Economic Evaluation of a Mobile Stroke Unit Service in Germany

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Background: Lower global disability and higher quality of life among ischemic stroke patients was found to be associated with the dispatch of mobile stroke units (MSUs) among patients eligible for recanalizing treatments in the Berlin_Prehospital Or Usual Delivery of stroke care (B_PROUD) study. The current study assessed the cost-utility and cost-effectiveness of additional MSU dispatch using data from this prospective, controlled, intervention study.
Methods: Outcomes considered in the economic evaluation included quality-adjusted life years (QALYs) derived from the 3-level version of EQ-5D (EQ-5D-3L) and modified Rankin Scale (mRS) scores for functional outcomes 3-months after stroke. Costs were prospectively collected during the study by the MSU provider (Berlin Fire Brigade) and the B_PROUD research team. We focus our results on the societal perspective. As we aimed to determine the economic consequences of the intervention beyond the study's follow-up period, both care costs and QALYs were extrapolated over 5 years.
Results: The additional MSU dispatch resulted in an incremental €40,984 per QALY. The best-case scenario and the worst-case scenario yielded additional costs of, respectively, €24,470.76 and €61,690.88 per QALY. In the cost-effectiveness analysis, MSU dispatch resulted in incremental costs of €81,491 per survival without disability. The best-case scenario and the worst-case scenario yielded additional costs of, respectively, €44,455.30 and €116,491.15 per survival without disability.
Interpretation: Among patients eligible for recanalizing treatments in ischemic stroke, MSU dispatch was associated with both higher QALYs and higher costs and is cost-effective when considering internationally accepted thresholds ranging from an additional €40,000 to €80,000 per QALY.

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Stroke is the second leading cause of death, and the third cause of disability-adjusted life-years (DALYs) worldwide.[1] Intravenous thrombolysis treatment with recombinant tissue plasminogen activator (tPA) is the only approved pharmacologic treatment in acute ischemic stroke and recommended for up to 4–5 hours after

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symptom onset when no contraindications are present.[2] Studies have shown that earlier treatment initiation results in better outcomes.[2,3] From symptom onset, time-to-treatment can be reduced by deploying "mobile stroke units" (MSUs) equipped with computed tomography scanners and trained personnel, enabling acute stroke work-up and administration of thrombolytic treatment prior to hospital arrival.[4,5]

For healthcare systems to justify reimbursement of MSU deployment, MSU dispatch must be clinically effective and demonstrate cost-effectiveness. The cost-utility analysis in the PHANTOM-S study (Berlin, Germany, 2011–2013) estimated an incremental cost-effectiveness ratio (ICER) of €32,456/quality-adjusted life-year (QALY; $32,306.70; EUR 1 = US$ 0.9954) based on shorter onset-to-treatment times and increased thrombolysis rates due to MSU deployment.[6] This estimate fell below the cost-utility threshold for the UK (£30,000/QALY),[7] the Netherlands (up to €80,000/QALY),[8] and the United States (a study proposed a threshold of either $100,000/QALY or $150,000/QALY).[9] A 2020 Australian study by Kim et al estimated that MSUs cost an additional AU$30,982 per additional DALY averted in comparison with standard care.[10] A recent Norwegian study analyzed the economic consequences of the dispatch of MSUs and reported an ICER between $38,660/QALY and $113,700/QALY, depending on the number of potentially treated patients.[11] None of these studies used prospectively collected data on quality of life (QoL) and long-term care costs. Hence, we are confident that our study adds a significant novelty to previously published MSU cost-effectiveness studies.[12]

Recent results from the Berlin-based B_PROUD study showed that the dispatch of MSUs, compared with conventional ambulances alone, was associated with significantly better functional outcomes and lower global disability 3 months after stroke among ischemic stroke patients with no contraindications to recanalizing treatments.[4] We now aimed to assess cost-utility, cost-effectiveness, and cost-benefit of the additional MSU dispatch compared with standard care for eligible acute ischemic stroke patients in Berlin, Germany.

Methods

Setting, Patients, and Study Design

We used data from B_PROUD, a prospective, non-randomized, controlled intervention study conducted in Berlin, Germany. Study inclusion commenced on February 1, 2017, until May 8, 2019, and follow-up data collection ended on October 30, 2019.

Three MSUs were consecutively rolled-out across Berlin over 17 months.[4] Exposure status was determined according to ambulance dispatch type (with/without MSU dispatch) in each MSU's catchment area, analogous to the intention-to-treat principle in a randomized controlled trial. Group allocation was determined by MSU availability at the time of dispatch; creating a natural experiment setting. In overlapping catchment areas, the geographically closest available MSU was sent to the event location. MSUs in our setting are staffed with a paramedic, a radiology technician with emergency training, and a neurologist with training in emergency medicine. Conventional ambulances are staffed with a paramedic and an ambulance technician, who are trained to stabilize and transport patients to hospitals.

Patients were included in the B_PROUD study if they had a final diagnosis of acute cerebral ischemia (ischemic stroke or transient ischemic attack, according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision) and were likely to be eligible for thrombolysis or thrombectomy.[4] Other criteria for enrollment in the trial included being at least 18 years old; the emergency call had to prompt an MSU dispatch code during the MSU's operating hours; stroke onset within the previous 4 hours; patients had to be within the catchment area of an MSU; patients had to have been ambulatory before their stroke (a rough proxy of modified Rankin Scale scores [mRS]). Other stroke subtypes were excluded from the primary study population. Patients with final non-stroke diagnoses or stroke patients not eligible for recanalizing treatments were not included because no differences in short term outcomes were found in the preceding study.[6] We therefore assumed that the dispatch of MSUs had no effect on outcomes for these patient groups. The intervention group consisted of ischemic stroke and TIA patients for whom an MSU and a conventional ambulance were simultaneously dispatched (n = 749). The comparator group consisted of those for whom only a conventional ambulance was dispatched (n = 794).[4] Further details on the study design, and study population characteristics were published elsewhere.[4]

Outcomes

For the cost-utility analyses, the outcome of health-related QoL was measured with the 3-level version of EQ-5D (EQ-5D-3L) 3 months after the index event, using the German Visual Analogue Scale value set.[13] This questionnaire comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression—and was assessed by trained study nurses using telephone interviews or paper questionnaires. A previous study investigating QoL changes according to stroke symptom severity found that the differences in EQ-5D-3L scores and survival probabilities after the initial months remained relatively constant between stroke severity categories over a 5-year period.[14] Thus, we considered a 5-year time horizon in our analyses. This time horizon allowed us to take into account care costs, for which the financial burden extends beyond the 3-month follow-up (see the Costs section). While QoL in the Luengo-Fernandez study was not assessed at the 3-month follow up, at which times QoL information was collected in B_PROUD, it falls within their 1- and 6-month follow-up interval.[14] QALY scores for 5 years were calculated by multiplying the EQ-5D-3L score at 3 months by 5. We recognize that this extrapolation implies that the EQ-5D-3L scores for each patient remains constant over a 5-year period. However, this approach was suitable for the present study because the ICER denominator corresponds to the difference in QALYs between groups after confounding adjustment. Therefore, the relevant assumption in our approach was that the variation in the amount of QALYs due to death or to QoL changes after confounding adjustment was the same in both groups across the 5-year period.

The primary outcome measure in the cost-effectiveness analyses was the 3-month mRS, a measure of the degree of disability or dependence in the daily activities among people who have suffered a stroke (range 0, no neurological symptoms, to 6, death). In the B_PROUD study, patients in the MSU dispatch group had significantly less global disability as measured by mRS score compared with those in the standard care dispatch group (odds ratio [OR] 0.71; 95% confidence interval [CI], 0.58 to 0.86).[4] For the cost-effectiveness analysis, this score was dichotomized in two levels: 0–1 ("excellent" or/"survival without disability") and 2–6 ("not excellent"/"survival with disability" or "dead").[15] Determination of 3-month mRS scores was performed as the median of three independent neurologists rating outcomes in a blinded manner whenever possible.[4] For the dichotomized mRS outcome, we assumed that the difference in the number of survivals without disability between groups, after confounding adjustment, remained constant over the 5-year period.

Costs

Costs were prospectively documented throughout the study period by the MSU provider (Berlin Fire Brigade) and by the B_PROUD study personnel. These included MSU-related investment and running costs, prehospital medication costs, and prehospital imaging costs. For the MSU investment costs, we obtained the annualized cost (per 12 months) of an MSU and multiplied it by the running duration of all MSUs (56 months of operation), as shown in Table S3.3.

Our analyses present cost from two different perspectives: the societal perspective and the statutory health insurance perspective. Taking the societal perspective, we considered all additional MSU-related costs incurred by the Berlin Fire Brigade (including value-added tax). Taking the statutory health insurance perspective, we used the fee calculated per MSU dispatch by the Berlin Fire Brigade for reimbursement by the statutory health insurances (assuming that 97% of all dispatches with patient care were actually billable and reimbursed). As analyses from the statutory health insurance are specific to Germany, we present them in the Supplementary Material and focus on the societal perspective in the manuscript.

We also accounted for projected costs associated with long-term (nursing) care in the 5-year period following the index event. To denote the extent of the need for care, we used unpublished information from another large German stroke outcome study[16] and converted mRS values into different levels of care dependency called "Pflegestufen," used in Germany until 2017. In Germany, the levels of care dependency are determined by the Medical Service of the Health Insurance (MDK) and are used to calculate long-term care insurance benefits for care provision. Since Germany changed the way of categorizing these levels in 2017, we converted the original "Pflegestufe" levels to the contemporary "Pflegegrad" (care grade) according to official, published conversion tables.[17] Synthesizing information from 3-month follow-up on individual's care-grade and information on each patient's living situation (at home being cared for by a relative, at home being cared for by a professional, in a nursing care home, or in hospital), we calculated total care service costs.

We applied a 3% discount rate to long-term (nursing) care costs for the years following the intervention, as recommended by the German Institute for Quality and Efficiency in Health Care.[18] Furthermore, we used the 3% rate to convert 2020 costs (which we received from the named data sources) to 2019, which is the base year for our analyses. We report all costs in Euros.

We considered a base-case, a best-case, and a worst-case scenario (detailed in Supplementary Appendix 1). Under the base-case scenario, we analyzed outcomes in the primary study population.[4] We therefore accounted for additional costs incurred by MSU operation for all code stroke patients. Furthermore, we assumed that medication costs for individual tPA treatment were the same in the pre-hospital and in-hospital settings and that costs for nursing care depended on the mRS score. A best-case scenario was created following the base-case scenario, but calculating long-term care costs with a less conservative conversion from 3-month disability to nursing costs was used (Supplementary Appendix 2). We further assumed that the frequency of MSU dispatches can be increased by a factor of 1.8, corresponding to the higher tPA treatment frequency per MSU operation week, as seen during the PHANTOM-S study period.[6] The worst-case scenario used the base-case scenario's assumptions with several modifications. As we assumed that the effects observed in B_PROUD only applied to patients with full 3-month follow-up information, we restricted the analysis to complete cases only instead of using multiple imputation under this scenario. Moreover, we assumed that effects on mRS (and levels of care dependency) only remained stable over 18 months (according to the observation period in IST-3).[19] Finally, we assumed that half of the imaging examinations would have to be repeated in-hospital.

Statistical Methods

We used the parametric G-formula to estimate incremental costs and incremental outcomes due to MSU dispatch for all analyses.[20] We fitted a linear regression model with costs as the dependent variable, and MSU dispatch, and a set of covariates that have been selected in the clinical effectiveness study (age, sex, arterial hypertension, diabetes mellitus, atrial fibrillation, neurological symptoms at emergency medical services or MSU arrival, and living situation before stroke) as independent variables.[4] We then used this model to predict the expected costs for each individual for both hypothetical scenarios in which the MSU was dispatched in addition to a conventional ambulance to all code-stroke patients versus dispatch of a conventional ambulance alone for all code-stroke patients. In order to obtain overall costs, we summed the predicted costs across all individuals in each scenario and computed the difference between the overall costs to obtain incremental costs related to MSU dispatch. We used the same procedure to compute incremental QALYs due to MSU dispatch in addition to a conventional ambulance, since QALYs is also a numeric variable.

For the dichotomized mRS, we ran a logistic regression model to predict each individual's probability of surviving without disability (mRS 0–1) under each scenario and to estimate the absolute number of individuals who survived without disability per scenario. Finally, we computed the incremental number of survivors without disability due to MSU dispatch as the difference.

Incremental overall costs and incremental overall effects (QALYs in the cost-utility analysis and dichotomized mRS in the cost-effectiveness analysis) were used to estimate ICERs.

As care cost calculations depended on individual patient data, some of which had missing values, there were missing values in the costs and in other outcomes (QALY and dichotomized mRS). Assuming missing at random data, we used multiple imputation by chained equations to impute missing values for the base-case and best-case scenarios. Point estimates for incremental costs, incremental QALYs, and incremental survivals were obtained as averages across the five imputed datasets. In accordance with the guidelines,[21] imputation models included all covariates that were included in the regression models in the primary effectiveness publication (see above).[4]

To compute 95% CIs, we performed nonparametric bootstrapping with 5,000 replications according to the BootMI method.[22] On each bootstrapped dataset, after multiple imputation, the 2.5% and 97.5% percentiles of the resulting distribution of the average metric (across 5 imputed datasets) were considered as confidence limits. We further used cost-utility and cost-effectiveness planes to illustrate the bootstrapped cost-utility and cost-effectiveness pairs resulting from the bootstrapping replication runs, depicting the joint uncertainty surrounding costs and outcomes.[23] Data points falling into the "northeast" quadrant of these figures indicate that the intervention generates more health gains but is also more expensive, while points in the "southwest" quadrant indicate a cost-saving intervention that generates less health gains. An intervention that is associated with higher health gains and lower costs ("southeast" quadrant), is considered to be an economically "dominant" strategy. We also report the percentage of data points that fell into each quadrant.

Furthermore, we conducted a sensitivity analysis, in which the models were only adjusted for MSU coverage, operationalized as the number of MSUs covering the location (zip code) during the specific quarter of the calendar year at the moment of the patient's stroke (due to overlapping of MSU catchment areas). We assumed no relevant change in the MSU availability occurred after the introduction of the GPS system. To create the imputed datasets, we used information from all covariates in the main analyses (see above) plus the MSU coverage variable.

All analyses were conducted using R version 4.0.3 and RStudio.[24]

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Charité Ethics Committee (EA4/109/15). The economic evaluation was conducted in accordance with the statistical analysis plan.

Results

Patients' baseline parameters, clinical, and process information can be found in Supplementary Appendix 3, Table S3.1.

Costs

Cost breakdown per patient and exposure group under the base-case scenario is shown for the societal perspective, in Table 1. Under this scenario, the largest cost contributors in the MSU group were medical costs/reimbursement of expenses, which included costs for hospital employed personnel (neurologists, technicians, teleradiology, and project management) and amounted to €4,383.08 per included stroke patient. The MSU investment costs were the second-largest cost contributor (€1,286.02 per patient). The total costs (excluding long-term care costs) were estimated to be on average €8,491.58 during the 56-month study period per patient allocated to the MSU group. In the standard care group, the total costs amounted to €1,274.54 per patient.

Outcomes

The average EQ-5D-3L score was higher in the MSU group than in the standard care group (0.63 vs 0.59). The percentage of patients who reported a "good outcome" as measured with the mRS was also higher in the MSU group than in the standard care group (50.92% vs 42.31%) (Table 2).

Cost-Utility Analyses

Results under the base-case scenario are shown in Table 3, which shows that MSU dispatch was associated with both higher costs and QALYs. Incremental overall costs due to MSU dispatch amounted to €10,759,089.49 (9,912,284.42; 11,997,571.30). Incremental QALYs due to MSU dispatch were 262.52 (−41.06; 479.92), and the resulting ICER per QALY was €40,983.82. A large majority (95.16%) of the bootstrapped replications, showed that MSU dispatch was associated with both higher QALYs and higher costs (Figure).

As expected, given our assumptions (Supplementary Appendix 1), the ICERs under the best-case scenario yielded the lowest values (€24,470.76 per QALY), mostly attributable to lower incremental overall costs than in other scenarios. On the opposite, under the worst-case scenario, the ICER for the societal (€61,690.88 per QALY) was higher than in the base-case scenario due to higher incremental overall costs but also because of lower incremental overall QALYs.

Bootstrap replications' patterns were similar under all scenarios and between perspectives, with approximately 95% of the bootstrapped samples showing that MSU dispatch was associated with higher QALYs and higher costs.

Taking the statutory health insurance perspective, the ICER per QALY amounted to €28,029·51, which is lower than the ICER calculated when taking a societal perspective. Detailed results for the analyses taking the statutory health insurance perspective are given in Supplementary Appendix 3, Table S3.4.

Cost-Effectiveness Analyses

Cost-effectiveness analyses, under the base-case scenario, showed that incremental overall costs due to MSU dispatch amounted to €10,793,823.78 (9,809,757.36; 12,020,619.78) and incremental survivals to 132.45 (48.30; 199.85). Thus, an incremental survival without disability was associated with additional costs amounting to €81,491.49 (Table 3).

The best-case scenario and the worst-case scenario yielded, respectively, €44,455.30 and €116,491.15 per survival without disability.

The percentage of bootstrapped samples indicating higher incremental survivals and higher costs associated with MSU dispatch reached almost 100% (Figure).

Results for the analyses taking the statutory health insurance perspective are given in Supplementary Appendix 3, Table S3.4.

Sensitivity Analyses

Sensitivity analyses' results (Supplementary Appendix 3, Tables S3.6 and S3.7) were similar to the findings of the main analyses.

Discussion

For the primary population of the B_PROUD study, incremental costs and incremental QALYs generated an ICER of circa €41,000 per QALY. These values are similar to the results of a previous study conducted in Berlin/Germany, which estimated an ICER of €32,456 per QALY.[6] Overall, our findings support that MSUs can be considered cost-effective for thresholds greater than €40,000 per QALY. The interpretation of this number depends on the acceptable and setting-specific threshold, and the range of possible thresholds varies (eg, between €20,000 and €80,000 in the Netherlands or between $100,000 and $150,000 in the US). While Germany does not have an official threshold, the MSU implementation would be, for example, justified in the Netherlands, which has a similar healthcare system (with a mixed compulsory social insurance and private voluntary insurance) and where this ICER figure could lie in the official threshold range. In determining the cost-effectiveness of a health intervention, the WHO Commissions on Macroeconomics and Health

TABLE 1. Mean Additional Costs Per Patient Included in the B_PROUD Study (€, Unadjusted, Base-Case Scenario, Societal Perspective)

Societal Perspective	Mean Cost per Patient MSU Group (n = 749)	Mean Cost per Patient Standard Care Group (n = 794)
MSU-related costs		
Investment costs	€1,286.02	
Interest	€67.15	
Maintenance and repairs	€698.90	
Fuel	€77.75	
Personnel	€974.35	
Medication	€654.40	€481.11*
Consumables	€76.93	
Other operating costs	Facility expenses: €81.99 Medical attire for MSU personnel: €33.92 Medical costs/reimbursement of expenses (neurologists, technicians, teleradiology and project management): €4,383.08 Personnel pension provisions and allowances: €397.09 Internal costs incurred by the Fire Brigade†: €511.44	
Savings through the assignment of MSU emergency physicians to conventional emergency cars when MSUs were out of service‡	−€371.31	
Savings by avoiding repeated imaging in hospitals§	−€380.13	
Costs for additional emergency physician car deployments¶		€620.35
Costs for additional rescue helicopter deployments		€145.40
Costs for additional auxiliary vehicle deployments		€27.68
Long-term care costs over 5 years	Depends on patient's mRS, living situation and time after index event (Supplementary Appendix 2)	Depends on patient's mRS, living situation and time after index event (Supplementary Appendix 2)

Note: All costs are reported per participant over a 56-month running period except for the nursing care costs, which were projected over the 5-year period after the index event.

*There were 382 patients in the standard care group who received tPA at the hospital, with a cost of €1,000 and there are 794 patients in this group: €1,000 × 382/794.

†Internal costs incurred by the Fire Brigade, including administration, insurance, dispatch, housing, trainings, and routine emergency medical services' data collection (excluding costs for command operations).

‡During B_PROUD, the three MSUs accumulated a total of 535 off-duty working days. During this period, MSU physicians worked on conventional physician staffed ambulances.

§We used internal cost calculation fees of Charité Universtätsmedizin Berlin in order to quantify the in-hospital cost savings by shifting brain imaging to the prehospital setting.

¶MSUs with an emergency physician aboard were dispatched to all patients with code stroke in the coverage area during operational times. In cases when no MSUs were available, Berlin regulations stipulate that a conventional ambulance without an emergency physician on board is to be dispatched to code stroke patients who do not present with compromised vital signs nor reduced vigilance, while a conventional ambulance plus an emergency physician car are dispatched to patients with compromised vital signs or with reduced vigilance. In the latter case, if no emergency physician cars are available, helicopters are sent to the scene.

Abbreviations: MSU = mobile stroke unit; mRS = modified Rankin Scale; tPA = recombinant tissue plasminogen activator.

TABLE 2. Quality of Life Outcomes (Available Case, Per Participant, Unadjusted)

	MSU group (Available Case, per Patient)	Standard Care Group (Available Case, per Patient)
No.	618	649
EQ-5D-3L	0.63	0.59
No.	654	683
Lives saved without disability, mRS 0–1 (%)	50.92% (n = 333)	42.31% (n = 289)

Abbreviations: mRS = modified Rankin Scale; MSU = mobile stroke unit.

suggests a threshold of one to three times the GDP per capita.[25] For Germany, this threshold would amount from $58,386 to $175,158. Our ICER result would also be considered cost-effective using these reference values.[26]

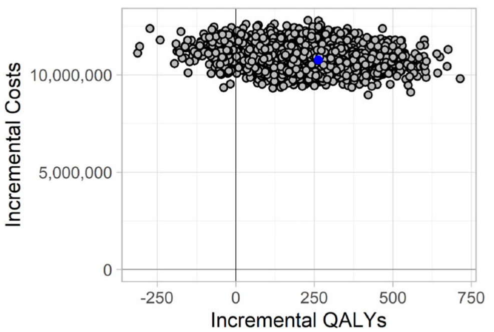
Previous studies (1) relied on extrapolations of IVT treatment effects in the rather crude 60 or 90 minutes onset to treatment time intervals, (2) projected disability scores to estimate QoL and/or (3) used probabilistic models to estimate the incremental costs per QALY. The present analysis makes use of prospectively measured outcomes and is therefore more robust compared with previous evaluations.

One challenge for economic evaluations based on trials is how they can be applied to other settings. On the cost side, we have shown cost data whenever possible, with a clear indication of unitary costs and the amount of resource consumption. This allows decision-makers in other healthcare systems to apply their own prices to the

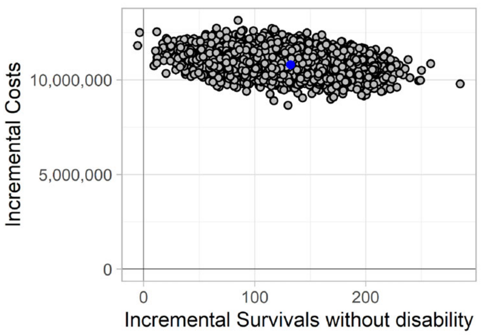
TABLE 3. Cost-Utility and Cost-Effectiveness Analyses for the Societal Perspective

	Incremental Overall Cost in € (Bootstrapped 95% CI) for 1,543 Patients*	Incremental Overall QALY or Survival Without Disability (Bootstrapped 95% CI) for 1,543 Patients*	ICER per QALY or per Incremental Survivals Without Disability in €	NE %	NW %
Cost-utility analysis					
Base-case scenario	10,759,089.49 (9,912,284.42; 11,997,571.30)	262.52 (−41.06; 479.92)	40,983.82	95.16	4.84
Best-case scenario	5,839,431.83 (4,351,335.96; 7,553,436.36)	238.63 (−35.09; 484.01)	24,470.76	95.36	4.64
Worst-case scenario	13,129,271.81 (12,072,370.83; 14,205,721.97)	212.82 (−46.27; 471.22)	61,690.88	94.7	5.3
Cost-effectiveness analysis					
Base-case scenario	10,793,823.78 (9,809,757.36; 12,020,619.78)	132.45 (48.30; 199.85)	81,491.49	99.96	0.04
Best-case scenario	5,912,181.64 (4,261,885.24; 7,592,776.25)	132.99 (57.46; 208.94)	44,455.30	99.98	0.02
Worst-case scenario	13,129,271.81 (12,072,370.83; 14,205,721.97)	112.71 (37.56; 188.15)	116,491.15	99.86	0.14

Abbreviations; CI = confidence interval; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-years; NE = Northeast Quadrant; NW = Northwest Quadrant.
*The figure "1,543 patients" corresponds to the pseudo-population created when using the G-formula method[18] (see the Methods section).



A Cost-utility analysis (base-case scenario, societal perspective)



B Cost-effectiveness analysis (base-case scenario, societal perspective)

FIGURE: Cost-utility and cost-effectiveness planes.

same units of resource use. Furthermore, we focused our analyses on the societal perspective, which is less country-specific than statutory-health insurance (reported in the Supplementary Appendix only). The completeness of MSU coverage in Berlin makes it generalizable for the whole city. All hospitals with a stroke unit in Berlin participated in the data collection. With regard to catchment areas, once all MSUs were in operation, they covered more than 94% of the Berlin population (according to the Berlin Fire Brigade).[4]

Several limitations to our study should be considered when interpreting our results. First, one challenge for economic evaluations is their generalizability to other settings.[27,28] In terms of costs, we reported results from a societal and a statutory health insurance perspective. In the Berlin setting, emergency physician cars are dispatched to the scene in addition to conventional ambulances in selected cases with unstable vital parameters or loss of consciousness. We recognize that in other settings, ambulances may only be paramedic-staffed. Thus, related costs in the conventional care group may be higher in our case. On the other hand, several MSUs are operated using telemedicine in order to avoid neurologist staffing of the MSU. This is likely to largely reduce the costs of MSU care, but there may be other disadvantages.

We made some simplifying assumptions due to limitations in data availability. First, we did not account for possible in-hospital savings related to MSU dispatch due to shorter lengths of stay in costly high care monitoring units or rehabilitation hospitals as a consequence of improved functional outcomes (Supplementary Appendix 3, Table S3.8). Furthermore, we did not account for reduced resource consumption regarding consumables nor for potential benefits in terms of time savings in emergency departments created by pre-hospital stroke work-up and medical treatment. Second, although the average age of patients in this study was 73.5 years, a total of 385 included patients were less than 65 years old, which is the current standard retirement age in Germany. Our computations are therefore conservative, as they do not reflect potential savings in terms of productivity gains when taking a societal perspective.

Third, under the base-case scenario, we used the most conservative approach in converting costs from level-of-care to grade-of-care (Supplementary Appendix 1). A substantial proportion of patients would likely have received a larger amount of care benefits because mental and communication deficits mean higher care benefits in the currently used "grade-of-care" system, but not in the old "level-of-care" system used for the conversion in this analysis. With less global disability in the MSU dispatch arm, this would have resulted in a higher cost load in the conventional dispatch group. Fourth, relating again to the base-case scenario, we did not account for possible transport savings, which are likely to have been incurred since stroke work-up on the dispatch of MSUs improves the direct transport of patients to the most appropriate hospital.[29] Hence, secondary transports of patients for specific treatments such as thrombectomy and the dispatch of costly emergency physician cars, which is commonplace in the German setting, were not included. Fifth, we did not account for benefits in terms of time savings in emergency departments created by pre-hospital stroke work-up and medical treatment.

Furthermore, due to the B_PROUD eligibility criteria, we only considered the primary study population without absolute contraindications to recanalizing treatments, which does not capture effects in other subgroups with MSU dispatch such as intracranial hemorrhage patients or patients with final diagnoses of non-stroke diseases. We have, however, accounted for costs incurred by these patients. As the information about EQ-5D-3L was collected 3 months after the index event, our use of a 5-year time horizon relies on extrapolation beyond the collected data with the theoretical assumption that QoL remains constant and without additional mortality over the 5-year period. Our interest lies in comparing the average difference in QALYs between the MSU and non-MSU groups after confounding adjustment. For our estimate to be accurate, it is sufficient that any possible violations of this assumption lead to a change of the same amount of QALY in both groups across the 5-year period. Luengo-Fernandez et al have shown a relative stability in survival probability and QoL (as measured by the EQ-5D-3L) during the 5-year period after stroke in different categories of stroke severity.[14]

In summary, our findings indicate that the dispatch of MSU to patients with suspected acute stroke is cost-effective compared with conventional care only, considering internationally accepted thresholds higher than additional €40,000 per QALY. These findings can inform decision-makers planning future pre-hospital stroke care in metropolitan areas. Similar to the results of previous health economics analyses of MSUs, the present study indicates that their cost-effectiveness depends on the volume of ischemic stroke patients who can be treated with intravenous thrombolysis in these vehicles. It is therefore crucial to optimize the identification of acute stroke patients on a dispatcher level and to streamline the related processes of MSU operations.

Currently, most MSUs in service are financed on a charitable basis or with research grants. However, results from several economic evaluations of MSUs in different jurisdictions have shown that this intervention can be cost-effective. By establishing a transparent decision-making process, policy-makers in local settings may therefore take these results into consideration and act in the interest of patients.

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Author Contributions

A.S.O.G., J.L.R., R.B., and H.J.A. were responsible for the study conception and design. A.S.O.G., J.L.R., M.P., T.K., E.F., P.H., I.R.N., I.L.M., R.B., and H.J.A. contributed to the acquisition and analysis of data. All authors contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

H.J.A reported personal fees from Boehringer Ingelheim, the manufacturer of Alteplase, which is used for intravenous thrombolysis in ischemic stroke. He also reported personal fees from NovoNordisk, the manufacturer of NovoSeven (factor VIIa), a drug that is used for acute life-threatening bleedings and with an ongoing study in patients with spontaneous intracerebral hemorrhage. The other authors have nothing to report. Full disclosures are listed in the submitted ICMJE forms.

Data Availability Statement

Pseudonymized participant data that underlie the results reported in this article can be made available in a de-identified manner upon request to researchers who provide a methodologically sound proposal after de-identification beginning at 12 months and ending 5 years after publication. Proposals should be directed to heinrich.audebert@charite.de. The statistical analysis plan for the analyses presented in this manuscript, is available in an online repository. A sample of the code used to analyze the data is available as a Supplementary Appendix 4.

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