Health economic evaluation of the ‘Flying Intervention Team’ as a novel stroke care concept for rural areas: study protocol of the TEMPiS-GÖA study

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INTRODUCTION

Stroke is one of the most common causes of acquired functional and cognitive disability, which is not only an extraordinary burden for patients and their families, but is also associated with high healthcare costs.1 Despite far-reaching developments and medical innovations in prevention and healthcare, stroke remains one of the most common causes of death and accounts for the largest proportion of disability-adjusted life year loss worldwide.2 3 Among the patients who survive the initial stroke, a quarter of patients die within the first year, and more than one-third of survivors suffer from permanent restrictions to the individual burdens and the economic impact of premature deaths, chronic consequences and disabilities are associated with high personnel and financial challenges for the healthcare system, causing one of the largest direct cost blocks compared with all other diseases.4 In 2017, total healthcare costs of stroke amounted to over 9.1 billion Euros.

METHODS AND ANALYSIS

The within-trial cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) will be performed from a statutory health insurance perspective as well as from a societal perspective over the time horizon of 12 months after the patients’ hospital discharge. Direct costs from outpatient and inpatient care are collected from routine data of the participating health insurance funds, while medical and non-medical costs from a patient’s perspective are retrieved from primary data collected during the TEMPiS-FIT study and follow-up questionnaires. Results will be presented as incremental cost-effectiveness ratio and incremental cost-utility ratio quantifying the incremental costs and health benefits compared with standard care practice. The outcome of the CEA will be measured in costs per minute reduction in mean process time to thrombectomy. The outcome of the CUA will be presented as costs per quality-adjusted life year gained.

ETHICS AND DISSEMINATION

Ethical approval for the TEMPiS-FIT study was granted by the Bavarian State Medical Association Ethics Committee (# 17056). Results will be disseminated via reports, presentations of the results in publications and at conferences and on the TEMPiS website. Trial registration number: German Clinical Trials Register DRKS00023885. Registered on 2 July 2021 — retrospectively registered.
in Germany and accounted for 2.60% of total healthcare expenditure.6

One key factor in the treatment of an ischaemic stroke is the rapid restoration of blood supply to the affected brain area, as it can reduce or even eliminate short-term and long-term impairments.5–8 Although healthcare systems in the USA and Europe have been developed to deliver comprehensive intravenous thrombolysis treatment in case of a cerebral infarction, several contraindications as well as a short time window (4.5 hours) still introduce limitations and challenges to the treatment of patients who had an ischaemic stroke.10–12 Since 2015, a new interventional therapy for strokes with large vessel occlusions has been available in the form of mechanical thrombectomy (MT), and this has initiated a paradigm shift in stroke treatment. The efficacy of the new procedure has been demonstrated as a result of several independent randomised controlled trials indicating, among other things, improved functional outcomes and reduced mortality compared with standard care procedures.13–20 Nevertheless, MT is, analogous to thrombolysis, very time critical and, according to current research, can only be successfully performed within a short time window after the onset of stroke symptoms.9 19 In addition, the procedure itself is medically demanding and requires specialised and well-trained personnel on site. Enabling the nationwide provision of this interdisciplinary treatment approach within the shortest possible time represents a major organisational and health policy challenge. In particular, for patients in rural areas, a comprehensive distribution of MT treatment is not feasible financially or in terms of personnel and is often performed with enormous delays because of the transfer to specialised, comprehensive stroke centres.21 Therefore, new strategies are necessary to provide stroke care in a timely manner independent of the geographical circumstances.

**Context TEMPiS–Flying Intervention Team (TEMPiS-FIT)**

The ‘TEMPiS-FIT’ project aims to close the gap in the treatment of patients who had an ischaemic stroke with large vessel occlusion in rural areas of Southeast Bavaria. To avoid the time-consuming transportation of severely ill patients to the nearest comprehensive stroke centre, a team of interventional neuroradiologists is located centrally with continuous availability during service hours. In case a patient is telemedically identified as a candidate for endovascular treatment, a helicopter flies the intervention team to the patient who had an ischaemic stroke, where the catheter-based thrombectomy is performed at the angiography facility on site. Staff familiar with the local angiography equipment and an anaesthetist are present and supportive during the intervention in the local clinic. Following the intervention, the local stroke or intensive care unit provides postprocedural care with telemedicine support if needed.16 22 Recently published results of the TEMPiS-FIT study provide evidence that the deployment of the Flying Intervention Team is associated with reduced time to endovascular thrombectomy for patients who had an ischaemic stroke compared with interhospital patient transfer. Additionally, post hoc analyses suggest an association of the FIT intervention with an improved median modified Rankin Scale (mRS) score at 3 months of follow-up.23

Despite the promising results of the TEMPiS-FIT study in terms of its effectiveness, the intervention is associated with significant costs. In particular, the use of the helicopter for the transport of the intervention team and the necessary personnel (including the pilot, the interventionalist and assistants) is a high additional cost factor not yet covered by standard care.

Owing to the innovative and unique structure of the project, previously published research on the cost-effectiveness of helicopter transfer of patients who had an acute ischaemic stroke is limited. Several studies across Europe and in the USA have demonstrated the effectiveness of mobile intervention teams for the treatment of patients who had an ischaemic stroke in rural areas.24–28 However, evidence on the cost-effectiveness of alternative transfer methods using a helicopter in the treatment of patients who had an ischaemic stroke is rare and differs in at least one of the main project characteristics. Investigating the cost-effectiveness of physician-staffed helicopter emergency medical services (HEMS) compared with emergency medical services independent of the medical indication, a prospective cohort study found HEMS to be cost-effective using an acceptance threshold of £75 000 per quality-adjusted life year (QALY).29 Specifically considering the helicopter transfer of patients who had an ischaemic stroke itself instead of an intervention team, Coughlan et al provide evidence that using HEMS to transfer patients who had a stroke eligible for MT is cost-effective compared with ground emergency medical services when travel time is reduced by at least 60 min and a threshold of £30 000 per QALY is used for decision-making.30 Similarly, Silbergleit et al found that ‘helicopter transfer of patients with suspected acute ischaemic stroke for potential thrombolysis is cost-effective for a wide range of system variables’.31 To our knowledge, no study has yet investigated the cost-effectiveness of flying a specialised intervention team to the patient who had an ischaemic stroke.

**Study aim**

The present study protocol aims to describe the economic evaluation (TEMPiS-GÖA) alongside the TEMPiS-FIT study. The relevance of this project lies in the comparison of the incremental cost items resulting from the transport of the specialist to the patient and its effect/benefit compared with the conventional care system. The economic evaluation will address the main question of interest of whether thrombectomy on site by the flying interventionalist represents a cost-effective improvement in the care situation of patients who had an ischaemic stroke in rural areas over a period of 12 months compared with standard care. Owing to the optimised care processes, the intervention of the TEMPiS-FIT study is expected to
lead to improved outcomes, which is reflected in cost-effective patient care from a statutory health insurance (SHI) and societal perspective within 1 year.

METHODS AND ANALYSIS

TEMPiS-FIT study design
The TEMPiS-FIT study design corresponds to a prospective study with quasi-randomised assignment to the respective treatment technology. On account of limited helicopter use capacity and financial and human resource restrictions, the a priori quasi-randomised allocation into flight and transfer treatment is determined by the calendar week in which the ischaemic stroke occurs instead of on a patient-level basis randomisation (see figure 1). Resulting in a predefined weekly intervention schedule, the ‘Flying Intervention Team’ is available 26 weeks/year, while conventional care is used during the remaining 26 weeks ensuring an even allocation ratio of 1:1 (amendment: owing to the impact of the COVID-19 pandemic, intervention days with helicopter availability had to be reduced from the initially planned 182 days to 170 days). Consequently, whether a patient receives the innovative form of care or conventional care primarily depends on the occurrence of the stroke itself, which is assumed to be independent of the predefined intervention team availability weeks.

The quasi-randomised allocation of the flight and transfer weeks attempts to ensure the comparability of the two groups with regard to confounding variables, for example, seasonal effects or the intervention team on duty. Because of the project design, neither the patients nor the referring medical staff (teleconsultants in cooperation with the neuroradiologists and the treating physicians on site) can be blinded.

The selected target population of the clinical trial compromises all ischaemic stroke patients with intracranial ICA, M1, proximal M2, carotid-T or basilar artery occlusion (especially ICD I63), who are admitted to one of the TEMPiS-FIT hospitals with an indication for thrombectomy treatment during the project period. Patients above the age of 85 or with concomitant diseases significantly increasing mortality are excluded from the study.

As the efficacy of the MT has been demonstrated by several randomised controlled trials,13–20 the primary outcome of interest is the mean process time to thrombectomy. Secondary outcomes include the self-reported QALYs and the functional outcome measured by the mRS after 3 months.

An interim analysis of the TEMPiS-FIT study workflow and safety was performed after 12 months. Because of a large significant reduction in time to treatment, the ethical review board recommended termination of recruitment for loss of equipoise. The TEMPiS-FIT study was discontinued on 24 October 2019, leading to a temporal divergence between the effectiveness study and the ensuing economic evaluation. After the discontinuation of the TEMPiS-FIT study, patients were enrolled in an ongoing registry. As there was no funding available for additional service weeks, the quasi-randomised allocation of service weeks was upheld until January 2021, covering the entire recruitment period of the TEMPiS-GÖA study.

TEMPiS-GÖA design
The primary objective of TEMPiS-GÖA is the within-trial cost-effectiveness analysis (CEA) and cost–utility analysis (CUA) of the Flying Intervention Team estimating the incremental costs and health benefits of the new health technology compared with existing standard care practice. Subsequent objectives are

- The quantification of the direct cost items from the SHI perspective in outpatient and inpatient care of the new health technology compared with standard care using routine data from the participating health insurance funds.
- The analysis of the incremental cost-effectiveness ratio (ICER) of the TEMPiS-FIT study on the primary outcome parameter compared with standard care.
The analysis of the incremental cost-effectiveness ratio (ICER) of the TEMPiS-FIT study based on the self-reported QALYs of the intervention patients compared with standard care.

The CEA and CUA will be performed from an SHI perspective (ie, the payer perspective) as well as from a societal perspective over the time horizon of 12 months after hospital discharge, including data from the price years 2017–2021. Results will be presented as ICERS and ICURs and are examined with regard to the transferability to the entire SHI population, as only a limited number of insurance funds are included in the study (see the Study population and sample size section). Table 1 provides a comprehensive summary of the economic evaluation framework. The reporting of the TEMPiS-GÖA study protocol and results is developed in accordance with the established Consolidated Health Economic Evaluation Reporting Standards. The analysis is scheduled to take place between April and October 2023.

### Study population and sample size
Because of cost data availability limitations, the study population includes the respective participants from the TEMPIS-FIT study and subsequent registry who are insured with one of the participating SHI funds (AOK Bavaria, BARMER, BKK) covering about 70% of the patients who had a stroke treated by TEMPIS-FIT. The sample size calculation is based on the primary endpoint, namely, the mean process time from the decision to thrombectomy until the start of the procedure. A 50 min time difference in the mean process time from thrombectomy between the intervention and control groups was assumed with a standard deviation of 60 min (TEMPIS, 2019). Following standard sample size calculation procedures for two independent samples using a t-distribution and employing an alpha error of 0.05 and a statistical power of 90%, the minimum sample size required for the economic analysis is a total of 60 patients. Based on estimates of the current patient population available at the time of the sample size calculation (2019), about 60% of the patients are covered by the participating health insurance companies, which leads to an adjustment of the required number of cases to 100 participants. Furthermore, owing to the patients’ demographic characteristics and the severity of the considered indication, a loss to follow-up rate of about 20% is assumed, which leads to a minimum case number of about 65 participants per group and 126 in total.

### Data collection
Relevant data for the economic evaluation are taken from two main sources: clinical data provided by the TEMPIS Network and routine data provided by the participating SHI funds. Data on clinical outcomes will be collected...
at three points in time (t0=initial hospitalisation, t1=3-month follow-up and t2=12-month follow-up) during the trial. Cost and resource use data are provided by the participating health insurance companies in the form of routine data. In order to record pre-existing variation in patient characteristics at baseline, routine data include a 1-year preobservation period in addition to the 12-month follow-up period after the procedure. For incomplete and missing data sets, appropriate imputation methods, such as multiple imputation and inverse probability weighting, depending on the underlying missing data mechanism, are used in line with best practice guidance. The collection of additional patient characteristics, such as sociodemographic parameters, which are not part of the working hypothesis, serves to identify possible differences between the intervention and control groups. This allows adjustment for potential bias and the presentation of the effects stratified by relevant groups.

**Outcome data**

The within-trial clinical outcome measure for the CEA is the incremental change in the primary endpoint of the study between the intervention and control groups. As the main goal of the Flying Intervention Team is to provide comprehensive care for patients who had a stroke in rural areas, the mean process time to thrombectomy is a process measure that correlates highly with the treatment effectiveness and thus provides a reasonable primary endpoint for the new health technology. To measure health-related quality of life as part of the CUA, QALYs are calculated based on the commonly used EQ-5D-5L questionnaire surveyed by telephone. The EQ-5D-5L consists of five quality of life dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) measured in five levels (no problems, slight problems, moderate problems, severe problems and extreme problems). Self-reported patient answers are then converted to a utility score ranging from −0.59 to 1.0 using predetermined value sets, where 1 represents full health and 0 represents death.

In addition to the primary outcome and the QALYs, the mRS serves as a secondary outcome measure for the incremental effect change in the CEA. Owing to its standardised and stroke-specific set-up, the mRS allows a valid quantification of neurological and functional deficit after an ischaemic stroke and is widely used as a parameter for economic analyses in the international stroke literature.

**Healthcare resource use, unit costs and intervention costs**

For the primary data collection from the SHI perspective, we will gather information on the incremental resource use and costs invested to provide the new form of care compared with standard care. Using the documentation alongside the clinical trial and the routine data provided by the participating SHIs, we will identify relevant parameters of direct medical and intervention costs of the new health technology as well as conventional care.

Available cost categories include treatment costs, emergency medical services, inpatient and outpatient medical care, pharmaceuticals and medicines, remedies, medical auxiliary aids, domestic and ambulant patient nursing care, as well as rehabilitation. After identifying all relevant cost items, unit costs and the respective quantities are presented as a quantity structure to provide an overview of investments that would be necessary to transfer the new care system into standard care. In addition to the cost information provided by the routine data, we will use standard cost rates for the German public health insurance system to verify and validate total incremental costs incurred.

In addition to the perspective of the health insurance funds, we will collect supplementary information on direct and indirect medical and non-medical costs from a patient’s perspective as well as implementation costs caused by the new care structure not covered by the health insurance expenses to provide a macroeconomic view. Direct patient and relatives’ cost items considered include, for example, medical copayments and travel time and are estimated using prestructured questionnaires, telephone interviews and relevant literature. Indirect costs, on the other hand, are estimated as productivity losses associated with the reduced ability or inability to work based on routine data. Costs related to the implementation of the new health technology and its recurrent costs necessary for ongoing provision will be considered as running cost items.

**Analysis**

**Cost analysis**

Combining the relevant information on resource use and unit costs, cost data will be reported as average total costs per patient in each trial group measured in Euros. With regard to the CEA and CUA, incremental costs will be calculated by taking the difference between the mean per-patient costs of the two study groups. Costs directly related to the administration of the trial, and thus solely for research purposes, will be excluded from the analysis. Owing to the available data time span of five consecutive years (2017–2021), costs will be inflated based on the Harmonised Index of Consumer Prices of the German Federal Statistical Office using 2021 as the reference year.

Table 2 provides an overview of the respective cost parameters that will be collected as part of the TEMP-iS-GÖA project.

**Cost-effectiveness and cost-utility analysis**

As the quasi-randomisation of patients is based on the calendar weeks of the intervention and not at the patient level, generalised linear models are used prior to the main analysis to extensively check whether an adjustment due to an unequal distribution of the baseline characteristics from the routine data or clinic-specific data is necessary in order to ensure results that are as unbiased as possible with regard to the defined endpoints. If necessary,
Table 2  Summary of cost parameters

| Cost parameters                                      | Collection strategy/source of data                      |
|------------------------------------------------------|--------------------------------------------------------|
| Statutory health insurance fund perspective          |                                                        |
| Direct medical costs                                 | Inpatient and outpatient medical care, pharmaceuticals, remedies, medical auxiliary aids, domestic and ambulant patient nursing care, rehabilitation and emergency medical services | Routine data from the participating SHI funds           |
| Running costs                                        | Helicopter availability, intervention team availability and personnel training | Routine data from the participating SHI funds, financial data provided by the hospital |
| Societal perspective                                 |                                                        |
| Medical costs (patients’ perspective)                | Copayments and care provided by relatives              | Patient questionnaires during the follow-up (t1 and t2) |
| Non-medical costs (patients’ perspective)            | Travel/transportation costs and time, productivity loss | Patient questionnaires during the follow-up (t1 and t2) |
| Implementation costs                                 | Telemedicine IT equipment, quality management and administration | Financial data provided by the hospital                 |
| Statutory health insurance fund perspective          |                                                        |
| Direct medical costs                                 | Inpatient and outpatient medical care, pharmaceuticals, remedies, medical auxiliary aids, domestic and ambulant patient nursing care, rehabilitation and emergency medical services | Routine data from the participating SHI funds           |
| Running costs                                        | Helicopter availability, intervention team availability and personnel training | Routine data from the participating SHI funds, financial data provided by the hospital |
| Societal perspective                                 |                                                        |
| Medical costs (patients’ perspective)                | Copayments and care provided by relatives              | Patient questionnaires during the follow-up (t1 and t2) |
| Non-medical costs (patients’ perspective)            | Travel/transportation costs and time, productivity loss | Patient questionnaires during the follow-up (t1 and t2) |
| Implementation costs                                 | Telemedicine IT equipment, quality management and administration | Financial data provided by the hospital                 |

Subgroup and sensitivity analysis

In addition to the main analysis, we will perform sensitivity analyses and subgroup analyses to test the robustness as well as the reliability of our results. The statistical uncertainty of the cost and effect measures as well as the ICER will be explored using deterministic and probabilistic sensitivity analyses. To determine the influence of estimated changes on the overall results, we will conduct scenario analyses with variations in potentially influential variables across plausible ranges (i.e., 50%-150%). Using non-parametric bootstrapping techniques to generate 95% CIs, we will plot results on a cost-effectiveness plane to graphically depict uncertainty. In addition, cost-effectiveness acceptability curves (CEACs) are used to visually represent the probability of cost-effectiveness of the new health technology compared with standard care in terms of various willingness to pay thresholds. Furthermore, we will conduct explorative subgroup analyses disaggregated by demographic characteristics, socioeconomic status and study group to allow for a provision of differentiated results and an indication for the transferability to the German SHI population.

Strength and limitations

While the TEMPIS-FIT study focuses on the analysis of the processes and the clinical outcome of the new health technology in the form of the Flying Intervention Team for patients who had an ischaemic stroke in rural areas of Southeast Bavaria, the TEMPIS-GÖA study will provide evidence on the cost-effectiveness from both the SHI and the societal perspective. Designed alongside the quasi-experimental, cluster-randomised TEMPIS-FIT study and subsequent registry, the quasi-randomised allocation into intervention and transfer weeks as well as the strict definition of inclusion and exclusion criteria are intended to minimise possible selection bias. In addition, the use of generalised linear models prior to the health economic analysis allows for possibly necessary adjustments resulting from an unequal distribution of the study groups’ baseline characteristics. As an independent evaluation institute and by prespecifying the parameters and outcomes of interest with respect to the CEA and CUA, we additionally reduce potential hypothesis-driven bias. The simultaneous collection of clinical trial data and routine data allows us to systematically validate cost-related and outcome-related data as well as minimise potential problems with missing data. In contrast to an artificial study environment, the use of routine data provides further indications about the transferability of the results to the entire German SHI population.

Some aspects of our study design have potential limitations. The effect measure for the CUA (QALYS) as well...
as incurred patient costs are self-reported and thus susceptible to recall bias. In particular, when considering the societal perspective, a complete representation of accrued costs is often unfeasible for ethical and intangibility reasons. Considering the relatively short time horizon of the 12-month follow-up period and the high initial investment costs for helicopter availability, further research might be necessary to investigate the long-term cost-effectiveness of the Flying Intervention Team.

Following the publication of the clinical trial, the evaluation of the economic data in the form of the CEA and CUA provides useful information to healthcare policymakers as a decision aid for a nationwide and comprehensive provision of the unique and innovative care system for patients who had an ischaemic stroke in rural areas. Consequently, TEMPiS-GÖA aims to add valuable evidence on the cost-effectiveness of alternative transfer methods using a helicopter in the treatment of patients who had an acute ischaemic stroke in rural areas to the relatively limited evidence base.

**Patient and public involvement**

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

**ETHICS AND DISSEMINATION**

**Approval, registration and consent to participate**

The TEMPiS-GÖA study has been registered with the German Clinical Trials Register. Ethical approval for the TEMPiS-FIT study has been granted by the Bavarian State Medical Association Ethics Committee (# 17056). According to §15 of the Bavarian Medical Association’s code of conduct, further ethical approval for the TEMPiS-GÖA study was not required (consultation of the Bavarian State Medical Association Ethics Committee from 20 October 2020). Our application to use routine data for the TEMPiS-GÖA study was approved by the regulatory authorities of the participating SHIs (Regional Association of SHI Physicians in Bavaria, granted 13 April 2021; Federal Office for Social Security, granted 12 July 2021). Both authorities also confirmed that, according to Section 75 of Book X of the German Code of Social Law (§75 GSB X), obtaining informed consent from the patients prior to the follow-up questionnaire is not required because it would be unreasonable on account of the severity of the disease and would additionally lead to relevant statistical biases in the analyses. Results of the health economic evaluation will be disseminated via reports, presentations of the results in peer-reviewed journals, at conferences, in public relations as well as on the TEMPiS project website (https://www.tempis.de/wissenschaft/).

**Data management and protection**

The data provided are processed exclusively for scientific research purposes within the framework of the Innovation Fund project ‘Health Economic Analysis of the Flying Interventionist as a New Stroke Care System in Rural Areas/TEMPiS – GÖA’. The legal basis for the processing is Section 75 of Book X of the German Code of Social Law (§75 GSB X: Transfer of Social Data for Research). The data transmission from the participating health insurance funds and the TEMPiS Network to the evaluating institute is organised via the TUM Trust Centre, where the pseudonymised primary data from the TEMPiS Network are linked with the pseudonymised routine data from the respective health insurance fund. To prevent reidentification, pseudonymised trial-based and economic data will be pseudonymised again after the linkage and maintained in password-protected, encrypted containers. Inferences to individuals are excluded.

**Acknowledgements**

We thank the participating health insurance funds AOK Bayern–Die Gesundheitskasse, BARMER and BKK Landesverband Bayern for the data preparation.

**Contributors**

LS, GJH and NDH planned this study and developed the intervention. LS, MC, RF and WS conceptualised the economic evaluation. MC drafted the manuscript together with RF, WS and LS. All authors reviewed and edited the original manuscript. All authors provided input and read and approved the final manuscript.

**Funding**

The study is fully funded by the German Federal Joint Committee (GBA), grant number 01VSF19044.

**Competing interests**

None declared.

**Patient and public involvement**

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

**Patient consent for publication**

Not applicable.

**Ethics approval**

This study involves human participants, but Ethical approval for the TEMPiS–Flying Intervention Team study has been granted by the Bavarian State Medical Association Ethics Committee (# 17056). According to §15 of the Bavarian Medical Association’s code of conduct, further ethics approval for the TEMPiS-GÖA study was not required (consultation of the Bavarian State Medical Association Ethics Committee from 20 October 2020). Our application to use routine data for the TEMPiS-GÖA study was approved by the regulatory authorities of the participating statutory health insurances (Regional Association of SHI Physicians in Bavaria, granted 13 April 2021; Federal Office for Social Security, granted 12 July 2021). Both authorities also confirmed that, according to Section 75 of Book X of the German Code of Social Law (§75 GSB X), obtaining informed consent from the patients prior to the follow-up questionnaire is not required because it would be unreasonable on account of the severity of the disease and would additionally lead to relevant statistical biases in the analyses.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Data availability statement**

No data are available.

**Open access**

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