MSU and conventional care in mean minutes from alarm to CT was around 27 minutes (95% CI -51 to -3) (low certainty of the evidence), and from alarm to thrombolysis around 31 minutes (95% CI -43 to -18) (moderate certainty of the evidence). Similarly, one of the RCTs, investigating time from symptom onset to imaging, detected a reduction in time, in favor of MSU (39 minutes difference in median, 95% CI IQR 26 to 52) (certainty of the evidence not graded). No statistically significant difference between groups in time from symptom

onset to thrombolysis was detected (-50 mean minutes, 95% CI -117 to 18) (low certainty of the evidence). However, the effect direction of the two included RCTs investigating this outcome was the same, favoring MSU.

Based on the evidence, in total, 11% more patients received thrombolysis with MSU care, compared to those who received conventional care (32% vs. 21%) (moderate certainty of the evidence). Among those who received thrombolysis, MSU patients were more than five times more likely (31% vs. 5.5%) to receive thrombolysis within 60 minutes (golden hour), than those who received conventional care (low certainty of the evidence). Furthermore, compared to conventional care, MSU care improved triage of patients with stroke to specialized hospitals (certainty of the evidence not graded), and increased the proportion of patients with 3-month modified Rankin Scale (mRS) score 0-3 (low certainty of the evidence). The mRS scale is used to measure physical function and runs from 0 to 6 (0 = no symptoms of disability, 6 = dead).

No differences in 90-day mortality (RR 1.35, 95% CI 0.84 to 2.15) (low certainty of the evidence) or hemorrhagic complications (RR 0.55, 95% CI 0.23 to 1.34) (certainty of the evidence not graded) were detected. Radiation exposure for MSU staff or the public did not exceed established dose limits.

We were not able to identify studies investigating the effectiveness of CT scanners localized in decentralized CT stations outside hospitals, or the use of prehospital CT in suspected severe head injuries.

Health economic evaluation

The estimated annual cost of one MSU is approximately 6.4 million Norwegian kroner, and includes both daily operation- and depreciation costs on the investment. The health economic model simulation resulted in a quality-adjusted life-year (QALY) gain of 0.3 per patient who received thrombolysis through MSU care compared with conventional care. We calculated an absolute shortfall of 5.5 QALYs. We found that the expected cost per QALY is about 385,000 Norwegian kroner or lower if one MSU successfully reaches at least 35-40% (145-171) of thrombolysis patients per year. We assume that efficacy results are transferable to metropolitan areas in Norway. Our one-way sensitivity analyses indicate that the required patient proportion to achieve an incremental cost-effectiveness ratio (ICER) of 385,000 Norwegian kroner would decrease when the MSU costs decrease and increase when the MSU costs increase.

Discussion

Based on the findings presented in this HTA, MSU care probably shortens the time to imaging and treatment, and results in higher frequency of thrombolysis administration. The included studies took place in two larger cities in Germany. We assume that the effectiveness of MSU care could be, to some extent, transferrable to metropolitan areas of Norway. However, the degree to which these outcomes can be achieved depends on several context-specific factors. Thus, it will require local adaptations of processes and workflow, and a close cooperation between emergency dispatch center, hospitals,

MSUs and regular ambulances. Furthermore, issues related to MSU staffing and required competence, as well as use of telemedicine, must be considered.

To ensure that equal healthcare is offered to the entire population in Norway, different options may need to be considered in rural and remote areas. “A rendezvous model” where an MSU travels to meet the incoming ambulance or helicopter, or establishment of CT stations outside hospitals, such as the CT scanner currently placed in the district medical center in Ål, are some alternatives to consider. However, robust studies are needed to determine the effectiveness of these options.

While producing this HTA, we identified five ongoing studies with estimated completion dates within the next few years. Two of these studies are conducted in Norway. One is a prospective controlled intervention study on MSU care, taking place in Østfold, with 400 participants. The other is an observational study on rural CT examination and thrombolytic treatment for stroke (CT station in Ål), with 200 participants. The estimated completion dates for these studies are May and April 2021, respectively.

It must be emphasized that prehospital CT represents a supplementary tool to increase the efficiency of stroke management, and cannot replace any other efforts to improve intrahospital and prehospital stroke management. In Norway, the dispatch guidelines (index) used by the emergency medical communication centers (EMCCs) are known to identify just over half of the acute stroke patient population at dispatch. This in turn may result in transportation delay. Moreover, the period before contact with EMCC is important and will not be directly affected by the prehospital CT strategy. Thus, it is crucial to increase public awareness of stroke symptoms.

Conclusion

Compared with conventional care of acute stroke, MSU care probably reduces the time from a patient’s first contact with the emergency dispatch center to thrombolysis, and increases the number of patients who receive thrombolysis. It may also lead to reduced time from a patient’s first contact with the emergency dispatch center to CT imaging, and to better functionality at 3 months after stroke (mRS score 0-3).

We found an absolute shortfall of 5.5 QALYs for ischemic stroke patients, and that the expected cost per QALY is about 385,000 Norwegian kroner or lower if one MSU successfully reaches at least 35-40% (145-171) of thrombolysis patients per year. Decision makers must consider whether they think it is plausible that a minimum of 35-40% of patients could receive the intervention.

Due to the lack of evidence, the effectiveness of decentralized CT stations outside hospitals and of prehospital CT in suspected severe head injuries is unknown.

Hovedbudskap (Norwegian)

Hvert år blir anslagsvis 12 000 personer rammet av hjerneslag i Norge. Ved mistanke om hjerneslag er det viktig å komme til behandling så fort som mulig. I slike situasjoner er anbefalingen akutt innleggelse i sykehus for å få utført computertomografi (CT) av hodet.

Slagambulanse (ambulanse utstyrt med en CT-skanner) kan «ta med seg» sykehuset til pasienten. Forskningen viser at slagambulanse trolig fører til:

- Redusert tid fra melding om mistanke om hjerneslag mottas hos akuttmedisinsk kommunikasjonssentral til trombolyse (blodproppløsende behandling) gis
- Økt andel slagpasienter får trombolysebehandling

Slagambulanse kan også føre til:

- Redusert tid fra melding om mistanke om hjerneslag mottas hos akuttmedisinsk kommunikasjonssentral til CT utføres
- Bedre funksjonalitet tre måneder etter hjerneslag.

Vår kostnads- og terskelanalyse fant at:

En slagambulanse i drift er estimert til å koste omkring 6,4 millioner norske kroner per år. Helsegevinst målt i kvalitetsjusterte leveår (QALYs) er 0,3 per pasient som mottar trombolyse ved hjelp av slagambulanse, sammenlignet med nåværende praksis ved hjelp av standard ambulanse. Vi har kvantifisert alvorlighet ved å kalkulere et absolutt prognosetap på 5,5 QALYs for iskemiske slagpasienter, som mottar trombolyse ved hjelp av standard ambulanse. Vi fant at forventet kostnad per QALY er om lag 385 000 norske kroner eller lavere hvis en slagambulanse lykkes med å nå ut til minst 35-40 % (145-171) trombolyse pasienter per år.

Tittel:
Prehospital CT for tidlig diagnostikk og behandling ved mistanke om hjerneslag eller alvorlige hodeskader. En metodevurdering.

Publikasjonstype:
Metodevurdering
En metodevurdering er resultatet av å
- innhente
- kritisk vurdere og
- sammenfatte

relevante forskningsresultater ved hjelp av forhåndsdefinerte og eksplisitte metoder.

Svarer ikke på alt:
Vi har ikke sett på etiske, juridiske eller sosiale aspekter ved prehospital CT

Hvem står bak denne publikasjonen?
Folkehelseinstituttet har gjennomført oppdraget etter forespørsel fra Bestillerforum RHF.

Når ble litteratursøket utført?
Søk etter studier ble avsluttet i desember 2018

Eksterne fagfeller:
Professor Jan Malm, Umeå Universitet
Førsteamanuensis Eline Aas, Universitetet i Oslo

Sammendrag (Norwegian)

Bakgrunn

Hjerneslag er den nest hyppigste dødsårsaken i de fleste vestlige land, og en viktig årsak til funksjonshemming hos voksne. I Norge rammes rundt 12 000 personer hvert år av akutt hjerneslag. I 2017 ble det registrert 8 789 tilfeller av akutt hjerneslag i Norsk hjerneslagregister (dekningsgrad på 86 %). Pasienter med hodeskader utgjør også en stor gruppe som kommer til akuttavdelingen, og hodeskader den viktigste dødsårsaken hos personer under 44 år. Ved mistanke om alvorlig hodeskade skal pasienten raskt legges inn i en nevrokirurgisk avdeling.

Ved akutt hjerneslag og alvorlige hodeskader er det avgjørende at pasienten diagnostiseres og behandles så fort som mulig ("time is brain"). Ved mistanke om akutt hjerneslag eller alvorlig hodeskade er det anbefalt akutt innleggelse i sykehus for å få utført computertomografi (CT) av hodet. Ved hjerneslag forårsaket av blodpropp (iskemisk hjerneslag eller hjerneinfarkt) bør blodproppløsende behandling (trombolyse) gis så raskt som mulig, og innen 4,5 timer etter symptomdebut. Dersom hjerneslaget er forårsaket av en hjerneblødning kan trombolyse gi livstruende komplikasjoner og er derfor kontraindisert. Det er derfor viktig å få avklart så fort som mulig hva hjerneslaget skyldes for å kunne gi riktig behandling. Ved hodeskader benyttes CT for å identifisere pasienter med behov for rask innleggelse i en nevrokirurgisk avdeling.

Prehospital CT, utført enten i en slagambulanse (ambulanse utstyrt med en CT-skanner) eller en «CT-stasjon» utenfor sykehus, er en ny tilnærming som bringer sykehuset nærmere pasienten. Prehospital CT har som mål å korte ned tid til diagnose og behandling, samt å bidra til å bestemme riktig behandlingssted.

Problemstilling

Formålet med denne metodevurderingen er å oppsummere og vurdere dokumentasjonen for klinisk effekt og sikkerhet av prehospital CT ved mistanke om hjerneslag eller alvorlige hodeskader, og eventuell igangsetting av behandling før ankomst i sykehus, sammenliknet med dagens praksis der både billeddiagnostikk og behandling gjøres i sykehus. I tillegg belyser metodevurderingen organisatoriske og helseøkonomiske konsekvenser knyttet til en eventuell innføring av prehospital CT i Norge.

Metode

Klinisk effekt og sikkerhet

I fravær av relevante systematiske oversikter og metodevurderinger utførte vi systematiske søk etter primærstudier i et utvalg av relevante databaser og studieregistre, tidsavgrenset fra 2010 til i dag. Søkene ble ikke avgrenset til spesifikke typer studiedesign. To medarbeidere vurderte uavhengig av hverandre søkeresultatene opp mot inklusjonskriteriene, og utførte kvalitetsvurdering av de inkluderte studiene. Dataekstraksjon ble utført av en medarbeider, og sjekket av en annen. For fire utfall kunne vi sammestille resultatene ved hjelp av metaanalyser. For andre utfall ble resultatene presentert i tabeller og tekst. Tilliten til dokumentasjonen for de viktigste kliniske utfallene ble vurdert med GRADE (Grading of Recommendations Assessment, Development and Evaluation). I GRADE blir tilliten til dokumentasjonen oppgitt som høy, moderat, lav eller svært lav, basert på vår vurdering av hvilken grad vi kan stole på effektestimatene.

Helseøkonomisk evaluering

Vi utførte en kostnads- og terskelanalyse. Analysen har som mål å undersøke gjennomsnittlige inkrementelle kostnadseffektivitets-ratioer (ICERs) ved ulike verdier for andeler av iskemiske slagpasienter som mottar trombolyse ved hjelp av slagambulanse sammenlignet med dagens praksis (trombolyse mottatt ved hjelp av standard ambulanse). Denne metoden gjør det mulig å identifisere en terskelverdi for den andelen som er nødvendig for at slagambulansen skal oppnå en ICER på et forhåndsbestemt nivå. Vi kalkulerte absolutt prognosetap for iskemiske slagpasienter som mottar trombolyse ved hjelp av standard ambulanse, for å kvantifisere alvorlighet for den relevante pasientpopulasjonen. Videre utførte vi en enveis sensitivitetsanalyse for å undersøke slagambulansekostnadens innvirkning på resultat. Vi tilpasset en eksisterende probabilistisk Markov beslutningsanalytisk modell for iskemiske slagpasienter, utviklet som en del av en metodevurdering om mekanisk trombektomi utført av Folkehelseinstituttet i 2016. Analysene vurderer ikke konsekvenser av å introdusere slagambulanse utenfor storbyområder i Norge, og inkluderer ikke pasienter med andre indikasjoner som kan få nytte av slagambulanse.

Resultater

Klinisk effekt og sikkerhet

Litteratursøkene etter primærstudier resulterte i totalt 2 628 unike referanser. Av disse ble åtte publikasjoner (fire studier) valgt for inklusjon. De fire inkluderte studiene omfattet to randomiserte kontrollerte studier (RCTer) og en observasjonell registerstudie fra Tyskland, samt en dosimetristudie (måling av strålingseksponering) fra USA. I alle studiene bestod intervensjonen av en slagambulanse.

Slagambulanse førte til en reduksjon av tid fra alarm til CT og fra alarm til trombolyse. Basert på studieresultatene var forskjellen i tid fra alarm til CT mellom slagambulanse og konvensjonell behandling ca. 27 minutter i gjennomsnitt (95 % KI -51 til -3) (lav tillit til dokumentasjonen), og fra alarm til trombolyse ca. 31 minutter i gjennomsnitt (95 % KI -43 til -18) (moderat tillit til dokumentasjonen). Slagambulanse førte også til en reduksjon i tid fra symptomdebut til CT (39 minutter forskjell i median, 95 % KI IQR 26 til 52) (tillit til dokumentasjonen ikke vurdert med GRADE). Dette resultatet var basert

på en RCT. Ingen statistisk signifikant forskjell ble funnet i tid fra symptomdebut til trombolyse (-50 minutter i gjennomsnitt, 95% KI -117 til 18) (lav tillit til dokumentasjonen). Begge RCTene som målte dette utfallet viste imidlertid positiv effekt, til fordel for slagambulanse.

Basert på studieresultatene, fikk totalt 11 % flere pasienter trombolyse med slagambulanse sammenlignet med pasienter som mottok konvensjonell behandling (32 % vs. 21 %) (moderat tillit til dokumentasjonen). Blant pasienter som fikk trombolyse var det fem ganger mer sannsynlig (31 % vs. 5,5 %) at slagambulansepasienter mottok trombolyse innen 60 minutter («golden hour») enn pasienter som fikk konvensjonell behandling (lav tillit til dokumentasjonen). Sammenlignet med konvensjonell behandling førte slagambulanse til bedre triage til riktig behandlingssted for slagpasienter (tillit til dokumentasjonen ikke vurdert med GRADE), og økte andelen pasienter med modifisert Rankin skala (mRS) skår 0-3 tre måneder etter hjerneslag (lav tillit til dokumentasjonen). mRS er en skala fra 0 til 6 som brukes til å måle fysisk funksjon (0 = ingen funksjonshemning, 6 = død).

Ingen forskjeller i 90-dagers dødelighet (RR 1,35, 95% KI 0,84 til 2,15) (lav tillit til dokumentasjonen) eller blødninger (RR 0,55, 95% KI 0,23 til 1,34) (tillit til dokumentasjonen ikke vurdert med GRADE) ble oppdaget.

Vi fant ingen studier som undersøkte effekt av CT-stasjoner utenfor sykehus, eller av prehospital CT ved mistanke om alvorlige hodeskader.

Helseøkonomisk evaluering

Den årlige kostnaden av en slagambulanse er estimert til å være ca. 6,4 millioner norske kroner, og inkluderer både investeringer og daglig drift. Simuleringen av den helseøkonomiske modellen resulterte i en kvalitets-justerte leveår (QALY) gevinst på 0,3 per pasient som mottar trombolyse ved hjelp av slagambulanse sammenlignet med dagens praksis (trombolyse mottatt på sykehus ved hjelp av standard ambulanse). Vi kalkulerte et absolutt prognosetap på 5,5 QALYs. Vi fant at forventet kostnad per QALY er om lag 385 000 norske kroner eller lavere hvis en slagambulanse lykkes med å nå ut til minst 35-40 % (145-171) trombolyse pasienter per år. Vi antar at effektresultater kan overføres til storbyområder i Norge. Våre enveis sensitivitetsanalyser indikerer at nødvendig pasientandel for å oppnå en inkrementell kostnadseffektivitetsratio (ICER) på 385 000 norske kroner vil reduseres når slagambulansekostnaden reduseres og øke når slagambulansekostnaden øker.

Diskusjon

Basert på studieresultatene presentert i denne metodevurderingen, korter slagambulansen trolig ned tid til diagnose og behandling, og fører til økt andel pasienter som mottar trombolyse. De inkluderte studiene fant sted i to større byer i Tyskland. Vi antar at resultatene til en viss grad vil være overførbare til storbyområder i Norge. Hvorvidt man oppnår den samme effekten for de ulike utfallene vil være avhengig av flere kontekstuelle faktorer. Implementering av slagambulanse vil kreve lokale tilpasninger av

prosesser og arbeidsflyt, samt nært samarbeid mellom akuttmedisinsk kommunikasjonssentral, sykehus, slagambulanser og vanlige ambulanser. Man må i tillegg vurdere hva slags bemanning og kompetanse som trengs i en slagambulanse, og hvorvidt telemedisin bør brukes.

Ulike alternative løsninger må eventuelt vurderes utenfor storbyområder for å sikre likt helsetjenestetilbud for hele befolkningen i Norge. "En rendezvous-modell" der slagambulansen møter en innkommende ambulanse eller et helikopter, eller etablering av CT-stasjoner utenfor sykehus, slik som CT-skanneren som i dag er plassert i det distriktsmedisinske senteret i Ål, er noen alternativer som kan vurderes. Robuste studier trengs imidlertid for å kunne si noe om effekten av slike løsninger.

I denne metodevurderingen identifiserte vi fem pågående studier som er estimert til å bli ferdigstilt i løpet av noen få år. To av disse pågår i Norge. En av studiene er en prospektiv kontrollert studie om effekt av slagambulanse (i Østfold), med 400 pasienter. Den andre er en observasjonell studie om effekt av CT stasjon utenfor sykehus (CT stasjonen i Ål), med 200 pasienter. Forventet ferdigstillelse er henholdsvis mai og april 2021.

Det må påpekes at prehospital CT bør betraktes som ett av flere verktøy for å øke effektiviteten av slagbehandlingen, og kan ikke erstatte andre tiltak som sikter på å forbedre slagbehandlingen prehospitalt og på sykehus. Forskningen viser at indeksen brukt av operatørene ved akuttmedisinsk kommunikasjonssentral i Norge avdekker mistanke om slag kun hos litt over halvparten av slagpasientene, noe som kan medføre forsinkelser i pasienttransport. Hvor lang tid det går før akuttmedisinsk kommunikasjonssentral kontaktes er også en avgjørende faktor og vil ikke bli direkte berørt av en eventuell innføring av prehospital CT. Det er viktig å øke bevistheten hos befolkningen om hjerneslagsymptomer.

Konklusjon

Sammenlignet med konvensjonell behandling av akutt hjerneslag fører slagambulanse trolig til redusert tid fra melding om mistanke om hjerneslag mottas hos akuttmedisinsk kommunikasjonssentral til trombolyse og en økt andel pasienter som får trombolysebehandling innen rett tid. Slagambulanse kan også føre til redusert tid fra melding om mistanke om hjerneslag mottas hos akuttmedisinsk kommunikasjonssentral til CT, og bedre funksjonalitet tre måneder etter hjerneslag (mRS score 0-3).

Vi fant et absolutt prognosetap på 5,5 QALYs for iskemiske slagpasienter, og at forventet kostnad per QALY er om lag 385 000 norske kroner eller lavere hvis en slagambulanse lykkes med å nå ut til minst 35-40 % (145-171) trombolyse pasienter per år. Beslutningstakere må vurdere om de mener det er plausibelt at minst 35-40 % pasienter kan motta intervensjonen.

På grunn av manglende kunnskapsgrunnlag vet vi ingenting om effekt av CT-stasjoner utenfor sykehus eller av prehospital CT ved mistanke om alvorlige hodeskader.

List of abbreviations and acronyms

ADL	Activities of daily living
AS	Absolute shortfall
CEA	Cost-effectiveness analysis
CI	Confidence interval
CT	Computed tomography
CTA	Computed tomography angiography
CTDI	Computed tomography dose index
DRG	Diagnosis Related Group
EMCC	Emergency medical communication center
EMS	Emergency medical service
EMT	Emergency medical technician
GB	General practitioner
GCS	Glasgow Coma Scale
GRADE	The Grading of Recommendations Assessment, Development and Evaluation
HEMS	Helicopter emergency medical service
HISS	Head Injury Severity Scale
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICH	Intracerebral hemorrhage
IQR	Interquartile range
IV rtPA	Intravenous recombinant tissue plasminogen activator
KI	Konfidensintervall
kVp	Kilovoltage peak
LQ	Lower quartile
mA	milliAmpere
MD	Mean difference
mGy	Milligray
MR	Magnetic resonance
mRS	Modified Rankin Scale
MSU	Mobile stroke unit
mSv	Millisievert
µSv	Microsievert
NIHSS	National Institutes of Health Stroke Scale
NOK	Norwegian kroner
NR	Not reported

NSR	Norwegian Stroke Registry
OR	Odds ratio
PRESS	Peer Review of Electronic Search Strategies
PSA	Probabilistic sensitivity analysis
QALYs	Quality adjusted life years
RCT	Randomized controlled trial
RevMan	Review Manager (software)
RoB	Risk of bias
RR	Risk ratio
SAH	Subarachnoid hemorrhage
S100B	S100 calcium-binding protein B
TBI	Traumatic brain injury
UQ	Upper quartile
WHO	World Health Organization
WTP	Willingness to pay

Preface

The Division of Health Services in the Norwegian Institute of Public Health was commissioned in 2016 by the The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway to conduct a health technology assessment on mobile prehospital CT for diagnosis and treatment of suspected acute stroke (Nye metoder ID2016_009). After consultation with clinical experts, the scope of the assessment was expanded to include prehospital CT - both mobile and stationary CT units – in suspected acute stroke or severe head injury.

The work on the commission started in October 2016 and an introductory meeting with the project group took place in December, 2016. However, in January 2017, the assignment was put on hold due to internal priorities. The project was resumed in October 2017.

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We wish to thank Senior Consultant Einar Johan Tveit and the Head of Stroke Unit Martin Kurz from the Stavanger University Hospital, and Senior Consultant Hans Julius

Heimdal from the Oslo University Hospital, for contributing with their expertise at the scoping phase of the project and for providing input to the draft project plan. We also wish to thank Researcher Christopher Rose (CR) from the Norwegian Institute of Public Health for providing valuable statistical support in the data analyses. We would also like to thank Professor Jan Malm from the Umeå University and Associate Professor Eline Aas from the University of Oslo for their expertise and comments as external peer reviewers of the draft report. Furthermore, we would like to acknowledge Director of Reviews and Health Technology Assessments Kåre Birger Hagen and acting Department Director Hege Kornør from the Norwegian Institute of Public Health for internal peer review of the draft report. Lastly, we would like to thank Arna Desser from the Norwegian Institute of Public Health for English editing of the document before publication.

Declaration of interest:
None of the authors, contributors or peer reviewers state any conflicts of interest.

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Progress log

Date	Correspondence
February 2016	Proposal submitted to Nye Metoder
March 2016	The Ordering Forum commissioned a health technology assessment
October 2016	The work on the commission started
October 2016	First contact with clinical experts
December 2016	First meeting with clinical experts
January 2017–October 2017	The assignment on hold due to internal priorities
October 2017	The project resumed
February 2019	External review process
February 2019	Internal review process
May 2019	Report submitted to Nye Metoder

Objectives

In this health technology assessment (HTA), we aimed to compare the clinical effectiveness and safety of prehospital CT for early diagnosis and potential prehospital treatment of suspected acute stroke or severe head injury with current practice of diagnosis and treatment carried out after arrival in the hospital.

Furthermore, our goal was to shed light on organizational consequences related to the implementation of prehospital CT, present organizational models relevant to Norway, and carry out health economic evaluations related to the intervention.

By ‘prehospital CT’ we mean mobile CT scanners adapted for use in ambulances, and CT scanners localized in decentralized "CT stations" outside hospitals.

Background

In acute stroke and severe head injuries, rapid diagnosis and treatment is crucial ("time is brain"). In stroke caused by blood clots (ischemic stroke or cerebral infarction), thrombolytic treatment (thrombolysis) should be given as soon as possible, and at most within 4.5 hours after the onset of symptoms. In hemorrhagic stroke (bleeding), on the other hand, thrombolytic treatment is contra-indicated as it may cause life-threatening complications (1).

On suspicion of acute stroke or a severe head injury, rapid admission to a hospital to undertake a computed tomography (CT) scan is recommended. In cases of acute stroke, thrombolytic treatment should be provided as soon as hemorrhagic stroke has been ruled out. Rapid diagnosis and treatment is essential to minimize the damage caused by stroke (1). In head injuries, CT performed as soon as possible is also important as it allows identification of those patients who require urgent admission to a neurosurgical department (triage) (2).

Prehospital CT, either performed with mobile CT scanners adapted for use in ambulances or in "CT scanner stations" located outside hospitals, may help determine which hospital (what kind of facility) the patient should be directed to. Prehospital CT also seeks to shorten the time from the patient's first contact with the emergency dispatch center to provision of thrombolysis or other appropriate treatment, either during transportation or at the hospital.

Acute stroke and severe head injuries

Acute stroke

Stroke is the second leading cause of mortality in most Western countries, and a major cause of adult disability (3). A growing burden of stroke (4) along with new therapies in development (5;6) have led to increased focus on the need for new diagnostics models in close relation to symptom onset. As a consequence, better utilization of the prehospital phase has aroused growing interest.

Stroke is caused by lack of oxygen supply to smaller or larger parts of the brain.
The extent of brain damage as a result of stroke depends critically on how long the brain tissue remains without oxygen. In acute stroke diagnostics, three subcategories can be identified: 1) ischemic stroke caused by focal infarction, 2) intracerebral hemorrhage (ICH) due to a focal collection of blood within the brain parenchyma that is not

caused by trauma, or 3) stroke caused by a subarachnoid hemorrhage (SAH) with bleeding into the subarachnoid space (7). Approximately 84% of all strokes are ischemic, due to an acute atherothrombotic lesion in pre- or intracerebral arteries, or embolus from the heart or proximal arteries (8). The occlusion results in reduced blood flow in proximal parts of the clogged vessel leading to reduced perfusion and focal ischemia in the surrounding brain tissue. In severe or prolonged cases, ischemic lesions may end up as irreversible damage (infarction) (9).

Brain cells are extremely sensitive to hypoxia secondary to insufficient blood supply. Ischemia in the brain will trigger a cascade of biochemical changes which potentiate cell death leading to infarction within a few minutes (9). However, due to cerebral collateral flow a significant brain volume ("the penumbra volume") may survive for some hours (10). To save the penumbra volume a sufficient blood flow must be restored as fast as possible (11). Thus, restoring of sufficient blood flow is the main goal of revascularization therapy. By reopening clogged vessels, threatened tissue not yet transformed to infarction, may survive and function can be restored (9). In recent years, revascularization therapy with thrombolytic agents and/or thrombectomy has been established as state of the art treatment (12;13). However, due to the pathophysiological mechanisms in ischemic brain tissue, the treatment window is very narrow, and clinical effect is highly dependent on early initiation (11).

Acute stroke is a clinical diagnosis and defined by the World Health Organization (WHO) as rapidly developing clinical sign of focal (or global) disturbance of cerebral function (7). Acute stroke is a time critical situation demanding a high level of competence and rapid assessment in the very early phase of symptom progression. Symptoms are characterized by acute onset of muscle weakness, sensory loss, facial paresis, dysarthria and diplopia (7).

In Norway, approximately one in five patients experiencing stroke die within three months (8). Among those who survive many suffer from considerable and often irreversible functional disabilities. Stroke is the most common cause for long lasting function impairment in adults, often resulting in decreased quality of life, and requiring extensive care and rehabilitation. Early treatment and appropriate follow-up improves the prognosis (1).

According to the National guideline for stroke, approximately 12,000 persons experience stroke each year in Norway (1). In 2017, the number of acute strokes recorded was 8,789 in 51 Norwegian hospitals (covering 86% of acute stroke patients). Among these acute cases of stroke, 94% were treated in a stroke unit (8). Stroke occurs both in young and older people, however 79% have passed the age of 65 years when encountered (8). Mean time spent at the hospital was seven days, and mortality during hospitalization was 8% (8). Compared with other conditions, stroke causes the highest number of hospitalization days in the somatic health care services.

Head injuries requiring rapid assessment with a CT scan

Traumatic brain injury (TBI) is a leading cause of disability and death in the younger adult population and accounts for over 1 million consultations at the emergency department in both the US and UK each year (2). In Norway, TBI represents a large group of patients who arrive at emergency wards, and is the leading cause of death in persons under the age of 44 years (14). A study from Oslo in Norway has shown an incidence of hospital admissions due to TBI of 83 per 100,000 inhabitants (15). Moreover, an assessment on biomarker S100 calcium-binding protein B (S100B) in patients with milder head injuries have reported around 16,000 cases of TBI admitted to emergency units in Norwegian hospitals per year (16). Among these TBIs, 80-90% were considered to be milder TBIs (16).

Head injuries are mostly caused by road accidents, assaults or falls. In cases of TBIs, it is important to determine as soon as possible any intracranial damage, which is assessed with CT or magnetic resonance (MR) imaging. Rapid radiologic diagnosis may save patients who need neurosurgical treatment by allowing them to immediately be transported to facilities with appropriate equipment and expertise.

Brain injury is often classified clinically by the Glasgow Coma Scale (GCS) based on eye opening, motoric and verbal response. The GCS goes from 0 to 15, i.e. patients with no reaction to stimuli scores 3 or less, and an awake alert patient scores 15. The GCS can be transferred into the Head Injury Severity Scale (HISS), by dividing the score levels in to four categories as minor, mild, moderate and severe (17).

Current diagnostic and treatment pathways

Acute stroke

Stroke is a clinical diagnosis determined through a structured clinical examination and anamnestic information about the patient, however it is not possible to distinguish an infarction from a hemorrhage. Thus imaging is required to establish the cause of the stroke, and the patient must be transported as soon as possible to the nearest hospital to have a radiological examination of the head (1).

Stroke caused by an occluding blood clot (thrombus or embolus) should be treated with a clot dissolving agent, i.e. tissue plasminogen activator (thrombolytic treatment or thrombolysis) as soon as possible, and at most within 4.5 hours after symptom onset, provided that there are no contraindications or no serious risk factors. Thrombolytic treatment increases the risk of bleeding, and may therefore be fatal if the stroke is caused by cerebral hemorrhage. Thus it is crucial to find out as soon as possible what the stroke is caused by to provide the patient with the appropriate treatment (1). In some cases thrombolysis does not succeed in dissolving the occluding clot (this might occur with larger clots in the large proximal segments of the cerebral arteries), and thrombectomy may be needed. Thrombectomy is also the treatment alternative when thrombolysis is contraindicated, as mentioned above. Contraindications are ongoing

anticoagulant treatment, pregnancy, and unknown time of symptoms onset. Thrombectomy is an endovascular treatment where the thrombus is mechanically removed to allow blood to reach the region the clotted artery is supplying (18). In Norway today, most of the emergency treatments of stroke take place in local hospitals, however patients who need thrombectomy have to be transported to specialised centres with more expertise. As for thrombolysis, time is crucial, since thrombectomy has to be effectuated within 6 hours after symptom onset (18), however recent data from the DAWN study have shown effect of thrombectomy in some cases after 24 hours (19). In 2017, 3.3% of patients with acute ischemic stroke were treated with thrombectomy in Norway (8). Today the proportion of stroke patients eligible for thrombectomy is estimated to be around 5-7% (1).

Acute stroke diagnostics and treatment has developed rapidly during the last decade. As mentioned above, the acute assessment of patients with suspected stroke includes a mandatory cerebral CT or MR examination when admitted at the hospital (20;21), clinical work-up with structured neurological examination, blood testing and vital support. Computed tomography angiography (CTA) is considered as standard procedure when selecting patients for thrombectomy (1). This complex diagnostic approach aims to identify patients eligible to treatment, and the appropriate level of care. Delay to final diagnosis is one of the most important factors in delay to treatment and may result in poor outcome (22). Delay to treatment in acute stroke is multi factorial and may distribute differently in urban and rural settings. Data from a Norwegian study showed that prehospital delay alone accounted for up to 50% of the total delay (23) and the Norwegian Stroke Registry (NSR) reports that less than 50% reaches hospital within the therapeutic window (4 hours) (8). Hence, it is essential to reach more patients in the early phase of disease progression to improve this rate.

Head injuries requiring rapid assessment with a CT scan

Head injuries occur at all ages and may be due to a variety of different causes. Treatments differ according to the severity of the injury and damages incurred. In patients with clinical evidence or high risk of intracranial injury after head trauma a non-contrast cerebral CT scan has become the consensus choice in the acute assessment (24). CT is rapid, easily performed and accessible. A cerebral CT scan in TBI is suitable for detecting cranial fractures and intracranial lesions, and the method may be used to follow the dynamics of a lesion and give insights into corresponding pathological development of brain injury (25). In the acute diagnostics of TBI the non-contrast cerebral CT scan helps differentiate patients in need of specialized care from those who can safely be sent home (25).

Scandinavian guidelines on initial management of head injuries in adults produced by the Scandinavian Neurotrauma Committee suggests that all adult patients with mild to moderate head injury and GCS ≤ 14, loss of consciousness, repeated vomiting, anticoagulant therapy or coagulation disorders, clinical signs of depressed or basal skull fracture, post-traumatic seizures or focal neurological deficits should have a CT scan. To limit excessive use of cerebral CT in patients with low risk and mild head injury, the biomarker S100B was first introduced into practical guidelines in 2013, however S100B

should be used with a low cut off rate to predict the absence of CT pathology and neurosurgical intervention (2). When severe head injury is suspected, the patient should be directed as soon as possible for observation at a neurosurgical department (2).

Patient transport

Minimizing prehospital time delay has been proven to positively influence thrombolytic rates in acute ischemic stroke (26-28). Stroke severity, transportation by ambulance (29) and younger patients are associated with reduced prehospital delay (23). Prehospital delay can be divided into decision delay and transportation delay, and covers the time line from symptom onset to hospital admission. Decision delay starts with patients hesitating to seek emergency medical assistance, often due to failure in recognizing acute stroke symptoms and not acknowledging the symptoms as serious. Transportation delay covers dispatch, on-scene time and transportation to treatment facility. The emergency medical communication center (EMCC) is known to identify only half of the acute stroke patient population at dispatch (30) resulting in a great proportion of transportation delay. A review paper of three retrospective and four prospective cohort studies enrolling a total of 16,382 patients, concluded that dispatch accuracy in detecting acute stroke patients were suboptimal (31). Moreover, pre-notification by the emergency medical service (EMS) and stroke education in order to facilitate recognition of stroke (stroke scoring tools) is recommended to reduce prehospital delay (32-34).

In Norway, patients are usually transported in ambulances, either in cars, boats, helicopters or airplanes. Sometimes a combination of two means of transportation is necessary to reach the hospital as quickly as possible. Only 43% of stroke patients in Norway reach the hospital within 4 hours, and there are large variations among hospitals and regions (8). These variations may be explained by Norway's uneven population density, challenging topography and weather conditions. On average, only 21% of all patients with acute ischemic stroke in Norway receive thrombolysis (8).

Prehospital CT

Prehospital CT may be particularly useful in cases where acute stroke or severe head traumas are suspected. Prehospital CT may be used to determine the need for treatment, reduce time between onset of symptoms and treatment initiation, and allow triage to the appropriate follow-up treatment.

For strokes due to brain infarction, the thrombolytic treatment has to be initiated as soon as possible, but it might be challenging to get the patient rapidly enough to a hospital in order to determine the diagnosis through CT imaging. Logistics within a hospital may also not be efficient enough, and "door-to-needle time" can be unnecessarily long and have a significant impact on the total lag time, i.e. from onset of symptoms to start of thrombolysis. Giving the possibility to determine the diagnosis earlier and to establish the type of stroke the patient is suffering from, prehospital CT may be an alternative or a supplement to what is offered to these patients today. The thrombolytic treatment can be performed outside the hospital or just after admission to the hospital.

In cases where the stroke is caused by hemorrhage, prehospital CT may help indicate where to direct the patient, i.e. if there is need for a neurosurgical facility. In the same way, for head traumas, prehospital CT may allow the identification of patients with need for neurosurgical competence, and may be particularly beneficial in unclear cases where a severe head injury is suspected.

In the context of this report, two organizational models for prehospital CT are considered: mobile CT scanners adapted for use in vehicles (mobile stroke units), and CT scanners localized in decentralized "CT stations" outside hospitals.

Mobile stroke unit

Prehospital CT in an ambulance includes only CT of the head (a whole-body CT scanner is too large and heavy to be installed in any kind of ambulance). Large ambulance vehicles have been adapted in order to fit a head CT scanner and necessary equipment. Such specially equipped ambulances or mobile stroke units (MSU) have been used in Germany and the USA, among others, and are now being tested in the South-East region of Norway (Østfold) (Figure 1). The CT scan itself can be performed in the ambulance by, for example, paramedics, and resulting images sent to radiologists in hospitals for assessment. This procedure is entirely dependent on a well-functioning telemedicine system. An alternative approach has been tested in a study in Østfold, where the MSU was staffed with anesthesiologists from the Norwegian helicopter emergency medical service (HEMS). In this study, anesthesiologists were trained in prehospital critical care to perform acute stroke diagnostics (cerebral CT and clinical assessment), and CT images were analyzed in the vehicle (35-37).

Figure 1. *MSU used in Østfold, South-East region of Norway*

Source: Karl Meyrs / Norwegian Air Ambulance Foundation

The head CT scanners in use today weigh approximately 350 kg, which exceeds the loading capacity in most ambulance helicopters that are in use in Norway today. Today, 13 helicopters (type EC135 T3, type EC145 T2 and type AW139) are in operation in Norway (38). The first two models do not have enough capacity for a head CT scanner - only the AW139 helicopters along with another model, i.e. the rescue AW101-helicopters, could potentially have the capacity to transport a head CT scanner, based on volume and weight. Currently, no head CT is in operation in a helicopter anywhere in the world. In Norway, there is an ongoing project to create a prototype (39), however there are challenges, as these helicopters may be exposed to radiation emitted by the CT scanner, which could interfere with the helicopter's electronic navigation devices. Rules are very strict in terms of what devices may be installed in today's helicopters. Each device requires separate approval in order to be placed in Norwegian helicopters currently in use. Obtaining this approval would require modification or adaptation of some parts of the CT-related equipment, or at least that the equipment be properly shielded.

«CT stations» outside hospitals

So-called «CT stations» outside hospitals will reduce challenges related to transportation of equipment. Today, CT scanners have been installed at two medical centers in remote districts in Norway. A research project is taking place in the community of Ål in Hallingdal (mid-South of Norway), where patients are receiving thrombolysis at the local medical center following CT imaging analysed and diagnosis sent via telemedicine (40). So far, no data have been published from this study.

Radiation protection regulations

All medical use of radiation must be justified according to the radiation protection regulations (41)**.** This means that the benefit of the medical examination or treatment must be greater than the risks involved with irradiating the patient. The overall quality of the examination must be high to fulfill the justification requirement. The quality of the examination depends on several factors. The choice of modality must be appropriate according to present clinical symptoms, the image quality must be good enough and the radiation doses must be as low as possible without losing important diagnostic details. A competent person must also interpret the images so that the patient receives the correct treatment and care. The radiation protection regulation paragraphs §§ 47 and 48 (41) states that health professionals with competence in radiology and radiography must be included in the medical radiation practice. Replacing these professionals with anesthesiologists and paramedics requires training and education, and this is only permitted where the use of radiation is said to be simple. One can use teleradiology as an alternative to an onsite radiologist, but this involves a certain risk of technical problems.

There is no inherent increase in radiation risk for the patient by transferring the CT examination into the ambulance/pre-hospital services, but it is important to survey the practical and organizational changes with respect to the overall quality of the medical examination. The changes may also affect the exposure of personnel and the public.

One needs to consider where the CT operator will stand during scans, what shielding will be applied, and whether the ambulance walls stop the radiation such that the levels outside are acceptable.

The quality of CT images taken in an ambulance and the corresponding exposure level must be compared to in-hospital imaging. The quality must be good enough within the acceptable radiation dose so that the imaging is still justified. Mobile CT scanners are already in use in hospitals where patients, for medical reasons, cannot come to regular CT laboratories. Mobile CT scanners are smaller and lighter and are therefore suitable for use in an ambulance. The potential difference in use is that the ambulance will lead to increased movement during transportation on roads of varying quality. It may also be parked on unlevel ground. The ambulance must be equipped with hydraulic legs for support and levelling, and the scanner must be properly secured during transport.

In a hospital the CT operator usually stands outside the laboratory – in the control room – and is shielded from exposure. In an ambulance one must consider room design and practical solutions like lead curtains and lead aprons so the personnel is properly shielded from unnecessary exposure. In some cases the personnel must accompany the patient, but this happens irrespective of where the scan takes place.

Clinical effectiveness and safety

METHODS

In the conduct of this HTA, we have used a methodology guidance prepared by the Norwegian Knowledge Centre for the Health Services. A detailed description of the guidance can be found in the methods handbook «Slik oppsummerer vi forskning» (42).

Otherwise, we have followed the methods described in the project plan (43) when undertaking this assessment. The few modifications that have been made during the process are presented in Appendix 1.

Inclusion criteria

For this HTA, we defined inclusion and exclusion criteria in collaboration with a group of clinical experts. The inclusion criteria are presented in Table 1.

The commission was initially limited to mobile prehospital CT for diagnosis and treatment of suspected acute stroke. After consultation with clinical experts, the scope of the assessment was expanded to include prehospital CT - both mobile and stationary CT units – in suspected acute stroke or severe head injury.

First, we aimed at finding relevant, recently published systematic reviews and HTAs of high quality. If eligible evidence syntheses were identified, we would disseminate results from these. In the absence of eligible systematic reviews and HTAs, we would perform systematic searches for primary studies. Only primary research published since 2010 was considered eligible as there was assumed to be little relevant research on this topic conducted before 2010.

Table 1. *Inclusion criteria*

Population	Patients with suspected acute stroke or severe head injury* (*patients with symptoms of mild, moderate or severe head injury who may require admission to a neurosurgical department)
Intervention	Prehospital CT: mobile or stationary units with CT*, with or without provision of prehospital thrombolysis for stroke (* includes ambulance and helicopter transport to the stationary unit)

Comparator	CT or MR performed after arrival in the hospital; one type of pre-hospital CT compared to another type of prehospital CT (e.g. mobile versus stationary)
Outcomes	**Clinical effectiveness:** • Time to diagnosis and treatment (thrombolysis/thrombectomy in stroke), from symptom onset or the first contact with the emergency dispatch center • Proportion of patients treated with thrombolysis • Delivery to an appropriate hospital (triage) • Mortality: at 30 days, 90 days or at a later point in time • Morbidity and functionality: *In acute stroke:* o Modified Rankin scale (mRS) upon hospital admission, at 24 hours, 7 days and 90 days after admission; o NIH Stroke Scale/Score (NIHSS) upon hospital admission, at 24 hours, 7 days and 90 days after admission; o Barthel ADL Index upon hospital admission, at 24 hours, 7 days and 90 days after admission *In severe head injury:* o Glasgow Coma outcome scale at 14 days, 6 months and 1 year after injury (44) • Quality of life: Health-related quality of life measured with EQ-5D or other standardized instruments for measuring quality of life • Resource utilization, e.g. use of specialized staff and length of hospital stay **Safety:** bleeding (in acute stroke), radiation dose to patients and staff
Study design	• Systematic reviews and HTAs • Primary studies (in absence of recently published systematic reviews and HTAs of high quality): o To assess mortality, morbidity and functionality, and quality of life: studies with a control group o To assess all other outcomes: studies with a control group; prospective case series and registry data (≥100 patients); studies measuring radiation exposure (dosimetry studies)
Language	English, German, French, Norwegian, Swedish and Danish
Time frame	2010 - present

Exclusion criteria

In cases where two or more types of studies, e.g. randomized controlled trials (RCTs) and observational studies, covering the same outcome(s) were identified, the study design placed highest in the hierarchy of evidence of clinical effectiveness (45) was chosen for inclusion.

Case series and registry data with fewer than 100 patients were excluded as they were considered to provide little valuable information on clinical effectiveness and safety.

Literature search

All literature searches were developed and executed by an information specialist (EH), in collaboration with the project team and external experts. Individual search strategies, combining both text words and database specific subject headings, were designed for each database.

In September 2017, we performed systematic searches for published systematic reviews and HTAs in the following databases: Cochrane Database of Systematic Reviews (Wiley), Database of Abstracts of Reviews of Effects (DARE) (Wiley), Embase (Ovid), Epistemonikos, HTA database (Wiley) and MEDLINE (Ovid).

We combined search terms characterizing prehospital setting and (CT) imaging (using the Boolean operator 'AND'), and combined those with search terms characterizing MSU (using the Boolean operator 'OR'). No language or date restrictions were applied.

In absence of eligible systematic reviews and HTAs, we conducted systematic searches for primary studies in the following databases:

- CINAHL (EBSCO)
- CENTRAL (Cochrane Central Register of Controlled Trials) (Wiley)
- Embase (Ovid)
- MEDLINE (Ovid)
- NHS Economic Evaluation Database (Wiley)
- PubMed
- Web of Science
- ClinicalTrials.gov (National Institutes of Health, U.S.)
- International Clinical Trials Registry Platform (ICTRP) (WHO)

The purpose of searching trials registers was to find both ongoing studies, and completed, but unpublished primary studies.

We combined search terms characterizing prehospital setting, CT and acute stroke/severe head injury using the Boolean operator 'AND'. Before any searches were run, all search strategies were peer reviewed by another information specialist (SSO) using the PRESS checklist (46).

We performed all searches for primary studies in December 2017, with the exception of searches in study registries, which were conducted in February 2018. Searches were limited to publication year 2010 – present, but no restrictions to language or study type were applied. To ensure up-to-date evidence base by the point in time of publication, searches in CENTRAL and MEDLINE were updated in December 2018.

The complete search strategies for all databases, information about database versions used, search dates, and number of hits in each database, can be found in Appendix 2.

In addition, we scanned reference lists of included publications for further relevant studies. We also checked all possibly relevant evidence syntheses for relevant primary studies.

Study selection

Three reviewers (SSO, EH and KKC) independently screened all titles and abstracts of retrieved records using the web application Rayyan (47), and evaluated them against the predefined inclusion criteria. Potentially relevant references were obtained, read in full-text, and independently evaluated by two reviewers (SSO and KKC). Based on the full-text assessment, studies that met the inclusion criteria were included in the HTA. Any disagreements were resolved through discussion and subsequent consensus with a third reviewer, when necessary.

If multiple publications had been published about one study, these publications were linked together and treated as one single study.

Assessment of risk of bias in included studies

Two reviewers (SSO and KKC) independently assessed the methodological quality (risk of bias) of the included RCTs and observational registry-based study using the Cochrane Risk of Bias (RoB) tool (48). We resolved disagreements through discussion and subsequent consensus with a third reviewer, when necessary.

We did not assess the risk of bias of the included uncontrolled study which measured radiation exposure to patients, MSU staff and the public (dosimetry study), because this is a preliminary safety study related to an ongoing study.

Data extraction

We extracted data from the included publications into a data extraction form using Microsoft Excel. One reviewer (SSO) extracted the data and a second reviewer (KKC) confirmed the accuracy of the extracted information.

We extracted the following data: citation, first author, publication year, clinical trials ID, study design, study duration, country, setting, information about participants (inclusion and exclusion criteria, number of participants randomized/enrolled in each group), intervention characteristics, comparator(s), and outcomes assessed (scales and measurement tools used, timing of measurements, results).

Data analysis

We chose a quantitative synthesis, by means of meta-analyses, to collate and summarize study findings if we were able to pool the results from two or more studies with similar interventions, populations, outcomes and study designs. Otherwise, we presented results in tables and text.

We conducted meta-analyses for the following outcomes using the Review Manager software, RevMan (49): number of patients with intravenous thrombolysis (thrombolysis rate), alarm to imaging (minutes), alarm to thrombolysis (minutes), and symptom onset to thrombolysis (minutes).

For dichotomous outcomes, we presented the results with risk ratio (RR) and the 95% confidence intervals. For continuous outcomes, we expressed the results with differences in means (in minutes), with 95% confidence intervals. Because one of the included studies presented its findings solely in medians and interquartile ranges (IQR), a statistician (CR) re-calculated the reported medians, and lower and upper quartiles (LQ and UQ) to corresponding estimated means, standard deviations, and 95% confidence intervals on the estimated means. The methods used for re-calculation are described by Wan et al. (50). The confidence intervals were calculated using z-statistics under the assumption that at the sample sizes considered, a normal distribution is a reasonable approximation of a t-distribution.

Due to the clinical heterogeneity within settings, the administrated interventions and comparators, we employed a random-effects model which takes both between-study and within-study variability into account (51). Statistical heterogeneity was analyzed using the I-Square (I^2) test, where values higher than 75% were considered to indicate substantial heterogeneity between studies (51).

Assessment of certainty of the evidence

Two reviewers (SSO and KBF) independently applied the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation), developed by the GRADE working group (52), to assess certainty of the evidence. Due to the large number of included outcomes, only those outcomes considered main clinical outcomes were graded. In GRADE, the certainty of the evidence is evaluated separately for each outcome of interest, and is expressed either as high, moderate, low, or very low (52):

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Findings from RCTs begin with a rating of high certainty evidence. This may be downgraded according to five criteria: 1) risk of bias as assessed by review authors, 2) degree of inconsistency (unexplained heterogeneity between studies), 3) indirectness (indirect comparisons; issues related to the generalizability of findings), 4) imprecision of estimates, and 5) presence of reporting bias. In observational studies, which begin with a rating of low certainty evidence, the level of certainty can also be upgraded when results show a large effect estimate, or a dose-response gradient, or if all possible confounders would likely only diminish the observed effect (53).

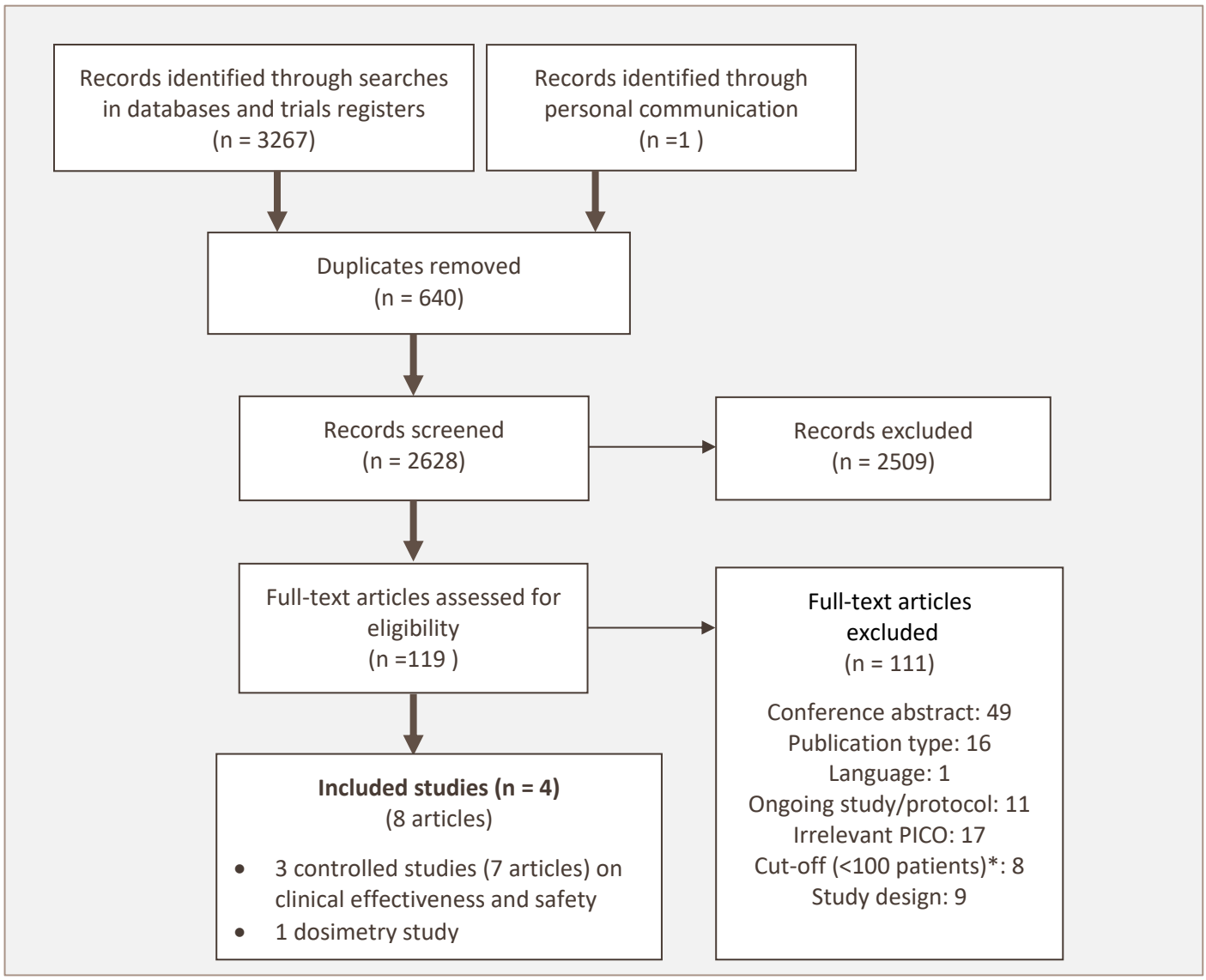
The GRADE assessments were done using the software GRADEpro (54).

RESULTS

Search results and selection of studies

Searches for systematic reviews and HTAs resulted in 616 records. 336 records were left after duplicates had been removed, and were screened for relevance. Of these, 25 records were considered potentially relevant and read in full-text. However, none of these met the inclusion criteria of this HTA.

Searches for primary studies resulted in a total of 2628 records, after duplicate records were removed (see Figure 2). Of these, we excluded 2509 irrelevant records at title and abstract screening. Out of the 119 assessed full-text publications, 8 publications, representing 4 studies, were considered eligible for inclusion.



* Case series and registry data with less than 100 patients were excluded

Figure 2. *Flow chart describing the selection process of primary studies*

A list of excluded full-text publications, with reasons for exclusion, can be found in Appendix 3.

Through the selection process, five ongoing potentially relevant studies were identified (40;55-58). A list of these is presented in Appendix 4.

We did not find any further relevant studies by scanning reference lists of possibly relevant evidence syntheses or the included publications.

Description of included studies

Two RCTs (59-63) and one observational registry study (64;65), conducted in Germany, were chosen for inclusion. In addition, we included an uncontrolled study from the USA (66) which measured radiation exposure to the MSU staff and the public (dosimetry study). An overview of the characteristics of the included studies is presented in Table 2.

Table 2. *Description of the included studies*

Study (first author and publication year of the main article, country)	**Population**	**Intervention**	**Comparator**	**Relevant outcomes**
RCTs				
Ebinger 2014 (59-61;63) Germany	Patients suspected for stroke (number of patients included in the analyses ranged between 213 and 2107, depending on the outcome)	An ambulance equipped with a CT scanner, point-of-care laboratory, and telemedicine connection, and a specialized pre-hospital stroke team (prehospital diagnosis and provision of thrombolysis)	Conventional care with an ambulance without prehospital capabilities (control group)	Time (min): alarm to CT/ thrombolysis; symptom onset to thrombolysis (in total and within different catchment zones) Number of patients with intravenous thrombolysis: in total/ treated within 60 min of symptom onset (golden hour thrombolysis) / treated within 90 min of symptom onset Number of patients ischemic stroke/intracranial hemorrhages delivered to hospitals without stroke unit/neurosurgery department (triage); number of secondary emergency referrals Number of patients with hemorrhagic complications; 90-day mortality

Study (first author and publication year of the main article, country)	**Population**	**Intervention**	**Comparator**	**Relevant outcomes**
Walter 2012 (62) Germany	Patients suspected for stroke (100 patients included in the analyses)	Mobile stroke unit (MSU): an ambulance equipped with a CT scanner, a point-of-care laboratory, and a telemedicine connection to the hospital (prehospital diagnosis and provision of thrombolysis)	Regular ambulance combined with optimized conventional hospital-based stroke management	Time (min): alarm / symptom onset to end of CT / intravenous thrombolysis Number of patients with intravenous thrombolysis Morbidity and function: NIHSS, Barthel index, and mRS scores at days 1 and 7 Safety endpoints related to secondary intracranial haemorrhage (ICH)
Observational registry study				
Kunz 2016 (64;65) Germany	Patients with ischemic stroke who received intravenous thrombolysis (264 patients with prestroke dependency and 658 patients not dependent on assistance before stroke included in the analyses)	An ambulance equipped with a CT scanner, point-of-care laboratory, and telemedicine connection, and a spe-cialized prehospital stroke team (prehospital diagnosis and provision of thrombolysis)	Conventional care: normal ambulances, diagnosis and provision of thrombolysis in the hospital (control group)	3-month functional outcome: number of patients with mRS score 0–1/ mRS score 0–3

Study (first author and publication year of the main article, country)	**Population**	**Intervention**	**Comparator**	**Relevant outcomes**
Dosimetry study				
Gutiérrez 2016 (66) **USA**	Setting: An ambulance equipped with a CT scanner (MSU) (measurements resulting from the care of 106 patients)	Measurements of radiation exposure (MSU staff equipped with personal dosimeters, area monitors positioned inside the vehicle, ion chamber measurements outside the MSU during scans of a head phantom)	Staff: Exposed worker in a high volume hospital setting (on average) (67) Public: Dose limit given by the American authorities (68;69) Patient: Typical adult head examination with a CT (70)	Radiation exposure (mSv, µSv) to MSU staff, the public and patients

Controlled studies on clinical effectiveness and safety

Participants and settings

Both RCTs (59-63) included patients with suspected stroke for whom the stroke dispatch was activated by the emergency call distpatcher (based on a pre-specified dispatcher algorithm). Both studies excluded patients under the age of 18, and Walter et al. (62) had an upper age limit of 80 years. The observational registry study (64;65) included only patients with ischemic stroke who had received intravenous thrombolysis (either in the MSU or a hospital). Separate analyses were performed for patients who had lived at home without any assistance before the event (64) and patients dependent on assistance before stroke (65). In all three studies, the time of symptom onset was a crucial factor for patient inclusion. If the symptom onset was more than 2.5 hours (62), 4 hours (59-61;63) or 4.5 hours (64;65), or unknown, the patients were excluded.

The RCT conducted by Walter et al. (62) was carried out in Homburg, Germany, covering a region of up to 30 km around the University Hospital of the Saarland. The two other studies (59-61;63-65) were performed in Berlin within a catchment area which covered around 1.3 million inhabitants, was defined as having a 75% probability of reaching the emergency site within 16 minutes from the MSU base (located in the middle of the catchment area), and contained altogether 28 hospitals and 14 stroke units.

We were not able to identify any studies dealing with prehospital CT in suspected severe head injuries.

Interventions and comparators

In all three studies (59-65), the intervention consisted of an MSU, i.e. an ambulance equipped with a CT scanner, a point-of-care laboratory, and a telemedicine connection to the hospital. In Walter et al. (62), the MSU team consisted of a paramedic, a stroke physician, and a neuroradiologist. The interpretation of the CT images was done at the scene. In the other two studies (59-61;63-65), the MSU staff included a neurologist, a paramedic, and a radiology technician. CT images were transmitted to a neuroradiologist at a hospital for interpretation. In all three studies, if the patient was eligible for thrombolysis, the treatment was provided directly at the emergency site.

In the two RCTs (59-63), during MSU randomized weeks, a regular ambulance was always also sent out in addition to the MSU (in parallel). In Ebinger et al. (59-61;63) the first responders were capable of cancelling the MSU based on their assessment, without providing further explanation. If the MSU was not available, due to simultaneous calls or maintenance, patients received conventional care during the MSU weeks (treatment group without MSU deployment).

Comparators consisted of conventional care with an ambulance without prehospital capabilities and in-hospital diagnostics and treatment. In Walter et al. (62), the conventional hospital-based stroke management was optimized by replacing centralized hospital laboratory testing with point-of-care laboratory testing. This was done to ensure that MSU care would not be compared with suboptimal in-hospital stroke management.

Outcomes

Differences in time (minutes) to diagnosis and treatment between treatment and control group were investigated by the two included RCTs (60-62). Both studies measured time from symptom onset to thrombolysis, and time from alarm to CT and to thrombolysis. In addition, Walter et al. (62) measured time from symptom onset to CT.

Thrombolysis rate was an outcome in both RCTs (59;60;62). Ebinger et al. (59;60) reported in addition number of patients treated within 60 minutes and 90 minutes of symptom onset. This study further investigated whether prehospital care in an MSU increased the number of stroke patients delivered to approriate treatment facilities (triage).

Further reported outcomes included 90-day mortality (60), hemorrhagic complications (60;62), and functionality at days 1 and 7 (mRS, NIHSS score, Barthel index) (62) and 3 months (mRS) (64;65).

None of the included studies measured quality of life, or resource utilization (e.g. use of specialized staff and length of hospital stay).

Dosimetry study

The dosimetry study by Gutierrez et al. (66) made measurements for radiation protection on an MSU in Houston, Texas. This dosimetry study was performed throughout an entire year to establish the exposure to the workers and to make sure that potential doses to the public did not exceed the yearly dose limits.

The CT technician stood at the side door, outside the MSU, and operated the CT scanner with a laptop computer. All other personnel stood outside the vehicle during the scan, unless medically necessary for the patients care, and then wearing lead aprons. The ambulance workers were equipped with personal dosimeters, and three area monitors were positioned inside the vehicle. In addition to this monitoring regime, ion chamber measurements were performed outside the ambulance during scans of a head phantom. The dosimeters and area monitors were from LUXEL, and the ion chamber was a Victoreen Fluke ion chamber.

For further details of the included studies, see Appendix 5.

Risk of bias in included studies

Figure 3 shows assessment results on each risk of bias item across all included controlled studies. Figure 4 shows the risk of bias for each included study.

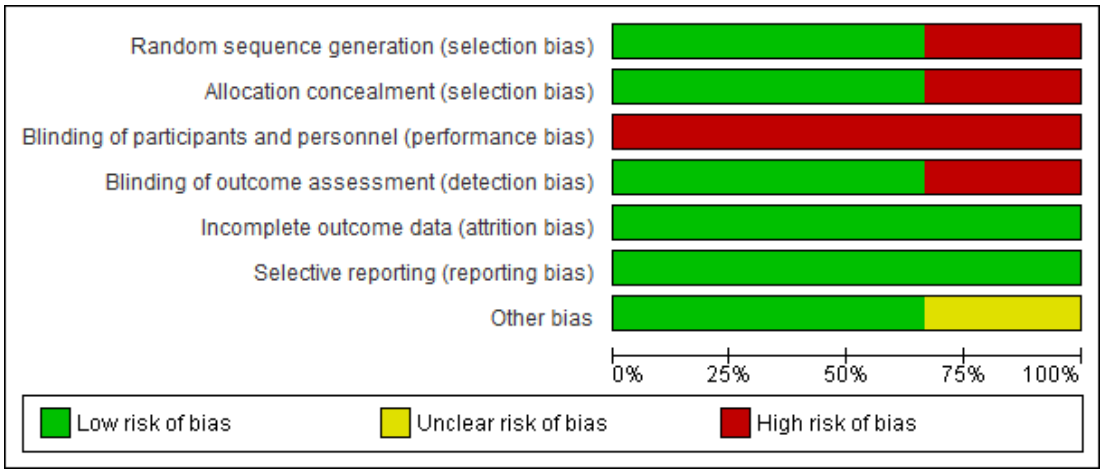


Figure 3. *Risk of bias across included studies*

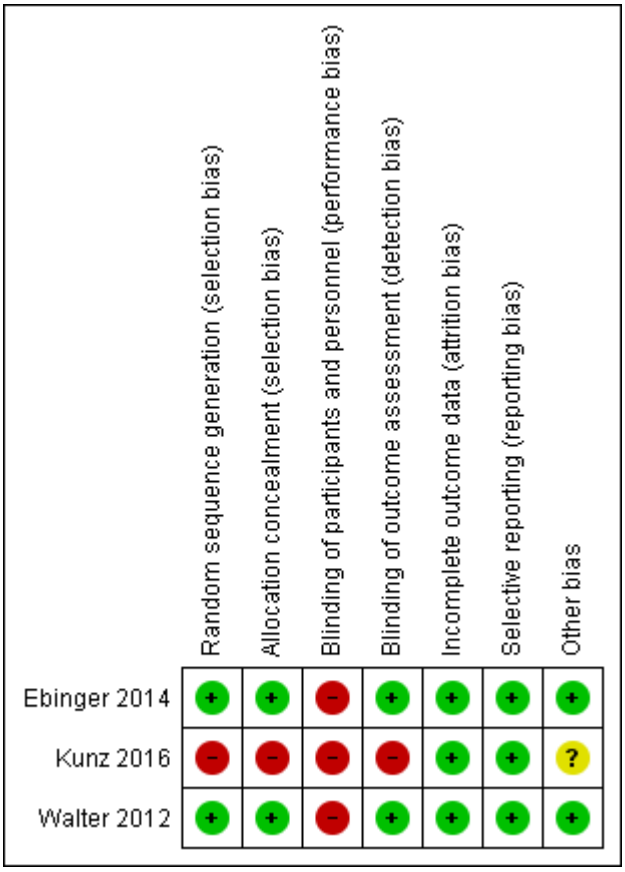


Figure 4. *Risk of bias for each included study*

Both RCTs (59-63) used randomized time periods (weeks) rather than randomization at patient level. This was due to the fact that informed consent cannot be given via telephone in Germany. Within both studies, the EMS dispatcher algorithm was the same during MSU and non-MSU weeks. Allocation was not concealed, but due to the week-wise randomization plans, and the fact that stroke occurs unexpected, the risk of selection bias is likely to be low. Furthermore, to avoid a selection bias in favor of MSU, Ebinger et al. (60) also included patients in the MSU deployment group who were not

treated in the MSU due to MSU cancellation (treatment group without MSU deployment). However, in both studies, neither the MSU nor the ambulance staff could be blinded, which may have introduced a performance bias.

In the included observational registry study (64;65), in addition to lack of both randomization, allocation concealment, and blinding of the EMS dispatcher, MSU/ambulance staff and patients (i.e. risk of selection and performance bias), the outcome assessment was unblinded. Outcome raters in the MSU group were also sometimes directly involved in patient care. The risk of information bias can therefore not be ruled out. Furthermore, the fact that not all baseline parameters were balanced, and some non-observed/non-documented confounders could not be included in adjusted analyses, may have introduced an additional bias.

For further details see Appendix 5.

Effectiveness and safety of prehospital CT

In this chapter, each of the subsections include a narrative summary of the findings for an outcome (or several similar outcomes), as well as presentation of the results by means of forest plots or tables. In addition, results of the GRADE assessment (our evaluation of the certainty of the evidence) are presented for each outcome.

Due to the large number of included outcomes, only those outcomes considered primary clinical outcomes were graded. Table 3 provides an overview of the conducted GRADE assessments. Further details can be found in Appendix 6.

Table 3. *Overview of the results from the GRADE assessments*

MSU care compared to conventional care for suspected stroke

Patient or population: Suspected stroke
Setting:
Intervention: MSU care
Comparison: Conventional care

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Certainty
		Conventional care	MSU care	**Difference**	
Time from alarm to imaging assessed with: minutes № of participants: 510 (2 RCTs)	-		-	MD **26.87 minutes lower** (50.98 lower to 2.77 lower)	⨁⨁◯◯ LOW [a,b,c]
Time from alarm to thrombolysis assessed with: minutes № of participants: 510 (2 RCTs)	-		-	MD **30.52 minutes lower** (43.04 lower to 18 lower)	⨁⨁⨁◯ MODERATE [a]

Time from symptom onset to thrombolysis assessed with: minutes № of participants: 520 (2 RCTs)	-		-	MD **49.84 minutes lower** (117.26 lower to 17.58 higher)	⊕⊕◯◯ LOW [a,d]
Total number of patients who received thrombolysis (thrombolysis rate) assessed with: number of patients № of participants: 1755 (2 RCTs)	**RR 1.53** (1.31 to 1.80)	21.0%	32.1% (27.5 to 37.7)	**11.1% more** (6,5 more to 16,8 more)	⊕⊕⊕◯ MODERATE [a]
Number of patients who received thrombolysis within 60 minutes assessed with: number of patients № of participants: 420 (1 RCT)	**RR 5.68** (3.16 to 10.23)	5.5%	31.0% (17.2 to 55.8)	**25.5% more** (11,8 more to 50,3 more)	⊕⊕◯◯ LOW [a,c]
90-day mortality assessed with: number of patients № of participants: 416 (1 RCT)	**RR 1.35** (0.84 to 2.15)	12.4%	16.7% (10.4 to 26.6)	**4.3% more** (2 fewer to 14,2 more)	⊕⊕◯◯ LOW [a,c]
3-month functionality (mRS 0-1) assessed with: number of patients № of participants: 658 (1 observational study)	**RR 1.12** (0.96 to 1.31)	47.0%	52.7% (45.1 to 61.6)	**5.6% more** (1,9 fewer to 14,6 more)	⊕⊕◯◯ LOW [e]
3-month functionality (mRS 0-3) assessed with: number of patients № of participants: 658 (1 observational study)	**RR 1.13** (1.04 to 1.22)	73.7%	83.2% (76.6 to 89.9)	**9.6% more** (2,9 more to 16,2 more)	⊕⊕◯◯ LOW [e]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Lack of blinding (patients and staff)
b. Same effect direction, but heterogenous effect estimates (however, not considered to be a reason for downgrading)
c. Large confidence interval
d. Heterogenous effect estimates and large confidence interval (0.5 points for each)

e. Not all baseline parameters were balanced, some non-observed or non-documented confounders could not be included in adjusted analyses (however, not considered to be a reason for downgrading)

Time to diagnosis and treatment

Both included RCTs (60;62) investigated whether there was a difference between groups in time (minutes) from alarm to imaging, and from alarm to thrombolysis. In total, 245 patients received MSU care and 265 patients received conventional care (control group). Within both outcomes, the meta-analyses (Figures 5 and 6) showed a difference between groups, in favor of MSU. The difference in means from alarm to CT was around 27 minutes (-26.87, 95% CI -50.98 to -2.77), and from alarm to thrombolysis around 31 minutes (-30.52, 95% CI -43.04 to -18.00).

Re-calculations of medians and interquartile ranges reported by Walter et al. (62) to corresponding estimated means and standard deviations (used in the meta-analyses) can be found in Appendix 7 Table A.

Based on the GRADE assessment (Table 3, Appendix 6), in time from alarm to imaging, the certainty of the evidence was assessed to be low. The reason for downgrading the evidence from high to low was the risk of bias in the included studies (lack of blinding) and large confidence interval. In time from alarm to thrombolysis, we assessed the certainty of the evidence to be moderate (due to lack of blinding).

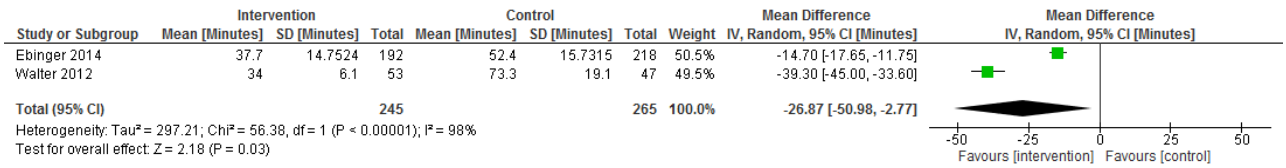


Figure 5. *Mean difference (in minutes) between groups from alarm to imaging*

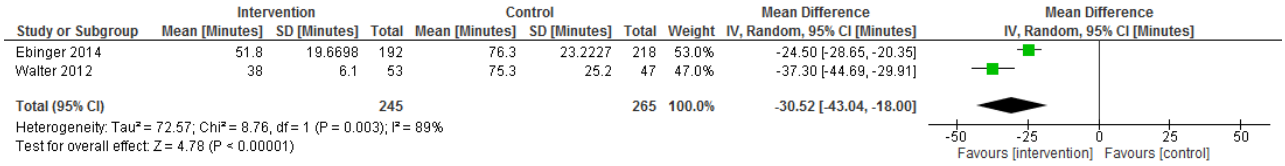


Figure 6. *Mean difference (in minutes) between groups from alarm to thrombolysis*

Walter et al. (62) measured time from symptom onset to imaging. The MSU group and the control group included 53 and 47 patients, respectively. The study found a difference in median minutes between groups (39, 95% CI IQR 26 to 52), in favor of MSU (Table 4). We did not however perform a GRADE assessment to assess certainty of the evidence for this outcome.

Table 4. *Difference between groups in time (minutes) from symptom onset to imaging, median (IQR) (62)*

MSU group (n=53)	Control group (n=47)	Difference (95% CI)	p-value
56 (43–103)	97 (74–156)	39 (26–52)	<0·0001

IQR = Interquartile range

The included RCTs (60;62) also investigated whether there was a difference between groups in time from symptom onset to thrombolysis. In total, 253 patients received care in the MSU and 267 patients received conventional care (control group). No statistically significant difference in means was detected between groups (-49.84 minutes, 95% CI -117.26 to 17.58) (Figure 7).

Based on the GRADE assessment (Table 3, Appendix 6), the certainty of the evidence was assessed to be low. The reason for downgrading the evidence from high to low was the risk of bias in the included studies (lack of blinding), heterogenous effect estimates and large confidence interval.

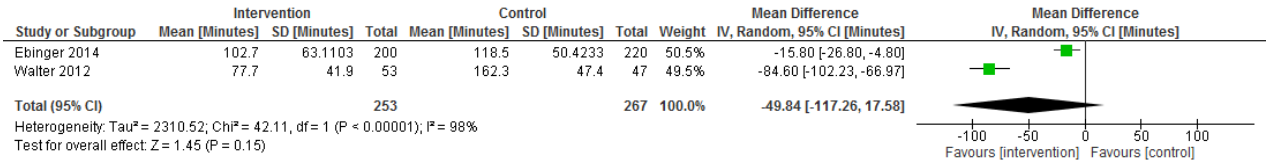


Figure 7. *Mean difference (in minutes) between groups from symptom onset to thrombolysis*

Further analyses by Ebinger et al. (60) on some of the outcomes above, comparing all patients in the intervention group, regardless whether they had received care in the MSU or not, with patients in the control group, showed similar results. For details, see Appendix 7 Table B.

Furthermore, a post hoc analysis (61) based on data from Ebinger et al. (60) investigated whether time benefits were sustained within the different zones in the catchment area. The area was divided into four distinct zones (zones 1-4) with respective expected arrival within 4, 8, 12, and 16 minutes from the MSU base station. Within all four zones, comparisons related to time from alarm to imaging and from alarm to thrombolysis showed differences in means between those who received care in the MSU and those who did not (Table 5). The latter included patients in the control group, as well as those in the MSU group who did not receive care in the MSU (because the MSU was not available). However, mean differences between groups in time from symptom onset to thrombolysis showed a sharper decrease from zone 1 (62.9 minutes) to zone 4 (8.1 minutes). We did not perform GRADE assessments to assess certainty of this evidence.

Table 5. *Differences between groups in time (minutes) within zones 1 and 4: comparison of patients who received care in the MSU and those who did not (regardless of group allocation) (61)*

Outcome	MSU group (with MSU deployment) (n=200)	Control group + MSU group (without MSU deployment) (n=330)	Mean Difference	p-value
Alarm to imaging, minutes, mean (median, IQR)				
Zone 1	37.6 (30, 24–40)	50.2 (49, 40–62)	12.6	0.001
Zone 4	51.2 (37, 33–47)	54.4 (52, 44–64)	3.2	<0.001
Alarm-to-treatment, minutes, mean (median, IQR)				
Zone 1	41.8 (39, 34–48)	76.5 (72, 63–84)	34.7	<0.001
Zone 4	59.3 (52, 45–63)	78.0 (72, 61–88)	18.7	<0.001
Symptom onset to treatment, minutes, mean (median, IQR)				
Zone 1	67.9 (60, 40–76)	130.8 (114, 80–179)	62.9	<0.001
Zone 4	108.9 (93, 62–135)	117.0 (105, 78–149)	8.1	0.051

IQR = Interquartile range

Delivery to an appropriate hospital (triage)

Ebinger et al. (63) investigated whether prehospital MSU care increased the number of stroke patients delivered to approriate treatment facilities (triage). Both among patients with ischemic stroke and patients with intracranial hemorrhages there were differences between those who received MSU care and those who did not, in favor of MSU (Table 6). Those who did not receive MSU care included patients in the control group, as well as those in the MSU group who could not be evaluated in the MSU (because the MSU was not available). MSU care reduced inadequate delivery of patients with ischemic stroke to a hospital without a stroke unit by more than 60% (relative risk reduction). In patients with intracranial hemorrhages, MSU care reduced delivery to a hospital without neurosurgery department by more than 70% (relative risk reduction). No statistically significant differences were detected between groups in the number of referrals to another hospital within two days from admission. We did not however perform GRADE assessments to assess certainty of the evidence for these outcomes.

Table 6. *Differences between groups in triage of stroke patients (63)*

Outcome	MSU group (with MSU deployment)	Control group + MSU group (without MSU deployment)	p-value[a]	RR (95% CI)	p-value
No. of patients with ischemic stroke	**610**	**1497**			

Delivered to hospitals without Stroke Unit, No. (%)	24 (3.9)	151 (10.1)	<0.01	0.39 (0.26-0.59)	< 0.0001
Secondary emergency referrals, No. (%)	11 (1.8)	33 (2.2)	0.56	0.82 (0.42-1.61)	0.56
No. of patients with intracranial hemorrhages[b]	**62**	**151**			
Delivered to hospitals without neurosurgery department, No. (%)	7 (11.3)	65 (43.0)	<0.01	0.26 (0.13-0.54)	0.0003
Secondary emergency referrals, No. (%)	3 (4.8)	19 (12.6)	0.09	0.38 (0.12-1.25)	0.11

RR = Relative risk
CI = Confidence interval
[a] = p-value for difference in proportions; Pearson $\chi 2$ test or Fisher exact test were used to compare these categorical variables
[b] = Consisting of spontaneous intracerebral hemorrhages, traumatic intracerebral hemorrhages, subdural and epidural hematoma, and subarachnoid hemorrhages

Proportion of patients treated with thrombolysis

Both included RCTs (59;60;62) reported proportion of patients who were treated with thrombolysis. In total, 667 patients received care in the MSU and 1088 patients received conventional care (control group). The former also included patients who were diagnosed in the MSU, but received thrombolysis first after arrival in the hospital. The results of the meta-analysis showed that MSU care had an effect on the thrombolysis rate, compared to conventional care (RR 1.53, 95% CI 1.31 to 1.80) (Figure 8). 32% of MSU patients received thrombolysis, whereas the proportion was 21% in conventional care.

Based on the GRADE assessment (Table 3, Appendix 6), the confidence in the pooled effect estimate was assessed to be moderate. The certainty of the evidence was downgraded because of the risk of bias in the included studies (lack of blinding).

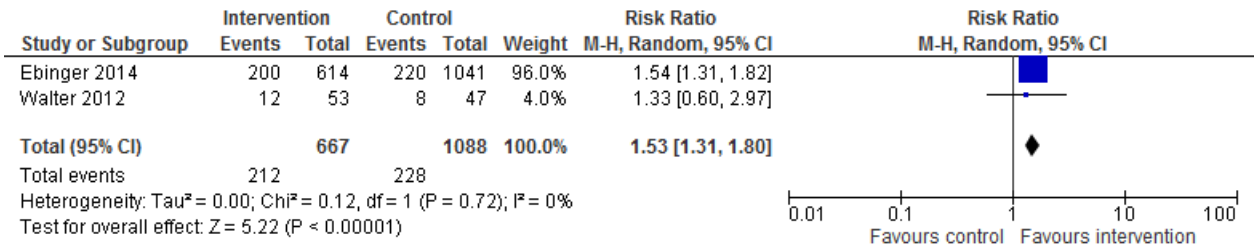


Figure 8. *Effect of prehospital CT on number of patients with intravenous thrombolysis*

Ebinger et al. (59;60) also investigated whether there were differences between groups in number of patients treated within 60 minutes (golden hour) and 90 minutes of symptom onset. The results showed that among those who received thrombolysis a higher proportion of patients received thrombolysis within 60 minutes (31.0% versus 5.5%, p <0.0001), as well as within 90 minutes (57.5% versus 37.4%, p < 0.001), in the MSU group compared to the control group (Table 7). Patients in the MSU group were more than five times as likely to receive thrombolysis within the golden hour, and approximately 1.5 times as likely to receive thrombolysis within 90 minutes, than patients in the control group.

Based on the GRADE assessment (Table 3, Appendix 6), the certainty of the evidence related to thrombolysis rate within 60 minutes was assessed to be low. The reason for downgrading the evidence from high to low was the risk of bias in the included studies (lack of blinding) and large confidence interval. No GRADE assessment was performed to assess certainty of the evidence for thrombolysis rate within 90 minutes.

Table 7. *Differences between groups in thrombolysis rate within 60 and 90 minutes of symptom onset (59;60)*

Outcome	MSU group (with MSU deployment)	Control group	p-value	RR (95% CI)	p-value
No. of patients who received thrombolysis	**200**	**220**			
Patients treated within 60 min of symptom onset, No. (%)	62 (31.0)	12 (5.5)	<0.0001[a]	5.68 (3.16-10.23)	< 0.0001
Patients treated within 90 min of symptom onset, No. (%)	115 (57.5)	82 (37.4[b])	< 0.001[c]	1.54 (1.25-1.90)	< 0.0001

RR = Relative risk
CI = Confidence interval
[a] = p-value for difference in proportions; 2-sample test for equality of proportions with continuity correction was used for calculation
[b] = The study authors have reported 37.4%. However, according to our own calculations the proportion should be 37.3%.
[c] = p-value for difference in proportions; Pearson $\chi 2$ test or Fisher exact test were used to compare categorical variables

Further analyses by Ebinger et al. (60) on some of the outcomes above, comparing all patients in the intervention group, including those patients who did not receive any care in the MSU (because the MSU was not available), with patients in the control group, showed statistically significant differences between groups as well. For details, see Appendix 7 Table C.

90-day mortality

Ebinger et al. (60) measured mortality at 90 days among patients who had received thrombolysis. The MSU group and the control group included 200 and 220 patients, respectively. No difference in 90-day mortality was detected between groups (16.7% versus 12.4%, p = 0.21) (Table 8). When age, sex, comorbidities and stroke severity (NIHSS score) were taken into account, there continued to be no group difference (60).

Based on the GRADE assessment (Table 3, Appendix 6), the certainty of the evidence was assessed to be low. The reason for downgrading the evidence from high to low was the risk of bias in the included studies (lack of blinding) and large confidence interval.

Table 8. *Difference between groups in 90-day mortality (60)*

Outcome	MSU group (with MSU deployment)	Control group	p-value[a]	RR (95% CI)	p-value
No. of patients who received thrombolysis	**198**	**218**			
90-day mortality, No. (%)	33 (16.7)	27 (12.4)	0.21	1.35 (0.84-2.15)	0.22

RR = Relative risk
CI = Confidence interval
[a] = p-value for difference in proportions; Pearson $\chi 2$ test or Fisher exact test was used to compare categorical variables

Further analyses by Ebinger et al. (60), comparing all patients in the intervention group, including those patients who did not receive any care in the MSU (because the MSU was not available), with patients in the control group, showed similar results. For details, see Appendix 7 Table D.

Functional status

Walter et al. (62) investigated functionality (mRS, NIHSS score, Barthel index) at days 1 and 7. The MSU group and the control group included 53 and 47 patients, respectively. No differences in 1-day and 7-day functionality were detected between groups (Table 9). We did not perform GRADE assessments to assess certainty of the evidence for these outcomes.

Table 9. *Differences between groups in 1-day and 7-day functionality (62)*

Outcome	MSU group	Control group	p-value
No. of patients	**53**	**47**	
Stroke severity, NIHSS score at day 1 [a]	3 (1–10)	4 (2–12)	0.48
Stroke severity, NIHSS score at day 7 [a]	2 (1–8)	4 (0–8)	0.94

Barthel index at day 1 [a]	65 (25–85)	75 (0–95)		0.98
Barthel index at day 7 [a]	70 (30–95)	80 (25–95)		0.79
No. of patients [b]	**41**	**41**	**OR (95% CI)**	**p-value**
mRS at day 1 [c]			1.00 (0.42–2.41)	0.99
mRS at day 7 [c]			0.89 (0.39–2.00)	0.77

CI = Confidence interval
NIHSS = National Institutes of Health Stroke Scale
mRS = modified Rankin scale
OR = Odds ratio
[a] = Based on the information provided by Walter et al. (62), we assume the presented data are median
[b] = Analyzed in a stroke patient subgroup
[c] = Logistic regression used with baseline mRS as categorical covariate

The included observational registry study (64;65) measured 3-month functionality (mRS) in patients with ischemic stroke who had received thrombolysis. Separate analyses were conducted for patients who had lived at home without assistance before the event (mRS 0-1 and mRS 0-3), and for patients dependent on assistance before stroke (mRS 0-3) (Table 10). In patients with no need of assistance before stroke, no difference was detected between the MSU and the control group in number of patients with mRS score 0-1 at 3 months (53% versus 47%, p = 0.14). The results showed, however, that a higher proportion of patients in the MSU group achieved 3-month mRS score 0-3, compared to the control group. This applied to both patients without pre-stroke dependency (83% versus 74%, p = 0.004) and with pre-stroke dependency (39% versus 25%, p = 0.01).
Similar results were found in adjusted analyses when age, sex, comorbidities, stroke severity (NIHSS score) and intra-arterial co-treatment were taken into account, including when pre-event institutional care was accounted for (64;65).

We performed GRADE assessments for 3-month mRS score 0-1 and 0-3 in patients who had lived at home without assistance before the event. Based on the GRADE assessments (Table 3, Appendix 6), the certainty of the evidence (both for mRS 0-1 and mRS 0-3) was assessed to be low. In GRADE, observational studies begin with a rating of low certainty evidence.

Table 10. *Differences between groups in 3-months functionality (mRS) (64;65)*

Outcome	MSU group	Control group	p-value[a]	RR (95% CI)	p-value
No. of patients without need of assistance before stroke	**305**	**353**			
3-month mRS score 0–1, No. (%)	161 (53%)	166 (47%)	0.14	1.12 (0.96-1.31)	0.14
3-month mRS score 0–3, No. (%)	253 (83%)	260 (74%)	0.004	1.13 (1.04-1.22)	0.004

No. of patients with pre-stroke dependency	**122**	**142**			
3-month mRS score 0–3, No. (%)	48 (39%)	35 (25%)	0.01	1.60 (1.11-2.29)	0.01

RR = Relative risk
CI = Confidence interval
mRS = modified Rankin scale
[a] = p-value for difference in proportions; Pearson $\chi 2$ test was used to compare categorical variables

Hemorrhagic complications

Both included RCTs (60;62) reported number of patients who experienced hemorrhagic complications secondary to thrombolysis (Table 11). In Walter et al. (62), one patient out of 53 died from secondary intracranial hemorrhage (ICH) in the MSU group, whereas two patients out of 47 experienced secondary ICH (change in NIHSS score less than 4) in the control group. In Ebinger et al. (60), 3.5% in the MSU group and 6.4% in the control group experienced hemorrhagic complications. The MSU group comprised patients who were diagnosed in the MSU, and received thrombolysis either in the MSU or first after arrival in the hospital. The difference between the groups was however not statistically significant (p = 0.18). When age and stroke severity (NIHSS score) were taken into account, there continued to be no group difference (60). We did not perform GRADE assessments to assess certainty of the evidence for these outcomes.

Table 11. *Differences between groups in hemorrhagic complications*

Outcome	MSU group	Control group	p-value[a]	RR (95% CI)	p-value
Walter 2012 (62)					
No. of patients	**53**	**47**			
Patients with fatal secondary ICH[b], No. (%)	1 (2)	0 (0)	NR		
Patients with non-fatal secondary ICH (change in NIHSS ≥ 4), No. (%)	0 (0)	0 (0)	NR		
Patients with secondary ICH (change in NIHSS < 4), No. (%)	0 (0)	2 (4)	NR		
Ebinger 2014 (60)					
No. of patients	**200[c]**	**220**			
Hemorrhagic complications No. (%)	7 (3.5)	14 (6.4)	0.18	0.55 (0.23-1.34)	0.19

ICH = Intracranial hemorrhage
NIHSS = National Institutes of Health Stroke Scale
NR = Not reported
[a] = p-value for difference in proportions; Pearson $\chi 2$ test or Fisher exact test was used to compare categorical variables

[b] = Subarachnoidal hemorrhage secondary to thrombolysis
[c] = Number of patients in the MSU group with MSU deployment

Radiation exposure

Gutierrez et al. (66) measured radiation exposure in an MSU in Houston Texas for one year (Table 12).

During the study only the CT technician was present on all runs in which the CT was used. Other MSU staff varied during the year so their exposure was lower. The CT technician had received a 1.14 mSv cumulative dose resulting from the care of 106 patients during a period of one year. This person stood in the door opening, outside the MSU, unless it was necessary to aid the patient. This dose level is comparable to an exposed worker in a high volume hospital setting, typically 1.5 mSv per year on average (67).

The area monitors inside the vehicle resulted in yearly doses from 0.23 – 1.38 mSv, which strongly overestimates the possible exposure of the public. The outside ion chamber measurements estimated a dose per scan around 0.33– 3.04 µSv right outside the MSU. Since the MSU will be parked on different sites for each run and there will likely be taken only one scan, the doses to any one individual will be well below the dose limit given by the American authorities, which is 1.0 mSv/year (68;69).

The dose to the patient was measured with a phantom and an ion chamber. The dose parameter CT-dose index (CTDI) was measured to 67.5 mGy (settings: 120 kVp, 6 mA, exposure time of 4 sec per rotation) and effective dose was estimated to 2.7 mSv. This is similar to typical adult head examinations with a CT scanner of a patient effective dose between 1 and 2 mSv (70).

Table 12. *Radiation exposure to staff, the public and patients (66-70)*

Outcome	MSU	Comparison
Dose to staff (CT technician)	1.14 mSv/ year	Exposed worker in a high volume hospital setting (on average): 1.5 mSv/ year
Dose to the public	Inside the MSU: 0.23 – 1.38 mSv/ year Outside the MSU: 0.33 – 3.04 µSv/ scan	Dose limit given by the American authorities: 1.0 mSv/ year
Dose to patient (effective dose)	2.7 mSv/ scan	Typical adult head examination with a CT: 1.0-2.0 mSv/ scan

mSv = Millisievert
µSv = Microsievert

Organizational aspects

Current diagnostic and treatment pathways in Norway

The Norwegian EMS is government-funded and includes the local emergency primary healthcare system (casualty clinics) in first line, the local ambulance system and a national air ambulance system, staffed by general practitioners (GP), emergency medical technicians (EMTs) or paramedics, or anesthesiologist and a specially trained paramedic, respectively (71).

Acute stroke

The emergency primary care center, EMCC and GP are the three main points of initial contact for patients experiencing stroke in Norway. When stroke is suspected or identified, patients are usually transported to the nearest treatment facility. Time to reach the facility depends on distance, topography, weather conditions and means of transportation. In some cases relatives drive the patient directly to the emergency room, but in most cases, patients are transported in regular ambulances either to the local hospital or to the regional university hospital (with a neurosurgical department), depending on what is the most nearby. In rural areas, however, patients are often far from any facility, and the helicopter emergency medical service (HEMS) may be required to shorten the time to treatment (39).

Most hospitals in Norway include specialized stroke units that consist of interdisciplinary-trained staff operating with a standardized treatment pathway. At these specialized stroke units, a logistical and management infrastructure supports all aspects of stroke treatment (8). At arrival, medical personnel initiate a clinical evaluation and perform a CT scan. This is to exclude hemorrhagic stroke, head trauma or any contraindications prior to thrombolysis treatment (1). Depending on the severity of the stroke and treatment options, patients are triaged to the appropriate treatment facility. If the patient is eligible for thrombolysis then treatment with thrombolysis is initiated at the hospital. If thrombolysis is contraindicated or thrombolysis does not have the desired effect (patients considered for thrombectomy), or if hemorrhagic stroke is considered severe, treatment within a neurosurgical department may be needed. This may require a second transportation, i.e. from a local hospital to a regional university hospital.

Severe head injuries

The treatment scheme for severe head injuries differs slightly from that of acute stroke, while the logistic pathways remain the same. In the case of head trauma, it is important

to triage these patients to the correct treatment facility. Patients with severe head trauma (TBI) are triaged to regional university hospitals, i.e. hospitals with a neurosurgical department (72).

The Norwegian setting

Figure 9 presents the distribution of Norwegian hospitals providing emergency care. There are currently five hospitals with a neurosurgical department, one in each regional health authority, except for the Western Region, which has two (Table 13). These have all the necessary competence and equipment to perform e.g. thrombectomies and treat patients with severe head traumas.

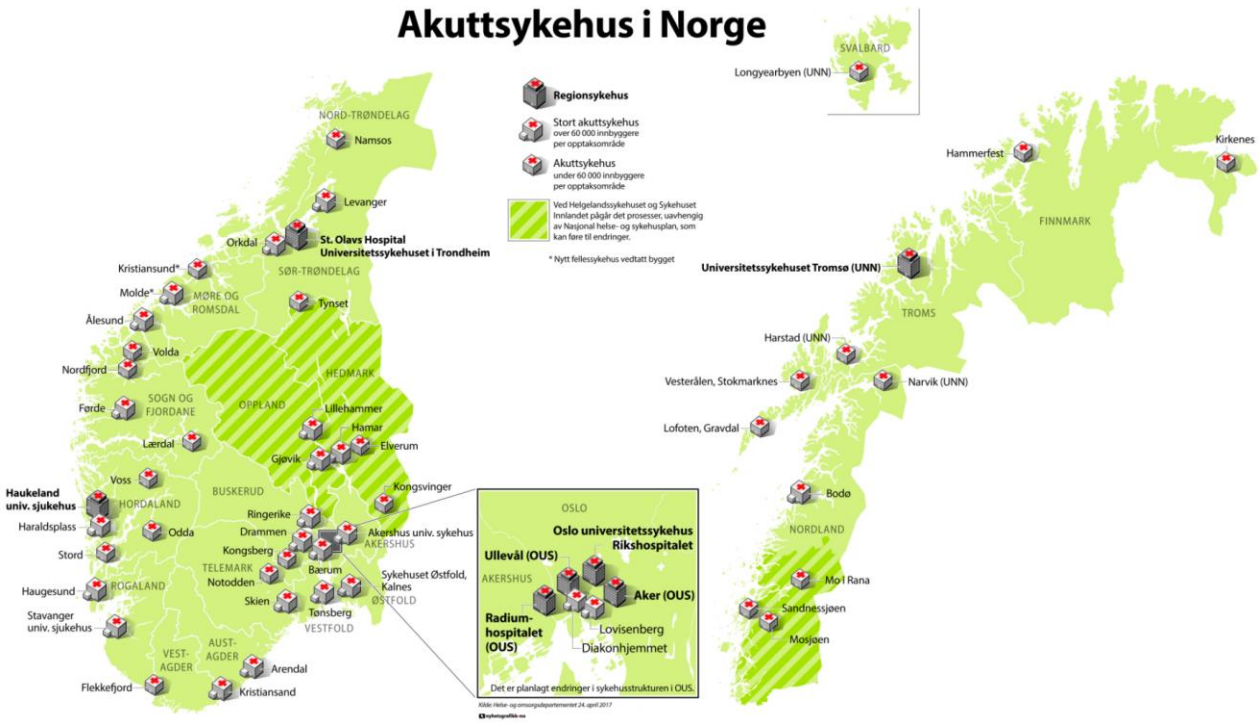


Figure 9. *The distribution of Norwegian hospitals providing emergency care (73)*

Table 13. *The regional health authorities and corresponding intervention center(s)*

Regional Health Authority	Hospital with Neurosurgical Department
South Eastern Region	Oslo University Hospital, Rikshospitalet
Western Region	Haukeland University Hospital Stavanger University Hospital
Northern Region	University Hospital of North Norway
Central Region	St. Olavs University Hospital

CT imaging can be carried out both at local and regional facilities, however patients with stroke eligible for thrombectomy or with severe head traumas need to be treated in a neurosurgical department. Hence some of these patients may suffer from having lost precious time as they may have been first directed to the local hospital for clinical assessment and CT, before being further transported to an appropriate treatment facility. Delays in triaging, registration at the hospital, diagnosis and treatment are all critical factors to consider in the treatment of both acute stroke and severe head injuries.

Implementation of prehospital CT

Mobile stroke unit

MSUs are equipped with a CT scanner device onboard, which assists determining the diagnosis prior to the transportation to the hospital. Introduction of prehospital CT will not only lead to identification of thrombolysis eligible strokes and following treatment initiation in the MSU, but helps also indicate to which facility the patient should be directed. If a hemorrhagic stroke or a head trauma is considered to be severe according to the CT scan, the MSU will allow direct transport towards the nearest hospital with a neurosurgical department.

«CT stations» outside hospitals

Norway consists of large rural and isolated coastal areas, where the people often live long distances from, or are isolated geographically from their affiliated hospital. Hence, some CT scanners have already been installed at district medical centers located strategically for quick access when needed. Such stationary CT scanners are currently placed in Finnsnes and Ål in Norway (the latter with acute preparedness) (39). They are connected to the nearest hospitals via telemedicine, allowing immediate access to the CT scan data and diagnosis set from distance. These stationary CT scanners are whole-body covering imaging devices, i.e. they are not restricted to the head and neck region as in the MSU. This increases their value as they may be used to detect and follow-up many other conditions and indications. Cancer patients for instance would no longer need to travel long distances for imaging. The CT scanner in Ål is currently included in a local stroke trial (40).

Implications of prehospital CT in Norway

In Norway, the introduction of prehospital CT (MSUs and/or telemedicine steered CT stations outside hospitals) will likely change the roadmap and lead to organizational changes to the health care services across the whole country. The impact will be location specific and will differ between urban and rural areas. As mentioned above, important factors to take into account especially in Norway are population density, topography and weather conditions. Norway consists of large areas with forest and mountains, and has at the same time long coastal areas with lots of islands only accessible by sea or air transport. This is challenging when it comes to deciding the best logistics for any hospital transport. Depending on where the patient is located geographically, different logistic options will be available.

The basic idea behind prehospital diagnosis is to shorten the time to CT, and this may be achieved in multiple scenarios, as the MSU and the conventional ambulance services will coexist. For instance, the MSU can meet the patient on site or an ambulance nearby could transport the patient towards an MSU. The latter would also be possible in difficult terrain with a helicopter. If there are stationary CT units located in the area, an ambulance or a helicopter could transport the patient to that location, perform imaging, and start treatment or transport the patient directly to an appropriate treatment facility (Figure 10).

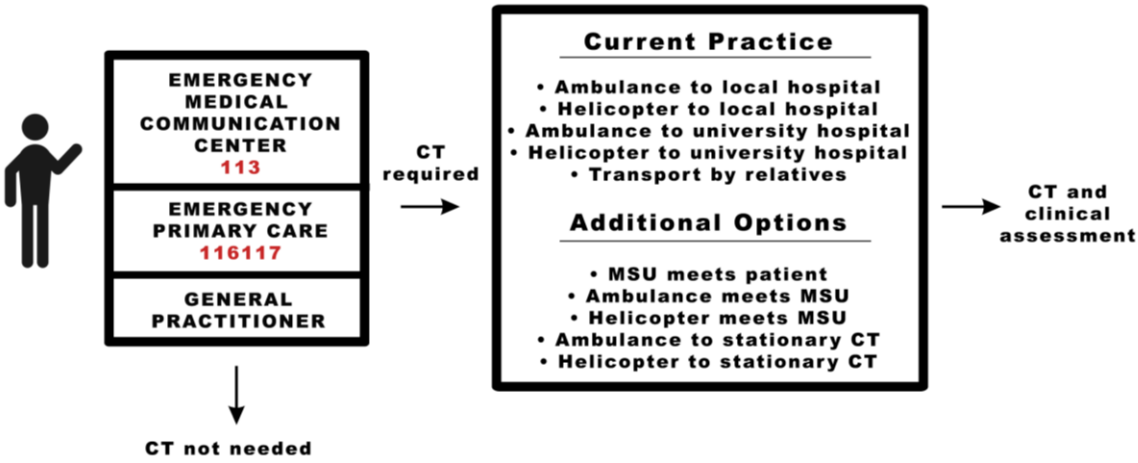


Figure 10. *Pathways to CT given prehospital CT is implemented*

If diagnosis is achieved earlier one could envision that triaging to the appropriate treatment facility could be achieved more accurately (Figure 11). Briefly, after the CT imaging (either in the MSU or at a stationary CT location) together with clinical assessment have identified probable diagnosis, patients are triaged to a suitable treatment facility. In the event of an acute ischemic stroke, treatment with thrombolysis is initiated and the patient is transported to a hospital with a specialized stroke unit for further treatment and follow-up (option 2 in the figure). If thrombolysis does not have the desired effect, thrombectomy becomes an option and the patient is transferred to a hospital with a neurological department. If large-vessel occlusion is suspected (option 3), patients are administrated thrombolysis and transferred directly to a hospital with a neurological department for thrombectomy. Similarly, if thrombolysis is contraindicated (option 4), the patient is transferred directly to a hospital with a neurological department for thrombectomy. In hemorrhagic stroke or head trauma, a decision of an appropriate treatment facility and need for neurosurgical treatment will be made based on the results of CT imaging, present symptoms and clinical assessment (options 5, 6 and 7).

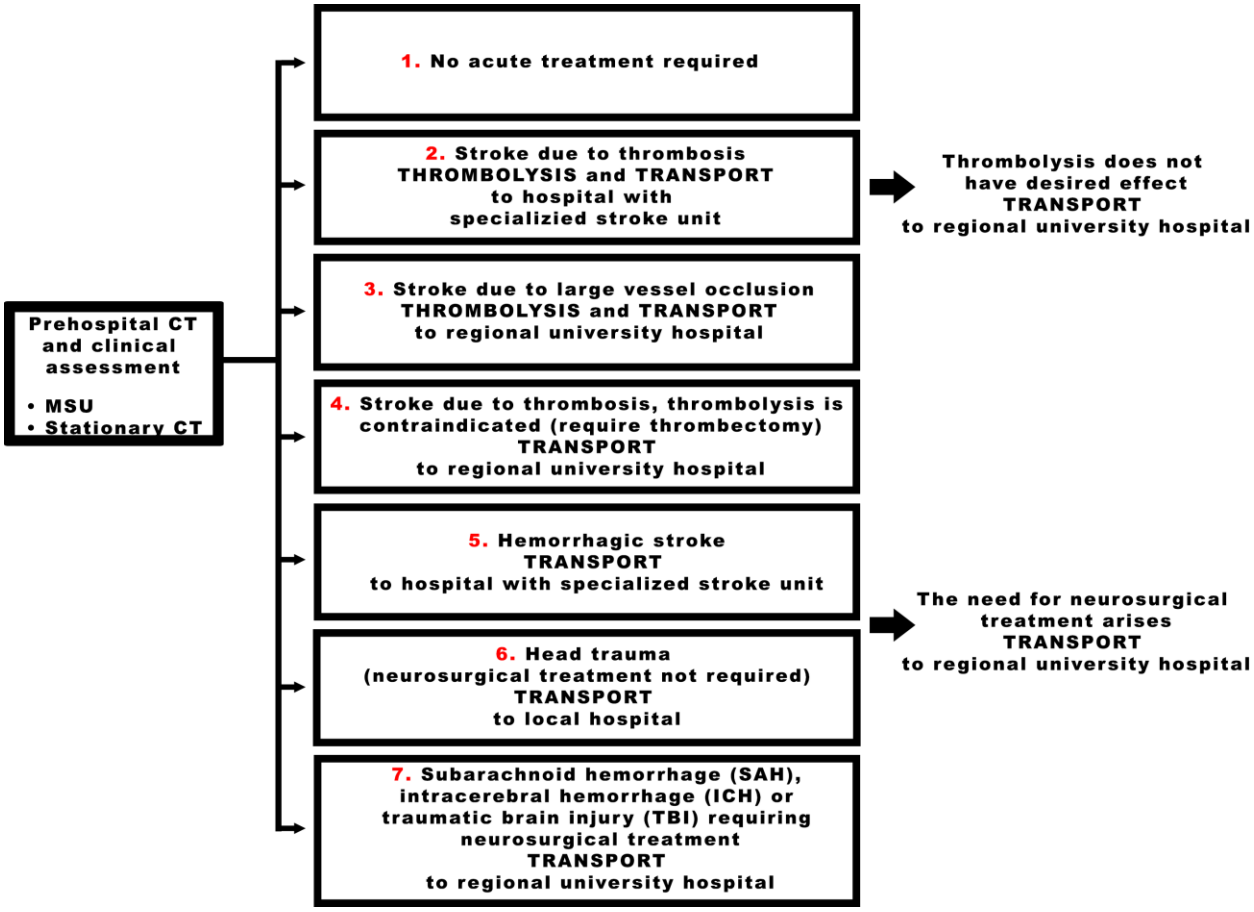


Figure 11. *Triaging of patients in the prehospital setting*

In Walter et al. (62), during the last study year, the MSU was equipped with a CT scanner allowing multi-modal imaging with CT angiography and CT perfusion. Given vascular imaging such as CTA was implemented in the MSU or at a stationary CT location, accurate triage of patients with large-vessel occlusion to appropriate target hospital (regional university hospital) could become possible (74). This would prevent having to perform two separate scans (CT and CTA) at two different locations, and could help avoid unnecessary second transportations (from a local hospital to a regional university hospital).

Required staff and competence

Several combinations of staff and competence have been tested in different clinical studies (74). One possibility is to have high clinical competence covering all needs in the MSU, including a neuroradiologist and stroke physician (62). Another option is to have a nurse or paramedics and CT technologist in the MSU, which would then be entirely dependent on telemedicine in every procedure carried out in the MSU (75). These are the two "extreme" scenarios, but combinations of the two can also be foreseen.

In a Norwegian study, trained non-neurologist physicians (anesthesiologists) were responsible for operating the CT scanner in the MSU and interpreting CT images (after extensive training) (35). Ongoing trials are testing what configuration of staffing achieves high quality in the decision-making aiding triaging and health outcomes, while still

keeping the costs low. In Norway, a configuration where anesthesiologists are the decision makers in the MSU has been tested (37), while in Houston in the U.S., a research nurse with telemedicine connection to an in-hospital vascular neurologist is currently being tested (76). Both options require staff onboard the MSU to undergo proper training in stroke recognition and stroke treatment. The MSU staff needs to be experienced in stroke treatment and in making decisions on whether to provide thrombolysis or not based on clinical criteria. In addition, training on how to use a CT scanner and how to interpret the resulting images will require formal training from expert radiologists and radiographers/radiation technicians. The (radiation protection/RP) regulations requirements on competence will only be open for dispensation if it affects the undertaking unreasonably, and is issued with great caution. When changing the organisation of tasks as might be the case in the MSU, the personnel competence must be risk evaluated, especially the radiology and radiography competence.

Technical challenges

The MSU will communicate with the hospital through a mobile device capable of sending CT images via the mobile network and accessing the hospital's record system. Operator errors or poor wireless network connection could interrupt the transfer of the CT images, which in turn would cause delays in determining the diagnosis. In addition, in some rural areas, mobile coverage may be insufficient. This would require the MSU to find a suitable location for the transfer of CT images, if the MSU is relying on in-hospital neurologists for interpretation of images. Of note, most of the studies on MSUs have been tested in urban areas, where the mobile data network coverage normally is very high, whereas in Norway, coverage could prove to be an issue if the MSU would solely rely on telecommunication. Thus, caution should be taken when using results from these studies and applying them in Norwegian settings.

Logistics

Implementation of an MSU as part of stroke management in Norway will require thoughtful reorganization and cooperation between the hospitals and the MSU. In order for the MSU to cover a specific geographic area, calculations must be made to find the optimal base station emplacement for the MSU.

EMCCs will require proper training to assess whether a patient is experiencing a stroke or not, preferably an interview algorithm based on a recognized stroke scale could be one solution. In Norway, EMCC has been using the Norwegian Index for Medical Emergency Assistance as a guideline for dispatch (77). When the MSU is dispatched, one should also consider whether both the MSU and the conventional ambulance are dispatched simultaneously in case the event is not stroke.

Hospitals within the region covered by the MSU will also require a stroke unit that can receive patients directly from the MSU and bypass the emergency unit. This might require access to hospital records from the MSU, so that the patient information is continuously updated.

Health economic evaluation

METHODS

Introduction to economic evaluations of health care programmes

The basic aim of an economic evaluation is to identify, measure and compare differences in costs and consequences of alternative strategies under consideration in a so called incremental analysis. Results of economic evaluations are often expressed as an incremental cost-effectiveness ratio (ICER), which is defined by the following equation:

$$ICER = \frac{Cost_{\text{intervention}} - Cost_{\text{comparator}}}{Effect_{\text{intervention}} - Effect_{\text{comparator}}} = \frac{\Delta C}{\Delta E}$$

The health care sector, like society in general, is constrained by scarce resources and fixed budgets. Therefore, economic evaluations can be important tools for decision makers facing questions of how to prioritize treatments in order to maximize health benefits, when faced with scarce resources. For an economic evaluation to be meaningful in a decision making process, the ICER must be judged with regard to a threshold that reflects the decision maker's maximum willingness to pay (WTP) for a health gain. The decision rule for an economic evaluation can be expressed as:

$$\frac{\Delta C}{\Delta E} \leq \lambda \quad ,$$

where λ represents willingness to pay (WTP), and means that if the ICER of an intervention is below or equal to the threshold, introducing the intervention represents good value for money.

Economic evaluations are often based on decision models, such as decision trees and Markov models, which are used to calculate ICERs based on important input parameters. Because there are always uncertainties related to the values of these parameters, analysing the potential consequenses of the uncertainty through sensitivity analyses is important. Determinististic sensitivity analysis illustrates how much the results vary when the values of individual parameters are changed, typically one at a time (one-way sensitivity analysis), while keeping all other parameters constant. In Probabilistic sensitivity analysis (PSA) it is possible to take the uncertainties of all of the model-parame-

ters into account simultaneously. The basic approach in probabilistic sensitivity analysis is to assign appropriate probability distributions to the model-parameters, which makes it possible to replace the "fixed" values of the parameters with values generated by random draws from the distributions in a process called Monte Carlo simulation. Results from PSA are typically presented as the probabilities that alternative interventions are cost-effective subject to various levels of WTP. In short, making a model probabilistic means that it is possible to estimate the uncertainty associated with a decision to implement alternative interventions. Another type of sensitivity analyses is a so-called threshold analysis. Threshold analyses are typically performed when the evidence for key parameters is particularly poor. The objective of a threshold is to identify the critical value(s) of parameter(s) that are central to the decision, i.e. the parameter value that will change a recommendation about whether or not to implement (78;79).

Priority setting criteria

There are three primary criteria for setting priorities in the Norwegian health care sector: the benefit criterion, the resource criterion, and the severity criterion (80).

- According to the benefit criterion, priority increases with the size of the expected health benefit of the intervention. The benefit criterion primarily refers to a technology's expected health gains: increased longevity and/or improved health-related quality of life. By combining these two types of health gains into a single outcome measure, the quality-adjusted life-year (QALY), it is possible to compare treatment outcomes across different diseases, patient groups and types of treatments.

- According to the resource criterion, priority increases, as fewer resources are needed for the intervention. The resource criterion focuses attention on how the health sector uses its limited resources. Introducing a new technology creates demands for personnel, equipment, facilities, etc. that could be used to provide treatments for other patients – a reality that is referred to as the "opportunity cost" of the new technology. The larger the quantity of resources allocated to a technology for one patient group, the fewer the resources available for treating others. In addition to resource use within the health sector, a technology may also engender costs for other parties. In practice, the resource criterion can also be taken into account by weighing costs against benefits in a cost-effectiveness analysis of the technology of interest. Resource use, measured as monetary costs, enters into the numerator of the cost-effectiveness ratio (see "Cost-effectiveness" below). In addition to the cost-effectiveness analysis, a budget impact analysis may help inform decisions.

- According to the severity criterion, priority increases with expected future health loss resulting from the disease. Severity is measured as "absolute shortfall", defined as the expected loss of future health (QALYs) associated with a specified diagnosis. For treatment of a diagnosed disease, severity is the average expected absolute shortfall for the relevant patient group given the current standard treatment. Generally, the greater the absolute shortfall associated with a disease, the more resources per QALY-gained the authorities may be willing to allocate (80;81).

We calculated absolute shortfall based on projections from the health economic model. Calculation of absolute shortfall has been described in more detail in the submission guideline for pharmaceutical reimbursements, and is based on a Norwegian life table and age adjusted quality of life information from a general Swedish population (82-84). Absolute shortfall is calculated as the difference in quality adjusted life expectancies at age (A) without the disease ($QALY_{sA}$), and prognosis with the disease (P_A):

$AS = QALY_{sA} - P_A$

Cost-effectiveness

Cost-effectiveness is an expression of the amount of health gains (in QALYs) created by a given amount of resources, or seen from an opportunity cost perspective, the cost per additional QALY gained. A health economic analysis evaluates a new technology relative to a comparator. The ratio between the incremental (additional) cost of the new technology and its incremental effect is referred to as the incremental cost-effectiveness ratio (ICER). The Norwegian White paper on priority setting (80) indicates that weighting of resource use against utility should be based on the opportunity cost principle, and that priority should be further increased according to severity (absolute shortfall).
The Norheim and Magnussen commissions suggested that an absolute shortfall of less than 2.0 QALYs should indicate diseases with the lowest level of severity, while an absolute shortfall above 20 QALYs would indicate diseases in the highest severity class (80;81).

There is no official societal willingness to pay threshold for health care interventions in Norway. However, for such considerations, the Norheim commission and Magnussen group assumed an opportunity cost of 275,000 Norwegian kroner per QALY, and suggested a weighting scale for the societal willingness to pay for different severity classes. The corresponding threshold for cost-effectiveness of MSU would accordingly be approximately 385,000 Norwegian kroner per QALY (80;81).

Summary of other economic evaluations

There is paucity of evidence regarding cost-effectiveness of MSU as an intervention. While the question has not been systematically evaluated in Norway, we have identified two economic evaluations from other countries.

A benefit-cost analysis was carried out by Dietrich and colleagues in 2014. A model was set up to consider five different scenarios regarding staffing of an MSU (with varying degrees of specialization and competence). The main parameters in the model were: direct incremental costs related to prehospital stroke treatment gathered during the trial, annual costs savings due to earlier thrombolysis sourced from the published studies, MSU operating distances, and population density. They estimated a benefit-cost ratio of 1.96 (scenario with neurologist and neuroradiologist on board), i.e. the value of benefits produced by the intervention were almost twice its costs. The benefit-cost ratio further improved in scenarios with reduced staff and increased use of telemedicine. The

benefit-cost ratio was also greater than one in rural areas with lower population density (85).

Gyrd-Hansen and colleagues considered the cost-effectiveness estimate of prehospital thrombolysis in Berlin, based on data from one of the included RCTs. The intermediate outcomes; time from onset to thrombolysis and treatment rates were used as basis to calculate numbers needed to treat and health gains in terms of number of avoided cases of disability (defined as score mRS>1). These results were then transformed into quality adjusted life years (QALYs) using data from a UK population-base study and UK population valuations (based on EQ-5D). Data on resource utilization was also gathered. The results show that the annual net cost of an MSU was 963,954 Euro (9.34 million Norwegian kroner), with an incremental cost-effectiveness ratio (ICER) of 32,456 Euro (approximately 314,450 Norwegian kroner) per QALY (86).

In Norway, final results from an ongoing study of MSU care in the Østfold district are expected in 2021. One case report from the study was published in 2018 (87). However, an economic evaluation has not been planned as part of this study (58). An ongoing observational study at Vestre Viken Hospital Trust, of rural CT examination and thrombolytic treatment for stroke, aims to assess medical and health economic effects. The results from this study are expected in 2021 (40).

General

Stroke accounts for considerable consumption of healthcare resources and has high economic consequences for patients, relatives, and society as a whole (88). Many attempts have been made to reduce onset-to-treatment time in acute stroke care. Studies summarized in this HTA have shown that stroke diagnostic investigation and treatment in specialized stroke ambulances with integrated CT scanners (MSU) is a strategy with the potential to reduce time to treatment and improve clinical outcomes compared with conventional care (60;62). The diagnostic clarification entails differentiation between cerebral infarction and cerebral haemorrhage on site. During the prehospital stage in conventional ambulances, the cause of stroke remains unknown. Acute stroke management involves multiple interfaces, such as complex multidisciplinary cooperation in various locations and multistep testing, before treatment can begin, all of which can contribute to delays and errors. The MSU concept, apart from reducing pre- and in-hospital transport times, can save crucial time by substantially reducing those interfaces. At one location, a single, specialized, interdisciplinary team performs the complete diagnostic investigation and acute treatment in a parallel workflow (74). Introducing MSU care represent substantial investments in infrastructure and training, so its cost-effectiveness needs to be demonstrated to justify prioritising its implemetation.

In this health economic evaluation we have conducted a cost- and threshold analysis. The analysis assesses mean incremental cost-effectiveness ratios (ICERs) at different values for proportions of ischemic stroke patients receiving thrombolysis through MSU care compared to conventional care. A threshold analytical approach was selected be-

cause this HTA failed to identify evidence of high validity for the proportion of Norwegian ischemic stroke patients who would actually receive MSU care (see further justification below).

We updated and modified the probabilistic Markov decision analytic model developed for ischemic stroke patients treated with thrombectomy, developed by the Norwegian Institute of Public Health (89). The model was developed in order to estimate costs and QALYs of a simulated cohort of acute ischemic stroke patients, based on their functional status assessment at 90 days, measured as mRS (decision tree only), in a lifetime perspective (decision tree and Markov model). To adjust the existing model to our research question, we used effectiveness parameters obtained from a registry study performed by Kunz et al. (2016) (64). Cost data was obtained from different sources described in the cost chapters below.

The cost analysis was carried out from a healthcare perspective. The health care perspective is relevant for prioritisation of interventions within a fixed budget if the aim of the decision maker is to maximize health. All costs and effects in the model are discounted using an annual discount rate of 4%, following the recommendation by the Norwegian Ministry of Finance and guidelines for health economic evaluation in the health sector (90). Costs are expressed in 2018 Norwegian kroner (NOK), and effects are expressed as quality-adjusted life-years (QALYs), a measure of disease burden that includes both the quality and the duration of life. QALY values are rounded to one decimal. As our primary health economic analysis is presented as a threshold analysis, probabilistic sensitivity analysis was inappropriate. The model was developed in, and the threshold- and sensitivity analyses, were conducted using TreeAge Pro ® 2018.

Cost- and threshold analysis

The result of the stroke model is driven by the proportion of ischemic stroke patients who receive thrombolysis through MSU care instead of conventional care. Norwegian data on this measure is not available yet and a standard cost-effectiveness analysis is therefore not possible without making very heroic assumptions about this key variable. However, the question of whether to implement stroke ambulance in Norwegian health care remains highly policy relevant. We therefore conduct cost- and threshold analyses, rather than a standard cost-effectiveness analysis (CEA). A threshold analysis is suitable for situations with extremely weak evidence for key parameters, but results must be interpreted differently. With standard cost-effectiveness analysis the following question can be answered: What is the cost-effectiveness of the intervention, when considering the best available evidence about important parameters? In a threshold analysis we can instead answer: What must the proportion of patients who receive thrombolysis through MSU care be (effective coverage) for the ICER to be at a predefined level? Technically, the threshold analysis is modelled in exactly the same way as a cost-effectiveness analysis (CEA), but results must be presented in a different format. In a threshold analysis we present a one-way sensitivity analyses for the key-parameters as our main finding rather than presenting the ICER-table that is standard in CEAs (78).

In this report we assess mean incremental cost-effectiveness ratios (ICERs) at different values for proportions of ischemic stroke patients receiving thrombolysis through MSU care compared to conventional care. This method makes it possible to identify a threshold value for the proportion that is required for the MSU to achieve an ICER of a predefined level. This decisive proportion is the threshold value of the parameter. An increase in the proportion of patients receiving MSU care reduces per patient costs. Therefore, values of the proportion can help assess cost-effectiveness. Ultimately, decision makers must consider whether they think it is plausible that the parameter is higher or lower than its threshold.

Epidemiology and patient flow assumptions

Provided that the intervention is introduced, we do not know well which patients that would receive thrombolysis, either as part of MSU care or conventional care, and in sum what the effective coverage of MSU would be. As mentioned, the clinical effectiveness data used in our analysis are from Berlin (64). Therefore, our analysis only considers MSU in a metropolitan area such as Oslo. As basis for further calculation, we used the number of patients receiving thrombolysis in the greater Oslo-area, which includes the city of Oslo and parts of Bærum and Akershus municipalities, with a total population of 1.1 million inhabitants. According to the Norwegian Stroke Registry (NSR), 263 of the 1,411 patients with acute ischemic stroke admitted to Ullevål Hospital, Bærum Hospital and Akershus University Hospital received thrombolysis in 2017 (19.7%, 21.4%, and 16.6% respectively). This registry only covers 86% of thrombolysis treatments (8). We therefore assumed that in reality 306 patients per year receive thrombolytic treatment in the Oslo-area and that all are treated in the conventional way today (Table 14).

We assumed that MSU would be introduced alongside conventional ambulances in the Oslo-area. We therefore considered the proportion of patients treated with thrombolysis through MSU care to vary between 10% and 50%, while the remaining (90% - 50%) were assumed to receive thrombolysis through conventional care. We further assumed that as the proportion of patients that receive treatment through MSU care increases, the total number of patients that receive thrombolysis increases by the same percent (Table 15). This implies that a number of patients that do not receive thrombolytic treatment today will receive treatment with an introduction of MSU. In addition, we assume that some of the patients who would receive thrombolysis the conventional way today, would receive it earlier with the presence of the MSU.

Table 14. *Reported number of ischemic stroke patients and proportion treated with thrombolysis in the Oslo-area in 2017.*

	Ischemic stroke patients (number)	***Ischemic stroke patients treated with thrombolysis (proportion in %)***	***Ischemic stroke patients treated with thrombolysis (number)***
Ullevål Hospital	610	19.7	120
Bærum Hospital	210	21.4	45

Akershus University Hospital	591	16.6	98
Total	1,411	-	263

The national data coverage in the registry was 86% in 2017. In our analysis we assume that 306 patients receive thrombolytic treatment in the Oslo-area per year (263 / 0.86 = 306). Source: Norwegian Stroke Registry Annual report 2017 (8).

Table 15. *Total number of patients receiving thrombolysis in the Oslo-area, and their distribution between MSU and conventional care, under different assumptions about MSU utilization rates*

MSU utilization rate	**10%**	**15%**	**20%**	**25%**	**30%**	**35%**	**40%**	**45%**	**50%**
Total number of patients who receive thrombolysis	337	352	367	383	398	413	428	444	460
Patients who receive thrombolysis through conventional care	303	299	294	287	278	269	257	244	230
Patients who receive thrombolysis through MSU care*	34	53	73	96	119	145	171	200	230

*MSU: mobile stroke unit. When patient proportion treated with thrombolysis through MSU care increases, the total number of patients who receive thrombolysis increases correspondingly (i.e. 10% more patients treated with thrombolysis through MSU care increases total number of patients that receive thrombolysis by 10%).

In order to translate the above numbers into information about health gains in quality-adjusted life-years, we have carried out simulation using the Markov model to find the average expected incremental effect for patients receiving treatment with use of MSU compared with conventional care. The key assumptions of this model are described in the subchapter below.

Markov model assumptions and parameters

Population

In the economic model, we assumed that the initial age for an acute ischemic stroke patient is 70 years, the average age of patients in Kunz et al. 2016. This study assessed German patients and took place in Berlin (64). The average age of the Norwegian stroke patients was 74 years in 2017 (8). In our economic model we have only assessed acute ischemic stroke, and not haemorrhagic stroke or head injury.

Interventions

In the model we assume that two diagnosis and treatment options are available for acute ischemic stroke patients:

- Intravenous thrombolysis delivered through MSU care. This option encompasses all patients transported by MSU, regardless of whether thrombolysis was ultimately given in the MSU or in the hospital (according to an intention-to-treat approach).
- Standard ischemic stroke care – intravenous thrombolysis given in the hospital following transport with conventional ambulance and in-hospital diagnosis.

The aim of MSU care is the delivery of state-of-the-art prehospital diagnosis and treatment, in addition to diagnosis-based triage of the patient to the most appropriate target hospital. This strategy is based on the use of an ambulance equipped with a point-of-care laboratory, an (brain) imaging system (CT scanner), a telemedicine connection with a hospital, and appropriate medication and assessment tools (74). The MSU used in Norway in the research project in Østfold is custom-built by a German company (Meytech) that furnish ambulances with tele-radiological solutions. This company also built the model used in the Berlin-study. The ambulance is approved according to Norwegian regulations for emergency vehicles and the inventory, as medical equipment meets the standard for air ambulance helicopter (91). Further, the MSU-concept also comprises a specialized interdisciplinary-trained staff together with a standardized treatment protocol. This team is supported by an infrastructure aiding in all aspects of stroke treatment (74). The use of MSU in the Østfold-study is restricted to daytime and evening hours, with operating hours being Monday to Friday from 8 am to 8 pm (91).

Model structure

We reconstructed an existing Markov-model combined with a decision tree (89). Our model is based on a hypothetic cohort of 10,000 patients diagnosed with stroke and followed over a period of 25 years. We assumed a cycle length of 12 months, meaning that any transition between different health states could happen once a year. At the end of each cycle the model evaluates how the cohort of patients move between the mutually exclusive health states based on transition probabilities, which vary with current health state, age and treatment. A health state is a defined clinical condition that a patient could have during a given cycle. Each health state and event generate costs as well as health gains which are being evaluated and summarised for both strategies at the end of each cycle.

We use the modified Rankin Scale (mRS) at 90 days following stroke to classify patients into 3 categories, which correspond to the 3 main health states in the Markov model: *independent*, *dependent*, and *dead*. The health state *independent* is defined as mRS score 0-2. Patients with this health state can be assumed to mainly be self-reliant in daily activities. The *dependent* health state is defined as mRS 3-5, and entails that the patient relies heavily on health care services. The state *dead* is modelled as an absorbing state. It is not possible to change state from the absorbing state. Once an individual makes a transition into the absorbing state, no further incurred costs or health outcome are included in the analysis. In addition, the model includes a transient state: recurrent

stroke, which opens for revision of current state. Upon completion of each cycle, all patients could, depending on transition probabilities, remain in the same state or transfer to another state until death or the end of the simulation. Transition from dependent to independent state is only possible through rehabilitation and spontaneous regression of neurological outcomes within the first year after stroke, modelled using a tunnel function (89). The Markov model structure with possible transitions is illustrated in Figure 12 and the decision tree structure is attached in Appendix 8.

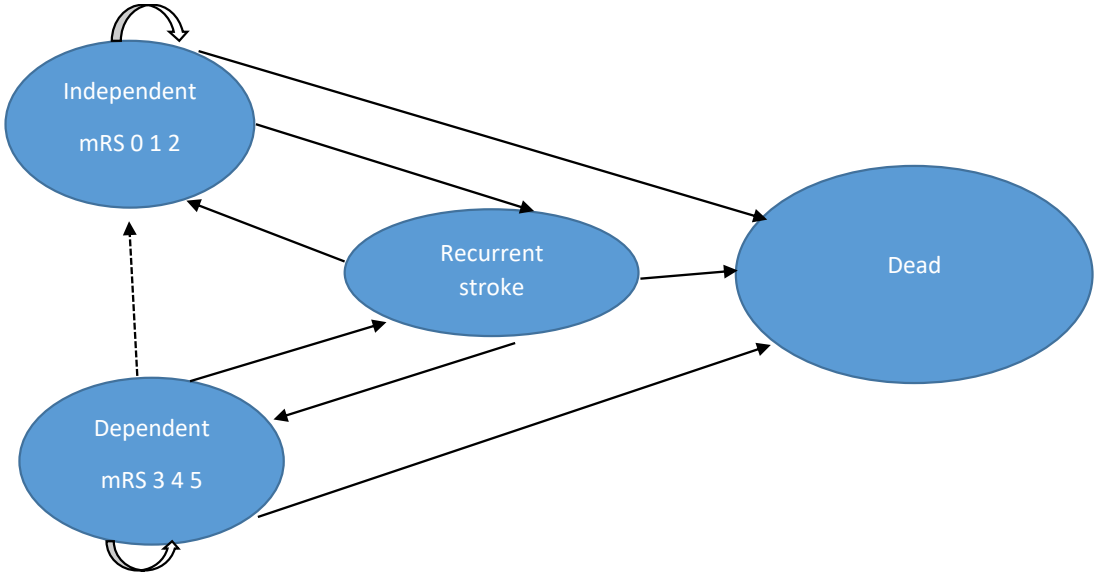


Figure 12. *State transition diagram, based upon a previous stroke model developed by The Norwegian Institute of Public Health and a British analysis from 2015 (89;92). The dotted line illustrates that transition from dependent to independent state only is possible within the first year after stroke.*

As mentioned, the model is based on an adaption of a probabilistic Markov decision analytic model for ischemic stroke patients (89). We assume that the stroke model has some generic properties regarding transition probabilitites and clinical outcomes, but have adapted parameters pertaining to costs and efficacy data to the stroke ambulance care.

Clinical efficacy

We based the clinical efficacy data on the results from Kunz et al. 2016, who conducted an observational registry study (64). The study aimed to compare patients with acute ischemic stroke who had received intravenous thrombolysis through MSU care with patients who had received thrombolysis through conventional care (normal ambulance and in-hospital thrombolysis at the Charité Campus Benjamin Franklin in Berlin). The mRS score at 90-days after intravenous thrombolysis was used as the main outcome measure. We have used this effect measure (Figure 13) to determine the initial probabilities in our health economic model (Table 16), i.e. the distribution of patients at the start of the first cycle for the two treatment strategies.

Table 16. *Number of patients at 90 days (3-month) mRS-score after stroke used in the health economic model*

	Independent, mRS 0-2 ***(proportion)***	**Dependent, mRS 3-5** ***(proportion)***	**Dead, mRS 6** ***(proportion)***	**Sum**
Mobile stroke unit	193 *(0.633)*	95 *(0.311)*	17 *(0.056)*	305 *(1.000)*
Conventional treatment	221 *(0.626)*	95 *(0.269)*	37 *(0.105)*	353 *(1.000)*

Source: Kunz et al. 2016 (64).

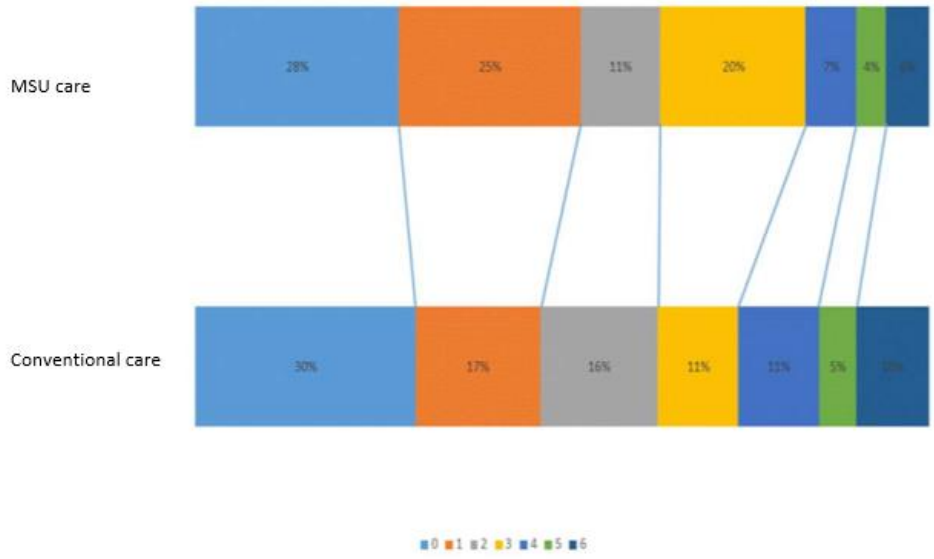


Figure 13. *Illustration of unadjusted outcome at 90 days according to modified Rankin Scale (mRS) by treatment group. Source: Supplementary webappendix to Kunz et al. 2016 (64).*

The MSU in the Berlin-study operated within a radius of a 16-minutes journey from the base fire station, which results in a catchment area of about 1.3 million inhabitants. 427 patients were treated within the MSU and 505 patients received conventional care between 5th of February 2011 and 5th of March 2015. 305 patients in the MSU group and 353 patients in the conventional care group met inclusion criteria and were included in the analysis. The results suggest that pre-hospital start of intravenous thrombolysis might lead to improved functional outcome in patients. Mean onset-to-treatment time was 33 minutes shorter in patients in the MSU group than in patients in the conventional care group, and significantly more patients in the MSU cohort received thrombolysis within 60 minutes or within 90 minutes of onset.

A second article based on the same data was published in 2018, in which the authors only include patients with pre-stroke dependency. We have not included those patients in our analysis (65).

Transition probabilities

In table 17 and 18 we have presented transition probabilities and state utilities used in the model. Data on mortality after 90 days was the same as in the previous economic model developed by The Norwegian Institute of Public Health. Stroke patients have an increased risk of death compared with general population. Death hazard ratios are dependent of mRS-status (Table 17) (89).

Table 17. *Probabilities used in the health economic model*

Parameter	Value (standard error)	Interval	Source
Hazard ratio of death beyond 1 year for independent patients (mRS 0-2)*	1.04 (0.08)	(0.89-1.30)	Based on hazard ratios used in Leppert et al. 2015 (93)
Hazard ratio of death beyond 1 year for dependent patients (mRS 3-5)*	1.78 (0.46)	(1.02-2.84)	Based on hazard ratios used in Leppert et al. 2015 (93)
Risk of recurrent stroke	0.05 (0.01)	(0.04-0.07)	(92-95)
Mortality when recurrent stroke (cycle-length 12 months)	0.19 (0.03)	(0.13-0.25)	(93)
Mortality between 90-365 days	0.07 (0.01)	(0.05-0.09)	(89)
Transition from dependent to independent (only first year)	0.11 (0.02)	(0.08-0.14)	Recalculated from Ganesalingam et al. 2015 (92)

*Mortality after 365 days: lifetables*hazard ratios

Table 18. *State utilities (QALY-values) used in the health economic model*

Utilities	Value (standard error)	Interval
Utility for patient in independent state (mRS 0-2)	0.74 (0.02)	(0.70 – 0.77)
Utility for patient in dependent state (mRS 3-5)	0.38 (0.05)	(0.29 – 0.47)

Source: Ganesalingam et al. 2015 (92).

Costs of mobile stroke unit

We estimated the total annual cost for one MSU as approximately 6,417,000 Norwegian kroner (Table 19), based on unpublished assumptions and discussions with experts. This estimate comprises three cost categories: operational costs, personnel costs, and

cost of medical devices. The costs do not include value added tax. The operational costs for one MSU include depreciation costs on the investment, insurance, annual fee, service agreements, parking, fuel, and variable maintenance. The post on medical devices includes depreciation costs on the investment, telemedicine (including tele-stroke assessment and tele-radiology), tablet, service agreement for CT scanner, and medical equipment follow-up. For mandatory controls of medical equipment, we assumed a hired medical engineer works five hours per month. A service agreement with the manufacturer is included. Personnel costs include costs of employees that are needed to operate one MSU: one physician (air ambulance physician with special competence in anesthesia and prehospital experience – average prehospital time about 11 years), one nurse with ambulance certificate, and one paramedic with a competency level above ambulance certification. The personnel cost is based on an assumption of 200 working days per year restricted to operating hours from 8 a.m. to 8 p.m., Monday to Friday, This cost was adjusted from trial data to a more realistic scenario based on advice from experts. We depreciated relevant medical equipment/devices over a period of seven years.

Table 19. *Annual cost estimates of one mobile stroke unit (MSU)*

Cost	Norwegian kroner (NOK)
Operational	1,138,555
Medical devices	1,277,920
Staffing	4,000,000
Total costs	**6,416,475**

Source: Assumptions and expert opinion.

Cost of conventional ambulance

We assumed that the unit cost per patient transported by a conventional ambulance is 3,921 Norwegian kroner, based on cost estimates in the previous health techonology assessment carried out by the Norwegian Institute of Public Health. The estimate is based on costs from Oslo and Akershus (89).

Cost of thrombolysis and rehabilitation

Based on DRG (Diagnostic Related Groups) information, we included a per-patient cost of thrombolysis of 89,462 Norwegian kroner in the model. We calculated this by multiplying 2.06 (the weight associated with DRG code 14A) by the 2018 unit price per DRG-point of 43,428 Norwegian kroner (96). We assumed that the cost of thrombolysis was the same for patients receiving MSU and conventional care.
In the absence of Norwegian estimates for overall costs associated with long-term follow-up, rehabilitation, secondary follow-up, nursing and care for patients who have undergone stroke, we have used cost data from a report compiled by the Swedish Tandvårds och Läkemedelsförmånsverket (TLV) (95). These costs reflect average costs for specialist- and municipal health services. We differentiate between costs during the first year of stroke treatment and costs that accrue annually after the first year. The

costs vary according to the patient's functional level. Table 20 provides a complete overview of costs used as input in the model.

Table 20. *Cost estimates used in the health economic model*

Parameter	Value (standard error)	Interval	Source
Standard treatment with intravenous thrombolysis	89,462 (13,693)	(62,623 – 116,300)	ISF 2018: Spesifikke karsykdommer i hjernen ekskl. TIA m/bk (96)
Costs first year in independent state (mRS 0-2)	103,328 (15,815)	(72,329 – 134,326)	TLV-report re-calculated to mean values and Norwegian kroner (95)
Costs first year in dependent state (mRS 3-5)	230,339 (35,256)	(161,237 – 299,440)	TLV-report re-calculated to mean values and Norwegian kroner (95)
Annual costs in independent state (mRS 0-2) after the first year	40,234 (6,158)	(28,164 – 52,304)	TLV-report re-calculated to mean values and Norwegian kroner (95)
Annual costs in dependent state (mRS 3-5) after the first year	102,964 (15,760)	(72,075 – 133,853)	TLV-report re-calculated to mean values and Norwegian kroner (95)
Costs associated with recurrent stroke	89,462 (13,693)	(62,623 – 116,300)	TLV-report re-calculated to mean values and Norwegian kroner (95)

Sensitivity cost- and threshold analysis

In order to investigate the impact of the key cost parameter, annual cost of an MSU, we performed a sensitivity analysis in which we adjusted the cost down and up by 25%.

Budget impact

The plausible organisational solutions related to introduction of MSUs in Norway are unknown, and we have therefore not estimated budget impact of the intervention. However, we assume that an investment in one MSU would cost approximately 6,417,000 Norwegian kroner annually (Table 19).

RESULTS

Severity considerations

In accordance with our economic model, we assume that patients are 70 years of age when entering the model. At this age, the expected quality adjusted life expectancy is 12.7 QALYs for a presumably health population. This is based on mortality rates from a Norwegian life table used in our model combined with age adjusted quality of life weight for a healthy population of 0.80 (82;83). The prognosis with disease with standard ambulance services is expected to be 7.2 QALYs, based on simulations from the health economic model developed for this analysis. The absolute shortfall with these assumptions is:

AS = 12.7 – 7.2 = 5.5 QALYs

Cost- and threshold analysis

We found different values for the proportion of patients diagnosed and treated with thrombolysis through MSU care, which corresponded with a range of levels of expected incremental cost-effectiveness ratios.

Costs

The expected incremental costs per patient among patients who receive thrombolysis through MSU care, compared to conventional care, is presented in table 21.

Outcome

The health economic model estimates an average incremental QALY-gain of 0.3 per patient who receives treatment with thrombolysis through MSU care, compared to conventional care (table 21).

Threshold analysis

Our cost- and threshold analysis for acute ischemic stroke treatment with intravenous thrombolysis through MSU care compared to conventional care, suggests that in order to achieve an incremental cost-effectiveness ratio of 385,000 Norwegian kroner, at least between 35% and 40% of patients who receive thrombolysis would have to receive this treatment through MSU care. For one MSU, 35-40% corresponds to 145-171 patients per year (Table 21 and Figure 14). Our result shows that as the proportion of patients that receive thrombolysis through MSU care increases, the incremental cost decreases and the intervention becomes more attractive in terms of cost-effectiveness.

Table 21. *Expected incremental costs, QALYs and -cost-effectiveness ratios (ICERs) at different values of proportions of patients receiving thrombolysis through MSU care.*

Proportion of patients that receive thrombolysis through MSU care*	Number of patients that receive thrombolysis through MSU care* (based on 306 patients)	Incremental cost (NOK**)	Incremental QALY-gain	ICER (NOK** per QALY)
10%	34	247,791	0.3	961,264
15%	53	178,723	0.3	693,328
20%	73	144,535	0.3	560,699
25%	96	124,265	0.3	482,066
30%	119	110,931	0.3	430,338
35%	145	101,543	0.3	393,920
40%	171	94,609	0.3	367,020
45%	200	89,301	0.3	346,428
50%	230	85,123	0.3	330,221

*MSU: mobile stroke unit. **NOK: Norwegian kroner.

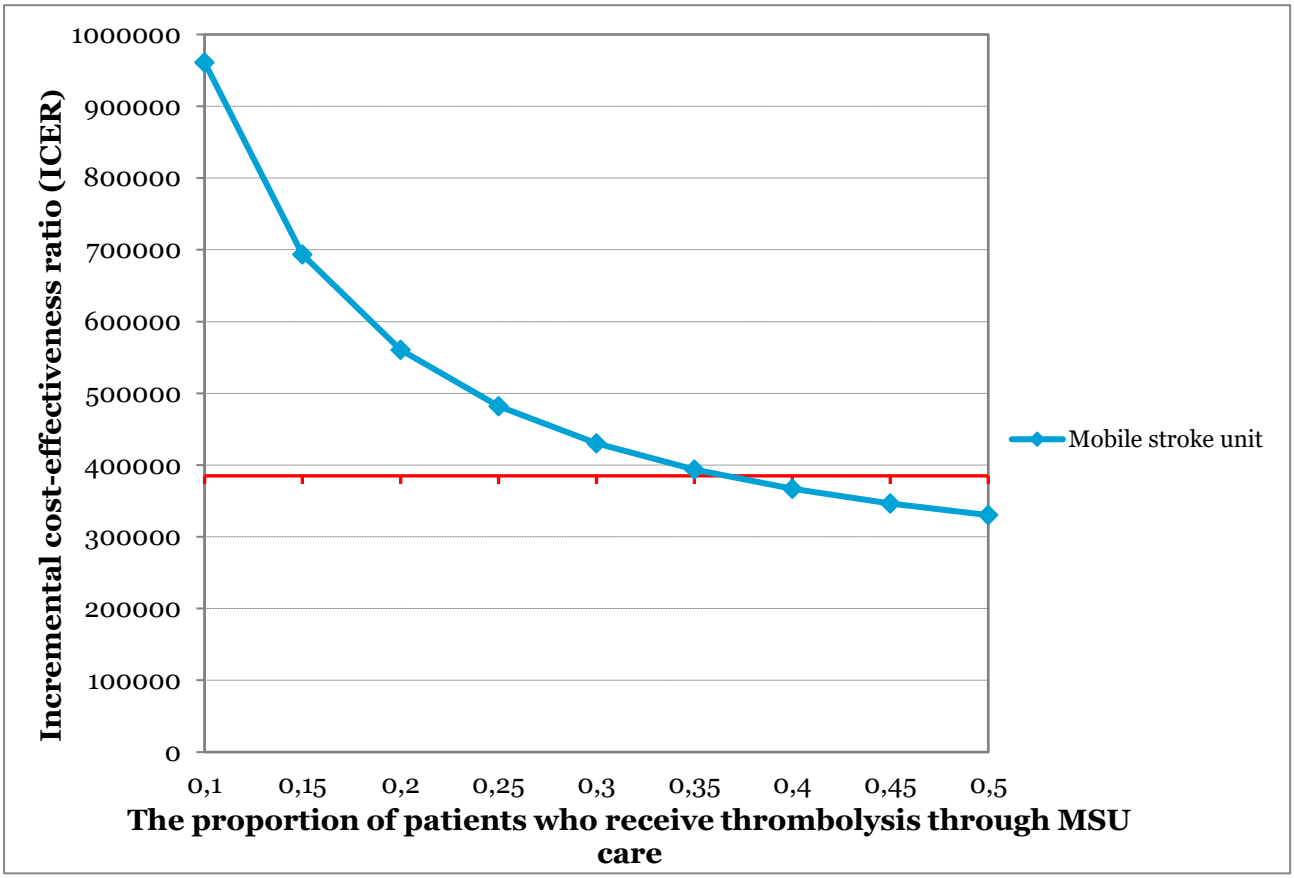


Figure 14. *Expected incremental cost-effectiveness ratios (ICERs) at different values of patient proportions receiving thrombolysis through MSU care. The red line illustrates an ICER of 385,000 Norwegian kroner per QALY. ICER values are expressed in Norwegian kroner (NOK).*

Sensitivity cost- and threshold analysis

Assuming that the MSU costs decrease by 25% (to 4,812,000 Norwegian kroner), the required proportion of patients receiving thrombolysis who have to receive this treatment through MSU care would be between 25 and 30%, in order to achieve an incremental cost-effectiveness ratio of 385,000 Norwegian kroner. 25-30% corresponds to 96-119 patients (Table 22 and Figure 15).

Table 22. *Expected incremental costs, -QALY and -cost-effectiveness ratios (ICERs) at different values of patient proportions that receive thrombolysis through MSU care, if the cost of an MSU decreases by 25%.*

Proportion of patients that receive thrombolysis through MSU care*	Number of patients that receive thrombolysis through MSU care* (based on 306 patients)	Incremental cost (NOK**)	Incremental QALY-gain	ICER (NOK** per QALY)
10%	34	200,123	0.3	776,347
15%	53	148,327	0. 3	575,410
20%	73	122,687	0. 3	475,946
25%	96	107,486	0. 3	416,975
30%	119	97,486	0. 3	378,182
35%	145	90,446	0. 3	350,870
40%	171	85,246	0. 3	330,697
45%	200	81,265	0. 3	315,254
50%	230	78,132	0. 3	303,100

*MSU: mobile stroke unit. **NOK: Norwegian kroner. The ICERs (expressed in Norwegian kroner) are calculated based on the fact that one mobile stroke unit has an annual cost of 4,812,000 Norwegian kroner (decreased by 25%).

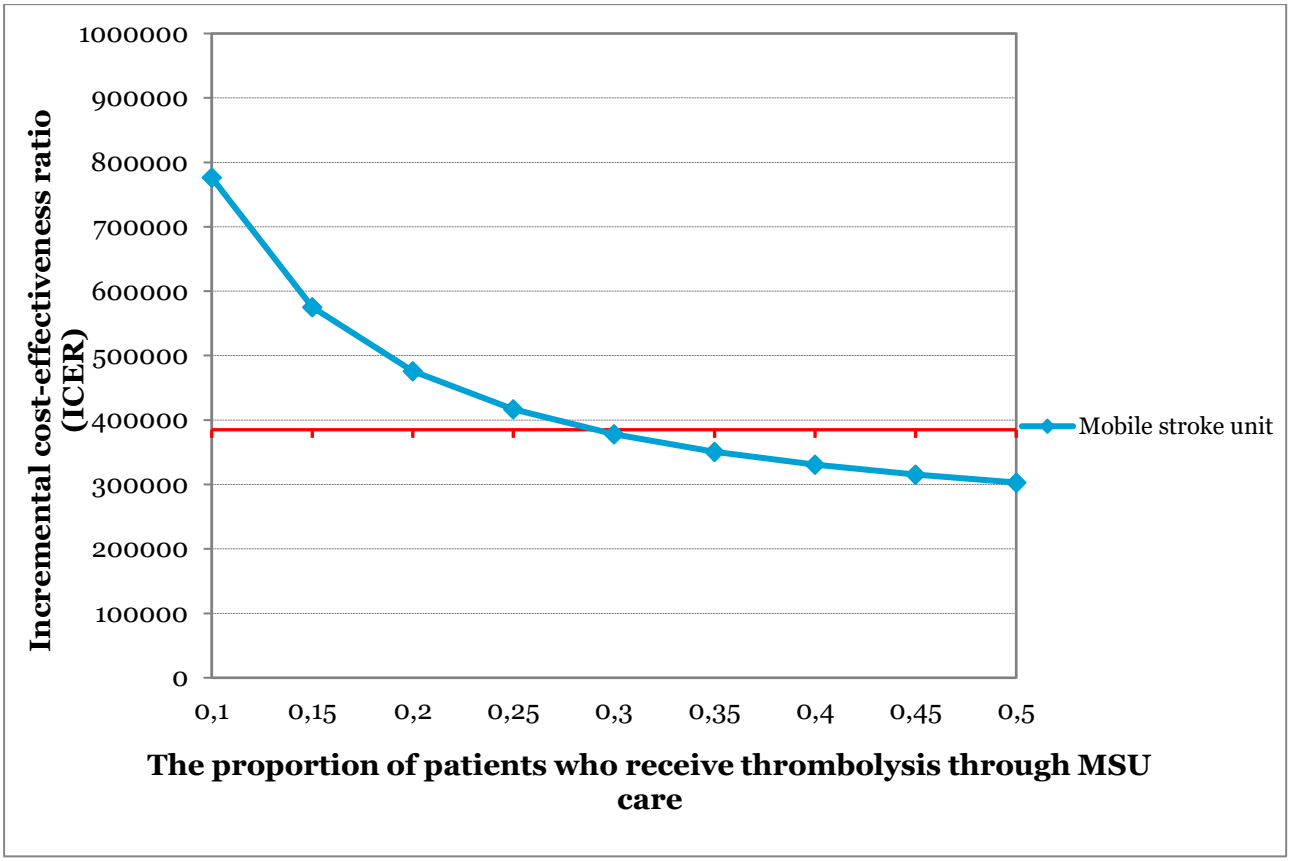


Figure 15. *Expected incremental cost-effectiveness ratios (ICERs) at different values of patient proportions that receive thrombolysis through MSU care, if the cost of an MSU decreases by 25%. The red line illustrates an ICER of 385,000 Norwegian kroner per QALY. ICER values are expressed in Norwegian kroner (NOK).*

If MSU costs increase by 25% (to 8,021,000 Norwegian kroner) the required proportion of patients receving thrombolysis who have to receive this treatment through MSU care would be between 40 and 45% in order to achieve an incremental cost-effectiveness ratio of 385,000 Norwegian kroner. 40-45% corresponds to 171-200 patients (Table 23 and Figure 16).

Table 23. *Expected incremental costs, -QALY and -cost-effectiveness ratios (ICERs) at different values of patient proportions that receive thrombolysis through MSU care, if the cost of an MSU increases by 25%.*

Proportion of patients that receive thrombolysis through MSU care*	Number of patients that receive thrombolysis through MSU care* (based on 306 patients)	Incremental cost (NOK**)	Incremental QALY-gain	ICER (NOK** per QALY)
10%	34	295,459	0. 3	1,146,186
15%	53	209,121	0. 3	811,249
20%	73	166,383	0. 3	645,456
25%	96	141,044	0. 3	547,158
30%	119	124,376	0. 3	482,496

35%	145	112,640	0. 3	436,971
40%	171	103,972	0. 3	403,344
45%	200	97,337	0. 3	377,602
50%	230	92,114	0. 3	357,343

*MSU: mobile stroke unit. **NOK: Norwegian kroner. The ICERs (expressed in Norwegian kroner) are calculated based on the fact that one mobile stroke unit has an annual cost of 8,021,000 Norwegian kroner (increased by 25%).

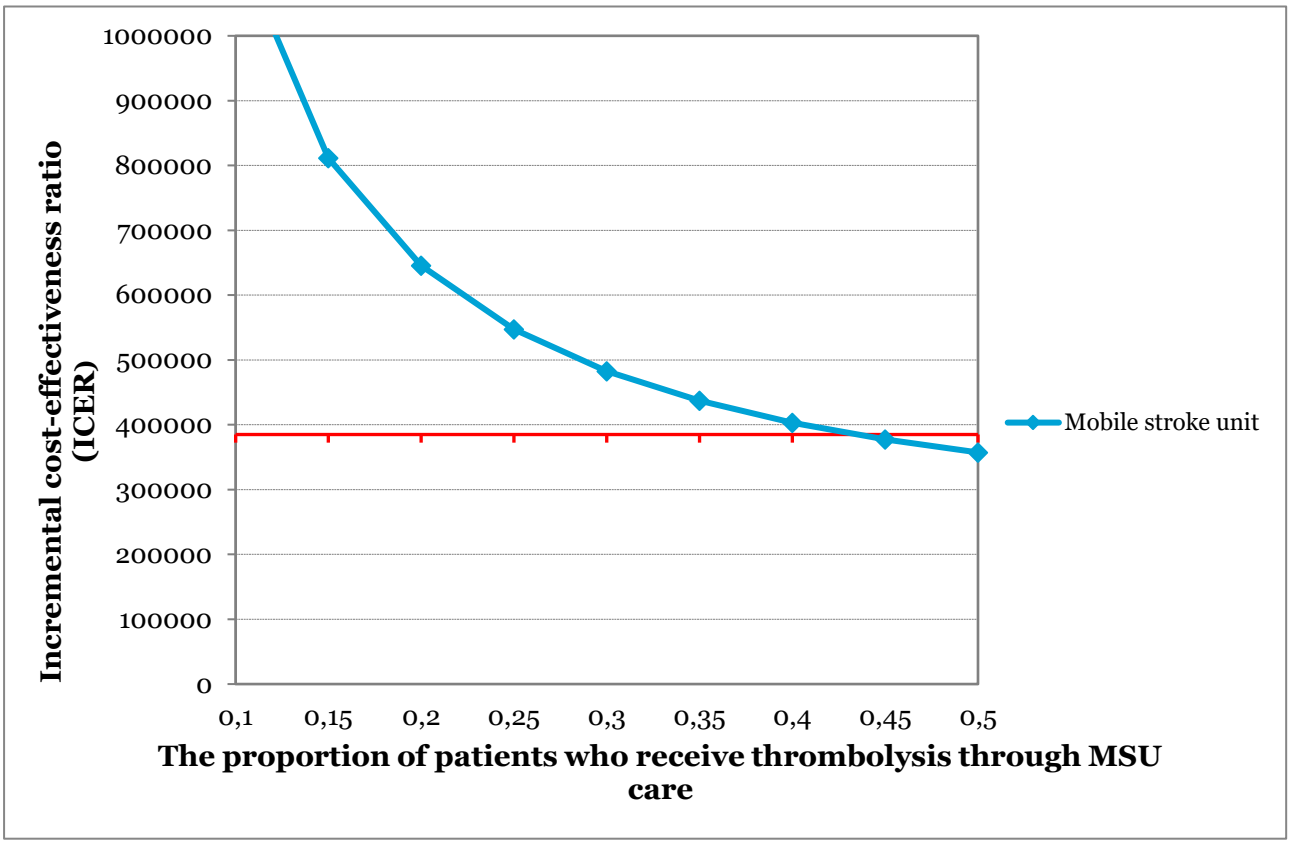


Figure 16. *Expected incremental cost-effectiveness ratios (ICERs) at different values of patient proportions that receive thrombolysis through MSU care, if the cost of an MSU increases by 25%. The red line illustrates an ICER of 385,000 Norwegian kroner per QALY. ICER values are expressed in Norwegian kroner (NOK).*

Discussion

Main findings and certainty of the evidence

Main results of the clinical effectiveness and safety and certainty of the evidence

In this HTA, we have systematically reviewed the literature on the clinical effectiveness and safety of prehospital CT for early diagnosis and potential prehospital treatment of suspected acute stroke or severe head injury, compared with conventional care. The evidence base comprised findings from two RCTs (59-63) and one observational registry study (64;65) from Germany, and one dosimetry study (66) from the U.S. Meta-analyses were conducted on four outcomes, including time (minutes) from alarm to imaging and from alarm to thrombolysis, time (minutes) from symptom onset to thrombolysis, and total number of patients who received thrombolysis. Due to the large number of included outcomes, only the eight outcomes that were considered to be main clinical outcomes, were graded (using the GRADE approach) to assess the certainty of the evidence (i.e. confidence we have in the effect estimates).

The results showed that MSU care reduced the time from alarm to imaging and from alarm to thrombolysis. The difference between MSU and conventional care in mean minutes from alarm to CT was approximately 27 minutes (95% CI -51 to -3) (low certainty of the evidence), and from alarm to thrombolysis was approximately 31 minutes (95% CI -43 to -18) (moderate certainty of the evidence) (60;62). Similarly, one of the RCTs (62), investigating time from symptom onset to imaging, detected a reduction in time, in favor of MSU (39 minutes difference in median, 95% CI IQR 26 to 52) (certainty of the evidence not graded). Meta-analysis on time from symptom onset to thrombolysis demonstrated no statistically significant difference between groups (-50 mean minutes, 95% CI -117 to 18) (low certainty of the evidence) (60;62). However, despite heterogenous effect estimates between the two RCTs included in the meta-analysis, the effect direction of the studies was the same, favoring MSU.

Due to the substantial heterogeneity among the studies, it is difficult to accurately estimate the effect size. Several factors may have contributed to this heterogeneity. For instance, the point in time of measurements varied somewhat between studies. Whereas Ebinger et al. (60) measured time from alarm to imaging, Walter et al. (62) measured time from alarm to end of CT. The limited number of studies, as well as differences in study settings and administrated interventions, may also have contributed to the variation in study results.

In addition, the use of means and standard deviations that have been estimated from medians and interquartile ranges reported by Walter et al. (62) have likely introduced some degree of error into the meta-analyses.

In total, 11% more patients received thrombolysis in the MSU group, compared to those who received conventional care (moderate certainty of the evidence) (60;62). Among patients who received thrombolysis, 31% of MSU patients were treated within 60 minutes (golden hour), whereas the proportion was 5.5% in conventional care (low certainty of the evidence) (59). Furthermore, MSU care reduced inadequate delivery of patients with ischemic stroke to a hospital without a stroke unit (by more than 60%), and of patients with intracranial hemorrhages to a hospital without neurosurgery department (by more than 70%) (certainty of the evidence not graded) (63).

No statistically significant differences between groups were detected in 1-day and 7-day functionality (certainty of the evidence not graded) (62). However, in the MSU group, a higher proportion of patients achieved 3-month mRS score 0-3, compared to the control group (low certainty of the evidence) (64;65). The results showed no statistically significant differences between groups in 90-day mortality (low certainty of the evidence) (60) or hemorrhagic complications (certainty of the evidence not graded) (60). Radiation exposure to MSU staff or to the public did not exceed established dose limits (66).

Reasons for downgrading the evidence to moderate or low included the risk of bias in the included studies, heterogenous effect estimates and large confidence interval.

We were not able to identify studies investigating the effectiveness of CT scanners localized in decentralized CT stations outside hospitals, or of prehospital CT in suspected severe head injuries.

Main results of the health economic evaluation

We performed an economic evaluation to explore the cost-effectiveness of MSU care compared to conventional care in a Norwegian setting, with the underlying assumption that the two are mutually exclusive. While this is clearly the case at the individual patient level, the assumption of mutual exclusiveness is less apparent at the population level in the catchment area of an ambulance service unit. In reality, the two modes of transportation and treatment will work in parallel, and the choice between an MSU and a regular ambulance will depend on availability, strength of symptoms, distance and other factors. In our model, these aspects are captured and controlled by the key parameter “proportion of patients who receive thrombolysis through MSU care”.

Due to lack of Norwegian data to inform key parameters like the distribution of patients between the two alternatives, we chose to undertake a cost- and threshold analysis. This study identified the premises on which a mobile stroke intervention would be cost-effective using different assumptions about the proportion of patients receiving the intervention.

Based on the model, we calculated the absolute shortfall to be 5.5 QALYs. There is no official cost-effectiveness threshold for health care interventions in Norway. Similarly, there is no official weighting function for severity. It is worth mentioning, however, that the proposal by the Magnussen Working Group implies a cost-effectiveness threshold of 385,000 Norwegian kroner per QALY at this level of absolute shortfall (80;81). Our cost- and threshold analysis shows that if 35 to 40% (or in absolute numbers, 145-171 per MSU) thrombolysis patients per year would receive this treatment through MSU care, the expected incremental cost per QALY would be 385,000 Norwegian kroner. The incremental health gain per patient is estimated to be 0.3 QALY compared to conventional ambulance and care.

For one MSU, the additional cost per year will be approximately 6.4 million Norwegian kroner. This estimate is based on unpublished data from an ongoing research project on MSU in the Østfold district. We did not estimate budget impact because of a lack of data and uncertainty about the effect some factors would have on costs. For example, costs are likely to increase in the short term for the specialist health services because of the cost of the MSU and the likelihood that the intervention will lead to more patients receiving thrombolysis. However, we could also assume that MSU care will shorten time to treatment for a proportion of patients, which could improve the patient's prognosis and reduce costs for rehabilitation and long-term care, especially in the community health services. Parameters where the uncertainty is particularly large include the proportion of patients that will receive thrombolysis through MSU care and through conventional care, the total number of new treated patients, MSUs versus stationary CT machines, as well as uncertainty about how the MSU-concept would be organised, if introduced into routine practice. The integration of MSU care with other air or road based ambulance services is also unclear.

The calculation of absolute shortfall is based on life expectancy and prognosis for patients receiving the current standard acute ischemic stroke care in the form of intravenous thrombolysis. These patients represent merely 20% of all ischemic stroke patients in Norway. It can be argued that for patients who, for various reasons, do not reach the hospital for acute treatment in time (but could potentially benefit from MSU care), the prognosis is worse, the absolute shortfall greater, and consequently, the severity class and acceptable willingness-to-pay threshold – higher. Calculating a separate absolute shortfall for this subgroup of patients and relcalculating a weighted shortfall for the total number of patients that can potentially benefit from MSU care, is methodologically challenging, as we do not know how many patients would reach thrombolysis in time if an MSU were available. Our calculated absolute shortfall and corresponding cost-effectiveness threshold are therefore potentially conservative.

We performed a one-way sensitivity analysis for the MSU cost parameter to investigate the impact of this parameter on the required proportion of patients receiving MSU care needed to achieve an ICER of 385,000 Norwegian kroner. Our sensitivity analysis showed that if the MSU cost decreased by 25%, an ICER of 385,000 Norwegian kroner per QALY could be achieved with a smaller proportion of patients receiving thrombo-

lysis through MSU care (Table 22). Assuming the MSU cost increased by 25%, an increase in the proportion of patients receiving thrombolysis through MSU care would be required to maintain the ICER of 385,000 Norwegian kroner per QALY (Table 23).

Based on evidence, we assumed that if more patients receive thrombolysis through MSU care, the total number of patients who receive thrombolysis increases correspondingly. Because MSU care could be introduced in addition to, and not at the expense of, conventional care, the development of prehospital acute stroke assessment should result in more patients treated in the essential time window (37). According to our results, MSU is not a cost-saving intervention, but rather lifesaving, as mortality decreases, and more patients end up in the dependent state, which is more expensive for the society as a whole (Table 16 and Figure 13). This is in accordance with the efficacy data from Kunz et al. 2016 (64), although the dependency following stroke was defined differently in the Kunz study (mRS 2-5 and not mRS 3-5, as in our model).

Certainty of the economic evaluation

Generalizability of our results needs to be confirmed in other settings. There is some uncertainty around the data used in our model, mainly related to the efficacy data. The efficacy data used in our economic model is taken from the German registry-based study of Kunz and colleagues (64). These data on 90-day functional outcomes of intravenous thrombolysis through MSU care were only available from Berlin. We assumed that the study effect could be to some extent transferrable to metropolitan areas of Norway, such as Oslo. Although we consider it reasonable to assume that the demography and biological characteristics of the study population is comparable to the Norwegian population, the transferability of results from this study to less urban Norwegian contexts is possibly the greatest limitation to its usefulness in support of decision-making.

In the Berlin-study, the MSU operated within a radius of a 16-minute journey from the MSU base, which results in a catchment area of about 1.3 million inhabitants. This is similar to our assumption about a catchment area of 1.1 million inhabitants. The exact impact of the introduction of an MSU in a specific setting will depend upon many factors, including, for example, geography, population density, local EMS protocols, hospital relationships, infrastructure and climate. Factors with substantial impact in Norwegian settings are distances, population density, topography, urbanization level and weather conditions. Norway has large areas with mountains and forest, which makes decisions about the best logistics for any hospital transport a challenge. Depending on where the patient is located geographically, different logistic options will be available, but prehospital models solely dedicated to acute stroke care and run by in-hospital specialists may be difficult to implement in rural areas. In some rural areas in Norway the use of air ambulance is essential for providing these services, and may be used independently of an introduction of MSU care in Norway.

In Norway, a health policy goal is to ensure that equal healthcare is offered to the entire population, which includes similar access to both emergency medical services and specialized treatment services regardless of place of residence. It is uncertain how many

patients currently miss the time window for thrombolysis, but who would be able to receive the treatment thanks to the earlier diagnosis through MSU care. This issue is particularly relevant outside metropolitan areas, where longer travel times to hospitals with stroke units are the norm. The efficacy data we had only allowed for a general assessment of the intervention that is valid for metropolitan areas, but not other parts of Norway. MSUs may have great potential in both urban and rural settings, but it is difficult to evaluate how including rural areas in our analysis would affect the results. Patients in regions with long travel times may benefit more from time saving than those in urban areas, with potentially higher health gains per patient. However, the per-patient costs of the intervention could also increase significantly. In areas, with even longer distances to the nearest appropriate hospital, neither MSU nor regular ambulance may be feasible, and air ambulance might be required to improve stroke outcomes.

There are some limitations related to registry-based studies, and lack of statistical significance for the primary outcome in the study that informed our model with efficacy data. In view of the limitations, further large-scale randomized trials are needed, to accumulate evidence of improvement in outcomes associated with prehospital stroke care (64). Our HTA could not identify any RCTs designed specifically to measure functional outcomes at 90-days on the mRS-scale. Ideally, data from Norwegian stroke-registry or Norwegian cohort studies should be used in the model, including information about travel distance and response times.

Strengths and weaknesses

Strengths and limitations of the review process

A strength of this HTA is its broad scope and inclusion criteria. We attempted to find and include research studies covering acute stroke and head trauma, mobile and stationary prehospital CT options, and a wide range of outcome measures.
Another strength of the review process was the use of two independent reviewers in the study selection process, data extraction, critical appraisal, and data analysis. This was to ensure that no unintentional errors or subjective assessments were introduced into this HTA. Furthermore, peer review of search strategies was conducted to detect any unintentional errors in search strategies, and to ensure comprehensiveness of searches.

A possible limitation of the review process is connected to the updated searches conducted in December 2018. Even though comprehensive searches in several databases, as well as searches for unpublished studies, were performed in December 2017 and February 2018, updated searches were only performed in two larger databases, CENTRAL (Cochrane Central Register of Controlled Trials) and MEDLINE. This may potentially have caused relevant newly published studies to be missed at the search stage. However, because none of the ongoing studies, which we had identified in clinical trials registries, had been finalized by the end of 2018, we are fairly sure that the evidence base in this HTA is complete.

Strengths and limitations of the health economic model

One of the strengths in this analysis is that we used a probabilistic Markov-model which is considered the appropriate approach to simulate the natural history of stroke. This economic model was previously used in a high-quality, published HTA report (89). The model structure and some assumptions have been revised to reflect MSU care as the intervention rather than thrombectomy. Further, the data is adapted to be relevant for a Norwegian setting based on Norwegian clinical practice. While the cost information is fairly comprehensive, there is an apparent paucity of effect data relevant for a Norwegian context. This is the reason for our choice to perform a cost- and threshold analysis instead of a regular cost-effectiveness analysis.

Due to the nature of the analysis (threshold analysis) and for the sake of simplicity we decided to run the analysis in deterministic mode. Although all parameters are characterized by a degree of uncertainty, we have chosen to only address uncertainty in the MSU cost parameter and in the proportion of patients receiving thrombolysis through MSU care.

We have assumed that 306 patients receive thrombolysis in the Oslo-area (8). The main reason that patients miss the narrow time window for thrombolysis treatment is that they arrive at the hospital too late (62). The time factor covers both time from symptom onset to alarm (patient delay) and response to alarm, transportation time and logistics (transportation delay) (35). The largest delay is often caused by late alarm, which is beyond the control of the emergency services. We do not know the exact potential of an MSU operating in the Oslo area to reduce time-to-treatment. We varied the proportion of patients that receive thrombolysis through MSU care between 10% and 50%. Because we do not know how many patients actually can be transported using one MSU per year, it is unclear whether there will be a need for additional MSUs. The introduction of MSU could lead to greater accessibility in the regular ambulance services, if the MSU can also be used for patients with less acute conditions. While this might allow for expanded ambulance services in general, it might result in a higher likelihood that the MSU is unavailable when needed for a stroke patient, which can give a greater likelihood of simultaneous requirements occurring (97).

Another assumption in our analysis is that patients entering the Markov-model have an initial age of 70 years, in accordance with the mean age in the study by Kunz and coworkers (64). The mean age in Norway for patients with stroke was 74 years in 2017 (8). Patient age is an important factor, especially in analyses with long time perspective, impacting both costs and health outcomes (89), but without Norway specific efficacy data it is difficult to know whether the difference in average age at time of stroke would have a major impact on our results.

The MSU described in the registry-based study conducted by Kunz et al. is largely comparable to the description of the MSU used for research in Østfold (64;91). An important aspect of MSU care is telecommunication between the unit and hospital, and staffing. In the Norwegian model “Norwegian Acute Stroke Prehospital Project”

(NASPP), the MSU was staffed with prehospital personnel from the Norwegian helicopter emergency medical service (HEMS) and Hov et al. demonstrated that anesthesiologists trained in prehospital critical care could perform acute stroke diagnostics (cerebral CT and clinical assessment) with high level of agreement compared to in-hospital specialists outcome (36;37;98).

We base the costing for an MSU on information from an ongoing research project in Østfold (58). This cost information was adjusted from a trial situation to a more realistic scale up scenario and are not peer reviewed or published. But since the intervention has not yet actually been implemented in Norway, and since there are unclarities regarding the organization set-up, there are still some uncertainties around the estimates. In addition, unit prices which amount to the total MSU cost could be negotiated in a potential introduction, adding to the uncertainty. Finally, we have used DRG code 14A as cost of thrombolysis in both the intervention and comparator arms. This approach may double count some cost items in the MSU arm.

We conducted the analysis from a health care perspective. Stroke has high health related and economic consequences both for the patient and the society as a whole. The societal costs will most likely increase in the coming years as a result of the changed age composition in the population (99).

Our model did not consider routes other than MSU and conventional ambulance for coming to hospital (i.e. physician referral, inpatient, walk into emergency department, and transfer from other hospitals). We have also not accounted for the possibility that MSU care could lead to better resource utilization by reducing unnecessary transportation, and unnecessary admissions and examinations in the hospital. Further, we only assessed prehospital treatment of ischemic stroke in our economic analysis, and excluded other indications such as hemorrhagic stroke and head injuries due to the lack of data. Subarachnoid haemorrhage is associated with higher mortality in the acute phase than other types of stroke. However, prehospital identification of subarachnoid haemorrhage in MSUs may benefit the patients by faster triage and direct transport to a neurosurgery centre. Haemorrhage enlargement occurs very early in the course of intracerebral haemorrhage, and the “time is brain” concept also applies to this type of stroke. MSU as an intervention may rapidly establish a diagnosis and select patients in need of neurosurgical care, which can significantly reduce time to treatment and give positive outcome (36). Other indications, such as hemorrhagic stroke and head injuries, may benefit from the intervention and costs could be allocated between different indications. In sum, these unaccounted factors tend to indicate that our cost-effectiveness considerations are conservative.

An alternative to MSU care could be to set up CT stations outside of hospitals, for example, localized in decentralized district medical centres. It was outside the scope of this study to consider this alternative, but it could be included in a more comprehensive evaluation at a later stage should the question become policy relevant.

Comparison with other studies

Consistency of the economic evaluation with other studies

We do not know of any Norwegian-based economic evaluations on MSU care and there is little transferability of the existing studies to Norway (they were conducted mainly in big cities in Germany). We have identified two studies from other countries which have examined the costs and cost-effectiveness of MSU compared to conventional care. However, we do not know any cost-effectiveness studies with outcome measured on the mRS-scale as we have done in this report. Gyrd-Hansen et al. (2015) did conduct a cost-effectiveness estimate of prehospital thrombolysis which shows that estimated annual net cost of an MSU was 9.34 million Norwegian kroner and the calculated incremental cost-effectiveness ratio (ICER) was equal to 314,450 Norwegian kroner per QALY (86). These results are similar to our results when the proportion of patients who receive thrombolysis through MSU care is around 50%.

Applicability of the findings and implications for practice

Based on the findings presented in this HTA, MSU care probably shortens the time to imaging and treatment, and results in higher frequency of thrombolysis administration. We assume that the effectiveness of MSU care could be to some extent transferrable to metropolitan areas of Norway. However, the degree to which these outcomes can be achieved depends on several context-specific factors. The MSU concept is complex and requires local adaptations of processes and workflow (100). A close cooperation with the local in-hospital stroke team(s) and the prehospital EMS is essential to ensure rapid care and continuity of patient management (100;101). In one of the included RCTs (60), in cases where a regular ambulance reached the emergency site before the MSU, 19% of MSU inquiries were cancelled based on the assessment done by the ambulance staff. Thus, close collaboration between MSU and regular ambulances is likely to be needed. Given telemedicine is used for interpretation of CT images and treatment decision-making, it is important to establish streamlined processes to avoid delays (102).

The demand for competence is essential in the radiation protection regulations. The requirement will only be open for dispensation if it affects the undertaking unreasonably, and is issued with great caution. This matter must be taken into consideration in planning for routine use of MSU in Norway. If changes to the organisation of tasks are required, the personnel competence, especially in radiology and radiography, must be risk evaluated. If the CT operator has a different background than radiography, he or she must be trained in radiation protection, correct handling of the scanner and other radiography related subjects. The different tasks must be well defined and limited in extent (41;103). It can be argued that this is the case for MSUs, where one can establish a strict set of CT protocols only for use on stroke patients. The same can be argued in case of trauma, the protocols can be pre-defined and limited to a defined group of patients.

The physical location of the CT operator varies in different MSU programs. If the CT operator on the MSU cannot stand behind a screen, the dose per scan to the CT operator will probably be slightly higher than the dose to a radiographer working in a shielded control room. Dose levels have been studied by Gutierrez et al. (66) and were found to be comparable to dose levels for exposed workers in a high volume hospital setting (1,5 mSv/year) and are reduced by shielding material (curtains and aprons). The dose levels are also in line with Norwegian levels, and will be far below dose limits for occupational exposure (41). When using the protective measures such as distance and shielding in an optimal way, the dose to the worker will not be of any concern. Due to the random nature of the ambulance location, the dose to the public will be far below the dose limits given in the radiation protection regulations (41).

To ensure that equal healthcare is offered to the entire population in Norway, different options may need to be considered in rural and remote areas. A current project in Edmonton, Canada, pilots an MSU program in a rural setting, with a catchment area within a 250 km radius of a university hospital. The program comprises "a rendezvous model" where the MSU travels to meet the incoming ambulance (104). Moreover, one of the ongoing studies we have identified (56) seeks to investigate the effect of MSU for delivery of specialized acute stroke care to patients in remote areas. Establishment of CT stations outside hospitals, such as the CT scanner placed in the district medical center in Ål (40), is another alternative to consider. However, robust studies are needed to determine the effectiveness of this option.

Lastly, it must be emphazised that prehospital CT for early diagnosis, and subsequent treatment, represents a supplementary tool to increase the efficiency of stroke management. It cannot replace any other efforts to improve intrahospital and prehospital stroke management (101). In Norway, the dispatch guidelines (index) used by the EMCCs are known to identify just over half of the acute stroke patient population at dispatch (77). This in turn may lead to transportation delay. Moreover, the period before contact with EMCC is important and will not be directly affected by the MSU strategy. A recently published Norwegian registry study (77) showed that the emergency line 113 was the initial EMCC access point for less than half of the stroke patients. Thus, it is crucial to increase public awareness of stroke symptoms.

Future research

Robust evidence (RCTs) is needed to determine the effectiveness of MSUs and CT stations for early diagnosis and treatment of stroke patients in rural and remote areas. Furthermore, randomized studies are required to determine effectiveness of prehospital CT for patients suspected severe head trauma. The feasibility and effect of using CTA in the MSU to identify and triage stroke patients with large vessel occlusion, could also be explored.

An ongoing prospective controlled intervention study on MSU care is currently taking place in Østfold, Norway. The estimated time of completion is May 2021 (58). There is

also an ongoing observational study at Vestre Viken Hospital Trust on rural CT examination and thrombolytic treatment for stroke (CT station in Ål). The estimated time of completion is April 2021 (40).

Conclusion

In acute stroke, prehospital CT in the form of an ambulance equipped with a CT scanner (MSU) probably reduces the time from a patient's first contact with the emergency dispatch center to thrombolysis, and increases the number of patients who receive thrombolysis. Among those who receive thrombolysis, MSU patients may be more than five times as likely to receive thrombolysis within 60 minutes (golden hour), than those who receive conventional hospital-based care. MSU care may also lead to reduced time from a patient's first contact with the emergency dispatch center to CT imaging. Furthermore, compared to conventional care, MSU care seems to improve triage of patients with stroke to specialized hospitals, and increase the proportion of patients with 3-month mRS score 0-3. A difference in 90-day mortality seems unlikely.

The present health economic analysis examined how the level of utilization of MSU (proportions of patients who would have to receive thrombolysis through MSU care) impacts cost-effectiveness ratio for this intervention compared with conventional care. The annual cost of one MSU is estimated to be approximately 6.4 million Norwegian kroner. The simulation of the health economic model resulted in a quality-adjusted life-year (QALY) gain of 0.3 per patient that received thrombolysis through MSU care compared with conventional care. We estimated an absolute shortfall of 5.5 QALYs. The expected cost per QALY is approximately 385,000 Norwegian kroner or lower, when a minimum of 35-40% (or, 145-171 per MSU) patients that receive thrombolysis per year would receive this treatment through MSU care. We assume that the efficacy results are transferable to metropolitan areas in Norway. Decision makers must consider whether they think it is plausible that a minimum of 35-40% patients could receive the prehospital intervention.

Due to the lack of evidence, the effectiveness of decentralized CT stations outside hospitals and of prehospital CT in suspected severe head injuries is unknown.

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Appendices

Appendix 1. Differences between project plan and assessment

Modification	Reason(s) for modification
Language of the HTA	We decided to write the HTA in English (i.e. not in Norwegian), as the assessment is likely to be of interest also internationally.
Inclusion criteria – study design: Cut-off (≥100 patients) for prospective case series and registry data was introduced	We considered case series and registry data with less than 100 patients to provide little valuable information on clinical effectiveness and safety.
Inclusion criteria – study design: "Studies measuring radiation exposure (dosimetry studies)" was added to the list of study designs	To include uncontrolled studies measuring radiation exposure to patients, MSU staff and the public (one of the included outcomes).
One exclusion criterion was introduced: Given two or more types of studies, covering the same outcome(s) were identified, the study design placed highest in the hierarchy of evidence was chosen for inclusion.	To present study results from types of studies which were least prone to bias for clinical effectiveness.
Not all included studies were assessed for risk of bias	Risk of bias assessment was limited to controlled clinical studies. We did not assess the risk of bias of the included dosimetry study, because this is a preliminary safety study related to an ongoing study.
Not all outcomes were graded (with GRADE)	Due to the large number of included outcomes, only those outcomes considered primary clinical outcomes were graded.

Appendix 2. Search strategies

1. Searches for systematic reviews and HTAs

Information specialist: Elisabet Hafstad

Database (provider) Search date: 25.09.2017	Number of hits
Cochrane Database of Systematic Reviews: Issue 9 of 12, September 2017 (Wiley)	3
Database of Abstracts of Reviews of Effect (DARE): Issue 2 of 4, April 2015 (Wiley)	14
HTA database: Issue 4 of 4, October 2016 (Wiley)	3
Epistemonikos	Broad Synthesis: 2 Structured Summary: 1 Systematic Review: 55
Embase 1974 to 2017 September 22 (Ovid)	86*
MEDLINE (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>)	452*
Total number of hits	**616**
Total number of hits after removal of duplicates	**336**

* After having removed duplicates in Ovid

Cochrane Database of Systematic Reviews

#1 ((([mh "Diagnostic Imaging"]) OR (imaging OR neuroimaging OR tomograph* OR microtomograph* OR echotomograph* OR angiograph* OR radiograph* OR ultrasonograph* OR sonograph* OR (diagnos* NEAR/2 ultraso*) OR MDCT OR ((CT OR CAT OR microCT OR PET) NEAR/3 (cine OR scan* OR x-ray* OR xray*))):ab,kw,ti) AND ((([mh ambulances] OR [mh ^"transportation of patients"]) OR (paramedic* OR ambulance* OR (emergency NEAR/3 (mobile OR vehicle* OR car OR cars OR transport*)) OR prehospital OR pre-hospital OR out-of-hospital OR helicopter* OR aeromedical OR ((patient* OR air) NEAR/3 transport*)):ab,kw,ti))

#2 ((([mh Stroke]) AND ([mh Ambulances])) OR (((stroke OR telestroke) NEAR/3 (mobile* OR ambulance*)) OR STEMO):ab,kw,ti)

#3 #1 OR #2

Database of Abstracts of Reviews of Effect (DARE); HTA database

#1 (((([mh "diagnostic imaging"]) OR (imaging OR neuroimaging OR tomograph* OR microtomograph* OR echotomograph* OR angiograph* OR radiograph* OR ultrasonograph* OR sonograph* OR (diagnos* NEAR/2 ultraso*) OR MDCT OR ((CT OR CAT OR microCT OR PET) NEAR/3 (cine OR scan* OR x-ray* OR xray*)))) AND (([mh ambulances] OR [mh ^"transportation of patients"]) OR (paramedic* OR ambulance* OR (emergency NEAR/3 (mobile OR vehicle* OR car OR cars OR transport*)) OR prehospital OR pre-hospital OR out-of-hospital OR helicopter* OR aeromedical OR ((patient* OR air) NEAR/3 transport*)))))

#2 ((([mh Stroke]) AND ([mh Ambulances])) OR (((stroke OR telestroke) NEAR/3 (mobile* OR ambulance*)) OR STEMO))

#3 #1 OR #2

Epistemonikos

[Title/Abstract] (((imaging OR neuroimaging OR tomograph* OR microtomograph* OR echotomograph* OR angiograph* OR radiograph* OR ultrasonograph* OR sonograph* OR (diagnos* AND ultraso*) OR MDCT OR ((CT OR CAT OR microCT OR PET) AND (cine OR scan* OR "x-ray" OR xray*))) AND (paramedic* OR ambulance* OR (emergency AND (mobile OR vehicle* OR car OR cars OR transport*)) OR prehospital OR pre-hospital OR "out-of-hospital" OR "out of hospital" OR helicopter* OR aeromedical OR ((patient* OR air) AND transport*))))

OR

[Title/Abstract] ("stroke ambulance" OR "mobile stroke unit" OR "mobile acute stroke unit" OR "mobile stroke treatment unit" OR "stroke emergency mobile" OR "mobile telestroke" OR STEMO))

Embase

1. ((((exp radiodiagnosis/) OR (imaging OR neuroimaging OR tomograph* OR microtomograph* OR echotomograph* OR angiograph* OR radiograph* OR ultrasonograph* OR sonograph* OR (diagnos* ADJ2 ultraso*) OR MDCT OR ((CT OR CAT OR microCT OR PET) ADJ3 (cine OR scan* OR x-ray* OR xray*))).tw,kw) AND ((exp ambulance/ OR air medical transport/) OR (paramedic* OR ambulance* OR (emergency adj3 (mobile OR vehicle* OR car OR cars OR transport*)) OR prehospital OR pre-hospital OR out-of-hospital OR helicopter* OR aeromedical OR ((patient* OR air) ADJ3 transport*)).tw,kw))) use oemezd
2. (((exp cerebrovascular accident/) AND (ambulance/ OR ambulance transportation/)) OR (((stroke OR telestroke) ADJ3 (mobile* OR ambulance*)) OR STEMO).tw,kw) use oemezd
3. ((systematic review/ OR meta analysis/) OR (((systematic* OR evidence OR research OR literature OR umbrella) ADJ3 (review* OR overview* OR synthes*)) OR meta-analys* OR metaanalys* OR technology assessment* OR HTA OR pubmed OR medline OR handsearch*).tw,kw) use oemezd

4. (conference abstract OR conference paper OR conference review).pt use oemezd
5. ((1 or 2) and 3) not 4

MEDLINE

1. ((((exp diagnostic imaging/) OR (imaging OR neuroimaging OR tomograph* OR microtomograph* OR echotomograph* OR angiograph* OR radiograph* OR ultrasonograph* OR sonograph* OR (diagnos* ADJ2 ultraso*) OR MDCT OR ((CT OR CAT OR microCT OR PET) ADJ3 (cine OR scan* OR x-ray* OR xray*))).tw,kw) AND ((exp ambulances/ OR "transportation of patients"/) OR (paramedic* OR ambulance* OR (emergency adj3 (mobile OR vehicle* OR car OR cars OR transport*)) OR prehospital OR pre-hospital OR out-of-hospital OR helicopter* OR aeromedical OR ((patient* OR air) ADJ3 transport*)).tw,kw))) use ppez
2. (((exp Stroke/) AND (exp Ambulances/)) OR (((stroke OR telestroke) ADJ3 (mobile* OR ambulance*)) OR STEMO).tw,kf) use ppez
3. ((meta-analysis.pt. OR review.pt. OR review literature as topic/ OR meta-analysis as topic/ OR technology assessment, biomedical/) OR (((systematic* OR evidence OR research OR literature OR umbrella) ADJ3 (review* OR overview* OR synthes*)) OR meta-analys* OR metaanalys* OR metanalys* OR technology assessment* OR HTA OR pubmed OR medline OR handsearch*).tw,kw) use ppez
4. (1 or 2) and 3

2. Searches for published and ongoing primary studies

Information specialist: Elisabet Hafstad

Database (provider) Search date: 15.12.2017	**Number of hits**
CINAHL (EBSCO)	70
CENTRAL (Cochrane Central Register of Controlled Trials): Issue 12 of 12, December 2017 (Wiley)	110
Embase 1974 to 2017 December 13 (Ovid)	1676*
MEDLINE (Epub Ahead of Print, In-Process & Other Non Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>)	429*
NHS Economic Evaluation Database: Issue 2 of 4, April 2015 (Wiley)	1
PubMed – limited to (pubmednotmedline[sb] or publisher[sb]) to capture the latest publications that had not yet been included in Ovid MEDLINE at the time of the search	192
Web of Science	489
Total number of hits	**2967**

Total number of hits after removal of duplicates	**2375**

* After having removed duplicates in Ovid

Trials registers Search date: 15.02.2018	**Number of hits**
ClinicalTrials.gov (National Institutes of Health, U.S)	136
International Clinical Trials Registry Platform (WHO)	10
Total number of hits	**146**
Total number of hits after removal of duplicates	**137**

CINAHL

Set	Query
S32	S24 OR S25 OR (S26 AND S27 AND S28) OR (S29 AND S30 AND S31) Limiters - Published Date: 20100101-; Exclude MEDLINE records
S31	S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23
S30	S12 OR S13 OR S14 OR S15 OR S16
S29	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
S28	(MH "Ambulances") OR (MH "Emergency Medical Services") OR (MH "Transportation of Patients") OR (MH "Aeromedical Transport") OR (MH "Mobile Health Units")
S27	(MH "Tomography, X-Ray Computed") OR (MH "Computed Tomography Angiography") OR (MH "Tomography, Spiral Computed+") OR (MH "Stroke+/RA")
S26	(MH "Stroke+") OR (MH "Head Injuries") OR (MH "Brain Injuries+") OR (MH "Intracranial Hemorrhage+")
S25	TI STEMO OR AB STEMO
S24	TI (((stroke or telestroke) N2 (mobile* or ambulance*))) OR AB (((stroke or telestroke) N2 (mobile* or ambulance*)))
S23	TI (patient* N3 transport*) OR AB (patient* N3 transport*)
S22	TI (((emergency or "EMS") N2 (mobile* or transport* or site*))) OR AB (((emergency or "EMS") N2 (mobile* or transport* or site*)))
S21	TI ((paramedic* or emergency-medical-technician* or physician-staffed-EMS)) OR AB ((paramedic* or emergency-medical-technician* or physician-staffed-EMS))
S20	TI ((scene or en-route or on-site or on-board or onboard)) OR AB ((scene or en-route or on-site or on-board or onboard))

S19 TI ((helicopter* or HEMS or aeromedic* or aero-medic* or air-medical)) OR AB ((helicopter* or HEMS or aeromedic* or aero-medic* or air-medical))

S18 TI ((ambulance* or (rapid-response W0 (car* or vehicle*)) or MSU)) OR AB ((ambulance* or (rapid-response W0 (car* or vehicle*)) or MSU))

S17 TI ((prehospital or pre-hospital or out-of-hospital)) OR AB ((prehospital or pre-hospital or out-of-hospital))

S16 TI ((neuroimag* or neuroradio* or neuro-imag* or neuro-radio*)) OR AB ((neuroimag* or neuroradio* or neuro-imag* or neuro-radio*))

S15 TI ((telestroke or teleradiolog* or tele-stroke or tele-radiolog*)) OR AB ((tele-stroke or teleradiolog* or tele-stroke or tele-radiolog*))

S14 TI (("MDCT" or "CT" or "CAT" or "CTA" or "CTP")) OR AB (("MDCT" or "CT" or "CAT" or "CTA" or "CTP"))

S13 TI ((microtomograph* or microCT or micro-CT)) OR AB ((microtomograph* or microCT or micro-CT))

S12 ((tomograph* or tomodensitometr*)) OR AB ((tomograph* or tomodensi-tometr*))

S11 TI ((((head or brain or cerebrovascular or cerebro-vascular) N3 (injur* or trauma*)) or TBI)) OR AB ((((head or brain or cerebrovascular or cerebro-vas-cular) N3 (injur* or trauma*)) or TBI))

S10 TI ((((brain or cerebellar or cerebral or hemisphere* or brainstem or intracra-nial or intra-cranial or intracortical or intra-cortical or subarachnoid* or subdu-ral or intracerebral or intra-cerebral or intraventricular or intra-ventricular or periventricular or peri-ventricular) N2 (hemorrhage* or haemorrhage* or bleed* or microbleed* or hematoma* or haematoma*)) or SAH)) OR AB ((((brain or cerebellar or cerebral or hemisphere* or brainstem or intracranial or intra-cranial or intracortical or intra-cortical or subarachnoid* or subdural or intracerebral or intra-cerebral or intraventricular or intra-ventricular or periventricular or peri-ventricular) N2 (hemorrhage* or haemorrhage* or bleed* or microbleed* or hematoma* or haematoma*)) or SAH)))

S9 TI Heubner-infarct* OR AB Heubner-infarct*

S8 TI ((large-vessel-occlusion* or LVO or large-artery-occlusion*)) OR AB ((large-vessel-occlusion* or LVO or large-artery-occlusion*))

S7 TI (((vertebrobasilar or carotid) N2 (aneurysm* or occlu* or thrombo* or in-farct* or insult* or embol* or ischemi* or ischaemi*))) OR AB (((vertebrobasi-lar or carotid) N2 (aneurysm* or occlu* or thrombo* or infarct* or insult* or em-bol* or ischemi* or ischaemi*)))

S6 TI (((cerebral or brain* or cortical or subcortical or cortex or cerebellar or hem-isphere* or intracranial or intra-cranial) N2 (infarct* or insult* or attack* or is-chemi* or ischaemi* or embol* or thrombo* or occlu* or hypoxia))) OR AB (((cerebral or brain* or cortical or subcortical or cortex or cerebellar or hemi-sphere* or intracranial or intra-cranial) N2 (infarct* or insult* or attack* or is-chemi* or ischaemi* or embol* or thrombo* or occlu* or hypoxia)))

S5	TI ((CVA or ((cerebrovascular or cerebro-vascular or cerebral-vascular) N2 (accident* or event* or infarct* or insult* or occlu*)))) OR AB ((CVA or ((cerebrovascular or cerebro-vascular or cerebral-vascular) N2 (accident* or event* or infarct* or insult* or occlu*))))
S4	TI acute-cerebral-vasculopath* OR AB acute-cerebral-vasculopath*
S3	TI apoplex* OR AB apoplex*
S2	TI ((transient-ischemic-attack* or transient-ischaemic-attack* or TIA)) OR AB ((transient-ischemic-attack* or transient-ischaemic-attack* or TIA))
S1	TI stroke* OR AB stroke*

CENTRAL; NHS Economic Evaluation Database

Set	Query
#1	([mh Stroke] or [mh "Intracranial Hemorrhages"] or [mh "Brain Ischemia"] or [mh "Craniocerebral Trauma"])
#2	([mh "Tomography, X-Ray"] or [mh ^"Tomography Scanners, X-Ray Computed"] or [mh Stroke/dg])
#3	([mh Ambulances] or [mh ^"Emergency Medical Services"] or [mh ^"Mobile Health Units"] or [mh ^"Transportation of Patients"])
#4	stroke*
#5	transient-ischemic-attack* or transient-ischaemic-attack* or TIA
#6	apoplex*
#7	acute-cerebral-vasculopath*
#8	(CVA or ((cerebrovascular or cerebro-vascular or cerebral-vascular) near/3 (accident* or event* or infarct* or insult* or occlu*)))
#9	((cerebral or brain* or cortical or subcortical or cortex or cerebellar or hemisphere* or intracranial or intra-cranial) near/3 (infarct* or insult* or attack* or ischemi* or ischaemi* or embol* or thrombo* or occlu* or hypoxia))
#10	((vertebrobasilar or carotid) near/3 (aneurysm* or occlu* or thrombo* or infarct* or insult* or embol* or ischemi* or ischaemi*))
#11	(large-vessel-occlusion* or LVO or large-artery-occlusion*)
#12	Heubner-infarct*
#13	(((brain or cerebellar or cerebral or hemisphere* or brainstem or intracranial or intra-cranial or intracortical or intra-cortical or subarachnoid* or subdural or intracerebral or intra-cerebral or intraventricular or intra-ventricular or periventricular or peri-ventricular) near/3 (hemorrhage* or haemorrhage* or bleed* or microbleed* or hematoma* or haematoma*)) or SAH)

#14	(((head or brain or cerebrovascular or cerebro-vascular) near/4 (injur* or trauma*)) or TBI)
#15	(tomograph* or tomodensitometr*)
#16	(microtomograph* or microCT or micro-CT)
#17	(MDCT or CT or CAT or CTA or CTP)
#18	(telestroke or teleradiolog* or tele-stroke or tele-radiolog*)
#19	(neuroimag* or neuroradio* or neuro-imag* or neuro-radio*)
#20	(prehospital or pre-hospital or out-of-hospital)
#21	(ambulance* or (rapid-response next (car* or vehicle*)) or MSU)
#22	(helicopter* or HEMS or aeromedic* or aero-medic* or air-medical)
#23	(scene or en-route or on-site or on-board or onboard)
#24	(paramedic* or emergency-medical-technician* or physician-staffed-EMS)
#25	((emergency or EMS) near/3 (mobile* or transport* or site*))
#26	(patient* near/4 transport*)
#27	((stroke or telestroke) near/3 (mobile* or ambulance*))
#28	STEMO
#29	#1 and #2 and #3
#30	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#31	#15 or #16 or #17 or #18 or #19
#32	#20 or #21 or #22 or #23 or #24 or #25 or #26
#33	#30 and #31 and #32
#34	#27 or #28 or #29 or #33 Publication Year from 2010, in Trials and Economic Evaluations

Embase & MEDLINE

Set	Query
1	exp Stroke/ or exp Intracranial Hemorrhages/ or exp Brain Ischemia/ or exp Craniocerebral Trauma/ use ppez
2	exp Tomography, X-Ray/ or Tomography Scanners, X-Ray Computed/ or exp Stroke/dg use ppez
3	exp Ambulances/ or Emergency Medical Services/ or Mobile Health Units/ or Transportation of Patients/ use ppez

4	exp cerebrovascular accident/ or brain ischemia/ or exp brain infarction/ or transient ischemic attack/ or occlusive cerebrovascular disease/ or brain haemorrhage/ or exp brain hematoma/ or exp intracranial aneurysm/ or head injury/ use oemezd
5	computed tomography scanner/ or portable computed tomography scanner/ or exp computer assisted tomography/ use oemezd
6	ambulance/ or ambulance transportation/ or air medical transport/ or exp emergency health service/ or patient transport/ use oemezd
7	stroke*.tw,kw,kf.
8	(transient ischemic attack* or transient ischaemic attack* or TIA).tw,kw,kf.
9	apoplex*.tw,kw,kf.
10	acute cerebral vasculopath*.tw,kw,kf.
11	(CVA or ((cerebrovascular or cerebro-vascular or cerebral vascular) adj3 (accident* or event* or infarct* or insult* or occlu*))).tw,kw,kf.
12	((cerebral or brain* or cortical or subcortical or cortex or cerebellar or hemisphere* or intracranial or intra-cranial) adj3 (infarct* or insult* or attack* or ischemi* or ischaemi* or embol* or thrombo* or occlu* or hypoxia)).tw,kw,kf.
13	((vertebrobasilar or carotid or intracranial or intra-cranial) adj3 (aneurysm* or occlu* or thrombo* or infarct* or insult* or embol* or ischemi* or ischaemi*)).tw,kw,kf.
14	(large vessel occlusion* or LVO or large artery occlusion*).tw,kw,kf.
15	Heubner infarct*.tw,kw,kf.
16	(((brain or cerebellar or cerebral or hemisphere* or brainstem or intracranial or intra-cranial or intracortical or intra-cortical or subarachnoid* or subdural or intracerebral or intra-cerebral or intraventricular or intra-ventricular or periventricular or peri-ventricular) adj3 (hemorrhage* or haemorrhage* or bleed* or microbleed* or hematoma* or haematoma*)) or SAH).tw,kf,kw.
17	(((head or brain or cranial or cerebrovascular or cerebro-vascular) adj4 (injur* or trauma*)) or TBI).tw,kw,kf.
18	(tomograph* or tomodensitometr*).tw,kw,kf.
19	(microtomograph* or microCT or micro-CT).tw,kw,kf.
20	(MDCT or CT or CAT or CTA or CTP).tw,kw,kf.
21	(telestroke or teleradiolog* or tele-stroke or tele-radiolog*).tw,kw,kf.
22	(neuroimag* or neuroradio* or neuro-imag* or neuro-radio*).tw,kw,kf.
23	(prehospital or pre-hospital or out-of-hospital).tw,kw,kf.
24	(ambulance* or (rapid response adj (car* or vehicle*)) or MSU).tw,kw,kf.
25	(helicopter* or HEMS or aeromedic* or aero-medic* or air medical).tw,kw,kf.
26	(scene or en route or on site or on board or onboard).tw,kw,kf.

27	(paramedic* or emergency medical technician* or physician staffed EMS).tw,kw,kf.
28	((emergency or EMS) adj3 (mobile* or transport* or site*)).tw,kw,kf.
29	(patient* adj4 transport*).tw,kw,kf.
30	((stroke or telestroke) adj3 (mobile* or ambulance*)).tw,kw,kf.
31	STEMO.tw,kw,kf.
32	1 and 2 and 3
33	4 and 5 and 6
34	(or/7-17) and (or/18-22) and (or/23-29)
35	or/30-34
36	remove duplicates from 35
37	limit 36 to yr="2010 -Current"

PubMed

Set	Query
#1	(("Stroke"[mh] or "Intracranial Hemorrhages"[mh] or "Brain Ischemia"[mh] or "Craniocerebral Trauma"[mh]) AND ("Ambulances"[mh] or "Emergency Medical Services"[mh:noexp] or "Mobile Health Units"[mh:noexp] or "Transportation of Patients"[mh:noexp]) AND ("Tomography, X-Ray"[mh] or "Tomography Scanners, X-Ray Computed"[mh:noexp] or "Stroke/diagnostic imaging"[mh]))
#2	(stroke*[tw] or transient-ischemic-attack*[tw] or transient-ischaemic-attack*[tw] or TIA[tw] or apoplex*[tw] or acute-cerebral-vasculopath*[tw] or (CVA[tw] or ((cerebrovascular[tw] or cerebro-vascular[tw] or cerebral-vascular[tw]) and (accident*[tw] or event*[tw] or infarct*[tw] or insult*[tw] or occlu*[tw]))) or ((cerebral[tw] or brain*[tw] or cortical[tw] or subcortical[tw] or cortex[tw] or cerebellar[tw] or hemisphere*[tw] or intracranial[tw] or intra-cranial[tw]) and (infarct*[tw] or insult*[tw] or attack*[tw] or ischemi*[tw] or ischaemi*[tw] or embol*[tw] or thrombo*[tw] or occlu*[tw] or hypoxia[tw])) or ((vertebrobasilar[tw] or carotid[tw]) and (aneurysm*[tw] or occlu*[tw] or thrombo*[tw] or infarct*[tw] or insult*[tw] or embol*[tw] or ischemi*[tw] or ischaemi*[tw])) or (large-vessel-occlusion*[tw] or LVO[tw] or large-artery-occlusion*[tw]) or Heubner-infarct*[tw] or (((brain[tw] or cerebellar[tw] or cerebral[tw] or hemisphere*[tw] or brainstem[tw] or intracranial[tw] or intra-cranial[tw] or intracortical[tw] or intra-cortical[tw] or subarachnoid*[tw] or subdural[tw] or intracerebral[tw] or intra-cerebral[tw] or intraventricular[tw] or intra-ventricular[tw] or periventricular[tw] or peri-ventricular[tw]) and (hemorrhage*[tw] or haemorrhage*[tw] or bleed*[tw] or microbleed*[tw] or hematoma*[tw] or haematoma*[tw])) or SAH[tw]) or (((head[tw] or

	brain[tw] or cerebrovascular[tw] or cerebro-vascular[tw]) and (injur*[tw] or trauma*[tw])) or TBI[tw]))
#3	((tomograph*[tw] or tomodensitometr*[tw]) or (microtomograph*[tw] or microCT[tw] or micro-CT[tw]) or (MDCT[tw] or CT[tw] or CAT[tw] or CTA[tw] or CTP[tw]) or (telestroke[tw] or teleradiolog*[tw] or tele-stroke[tw] or tele-radiolog*[tw]) or (neuroimag*[tw] or neuroradio*[tw] or neuro-imag*[tw] or neuro-radio*[tw]))
#4	((prehospital[tw] or pre-hospital[tw] or out-of-hospital[tw]) or (ambulance*[tw] or (rapid-response[tw] and (car[tw] or cars[tw] or vehicle*[tw])) or MSU[tw]) or (helicopter*[tw] or HEMS[tw] or aeromedic*[tw] or aero-medic*[tw] or air-medical[tw]) or (scene[tw] or en-route[tw] or on-site[tw] or on-board[tw] or onboard[tw]) or (paramedic*[tw] or emergency-medical-technician*[tw] or physician-staffed-EMS[tw]) or ((emergency[tw] or EMS[tw]) and (mobile*[tw] or transport*[tw] or site*[tw])) or (patient*[tw] and transport*[tw]))
#5	(((stroke[tw] or telestroke[tw]) and (mobile*[tw] or ambulance*[tw])) or STEMO[tw])
#6	((pubmednotmedline[sb] OR publisher[sb]))
#7	((#1 or (#2 and #3 and #4) or #5) and #6) [Filters activated: Publication date from 2010/01/01]

Web of Science

Set	Query
# 30	#29 OR #25 OR #24
	Indexes=SCI-EXPANDED Timespan=2010-2017
# 29	#28 AND #27 AND #26
# 28	#23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17
# 27	#16 OR #15 OR #14 OR #13 OR #12
# 26	#11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
# 25	TS=("STEMO")
# 24	TS=(("stroke" or "telestroke") NEAR/2 (mobile* or ambulance*))
# 23	TS=(patient* NEAR/3 transport*)

# 22	TS=(("emergency" or "EMS") NEAR/2 (mobile* or transport* or site*))
# 21	TS=(paramedic* or "emergency medical technician*" or "physician staffed EMS")
# 20	TS=("scene" or "en route" or "on site" or "on board" or "onboard")
# 19	TS=(helicopter* or "HEMS" or aeromedic* or "aero-medic*" or "air medical")
# 18	TS=(ambulance* or ("rapid response" NEAR/0 ("car" or "cars" or vehicle*)) or "MSU")
# 17	TS=("prehospital" or "pre-hospital" or "out-of-hospital")
# 16	TS=(neuroimag* or neuroradio* or "neuro-imag*" or "neuro-radio*")
# 15	TS=("telestroke" or teleradiolog* or "tele-stroke" or "tele-radiolog*")
# 14	TS=("MDCT" or "CT" or "CAT" or "CTA" or "CTP")
# 13	TS=(microtomograph* or "microCT" or "micro-CT")
# 12	TS=(tomograph* or tomodensitometr*)
# 11	TS=((("head" or "brain" or "cerebrovascular" or "cerebro-vascular") NEAR/3 (injur* or trauma*)) or "TBI")
# 10	TS=((("brain" or "cerebellar" or "cerebral" or hemisphere* or "brainstem" or "intracranial" or "intra-cranial" or "intracortical" or "intra-cortical" or subarachnoid* or "subdural" or "intracerebral" or "intra-cerebral" or "intraventricular" or "intra-ventricular" or "periventricular" or "peri-ventricular") NEAR/2 (hemorrhage* or haemorrhage* or bleed* or microbleed* or hematoma* or haematoma*)) or "SAH")
# 9	TS=("Heubner infarct*")
# 8	TS=("large vessel occlusion*" or "LVO" or "large artery occlusion*")
# 7	TS=(("vertebrobasilar" or "carotid" or "intracranial" or "intra-cranial") NEAR/2 (aneurysm* or occlu* or thrombo* or infarct* or insult* or embol* or ischemi* or ischaemi*))

# 6	TS=(("cerebral" or brain* or "cortical" or "subcortical" or "cortex" or "cerebellar" or hemisphere* or "intracranial" or "intra-cranial") NEAR/2 (infarct* or insult* or attack* or ischemi* or ischaemi* or embol* or thrombo* or occlu* or "hypoxia"))
# 5	TS=("CVA" or (("cerebrovascular" or "cerebro-vascular" or "cerebral vascular") NEAR/2 (accident* or event* or infarct* or insult* or occlu*)))
# 4	TS="acute cerebral vasculopath*"
# 3	TS=apoplex*
# 2	TS=("transient ischemic attack*" or "transient ischaemic attack*" or "TIA")
# 1	TS=(stroke*)

Clinical Trials.gov

(stroke ambulance OR mobile stroke OR stroke mobile OR stroke emergency mobile OR mobile acute stroke OR mobile hyperacute stroke)

International Clinical Trials Registry Platform

(stroke ambulance OR mobile stroke OR stroke mobile OR stroke emergency mobile OR mobile acute stroke OR mobile hyperacute stroke)

3. Update searches for primary studies

Information specialist: Elisabet Hafstad

Database (provider) Search date: 10.12.2018	**Number of hits**
CENTRAL (Cochrane Central Register of Controlled Trials): Issue 12 of 12, December 2018 (Wiley) Publication Year from 2017 to 2018; Date added to CENTRAL trials database 01/12/2017 – 10/12/2018	25
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to December 06, 2018> ("2017 12" or "2017/12" or 2018* or 2019*).dp,dt. use ppez	129

Total number of hits	**154**
Total number of hits after removal of duplicates (after removal of duplicates in the search update and in relation to the main search of Dec. 2017)	**115**

Details about how the original search strategies were updated (complete search strategies) can be obtained by contacting the project manager.

Appendix 3. Excluded publications and reasons for exclusion

1. Excluded publications found through searches for systematic reviews and HTAs

Reference	Main reason for exclusion
Amadi-Obi A, Gilligan P, Owens N, O'Donnell C. Telemedicine in pre-hospital care: a review of telemedicine applications in the pre-hospital environment. International Journal of Emergency Medicine 2014;7:29.	Irrelevant intervention
Audebert HJ, Fiebach JB. Brain imaging in acute ischemic stroke-MRI or CT? Current Neurology and Neuroscience Reports 2015;15(3):6.	Review
Audebert HJ, Saver JL, Starkman S, Lees KR, Endres M. Prehospital stroke care: new prospects for treatment and clinical research. Neurology 2013;81(5):501-8.	Review
Chang P, Prabhakaran S. Recent advances in the management of acute ischemic stroke. F1000Research 2017;6.	Review
Ebinger M, Fiebach JB, Audebert HJ. Mobile computed tomography: prehospital diagnosis and treatment of stroke. Current Opinion in Neurology 2015;28(1):4-9.	Review
El-Ghanem M, Al-Mufti F, Thulasi V, Singh IP, Gandhi C. Expanding the treatment window for ischemic stroke through the application of novel system-based technology. Neurosurgical Focus 2017;42(4):E7.	Review
Fassbender K, Grotta JC, Walter S, Grunwald IQ, Ragoschke-Schumm A, Saver JL. Mobile stroke units for prehospital thrombolysis, triage, and beyond: benefits and challenges. Lancet Neurology 2017;16(3):227-37.	Review
Hubert GJ, Müller-Barna P, Audebert HJ. Recent advances in TeleStroke: a systematic review on applications in prehospital management and Stroke Unit treatment or TeleStroke networking in developing countries. International journal of stroke: official journal of the International Stroke Society 2014;9(8):968-73.	Methods used not explicitely stated
Ip HL, Liebeskind DS. The future of ischemic stroke: flow from prehospital neuroprotection to definitive reperfusion. Interventional Neurology 2014;2(3):105-17.	Irrelevant intervention; review
John S, Stock S, Cerejo R, Uchino K, Winners S, Russman A, et al. Brain imaging using mobile CT: current status and future prospects. Journal of Neuroimaging 2016;26(1):5-15.	Review

Lahr MM, Luijckx GJ, Vroomen PC, van der Zee DJ, Buskens E. The chain of care enabling tPA treatment in acute ischemic stroke: a comprehensive review of organisational models. Journal of Neurology 2013;260(4):960-8.	Review
Lin MP, Sanossian N, Liebeskind DS. Imaging of prehospital stroke therapeutics. Expert Review of Cardiovascular Therapy 2015;13(9):1001-15.	Review
Mobile stroke units for prehospital care of ischemic stroke. Ottawa, CA: CADTH; 2017. CADTH issues in emerging health technologies. Issue 154.	Early warning
Nolte CH, Audebert HJ. [Prehospital care for stroke patients]. Medizinische Klinik, Intensivmedizin Und Notfallmedizin 2017;12:12	Review
Rajan SS, Baraniuk S, Parker S, Wu TC, Bowry R, Grotta JC. Implementing a mobile stroke unit program in the United States: why, how, and how much? JAMA Neurology 2015;72(2):229-34.	Review
Rangel-Castilla L, Rajah GB, Shakir HJ, Davies JM, Snyder KV, Siddiqui AH, et al. Acute stroke endovascular treatment: tips and tricks. The Journal of Cardiovascular Surgery 2016;57(6):758-68.	Irrelevant intervention; review
Rasmussen PA. Stroke management and the impact of mobile stroke treatment units. Cleveland Clinic Journal of Medicine 2015;82(12 Suppl 2):S17-21.	Review
Socialstyrelsen. Datortomografi, prehospitalt. I: Nationella riktlinjer för vård vid stroke: Rekommendationer och kunskapsunderlag: Remissversion: Bilaga. Stockholm: Socialstyrelsen; 2017.	Review
Schwindling L, Ragoschke-Schumm A, Kettner M, Helwig S, Manitz M, Roumia S, et al. Prehospital imaging-based triage of head trauma with a mobile stroke unit: first evidence and literature review. Journal of Neuroimaging 2016;26(5):489-93.	Review
Southerland AM. Clinical evaluation of the patient with acute stroke. CONTINUUM: Lifelong Learning in Neurology 2017;23(1, Cerebrovascular Disease):40-61.	Irrelevant intervention; review
Tai YJ, Yan B. Minimising time to treatment: targeted strategies to minimise time to thrombolysis for acute ischaemic stroke. Internal Medicine Journal 2013;43(11):1176-82.	Review
Theofanidis D, Savopoulos C, Hatzitolios A. Global specialized stroke care delivery models. Journal of Vascular Nursing 2016;34(1):2-11.	Review

Walter S, Grunwald IQ, Fassbender K. [Mobile stroke unit for prehospital stroke treatment]. Radiologe 2016;56(1):28-31.	Review
Weber J, Ebinger M, Audebert HJ. Prehospital stroke care: telemedicine, thrombolysis and neuroprotection. Expert Review of Neurotherapeutics 2015;15(7):753-61.	Methods used not explicitely stated; review
Yperzeele L, Van Hooff RJ, De Smedt A, Valenzuela Espinoza A, Van de Casseye R, Hubloue I, et al. Prehospital stroke care: limitations of current interventions and focus on new developments. Cerebrovascular Diseases 2014;38(1):1-9.	Review

2. Excluded publications found through searches for primary studies

Reference	Main reason for exclusion
Abdel-Halim E, Christopher M, Ashfaq S, Shy A, Laurel M, Hayrapet K, et al. Comprehensive Evaluation of a Stroke Ambulance (the ACHIEVE Project). International Journal of Stroke 2017;12(4):71.	Conference abstract
Alexandro AW, Dusenbury W, Swatzell V, Tsivgoulis G, Alexandrov AV. Staffing the mobile stroke unit: nurse practitioners measure up to physician-led care. International Journal of Stroke 2017;12(2):22.	Conference abstract
Alexandrov AW, Dusenbury W, Swatzell V, Rike J, Bouche A, Crisp I, et al. Born to run: advanced practice provider-led mobile stroke unit care measures up to vascular neurologists' diagnosis and management. Stroke 2017;48:ANS6.	Conference abstract
Almaghrabi T, Sarraj A, Bowry R, Parker S, Yamal JM, Grotta J. 90 day outcome after reperfusion therapy of stroke patients with baseline disability: unique observations from patients treated on the mobile stroke unit. Neurology 2016;86(16 Supplement):P6.052.	Conference abstract
Amlani S, Morrison L, Shuaib A, Jeerakathil T. Building Canada's first stroke ambulance: ACHIEVE (AmbulanCe Housed Ischemic Stroke trEatment with intraVEnous Thromoblysis). International Journal of Stroke 2017;12(4 Supplement 1):69.	Conference abstract
Aoun RJ, Bendok BR, Zammar SG, Hamade YJ, Aguilar MI, Demaerschalk BM. From delivering the patient to the hospital to delivering the hospital to the patient: acute stroke therapy in an ambulance. World Neurosurgery 2015;84(2):204-5.	Newsletter
Audebert H, Fassbender K, Hussain MS, Ebinger M, Turc G, Uchino K, et al. The PRE-hospital Stroke Treatment Organization. International Journal of Stroke 2017;12(9):932-40.	Review article

Audebert H, Kunz A, Nolte C, Erdur H, Fiebach J, Frederik G, et al. Time to treatment effects with ultra-early intravenous thrombolysis on outcome in acute ischemic stroke the stroke emergency mobile (STEMO) writing group. European Stroke Journal 2016;1(1):761-2.	Conference abstract
Audebert HJ, Kunz A, Winter B, Waldschmidt C, Weber J, Wendt M, et al. Ambulance based stroke thrombolysis compared to conventional care-results of PHANTOM-S (the prehospital acute neurological treatment and optimization of medical care in stroke patients). Cerebrovascular Diseases 2013;35(suppl 3):108.	Conference abstract
Bowry R, Grotta JC. Bringing emergency neurology to ambulances: mobile stroke unit. Seminars in Respiratory and Critical Care Medicine 2017;38(6):713-7.	Review article
Bowry R, Parker S, Rajan SS, Yamal JM, Wu TC, Richardson L, et al. Benefits of stroke treatment using a mobile stroke unit compared with standard management: the BEST-MSU study run-in phase. Stroke 2015;46(12):3370-4.	A non-randomized 10-week run-in phase of an ongoing RCT (pilot study); cut off (<100 patients)
Bowry R, Parker SA, Yamal JM, Hwang H, Appana S, Rangel-Gutierrez N, et al. Time to decision and treatment with tPA (Tissue-Type Plasminogen Activator) using telemedicine versus an onboard neurologist on a mobile stroke unit. Stroke 2018;49(6):1528-30.	Irrelevant comparator
Briggs F, Taqui A, Cerejo R, Itrat A, Donohue M, Organek N, et al. Pre-hospital imaging and thrombolysis in acute stroke in an urban us setting: results of the Cleveland pre-hospital acute stroke treatment (PHAST) study group. Neurology 2015;84(14 Supplement):S21.002.	Conference abstract
Buletko A, Cerejo R, Taqui A, Itrat A, John S, Toth G, et al. Early triage of acute ischemic stroke patients using mobile stroke unit shortens time to intra-arterial therapy. Neurology 2015;84(14 Supplement):P4.310.	Conference abstract
Cerejo R, John S, Buletko AB, Taqui A, Itrat A, Organek N, et al. A mobile stroke treatment unit for field triage of patients for intraarterial revascularization therapy. Journal of Neuroimaging 2015;25(6):940-5.	Registry data (with historic control); cut off (<100 patients)
Cho S, Cejero R, Taqui A, Itrat A, Donohue MM, Briggs F, et al. Feasibility of telemedicine on a mobile stroke treatment unit. Stroke 2015;46:ATP200.	Conference abstract
Chudyk J, Lylyk P, Bleise C, Cirio J. Establishing the first mobile stroke unit in Latin America. International Journal of Stroke 2016;11(3S):185.	Conference abstract

Coote S, Zhao H, Campbell B, Yassi N, Donnan G, Davis S. Nursing on-board a mobile stroke unit. International Journal of Stroke 2017;12(3S):10.	Conference abstract
Dietrich M, Walter S, Ragoschke-Schumm A, Helwig S, Levine S, Balucani C, et al. Is prehospital treatment of acute stroke too expensive? An economic evaluation based on the first trial. Cerebrovascular Diseases 2014;38:457–63.	Economic evaluation
Ebinger M, Harmel P, Nolte CH, Grittner U, Siegerink B, Audebert HJ. Berlin prehospital or usual delivery of acute stroke care - study protocol. International Journal of Stroke 2017;12(6):653-8.	Study protocol / ongoing study
Ebinger M, Lindenlaub S, Kunz A, Rozanski M, Waldschmidt C, Weber JE, et al. Prehospital thrombolysis: a manual from Berlin. Journal of Visualized Experiments 2013;(81):e50534.	A description of STEMO / review article
Ebinger M, Rozanski M, Waldschmidt C, Weber J, Wendt M, Winter B, et al. PHANTOM-S: the prehospital acute neurological therapy and optimization of medical care in stroke patients - study. International Journal of Stroke 2012;7(4):348-53.	Study protocol
Ebinger M, Weber J, Wendt M, Rozanski M, Winter B, Waldschmidt C, et al. Pre-hospital thrombolysis as a therapeutic option in acute stroke care results of the Pre-Hospital Acute Neurological Treatment and Optimization of Medical Care in Stroke (PHANTOM-S) pilot study. Cerebrovascular Diseases 2012;33(Suppl 2):40.	Conference abstract
Ebinger M, Wendt M, Rozanski M, Winter B, Waldschmidt C, Weber J, et al. Golden hour-thrombolysis by starting treatment before hospital arrival the pre-hospital acute neurological treatment and optimization of medical care in stroke study (PHANTOM-S). Stroke 2014;45(Suppl. 1): A104.	Conference abstract
Fassbender KC, Walter S, Ragoschke-Schumm A, Haass A, Dietrich M. Cost-efficiency of prehospital stroke treatment. Stroke 2015;46(Suppl. 1):AWP279.	Conference abstract
Gierhake D, Weber JE, Villringer K, Ebinger M, Audebert HJ, Fiebach JB. CT im Notarztwagen: technische Aspekte der prähospitalen radiologischen Schlaganfalldiagnostik vor systemischer Thrombolyse. Fortschr Röntgenstr 2013;185(1): 55-9.	Pilot study for one of the included RCTs (Ebinger)
Grotta J. Benefits of stroke treatment delivered using a mobile stroke unit. Neurology 2015;84(14 Suppl.):I1-3A.	Conference abstract

Grunwald IQ, Ragoschke-Schumm A, Kettner M, Schwindling L, Roumia S, Helwig S, et al. First Automated stroke imaging evaluation via Electronic Alberta Stroke Program Early CT Score in a mobile stroke unit. Cerebrovascular Diseases 2016;42(5-6):332-8.	Irrelevant PICO (the study evaluated the feasibility and clinical use of a software for image interpretation in the MSU)
Grunwald I, Ragoschke-Schumm A, Kettner M, Walter S, Shah S, Fassbender K. e-ASPECTS in pre-hospital stroke treatment on a mobile stroke unit. International Journal of Stroke 2016;11(4 Supplement 1): 46.	Conference abstract
Gyrd-Hansen D, Olsen KR, Bollweg K, Kronborg C, Ebinger M and Audebert HJ. Cost-effectiveness estimate of prehospital thrombolysis: results of the PHANTOMS Study. Neurology 2015;84:1090-7.	Economic evaluation
Hov MR, Lindner T, Lund CG. Prehospital radiological diagnosis of SAH and triage for neurosurgery. Cerebrovascular Diseases 2016;41(Suppl. 1):193.	Conference abstract
Hov MR, Nome T, Zakariassen E, Roislien J, Lossius HM, Russell D, et al. Assessment of acute stroke CT examinations by anaesthesiologists. Cerebrovascular Diseases 2014;37:506.	Conference abstract
Hov MR, Nome T, Zakariassen E, Roislien J, Lossius HM, Russell D, et al. Assessment of acute stroke CT examinations by anaesthesiologists. Cerebrovascular Diseases 2014;37(Suppl. 2):22.	Conference abstract
Hov MR, Nome T, Zakariassen E, Russell D, Røislien J, Lossius HM, et al. Assessment of acute stroke cerebral CT examinations by anaesthesiologists. Acta Anaesthesiologica Scandinavica 2015;59(9):1179-86.	Irrelevant outcome
Hov MR, Ryen A, Finsnes K, Storflor J, Lindner T, Gleditsch J, et al. Pre-hospital ct diagnosis of subarachnoid hemorrhage. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine 2017;25:21.	Cut off (<100 patients)
Hov MR, Zakariassen E, Lindner T, Nome T, Bache KG, Røislien J, et al. Interpretation of brain ct scans in the field by critical care physicians in a mobile stroke unit. Journal of Neuroimaging 2018;28(1):106-11.	Cut off (<100 patients)
Hughes S. PHANTOM-S: mobile stroke unit reduces time to tPA. 2013. Available from: https://www.medscape.com/viewarticle/805000	Newsletter
Itrat A, Taqui A, Cerejo R, Briggs F, Cho SM, Organek N, et al. Telemedicine in prehospital stroke evaluation and thrombolysis: taking stroke treatment to the doorstep. JAMA Neurology 2016;73(2):162-8.	Irrelevant outcome

John S, Stock S, Masaryk T, Bauer A, Cerejo R, Uchino K, et al. Performance of CT angiography on a mobile stroke treatment unit: implications for triage. Journal of Neuroimaging 2016;26(4):391-4.	Case study
Kalashyan H, Jeerakathil T, Elamy A-H, Amlani S, Morrison L, Bobyak J, et al. Canada's first stroke ambulance: the early experience of the achieve (ambulance housed ischemic stroke treatment with intravenous thrombolysis) study. International Journal of Stroke 2017;12(4 Supplement 1):31.	Conference abstract
Kettner M, Helwig SA, Ragoschke-Schumm A, Schwindling L, Roumia S, Keller I, et al. Prehospital computed tomography angiography in acute stroke management. Cerebrovascular Diseases 2017;44(5-6):338-343.	Cut off (<100 patients)
Kostopoulos P, Walter S, Haass A, Papanagiotou P, Roth C, Yilmaz U, et al. Mobile stroke unit for diagnosis-based triage of persons with suspected stroke. Neurology 2012;78(23):1849-52.	Cut off (<100 patients)
Kummer B, Lerario M, Ganzman A, Navi B, Ribaudo D, Mir S, et al. Clinical information systems integration in New York city's first mobile stroke unit. European Stroke Journal 2017;2(1 Supplement 1):243.	Conference abstract
Kummer BR, Lerario MP, Navi BB, Ganzman A, Ribaudo D, Mir SA, et al. Clinical information systems integration in New York City's first mobile stroke unit. Applied Clinical Informatics 2018;9(1):89-98.	Descriptive study
Kunz A, Nolte CH, Erdur H, Fiebach JB, Geisler F, Rozanski M, et al. Effects of ultraearly intravenous thrombolysis on outcomes in ischemic stroke: The STEMO (Stroke Emergency Mobile) Group. Circulation 2017;135(18):1765-7.	Study population included both those who received MSU and conventional hospital-based care (pooled analysis).
Kunz AK, Nolte C, Fiebach JB, Geisler F, Rozanski M, Scheitz JF, et al. Functional outcomes of pre-hospital stroke thrombolysis compared to conventional care; the Stroke Emergency Mobile (STEMO) Project. Stroke 2016;47(Suppl. 1):A179.	Conference abstract
Lin E, Calderon V, Goins-Whitmore J, Bansal V, Zaidat O. World's first 24/7 mobile stroke unit: initial 6-month experience at Mercy Health in Toledo, Ohio. Frontiers in Neurology 2018;9:283.	Study design (included RCTs covered the same outcomes than this case series)

Lorenz MW, Lauer A, Foerch C. Quantifying the benefit of pre-hospital rapid treatment in acute stroke: benchmark for future innovative clinical trials. Stroke 2015;46(11):3168-76.	Irrelevant PICO (this article aimed at determining the benchmark for innovative treatment options to set standards for future clinical trials)
Mathew J, Buletko AB, Taqui A, Reimer A, Winners S, Thacker T, et al. Prehospital timeline of mobile stroke treatment unit and traditional ambulance. Stroke 2017;48: ATP230.	Conference abstract
NCT00792220. "Mobile Stroke-Unit" for Reduction of the Response Time in Ischemic Stroke. 2008. Available from: https://ClinicalTrials.gov/show/NCT00792220.	Study protocol of a published study (Walter)
NCT01382862. PHANTOM-S: The Pre-Hospital Acute Neurological Therapy and Optimization of Medical Care in Stroke Patients - Study. 2011. Available from: https://ClinicalTrials.gov/show/NCT01382862.	Study protocol of a published study (Ebinger)
NCT01644019. Prehospital Telemedical Support in Acute Stroke. 2012. Available from: https://ClinicalTrials.gov/show/NCT01644019.	Irrelevant intervention
NCT02119598. Feasibility of AmbulanCe-based Telemedicine (FACT) Study. 2014. Available from: https://ClinicalTrials.gov/show/NCT02119598.	Irrelevant intervention and outcome
NCT02190500. BEnefits of Stroke Treatment Delivered Using a Mobile Stroke Unit. 2014. Available from: https://ClinicalTrials.gov/show/NCT02190500.	Relevant, but ongoing study
NCT02230852. Prehospital Stroke Study at the Universitair Ziekenhuis Brussel I (PreSSUB I). 2014. Available from: https://ClinicalTrials.gov/show/NCT02230852.	Irrelevant intervention and outcome
NCT02270541. Prehospital Study at the Universitair Ziekenhuis Brussel II. 2014. Available from: https://ClinicalTrials.gov/show/NCT02270541.	Irrelevant intervention
NCT02358772. Comparison of Pre-hospital and In-hospital Iv-tPA Stroke Treatment. 2011. Available from: https://ClinicalTrials.gov/show/NCT02358772.	Study protocol of a published study (Kunz)
NCT02465346. "Mobile Stroke Unit"-Concept for Delivery of Specialized Acute Stroke Care to Patients in Remote Areas. 2015. Available from: https://ClinicalTrials.gov/show/NCT02465346.	Relevant, but ongoing study
NCT02869386. Berlin PRehospital Or Usual Delivery of Acute Stroke Care. 2016. Available from: https://ClinicalTrials.gov/show/NCT02869386.	Relevant, but ongoing study

NCT03036020. The Norwegian Acute Stroke Prehospital Project. 2014. Available from: https://ClinicalTrials.gov/show/NCT03036020.	Irrelevant outcome (relevant for organizational aspects)
NCT03048292. New York City Mobile Interventional Stroke Team. 2016. Available from: https://ClinicalTrials.gov/show/NCT03048292.	Irrelevant intervention
NCT03158259. Prehospital Advanced Diagnostics and Treatment of Acute Stroke. 2017. Available from: https://ClinicalTrials.gov/show/NCT03158259.	Relevant, but ongoing study
NCT03370094. Tele-Stroke: Prehospital Identification of Patients With Suspected Stroke Using Onsite Mobile Telemedicine - Feasibility. 2017. Available from: https://ClinicalTrials.gov/show/NCT03370094.	Irrelevant intervention and outcome
NCT03577847. Rural CT Examination and Thrombolytic Treatment for Stroke (RURALCT). 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT03577847	Relevant, but ongoing study
New mobile stroke unit programs aim to improve outcomes. ED Management 2017;29(1):1-6.	Newsletter
New stroke ambulance hits Melbourne streets. Australian Nursing & Midwifery Journal 2017;25(6):8.	Newsletter
Nolte C, Kunz A, Erdur H, Fiebach J, Geisler F, Rozanski M, Scheitz JF, et al. Pre-hospital start of intravenous thrombolysis in acute ischemic stroke - Effect on outcome in patients with pre-stroke need of assistance. European Stroke Journal 2016;1(1 Supplement 1):765.	Conference abstract
Nour M, Starkman S, Sharma LK, Saver JL. Magnitude of benefit of prehospital mobile stroke unit vs conventional ED thrombolysis: preliminary estimate based on PHANTOM-S observational registry. Stroke 2017;48:A119.	Conference abstract
Nyberg EM, Cox JR, Kowalski RG, Vela-Duarte D, Schimpf B, Jones WJ. Mobile stroke unit reduces time to image acquisition and reporting. AJNR: American Journal of Neuroradiology 39(7): 1293-5.	Study design (included RCTs covered the same outcome than this non-randomized controlled trial)
Organek N, Taqui A, Uchino K, Itrat A, Cerejo R, Winners S, et al. Treatment of ischemic stroke in the mobile stroke treatment unit. Neurocritical Care 2015;23(1 SUPPL. 1): S131.	Conference abstract
Parker SA, Bowry R, Wu TC, Noser EA, Jackson K, Richardson L, et al. Establishing the first mobile stroke unit in the United States. Stroke 2015;46(5):1384-91.	An 8-week run-in phase of an ongoing RCT (pilot study); cut off (<100 patients)

Parker SA, Bowry R, Wu TC, Noser E, Presse D, Grotta JC. Benefits of stroke treatment delivered using a mobile stroke unit compared to standard management - BEST-MSU study. International stroke conference 2015.	Conference abstract
Parker S, Noser E, Presse D, Grotta J. Stroke treatment delivered using a mobile stroke unit. International stroke conference 2015.	Conference abstract
Parker S, Persse D, Noser E, Richardson L, Flanagan T, Grotta J. Establishing the first mobile stroke unit in the united states. Stroke 2015;46:A52.	Conference abstract
Ragoschke-Schumm A, Razouk A, Lesmeister M, Helwig S, Grunwald IQ, Fassbender K. Dosage calculation for intravenous thrombolysis of ischemic stroke: to weigh or to estimate. Cerebrovascular Diseases Extra 2017;7(2):103-10.	Irrelevant outcome
Rajan SS, Baraniuk S, Parker S, Wu TC, Bowry R, Grotta JC. Implementing a mobile stroke unit program in the United States: why, how, and how much? JAMA Neurology 2015;72(2):229-34.	Review article
Rothwell PM, Buchan AM. Mobile acute stroke units: bringing the hospital to the patient. Lancet Neurology 2012;11(5): 382-3.	Commentary
Rudd AG. Can emergency stroke care be delivered in an ambulance? The Lancet Neurology 2016;15(10): 998-1000.	Commentary
Schlemm L, Turc G, Audebert HJ, Ebinger M. Access to thrombolysis for non-resident and resident stroke patients-a registry-based comparative study from Berlin. Frontiers in Neurology 2017;30;8:319.	Irrelevant comparator
Sheikhi L, Itrat A, Cerejo R, Taqui A, Buttrick M, Stecker M, et al. Does portable CT imaging in a mobile stroke treatment unit (MSTU) provide adequate quality for early critical decision making? Stroke 2015;46(Suppl. 1):AWP31.	Conference abstract
Sheikhi LE, Winners S, George P, Russman A, Khawaja Z, Uchino K, et al. Early experience on intravenous tissue plasminogen activator delivery in mobile stroke unit patients with stroke mimics. Neurology 2017;88(16 Supplement 1):AWP72.	Conference abstract
Shuaib A, Jeerakathil T; for the Alberta Mobile Stroke Unit Investigators. The mobile stroke unit and management of acute stroke in rural settings. CMAJ Canadian Medical Association Journal 2018;190(28):E855-8.	Review article

Taqui A, Cerejo R, Itrat A, Briggs FB, Reimer AP, Winners S, et al. Reduction in time to treatment in prehospital telemedicine evaluation and thrombolysis. Neurology 2017;88(14):1305-12.	Study design (one of the included RCTs covered the same outcomes than this observational study)
Taqui A, Cerejo R, Itrat A, Uchino K, Donohue MM, Briggs F, et al. Reduction in time to imaging and intravenous thrombolysis by in-field evaluation and treatment in a mobile stroke treatment unit. Stroke 2015;46(Suppl. 1):A54.	Conference abstract
Tinsley M, Dunne J, Longworth M, Paddock B, Worthington JM. Early access to thrombolysis: Implementation of the NSW reperfusion programme. International Journal of Stroke 2013;8(Suppl. 1):46.	Irrelevant interventjon
Toth G, Taqui A, Cerejo R, John S, Donohue M, Uchino K, et al. Mobile stroke ambulance: high recanalization rates and excellent outcomes after early intravenous tpa administration in patients with acute large vessel occlusion. European Stroke Journal 2016;1(1 Supplement 1):766-7.	Conference abstract
Trujillo-Martin E, Exposito-Rodriguez M, Burillo-Putze G. Mobile stroke treatment units [Spanish]. Revista de Neurología 2015;60(9):430.	Language
Tsivgoulis G, Geisler F, Katsanos AH, Kõrv J, Kunz A, Mikulik R, et al. Ultraearly intravenous thrombolysis for acute ischemic stroke in mobile stroke unit and hospital settings. Stroke 2018;49(8):1996-9.	Non-prospective data collection (comparator); intervention group comprised of a subgroup of the included observational registry study (Kunz et al.)
Turc G, Cordonnier C, Ricard-Hibon A, Dubourdieu S, Oppenheim C, Chabriat H, et al. The ASPHALT study: rationale and design of a randomized controlled trial evaluating the cost-utility of a mobile stroke unit in the era of bridging therapy. European stroke organization conference. 2016.	Conference abstract
Turc G, Cordonnier C, Ricard-Hibon A, Dubourdieu S, Oppenheim C, Chabriat H, et al. The asphalt project: rationale and design of a randomized controlled trial evaluating the cost-utility of a mobile stroke unit in the era of bridging therapy. European Stroke Journal 2016;1(1 Supplement 1):779.	Conference abstract
Uchino K, Mathew J, Buletko AB, Taqui A, Reimer AP, Thacker T, et al. Patients with stroke missed in prehospital identification-missed opportunity for mobiles stroke unit. European Stroke Journal 2017;2(1 Supplement 1):247.	Conference abstract

Vela-Duarte D, Ramanathan RS, Zafar A, Taqui A, Winners S, Sheikhi L, et al. Prehospital diagnosis of intracerebral hemorrhage in a mobile stroke treatment unit. Stroke 2016;47(Suppl. 1):ATP358.	Conference abstract
Wahlster P, Niederlander CS, Kriza C, Kolominsky-Rabas PL. The framework for health economic modeling and multi-criteria decision analysis (MCDA) on the example of the mobile stroke unit (MSU). Value in Health 2013;16(7):A489-A490.	Conference abstract
Walter S, Grunwald IQ, Helwig SA, Ragoschke-Schumm A, Kettner M, Fousse M, et al. Mobile stroke units - cost-effective or just an expensive hype? Current Atherosclerosis Reports 2018;20(10):49.	Review article
Walter S, Kostpopoulos P, Haass A, Helwig S, Keller I, Licina T, et al. Bringing the hospital to the patient: first treatment of stroke patients at the emergency site. PLoS One 2010;5(10):e13758.	Preliminary study to one of the included RCTs (Walter); Cut off (<100 patients)
Walter S, Kostopoulos P, Haass A, Liu Y, Papanagiotou P, Roth C, et al. "Mobile Stroke Unit" for diagnosis-based triaging of persons with suspected stroke. European Journal of Neurology 19:27.	Conference abstract
Walter S, Kostopoulos P, Haass A, Papanagiotou P, Roth C, Grunwald I, et al. Bringing the hospital to the patient: stroke treatment directly at the emergency site. International Journal of Stroke 2010;5(2 Suppl.):109.	Conference abstract
Walter S, Kostopoulos P, Haass A, Papanagiotou P, Roth C, Grunwald I, et al. Bringing the hospital to the patient: stroke treatment directly at the emergency site. European Journal of Neurology 2010;17:142.	Conference abstract
Walter S, Kostopoulos P, Ragoschke-Schumm A, Haass A, Grundwald I, Reith W, et al. "Mobile stroke unit" for stroke treatment at the emergency site. Journal of the Neurological Sciences 2013;333:e190.	Conference abstract
Walter S, Kostopoulos P, Haass A, Papanagiotou P, Roth C, Grunwald I, et al. Bringing the hospital to the patient: stroke treatment directly at the emergency site. Journal of Neurology 2011;258:S45.	Conference abstract
Walter S, Ragoschke-Schumm A, Lesmeister M, Helwig SA, Kettner M, Grunwald IQ, et al. Mobile stroke unit use for prehospital stroke treatment-an update. Radiologe 2018;58(Suppl 1):24-8.	Review article

Weber JE, Ebinger M, Rozanski M, Waldschmidt C, Wendt M, Winter B, et al. Prehospital thrombolysis in acute stroke: results of the PHANTOM-S pilot study. Neurology 2013;80(2):163-8.	Pilot study for one of the included RCTs (Ebinger)
Weber JE, Ebinger M, Rozanski M, Waldschmidt C, Wendt M, Winter B, et al. Feasibility and safety on intravenous tissue plasminogen activator in the pre-hospital acute neurological therapy and optimization of medical care in stroke patients - study (PHANTOM-S) results of the Phantom-S pilot study. Stroke 2012;43(Suppl. 1):A64.	Conference abstract
Wendt M, Ebinger M, Rozanski M, Winter B, Waldschmidt C, Kunz A, et al. Effects of prehospital neurologist assessment on appropriate delivery to neurology facilities: the stroke emergency mobile (STEMO) project. Journal of the Neurological Sciences 2013;333(Suppl. 1):e285.	Conference abstract
Wu TC, Parker SA, Jagolino AL, Yu A, Yamal JM, Bowry R, et al. Can telemedicine replace an on-board vascular neurologist in deciding about tissue plasminogen activator treatment? A prespecified substudy of the BEST-MSU study. Stroke 2017;48(Suppl. 1):A21.	Conference abstract
Wu TC, Parker SA, Jagolino A, Yamal JM, Bowry R, Thomas A, et al. Telemedicine can replace the neurologist on a mobile stroke unit. Stroke 2017;48(2):493-6.	Irrelevant comparator and outcome
Yamal JM, Rajan SS, Parker SA, Jacob AP, Gonzalez MO, Gonzales NR, et al. Benefits of stroke treatment delivered using a mobile stroke unit trial. International Journal of Stroke 2018;13(3):321-7.	Study protocol / ongoing study
Zafar A, Udeh B, Reimer A, Ramanathan RS, Vela-Duarte D, Taqui A, et al. Hospital transfer cost savings from triaging selected stroke patients directly to the comprehensive stroke centers (CSCs) courtesy of the mobile stroke treatment unit (MSTU). Stroke 2017;48: ATP249.	Conference abstract
Zhao H, Coote S, Foster S, Smith K, Bernard S, Cadilhac D, et al. The first Australian mobile stroke unit: a novel platform for hyperacute stroke research. International Journal of Stroke 2017;12(3S):38.	Conference abstract
Zoler ML. Mobile stroke units becoming more common despite cost-effectiveness questions. Emergency Medicine 2017;49(4):150-1,179-80.	Newsletter
Zoler ML. Stroke ambulances speed treatment to U.S. patients. Emergency Medicine 2015;47(4):178-9.	Newsletter

Appendix 4. List of ongoing studies

Clinical Trials ID	**NCT02190500**
Title	BEnefits of Stroke Treatment Delivered Using a Mobile Stroke Unit Compared to Standard Management by Emergency Medical Services:The BEST-MSU Study https://clinicaltrials.gov/ct2/show/NCT02190500
Country	U.S.
Study design	Observational study
No. of participants	1200
Estimated completion date	August 2021
Clinical Trials ID	**NCT02465346**
Title	"Mobile Stroke Unit"-Concept for Delivery of Specialized Acute Stroke Care to Patients in Remote Areas https://clinicaltrials.gov/ct2/show/NCT02465346
Country	Germany
Study design	RCT
No. of participants	116
Estimated completion date	June 2019
Clinical Trials ID	**NCT02869386**
Title	Berlin PRehospital Or Usual Delivery of Acute Stroke Care - Functional Outcomes After Advanced Prehospital Stroke Care https://ClinicalTrials.gov/show/NCT02869386
Country	Germany
Study design	RCT
No. of participants	1500
Estimated completion date	August 2024
Clinical Trials ID	**NCT03158259**
Title	Advanced Diagnostics of Acute Stroke (Biomarkers, Blood Analysis, Stroke Scales and Cerebral CT Examinations) and Initiation of rtPa Treatment in an Air Ambulance Model https://ClinicalTrials.gov/show/NCT03158259
Country	Norway
Study design	Prospective controlled intervention study
No. of participants	400
Estimated completion date	May 2021
Clinical Trials ID	**NCT03577847**
Title	Rural CT Examination and Thrombolytic Treatment for Stroke: An Observational Study of Medical and Health Economic Effects https://clinicaltrials.gov/ct2/show/NCT03577847

Country	Norway
Study design	Observational study
No. of participants	200
Estimated completion date	April 2021

Appendix 5. Characteristics of included studies and risk of bias

Ebinger 2014 (59-61;63)

Clinical Trials ID	NCT01382862 (PHANTOM-S trial)
Methods	Randomized controlled trial
Participants	Patients suspected for stroke Sample size: *With a stroke dispatch and in-hospital documentation*: 1804 in treatment group with MSU deployment, 1409 in treatment group without MSU deployment, 2969 in control group *With cerebrovascular diseases*: 866 in treatment group with MSU deployment, 2110 in treatment group without MSU deployment AND control group *With ischemic stroke*: 614 in treatment group with MSU deployment, 456 in treatment group without MSU deployment, 1041 in control group *Received thrombolysis*: 200 in treatment group with MSU deployment, 110 in treatment group without MSU deployment, 220 in control group *Received thrombolysis at first assessment (those included in primary analysis)*: 192 in treatment group with MSU deployment, 108 in treatment group without MSU deployment, 218 in control group *With intracranial hemorrhages (including spontaneous intracerebral hemorrhages, traumatic intracerebral hemorrhages, subdural and epidural hematoma, and subarachnoid hemorrhages)*: 62 in treatment group with MSU deployment, 151 in treatment group without MSU deployment AND control group *Inclusion criteria:* stroke dispatch activated by the emergency call dispatcher; symptom onset within 4 hours or unknown *Exclusion criteria:* patients younger than 18 years; pregnancy; arrived at hospital with <10 admissions of patients; did not have matching data with hospital; did not have information on hospital destination, died before hospital arrival

Intervention	Mobile stroke unit (MSU): an ambulance (called Stroke Emergency Mobile, STEMO) equipped with a CT scanner, point-of-care laboratory, and telemedicine connection (between the MSU and a neuroradiologist on call), and a specialized prehospital stroke team The MSU staff included a neurologist, a paramedic, and a radiology technician. Neurologist assessed the patient and called the neuroradiologist for endorsement of CT indication (if stroke and time from onset within 4.5 hours confirmed). If no contraindications, patients received thrombolysis directly at the emergency site. During the MSU weeks, a regular ambulance was always sent out simultaneously. First responders were capable of cancelling MSU without further explanation based on their assessment. If MSU was not available, due to simultaneous calls or maintenance, patients received routine care (treatment group without MSU deployment).
Comparator	Conventional care with an ambulance without prehospital capabilities
Relevant outcomes	Time (min): alarm to thrombolysis (primary outcome); alarm to CT; symptom onset to thrombolysis Time (min) within different catchment zones (zones 1-4): alarm to CT/ thrombolysis; symptom onset to thrombolysis Number of patients with intravenous thrombolysis; number of patients treated within 60 min (golden hour thrombolysis) and within 90 min of symptom onset Number of patients with hemorrhagic complications 90-day mortality Number of patients with cerebrovascular diseases/ischemic stroke/intracranial hemorrhages delivered to hospital without stroke unit/neurosurgery department (triage to appropriate hospitals); number of secondary emergency referrals to another hospital (within 2 days from admission)
Setting	Berlin - 28 hospitals (14 stroke units)

	The study catchment area included about 1.3 million inhabitants, and was defined as being within 16 minutes of travel for ambulances from base. 4 different operation zones with expected arrival within 4, 8, 12, and 16 minutes from MSU base station were categorized for MSU deployment.	
Country	Germany	
Duration of study	May 1 2011 - January 31 2013	
Risk of bias		
Bias	**Reviewers' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "For randomization, we used 2 alternative blocks of 4 weeks, either "STEMO-control-STEMO-control" or "control-STEMO-control-STEMO."
Allocation concealment (selection bias)	Low risk	Allocation not concealed, but due to the week-wise randomization plan likely low risk of selection bias Quote: "Patients were included if the emergency call dispatcher activated a stroke dispatch, independent of randomized weeks or STEMO availability." Quote: "The dispatcher algorithm was the same during STEMO and control weeks."
Blinding of participants and personnel (performance bias)	High risk	Allocation was not masked from the EMS dispatcher, MSU/ambulance staff, or the patients (open-label trial)
Blinding of outcome assessment (detection bias)	Low risk	No systematic differences between groups in how outcomes were measured; data were de-identified Quote: "Data monitoring and audits were performed by an independent quality management team at the Center for Stroke Research Berlin."

Incomplete outcome data (attrition bias)	Low risk	Outcome data were missing among a low number of patients (1-4) in two outcomes. Which study arm the patients belonged to is not specified.
Selective reporting (reporting bias)	Low risk	The study protocol is available and, except for functional outcomes, all prespecified outcomes have been reported. The reason for not reporting functional outcomes has been explained.
Other biases	Low risk	The study appears to be free of other sources of bias.

Walter 2012 (62)

Clinical Trials ID	NCT00792220
Methods	Randomized, parallel-group, single-centre controlled trial
Participants	Patients suspected for stroke Sample size: 100 participants (53 in treatment group; 47 in control group) Distance to hospital (km) in median and IQR: 6 (4-10) in treatment group; 8 (6-15) in control group Symptom onset to alarm (min) in median and IQR: 21 (8-65) in treatment group; 23 (7-67) in control group Alarm to arriving at the scene (min) in median and IQR: 12 (9-16) in treatment group; 8 (6-11) in control group *Inclusion criteria:* patients aged 18–80 years, with one or more stroke symptoms (according to the modified recognition of stroke in the emergency room (ROSIER) scale); symptoms had started within the previous 2.5 hours; patient or patient's legal representative provided written informed consent *Exclusion criteria:* uncertain symptom onset, no focal stroke-like symptoms, pregnancy; if diagnosis and treatment options could not be offered because of defective key equipment in the MSU or the hospital, if unstable medical

	conditions needed immediate treatment in the intensive care unit, or if patients were secondarily transferred from primary hospitals
Intervention	Mobile stroke unit (MSU): an ambulance equipped with a CT scanner, a point-of-care laboratory, and a telemedicine connection to the hospital (enabling transmission of digital imaging and communication data obtained by CT scanning, or video of clinical examination, via the mobile telecommunication system to the picture archiving and communication system of the hospital). During the last study year, the MSU was equipped with a CT scanner allowing multi-modal imaging with CT angiography and CT perfusion. The MSU team included a paramedic, a stroke physician, and a neuroradiologist. The MSU team obtained the patient's history; undertook a neurological examination, CT scan, and laboratory examinations; and, if the patient was eligible, gave thrombolysis directly at the emergency site During the MSU weeks, a regular ambulance was always also sent out in addition to MSU (in parallel).
Comparator	Regular ambulance combined with optimized conventional hospital-based stroke management. Optimized management included point-of-care laboratory testing instead of testing by the centralized hospital laboratory.
Relevant outcomes	Time (min): alarm to therapy decision (primary endpoint); symptom onset to therapy decision; alarm to end of CT; symptom onset to end of CT; alarm to intravenous thrombolysis; symptom onset to intravenous thrombolysis; alarm to intravenous thrombolysis or intra-arterial recanalization (post hoc endpoint); symptom onset to intravenous thrombolysis or intra-arterial recanalization (post hoc endpoint) Number of patients with intravenous thrombolysis; number of patients with intravenous thrombolysis or intra-arterial recanalization (post hoc endpoint) Morbidity and function: NIHSS (cutoff value ≤1 or ≥8 points improvement), Barthel index (≥95 points), and mRS scores (≤2) at days 1 and 7 Safety endpoints (number of patients): Fatal secondary intracranial haemorrhage (ICH); non-fatal secondary ICH

	(change in NIHSS ≥ 4); secondary ICH (change in NIHSS < 4)	
Setting	Region of up to 30 km around University Hospital of the Saarland, Homburg	
Country	Germany	
Duration of study	November 2008 - July 2011	
Risk of bias		
Bias	**Reviewers' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Week-wise randomization plan (a block size of 4 weeks) Quote: "Our randomization list was created by an independent statistician (HS) with the SAS procedure PLAN."
Allocation concealment (selection bias)	Low risk	Allocation not concealed, but due to the week-wise randomization plan likely low risk of selection bias
Blinding of participants and personnel (performance bias)	High risk	Allocation was not masked from the EMS dispatcher, MSU/ambulance staff, or the patients
Blinding of outcome assessment (detection bias)	Low risk	No systematic differences between groups in how time, thrombolysis rate or ICH were measured; according to the study authors, there was no masking in assessment of "outcome-related secondary endpoints"; an independent statistician analyzed all data
Incomplete outcome data (attrition bias)	Low risk	No lost to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol is available and all pre-specified outcomes have been reported
Other biases	Low risk	Quote: "We stopped the trial after our planned interim analysis at 100 of 200

	planned patients (53 in the prehospital stroke treatment group, 47 in the control group), because we had met our pre-specified criteria for study termination."

Kunz 2016 (64;65)

Clinical Trials ID	NCT02358772
Methods	Observational registry study An ad-hoc continuation of the PHANTOM-S pilot study (Feb 5 to April 30, 2011) (105) and the PHANTOM-S trial (May 1, 2011, to Jan 31, 2013) (60)
Participants	Patients with ischemic stroke who received intravenous thrombolysis Sample size: *Received thrombolysis and had their data entered into a registry*: 932 (427 in treatment group; 505 in control group) *Patients with no prestroke dependency eligible for primary analysis:* 658 (305 in treatment group; 353 in control group) *Patients with prestroke dependency:* 264 (122 in treatment group; 142 in control group) *Inclusion criteria:* a) Patients who had lived at home without private or professional assistance before the event b) Patients dependent on assistance before stroke *Exclusion criteria:* Patients who arrived by private transport or who had a stroke in hospital; patients with stroke onset between 22:31 and 03:59 (these patients were unlikely to be cared for in the MSU, which operated between 07:00 and 23:00 for most of the study period); patients with 'last time seen well' not within past 4.5 hours (unknown time of symptom onset) who received intravenous thrombolysis when their diffusion-weighted imaging (DWI) and fluid attenuated inversion recovery (FLAIR) MRI was mismatched; patients not diagnosed with stroke according to their discharge

	notes; patients who denied or withdrew informed consent; patients who were not available at 3-month follow-up; patients with duplicate entry for second stroke; patients with stroke onset not within MSU catchment area; referral from other hospital; wake-up thrombolysis	
Intervention	Intravenous thrombolysis within an MSU (called Stroke Emergency Mobile, STEMO) (see the PHANTOM-S trial above (60) for further details); Patient data were documented in STEMO (pre-hospital) registry.	
Comparator	Intravenous thrombolysis within conventional care (normal ambulances and in-hospital care at the Charité Campus Benjamin Franklin); Patient data were documented in an in-hospital thrombolysis registry.	
Relevant outcomes	a) Patients who had lived at home without private or professional assistance before the event: 3-month functional outcomes after thrombolysis: number of patients with mRS score 0–1 (primary outcome); number of patients with mRS score 0–3 b) Patients dependent on assistance before stroke: 3-month functional outcomes after thrombolysis: number of patients with mRS score 0–3 mRS was assessed at 3 months by standardized telephone interview, via a standardized questionnaire returned by mail, via a discharge letter in patients who died in hospital, or by information from registration offices.	
Setting	MSU covering 1.3 million inhabitants of Berlin vs. normal ambulances and in-hospital care at the Charité Campus Benjamin Franklin in Berlin (located within the MSU service catchment area (zone 3), 9-min EMS transportation time to the MSU service base station; a wide overlap between its catchment area and the MSU catchment area)	
Country	Germany	
Duration of study	February 2011 – March 2015	
Risk of bias		
Bias	**Reviewers' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Observational registry study, no random sequence generation

Allocation concealment (selection bias)	High risk	Observational registry study, allocation was not concealed
Blinding of participants and personnel (performance bias)	High risk	Neither the EMS dispatcher, MSU/ambulance staff, nor the patients were blinded.
Blinding of outcome assessment (detection bias)	High risk	Quote: "Although data in both registries were collected with standardised mRS assessment by certified raters, data acquisition in both cohorts was done by different raters. Therefore, outcome assessment was not masked and we cannot rule out an information bias, particularly because raters in the STEMO group were sometimes directly involved in patient care."
Incomplete outcome data (attrition bias)	Low risk	There does not appear to be large differences between groups. 419 of 427 (98.1%) eligible patients in the treatment group and 493 of 505 (97.6%) eligible patients in the control group had complete outcome data.
Selective reporting (reporting bias)	Low risk	The study protocol is available and, except for 3 month mRS score 2-6 and 3 month mRS score 4-6, all pre-specified outcomes have been reported.
Other biases	Unclear risk	Quote: "...not all baseline parameters were balanced, some non-observed or non-documented confounders could not be included in adjusted analyses and the low loss-to-follow-up rate might have introduced an additional bias."

Gutiérrez 2016 (66)

Clinical Trials ID	Related to NCT02190500
Methods	Preliminary safety study related to an ongoing study (dosimetry study)
Participants	Setting: An ambulance equipped with a CT scanner (MSU) Sample size: Measurements resulting from the care of 106 patients
Intervention	Measurements of radiation exposure: The MSU workers were equipped with personal dosimeters. The CT technician stood at the side door, outside the MSU and operated the CT scanner with a laptop computer. All other personnel stood outside the vehicle during the scan, unless medically necessary for the patients care, and then wearing lead aprons. Three area monitors were positioned inside the vehicle. In addition to this monitoring regime, ion chamber measurements were performed outside the ambulance during scans of a head phantom.
Comparator	Staff: Exposed worker in a high volume hospital setting (on average) (67) The public: Dose limit given by the American authorities (68;69) Patient: Typical adult head examination with a CT (70)
Relevant outcomes	Radiation exposure (mSv, µSv) to MSU staff, the public and patients
Setting	MSU in Houston, Texas
Country	USA
Duration of study	July 2014 - June 2015

Appendix 6. GRADE evidence profiles

Question: MSU care compared to conventional care for suspected stroke

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MSU care	Conventional care	Relative (95% CI)	Absolute (95% CI)		
Time from alarm to imaging (assessed with: minutes)												
2	randomised trials	serious [a]	not serious [b]	not serious	serious [c]	none	245	265	-	MD **26.87 minutes fewer** (50.98 fewer to 2.77 fewer)	⊕⊕◯◯ LOW	
Time from alarm to thrombolysis (assessed with: minutes)												
2	randomised trials	serious [a]	not serious	not serious	not serious	none	245	265	-	MD **30.52 minutes lower** (43.04 lower to 18 lower)	⊕⊕⊕◯ MODERATE	
Time from symptom onset to thrombolysis (assessed with: minutes)												
2	randomised trials	serious [a]	serious [d]	not serious	Serious [d]	none	253	267	-	MD **49.84 minutes lower** (117.26 lower to 17.58 higher)	⊕⊕◯◯ LOW	
Total number of patients who received thrombolysis (thrombolysis rate) (assessed with: number of patients)												
2	randomised trials	serious [a]	not serious	not serious	not serious	none	212/667 (31.8%)	228/1088 (21.0%)	**RR 1.53** (1.31 to 1.80)	**111 more per 1 000** (from 65 more to 168 more)	⊕⊕⊕◯ MODERATE	
Number of patients who received thrombolysis within 60 minutes (assessed with: number of patients)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MSU care	Conventional care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	62/200 (31.0%)	12/220 (5.5%)	**RR 5.68** (3.16 to 10.23)	**255 more per 1 000** (from 118 more to 503 more)	⨁⨁◯◯ LOW	
90-day mortality (assessed with: number of patients)												
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	33/198 (16.7%)	27/218 (12.4%)	**RR 1.35** (0.84 to 2.15)	**43 more per 1 000** (from 20 fewer to 142 more)	⨁⨁◯◯ LOW	
3-month functionality (mRS 0-1) (assessed with: number of patients)												
1	observational studies	not serious [e]	not serious	not serious	not serious	none	161/305 (52.8%)	166/353 (47.0%)	**RR 1.12** (0.96 to 1.31)	**56 more per 1 000** (from 19 fewer to 146 more)	⨁⨁◯◯ LOW	
3-month functionality (mRS 0-3) (assessed with: number of patients)												
1	observational studies	not serious [e]	not serious	not serious	not serious	none	253/305 (83.0%)	260/353 (73.7%)	**RR 1.13** (1.04 to 1.22)	**96 more per 1 000** (from 29 more to 162 more)	⨁⨁◯◯ LOW	

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Lack of blinding (patients and staff)

b. Same effect direction, but heterogenous effect estimates (however, not considered to be a reason for downgrading)

c. Large confidence interval

d. Heterogenous effect estimates and large confidence interval (0.5 points for each)

e. Not all baseline parameters were balanced, some non-observed or non-documented confounders could not be included in adjusted analyses (however, not considered to be a reason for downgrading)

Appendix 7. Additional results tables

Table A: *Reported medians, lower and upper quartiles, and sample sizes (n) by Walter et al. (62), and corresponding estimated means, standard deviations, and 95% confidence intervals on the estimated means (in minutes)*

Outcome	Median	LQ	UQ	n	Estimated Mean	Estimated SD	Estimated 95% CI
Alarm to end of CT (intervention)	34	30	38	53	34.0	6.1	(32.4, 35.6)
Alarm to end of CT (control)	71	62	87	47	73.3	19.1	(67.9, 78.8)
Alarm to thrombo-lysis (intervention)	38	34	42	53	38.0	6.1	(36.4, 39.6)
Alarm to thrombo-lysis (control)	73	60	93	47	75.3	25.2	(68.1, 82.5)
Symptom onset to thrombolysis (intervention)	72	53	108	53	77.7	41.9	(66.4, 89)
Symptom onset to thrombolysis (control)	153	136	198	47	162.3	47.4	(149, 176)

LQ = Lower quartile
UQ = Upper quartile
SD = Standard deviation
CI = Confidence interval

Table B: *Time to diagnosis and treatment: comparison of all patients in the intervention group, regardless whether they received care in the MSU or not, with patients in the control group (60)*

Outcome	MSU group (with MSU deployment)	**Control group**	p-value	**MSU group (with and without MSU deployment)**	**p-value[a]**
No. of patients	(n=192)	**(n=218)**		**(n=300)**	
Alarm to imaging, min	Mean (95% CI): 37.7 (35.6-39.7) Median (IQR): 35 (30-42)	Mean (95% CI): 52.4 (50.3-54.4) Median (IQR): 50 (43-59)	<.001	Mean (95% CI): 44.0 (42.0-46.0) Median (IQR): 39 (32-52)	< .001

Alarm to thrombo-lysis, min	Mean (95% CI): 51.8 (49.0 - 54.6) Median (IQR): 48 (39 - 56)	Mean (95% CI): 76.3 (73.2-79.3) Median (IQR): 72 (62 - 85)	<.001	Mean (95% CI): 61.4 (58.7-64.0) Median (IQR): 55 (44-75)	< .001
No. of patients	(n=200)	**(n=220)**		**(n=310)**	
Symptom onset to thrombo-lysis, min	Mean (95% CI): 102.7 (93.9-111.5) Median (IQR): 81 (56-129)	Mean (95% CI): 118.5 (111.8-125.2) Median (IQR): 105 (81-145)	<.001	Mean (95% CI): 110.1 (103.4-116.8) Median (IQR): 95 (65-142)	.003

[a] = Tested against control group
IQR = Interquartile range
CI = Confidence interval
min = Minutes

Table C. *Thrombolysis rate in total and within 90 minutes of symptom onset: comparison of all patients in the intervention group, regardless whether they received care in the MSU or not, with patients in the control group (60)*

Outcome	MSU group (with MSU deploy-ment)	**Control group**	p-value	**MSU group (with and without MSU deployment)**	**p-value[a]**
No. of patients with ischemic stroke	(n=614)	**(n=1041)**		**(n=1070)**	
Patients who received thrombolysis No. (%)	200 (32.6)	220 (21.1)	< .001	310 (29.0)	< .001
Patients treated within 90 min of symptom onset, No. (%)	115/200 (57.5)	82/220 (37.4[b])	< .001	149/310 (48.1)	.02

[a] = Tested against control group
[b] = The study authors have reported 37.4%. However, according to our own calculations the proportion should be 37.3%.

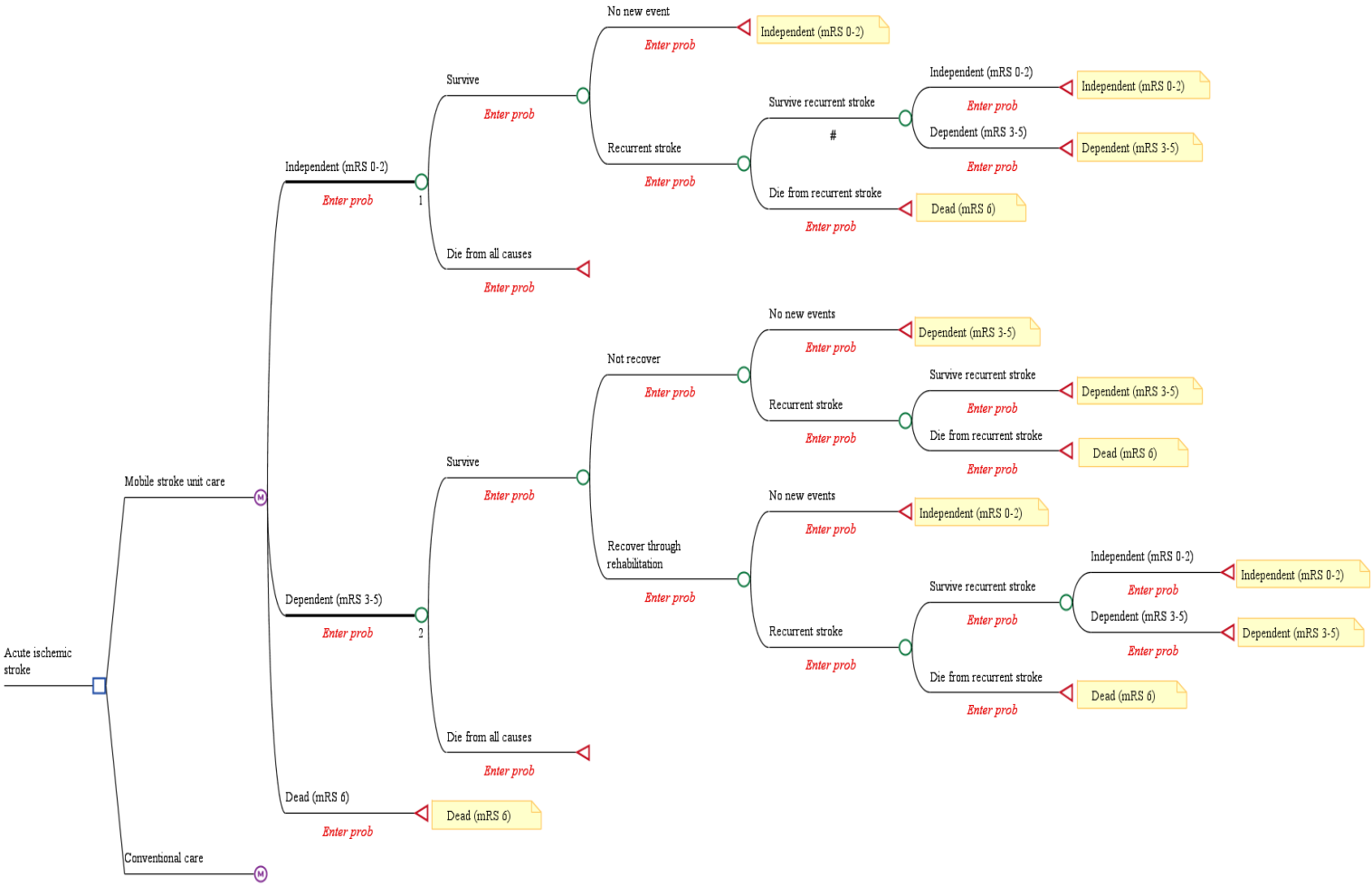
Table D. *90-day mortality among patient who received thrombolysis: comparison of all patients in the intervention group, regardless whether they received care in the MSU or not, with patients in the control group (60)*

Outcome	MSU group (with MSU deploy-ment)	**Control group**	p-value	**MSU group (with and without MSU deployment)**	**p-value[a]**

No. of patients who received thrombolysis	198	**218**		**308**	
90-day mortality, No. (%)	33 (16.7)	27 (12.4)	0.21	48 (15.6)	0.30

[a] = Tested against control group

Appendix 8. Decision tree illustrating the Markov model structure with possible transitions



Decision tree illustrating the model structure with possible transitions. The structure in the conventional care arm is identical to the structure in the mobile stroke unit arm.

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Published by the Norwegian Institute of Public Health
August 2019
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The report can be downloaded as pdf
at www.fhi.no/en/publ/