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ABSTRACT

Objectives Regional accessibility and distribution of endovascular thrombectomy (EVT) capable facilities, that is, comprehensive stroke centres (CSCs), may significantly influence time to treatment. We analysed the impact of adding CSCs in the north of the Netherlands, a region with roughly 1.7 million inhabitants currently served by one CSC and eight primary stroke centres (PSCs).

Design Monte Carlo simulation modelling was used to establish new CSCs in our region by hypothetically upgrading existing PSCs to CSCs and ensuing adjustments in health services set-up.

Setting One CSC and eight PSCs in the north of the Netherlands.

Participants 165 patients with acute stroke treated with EVT and underwent interhospital transfer between PSC and CSC (drip and ship patients).

Primary and secondary outcomes Time from onset to groin (OTG) puncture and predicted probability of favourable outcome (modified Rankin Scale 0–2) after 90 days. Sensitivity analyses were performed to assess uncertainty in workflow efficiency of CSCs.

Results Adding one or two CSCs would reduce the OTG time up to approximately 17 min and increases the predicted probability of favourable outcome by approximately 2%. Sensitivity analyses revealed that 'slow-acting' CSCs may reduce OTG by 3–5 min compared with 24–32 min for 'fast-acting' CSCs.

Conclusions This study suggests that adding one or two CSCs in the north of the Netherlands would have modest impact. Improving workflow efficiencies seems to be more potent when aiming to improve existing acute stroke care systems.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The results of this study adds important knowledge on the potential benefits of adding comprehensive stroke centres in underserved rural regions.
⇒ Input data for the developed models represent patient level data both from the hospital and prehospital setting thereby accurately representing clinical practice.
⇒ Simulation modelling is presented as a flexible and efficient methodological approach which has the potential for broader use by using input data from other regions.
⇒ Does not include the broader patients with stroke population of non-large vessel occlusion and haemorrhagic subtypes.
⇒ The simulation model includes time delay parameters on system performance that may have changed over time.

INTRODUCTION

Fast treatment of acute ischaemic stroke (AIS) due to large vessel occlusion (LVO) is pivotal to improve functional outcome.[1] The effects of both intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT) for AIS are highly time dependent. that is, every hour delay implies a 5%–6% decline in the chance of a favourable outcome.[2 3]

Two main organisational models for acute stroke care currently exist. In the mothership (MS) model, a patient with suspected stroke is directly transported to a comprehensive stroke centre (CSC), which can administer both IVT and EVT. In the drip and ship (DS) model, the patient is initially transported to the nearest IVT capable hospital, a primary stroke centre (PSC). In case the patient appears eligible for EVT, interhospital transfer by emergency medical services (EMS) is arranged between the PSC and CSC, which was shown to substantially increase the onset to groin (OTG) time and thus delaying the start of EVT.[4–7] The dominance of a certain organisational model and associated delays to EVT, mainly depend on region specific spread of hospitals, the geographic location of stroke onset and protocols used by EMS. In some regions there are concerns regarding timely access to EVT, as patients require relatively long travel times towards a CSC.[8] A possible solution is to upgrade other

Figure 1 PSCs, CSC and NSCs in the north of the Netherlands. CSC, comprehensive stroke centre; NSC, non-stroke centre; PSC, primary stroke centre.

hospitals presently acting as PSCs to meet the standard of a CSC, thereby aiming to reduce interhospital travel times or avoid inter-hospital transfer delay altogether.

The aim of this paper is to estimate the potential effects of adding one or more CSC(s) in the northern region of the Netherlands on the OTG puncture time and 90 days functional outcome in patients treated with EVT, using simulation modelling.

METHODS

Participants and setting

For the baseline model prospectively collected data of 183 patients from the MR CLEAN Registry was used.[9] All patients were treated with EVT between July 2014 and November 2017 and routed according to the DS model in the northern region of the Netherlands. In this region, the University Medical Centre Groningen (UMCG) is the only CSC. Its catchment area serves 1.7 million inhabitants (209 per square kilometre), including eight PSCs at distances between 6 and 84 kilometers (figure 1).

In order to acquire a complete overview of the acute stroke pathway, prehospital and interhospital transfer data was retrospectively collected at the regional EMS and subsequently linked. Inclusion criteria were prestroke modified Rankin Scale (mRS) score ≤2 and OTG time ≤390 min.

Baseline model

A Monte Carlo simulation model was developed based on DS time variables collected in the MR CLEAN Registry[9] and served as baseline model. Input variables for the model included time of: symptom onset or last seen well, CT, start IVT, CT angiography (CTA), arrival at angiography suite and groin puncture. EMS variables included time of: 911 call, arrival at the stroke onset location, departure to PSC, PSC arrival, transfer notification (second 911 call), arrival at PSC, departure to CSC, and arrival at the CSC.

Prior to development of the simulation model, conceptual modelling was applied to capture the real-world acute stroke pathway for DS patients (figure 2). For each patient various logistical routes can be defined, starting from the moment of stroke onset up to groin puncture. For example, stroke onset may occur inside or outside the hospital, patients may be eligible for IVT or not, undergo CTA before IVT treatment or the other way around. Also, after interhospital transfer, patients may be assigned directly to the angiography suite, or first undergo additional diagnostics. The conceptual model represented all these variations and was validated using stroke experts participating in the nationwide COllaboration for New TReatments of Acute Stroke (CONTRAST) consortium, and based on findings from previous publications.[10]

The Monte Carlo simulation model was coded using Plant Simulation software.[11] Time intervals were quantified and presented as statistical distributions using ExpertFit,[12] based on the original patient data (online supplemental table S1, online supplemental material).

Adding CSC(s): Data and experiments

To evaluate the impact of adding one or more CSCs in our region, the baseline model was modified and patient routing adapted towards the nearest new CSC (online supplemental table S2, online supplemental material). Based on the original prehospital routing strategy, two categories of patients were distinguished: (1) patients routed directly towards the new CSC (modified MS model), and (2) patients routed according to the DS model, and subsequently routed towards the nearest new CSC (modified DS model). The time distributions underlying the baseline model were changed accordingly, see figure 2 (parts 1–3). For patients routed according to the modified MS model interhospital transfer time and

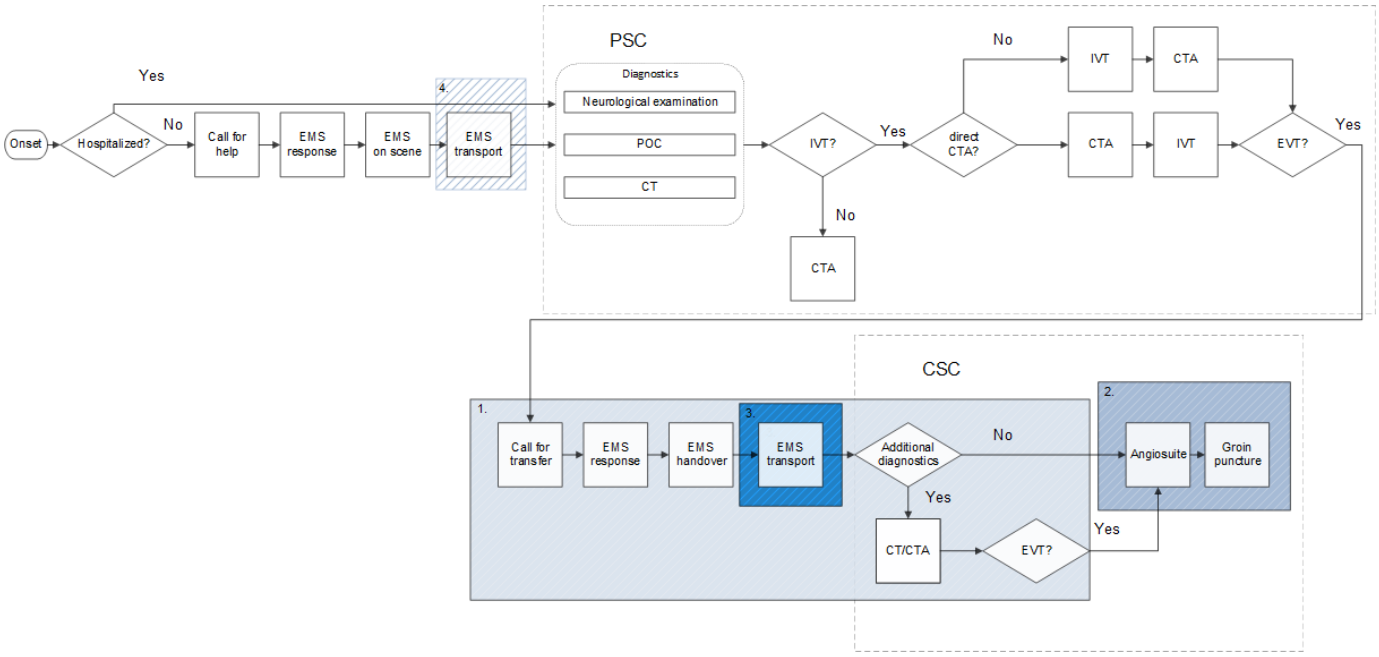

Figure 2 Conceptual model of the acute stroke pathway (DS patients), baseline model and adapted time variables. Time variables and patient routing for the baseline model are represented by rectangles and diamonds. Time variables adapted when upgrading PSCs to CSCs are marked as coloured parts, referring to one or multiple time variables. Part 1: steps omitted, when patient is routed directly to the new CSC. Part 2: steps for which time variables are set equal to the distributions found for the existing regional CSC, when patient is routed directly to the new CSC. Part 3: time distribution for EMS interhospital transport is adjusted for patients still routed according to the DS model but transferred to the nearest new CSC. Part 4: time distribution adapted when prehospital routing is adapted to routing directly to the nearest CSC. CSC, comprehensive stroke centre; CT, computed tomography; CTA, CT angiography; EMS, emergency medical services; EVT, endovascular thrombectomy; IVT, intravenous thrombolysis; POC, point of care; PSC, primary stroke centre.

time for additional diagnostics were set to zero (figure 2, part 1). In addition, for the new CSCs, we included time interval distributions from emergency department (ED) to angiography suite arrival and from angiography suite arrival to groin puncture (figure 2, part 2). For these distributions, we used data of MS patients (MR CLEAN Registry) treated with EVT in the UMCG.[9]

For patients still routed according to the DS model, but transferred to the nearest (new) CSC, the time distributions representing EMS interhospital transport were adapted (figure 2, part 3).

In addition, the strategy of prehospital routing to the nearest CSC was added. Prehospital routing was adapted when transportation times to the nearest CSC were shorter than 30–45 min,[13] both for added and existing CSCs. Transport times from stroke onset location to the added or existent CSC were based on times collected by a web-based route planner (figure 2, part 4),[14] and adjusted for presumed higher ambulance speeds by reducing transport times by 23% (calculated by comparing route planner car times and EMS time variables that were collected for our region). Furthermore, similar adaptions were made as for the modified MS model (figure 2, part 1 and 2).

Model scenarios

Three scenarios were tested to assess the impact of adding new CSC(s). The first two scenarios included selection of PSCs to be hypothetically upgraded to a CSC, based on their distance to the existing CSC, expected treatment volumes and available resources. Based on a distance of approximately 60 km from the UMCG and an expected treatment volume of 50 patients per year (based on collected patients with EVT of the last year in its catchment area),[9] scenario 1 adds a CSC in the western section of the region (figure 3A). Scenario 2 adds an additional CSC in the south-east section at approximately 60 km from the UMCG (figure 3B). This centre would have a treatment volume of approximately 15 patients per year,[9] but an increase in treatment volume is considered likely because this hospital is on a provincial border and thereby might attract patients from adjacent regions. In scenario 3, all PSCs are upgraded to CSCs.

In addition, a subscenario was to scenario 1 (1A) and 2 (2A) for adapted prehospital routing, that is, directly routed to the nearest CSC, when transportation time was shorter than30-45 minutes.

On adding CSC(s), we assumed that workflow efficiencies (time from door/last examination at the ED to groin) within the new CSCs would be comparable to the existing CSC in the region (the UMCG). However, as not every CSC will perform equal, we performed a sensitivity analyses representing practice variation observed in the Netherlands. Based on MR CLEAN Registry data of hospitals providing EVT in the Netherlands, we studied

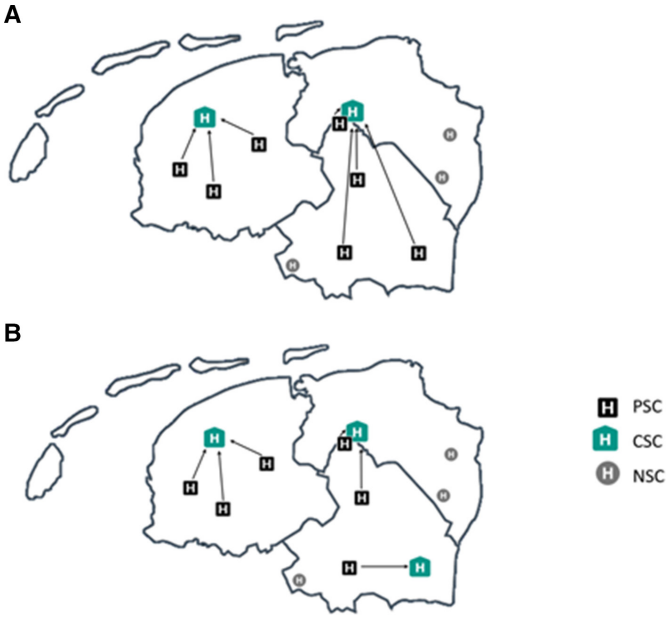

Figure 3 CSCs added in the north of the Netherlands. (A) One CSC is added in the western part of northern Netherlands (scenario 1). (B) Two CSCs are added in the western part and southern part of northern Netherlands respectively (scenario 2). CSC, comprehensive stroke centre; NSC, non-stroke centre; PSC, primary stroke centre.

the impact of a 25% increase and decrease in workflow efficiency.

Outcome measures

For each scenario, we calculated the clinical benefits in terms of reduction in OTG, and favourable functional outcome defined as mRS score of 0–2.

Statistical analysis

Missing values were excluded from analyses, as statistical imputation techniques were not necessary to obtain intact model distributions. Time distributions of the baseline model were numerically validated by comparing model output (mean, median, SD, minimum and maximum) with real-world data of patients.

Ordinal regression was used to estimate the likelihood of each of the seven outcomes according to the mRS score. Known prognostic variables were: OTG, age, National Institutes of Health Stroke Scale score and CTA collateral grading score in four categories. The predicted probability of favourable outcome (PPFO) was predicted using the formula obtained by ordinal regression, that is, still discerning all possible mRS and subsequently dichotomising.

Model outcomes for scenarios were compared with the baseline model. Testing for significance was deemed redundant since the aim was to assess the potential gains that may be expected based on a hypothetical cohort of 100.000 individuals.

Simulation model access

The simulation model will be available on reasonable request for other researchers.

Table 1 Characteristics, diagnostics and time delays of the baseline model

Patient characteristics		N
Age in years (SD)	70 (13)	165
Male (%)	99 (60)	165
IVT rate (%)	132 (80)	165
Patient diagnostics		
Baseline NIHSS score 1–15 (%)	71 (43)	165
Collaterals absent (%)	11 (7)	155
<50% filling of collaterals (%)	81 (49)	155
>50% filling of collaterals, less than 100% (%)	49 (30)	155
Process times EMS		
Symptom onset to 911 call	11 (3–33)	139
Response time	9 (7–12)	132
On scene time	16 (12–20)	126
Transport time	12 (7–15)	122
Process times in-hospital, PSC		
Hospital arrival to CT	15 (11–20)	125
Route 1		
CT to IVT	8 (4–19)	56
IVT to CTA	11 (5–19)	57
CTA to EMS call for transfer	31 (23–50)	56
Route 2		
CT to CTA	9 (5–11)	62
CTA to IVT	9 (4–15)	63
CTA to EMS call for transfer	21 (8–34)	61
Route 3		
CT to CTA	14 (9–30)	31
CTA to EMS call for transfer	33 (23–48)	31
Process times interhospital transfer		
Response time	8 (5–10)	140
Handover time	14 (10–16)	139
Transport time	27 (19–32)	150
Process times in-hospital, CSC		
CSC arrival to additional diagnostics	23 (17–45)	17
Additional diagnostics to angiography suite	29 (14–70)	18
CSC arrival to angiography suite	26 (16–38)	151
Arrival angiography suite to groin	30 (24–35)	163
Overall time		
OTG	230 (198–275)	165

Time variables are in minutes, median (IQR).
CSC, comprehensive stroke centre; CT, computed tomography; CTA, computed tomography angiography; EMS, Emergency Medical Services; IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale; OTG, time from stroke onset to groin puncture; PSC, primary stroke centre.

Table 2 Modelling results of adding CSC(s) and its effect on OTG and PPFO

Scenario	OTG (95% CI)	PPFO (95% CI)
All patients		
0. Baseline	240.9 (240.5–241.3)	52.4 (52.3–52.5)
1. Adding one CSC	227.4 (227.0–227.7)	54.0 (53.9–54.2)
A. Prehospital routing to nearest CSC	209.5 (209.2–209.9)	56.2 (56.1–56.4)
2. Adding two CSCs	222.3 (221.9–222.7)	54.7 (54.5–54.8)
A. Prehospital routing to nearest CSC	203.4 (203.0–203.8)	57.0 (56.8–57.1)
3. All PSCs upgraded to a CSC	197.9 (197.5–198.2)	57.6 (57.5–57.8)
All patients routed according to the DS model (to the new CSC and the original CSC)		
1. Adding one CSC	234.1 (233.8–234.5)	53.2 (53.1–53.4)
2. Adding two CSCs	231.7 (231.3–232.0)	53.5 (53.4–53.7)
3. All PSCs upgraded to a CSC	NA	NA
Patients routed according to the modified MS model		
1. Adding one CSC	198.1 (197.7–198.4)	57.6 (57.5–57.7)
2. Adding two CSCs	198.2 (197.8–198.6)	57.6 (57.4–57.7)
3. All PSCs upgraded to a CSC	197.9 (197.5–198.2)	57.6 (57.5–57.8)

CSC, comprehensive stroke centre; DS, drip and ship; mRS, modified Rankin Scale; MS, mothership; NA, not applicable; OTG, onset to groin puncture; PPFO, predicted probability of favourable outcome (mRS 0–2); PSC, primary stroke centre.

Public and patient involvement

Patients and the public were involved in the conception of the topics to be addressed in the CONTRAST consortium. Study results will be disseminated through newsletters, poster presentations and publications in newspapers, lay journals and publication in peer-reviewed journals.

RESULTS

Baseline characteristics

Out of the 179 patients, we included 165 patients. Fourteen patients were excluded because of an unknown or >2 prestroke mRS, and four because of an OTG >390 min. Baseline patient characteristics are presented in table 1.

Input data, adding CSC(s)

The median (IQR) time intervals from hospital arrival to angiography suite arrival and from angiography suite arrival to groin puncture were 58 (44–82) and 28 (25–35) minutes, respectively.

Simulation results, adding CSC(s)

Results for all simulated scenarios are presented in table 2. Adding a new CSC (scenario 1), would reduce OTG by 14 min and increase PPFO by 1.6%. For patients routed specifically according to the modified MS model, OTG would be reduced by 43 min and PPFO would increase by 5.2%. For all patients routed according to the DS model, OTG is reduced by 7 min and PPFO would increase by 0.8%. The strategy of direct prehospital routing to the nearest CSC would result in a 35 min reduction in OTG, and an increase by 4.1% in the PPFO.

Adding another CSC in the region (scenario 2) would lead to an overall reduction in OTG of 19 min and would improve PPFO by 2.2%. Modified MS patients would be treated 43 min faster and PPFO would increase by 5.2%. All patients routed according to the DS model would be treated 9 min faster and PPFO would increase by 1.2%. Using the adapted prehospital routing directly to the nearest CSC reduces OTG by 38 min and increases PPFO by 4.6%.

Upgrading all PSCs to CSCs effectively routing all patients according to the modified MS model (scenario 3), OTG would be reduced by 43 min and the PPFO increased by 5.5%. Increasing the number of CSCs showed a shift towards lower predicted mRS scores (online supplemental figure S1).

Sensitivity analysis

Results of the sensitivity analysis are presented in online supplemental table S3. When considering adding a new CSC in which workflow processes were 25% slower compared with the original CSC, OTG would be reduced by 3 min compared with the baseline model and PPFO would increase by 0.4%. In contrast, when implementing a CSC that is 25% faster, OTG would be reduced by 24 min and PPFO would increase by 3.0%. Adding two CSCs to the region, with 25% slower or faster workflow would reduce OTG by 5 and 32 min, respectively. PPFO would increase by 0.7% and 3.9%.

By upgrading all PSCs to CSCs, and assuming all the new CSCs would be 25% slower or faster compared with the baseline model, OTG would reduce by 19 and 67 min, respectively. PPFO would increase by 2.4% and 8.2%. In addition, if the original single CSC would achieve a 25% faster workflow, this would reduce OTG by 15 min and PPFO would increase by 1.8%.

DISCUSSION

This modelling study demonstrated that, adding one or two CSC(s) in our region with comparable workflow

efficiency as the current CSC, would reduce OTG between 15 and 20 min and improve PPFO at 90 days by 1%–2% (absolute benefit). A likely explanation for this modest effect may be the relatively short travel distances, the well-developed road network and the well-organised EMS within our region. Upgrading all PSCs to CSCs would have a much larger impact, reducing the OTG time by more than 40 min and improving PPFO by more than 5% (absolute benefit). This latter scenario is considered unfeasible, for reasons of low treatment volumes, which is related to the quality of EVT,[15] availability of staff and equipment and higher costs.

When prehospital routing was adapted to direct transfer to the nearest CSC, the OTG may be reduced by 30–40 min and PPFO at 90 days improves by 4%–4.5%. Although this option appears to be beneficial, we did not estimate onset to IVT times for non-LVO patients. In addition, the expected increased workload for CSCs when routing all patients with stroke directly towards CSCs was not taken into account. A more comprehensive simulation model would be needed to study this option further. Patients routed directly to the new CSCs (MS model) were observed to be treated much faster compared with patients routed according to the DS model. This is in line with previous research indicating that interhospital transfer significantly contributes to longer OTG times.[4–7] Analysing our data clarifies how the time interval from completing CTA to call for transfer explains more than one third of the difference among patient groups. Rapid LVO detection after CTA,[16] early EMS notification or even EMS waiting for release at the PSC[17] are therefore clear recommendations to further reduce the interhospital transfer time.

Importantly, sensitivity analyses revealed that workflow performance would have a major impact on performance of additional CSCs. Our sensitivity analysis revealed a difference of approximately 25 min in OTG times between 'slow' versus 'fast' acting CSC(s) compared with the baseline model. Given the practice variation between hospitals, the estimated impact might even be greater, and may be further enhanced by workflow improvements.[18] In addition, our sensitivity analysis suggests that improving workflow might be even more efficient than adding a second or third CSC. However, prior to offering clear-cut recommendations we suggest performing cost and cost-effectiveness studies.

Our results may be generalisable to other underserved rural regions, which indeed reflects 31% of the European population, and a higher proportion of the older population.[8] Using simulation modelling to obtain early estimates on the potential impact of implementation policies is in line with stroke guidelines indicating that organisation of stroke care should be analysed and/or adjusted per region.[13 19] Moreover, simulation could be applied to other regions using the same approach by repopulating the model with region-specific distributions and assumptions. For example, similar analyses might be performed using data from urban regions possibly overserved currently by an abundance of CSCs. Thus, the effect of reducing the number of CSCs may be assessed.

Limitations

Our study has limitations. Model input is only described for patients eligible for EVT, although in reality organising acute stroke care requires a comprehensive approach beyond this specific group. that is, by including a wider group of patients with stroke including non-LVO patients and haemorrhages. Also, our simulation study has a main focus on logistic gains implied by adding CSCs, leaving quality issues as reflected in outcome models out of scope.

Conclusions

Our study suggests that the impact of adding CSCs on treatment times and clinical outcome in the north of the Netherlands will be modest. Workflow efficiency and prehospital routing (using a prehospital triage scale) seems important when considering to add CSCs to existing infrastructures. Both the performance of the existing CSC(s) as well as additional CSC(s) are important in this consideration.

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Contributors WJM, D-JvdZ, EB, MU and MMHL designed the study with EB and MU as principal investigators. EB and MU applied for, received and organised study funding. WJM, D-JvdZ, MU and MMHL analysed the data. WJM drafted the manuscript, and D-JvdZ, EB, MU and MMHL revised the manuscript for intellectual content and approved the final version of the manuscript for publication. MMHL is responsible for the overall content as guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by central medical ethics committee and research board of Erasmus University Medical Centre (MEC-2014-235) Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The participants of this study did not give written consent for their coded data to be shared publicly, so due to the sensitive nature of the research supporting data is not available. Nevertheless, used distributions of the collected data are available in the supplemental material.

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Supplementary material; Modelling the impact of adding comprehensive stroke centres. Can we deliver endovascular thrombectomy sooner?

Introduction

The main text of the manuscript provides the most important findings of the study. This supplementary material provides details on the simulation modelling methodology, the estimation of the predicted probability of favorable outcome (mRS score, 0 to 2) at 90 days used in the manuscript, and extended tables of the results.

Simulation modelling methodology

Monte Carlo simulation modelling

Within the Monte Carlo simulation methodology random variables are used for solving stochastic or deterministic problems. The passage of time plays no substantial role, as there is no competition between patients.[1] Variety in patient diagnostics, characteristics, time delays towards endovascular thrombectomy (EVT) and routing patterns are incorporated into the model by probability distributions derived from real patient data. The Monte Carlo simulation modelling is to test 'what if' scenarios for workflow changes in the acute stroke pathway.

Distribution fitting

Activity durations and diagnostics are modelled by probability distributions, using data on individual patients. ExpertFit is used for distribution fitting, supporting the selection of statistical distributions, determining their parameters and testing candidate distributions for their goodness-of-fit.[2] Main steps in distribution fitting concerned:

- Importing of patient data into ExpertFit.
- Fitting theoretical distributions.

- Seeking further evidence in case goodness of fit tests are indeterminate, in an attempt to underpin the choice of a specific theoretical distribution.[3] Evidence considered includes conceptual usage of the candidate distribution(s), commonalities between highest ranked distributions, and consultation of domain experts. If such evidence is not found an empirical distribution was chosen.

Set-up of experiments

All experiments concern independent observations on a single run of 100.000 hypothetical patients. Independence of observations is guaranteed by modelling the stroke pathway as a non-queuing system reflecting the relatively low numbers of patients being treated in stroke centres, and priority rules that allow stroke patients to queue jump.[4]

Software

Plant Simulation was used to model the acute stroke pathway and perform experiments.[5] Expertfit[2] was used to find the probability distributions and their parameters.

Models

Baseline model

In the main text the conceptual model, the set-up of the baseline model, i.e. drip-and-ship model (DS), is visualized (figure 2). After stroke onset patients either enter the hospital from outside by ambulance transportation or are already hospitalised (9.1%). After distinguishing these patient routes (Table S1), the following time delay variable was modelled for hospitalised patients; 'time from stroke onset to computed tomography (CT)'. For patients outside the hospital the following were modelled; 'time from stroke onset to 911 call', 'emergency medical services (EMS) response', 'EMS on scene', 'EMS transport', 'time from hospital arrival to CT'.

After the time delay variables 'time from stroke onset to CT' (hospitalised patients) and 'time from hospital arrival to CT' (patients outside the hospital) patients were routed through the emergency department (ED) according to 3 routes; route 1 = CT-IVT- computed tomography angiography(CTA)-transfer call(EMS) , route 2 = CT-CTA-IVT-transfer call(EMS) and route 3 = CT-CTA-transfer call(EMS) (in case of a contraindication for IVT). The following percentages per routes are observed and used; 37.7%, 41.8% and 20.5 %, respectively.

After ED routing the following time delay variables are modelled; EMS response for transfer, EMS handover, and EMS transfer. EMS transfer was divided in 3 groups, i.e. the western subregion, north-east region and southern region. After comprehensive stroke centre (CSC) arrival patients receive additional diagnostics (AD) (10.9%) or are routed to the angiography suite. The following time variables are modelled for patients that receive AD; 'time from hospital arrival to last additional diagnostics' (CT or CTA time) and 'time from additional diagnostics to angiography suite'. Patients not receiving AD, 'time from hospital arrival to angiography suite' is modelled. Finally, 'time from angiography suite to groin puncture' is modelled for every patient. All distributions of the model are shown in Table S1.

In addition, patients age and diagnostics (National Institutes of Health Stroke Scale (NIHSS) and collaterals) are modelled to estimate the 7 scales of the mRS at 90 days. Collaterals are divided in 4 categories: absent of collaterals, less than 50% filling of occluded area, more than 50% filling but less than 100% filling of occluded area or 100% filling of occluded area, and NIHSS score and age are both continuous variables. Means (SD) are for NIHSS 15.3 (5.3), for age 70.2 (12.9) years and collateral categories were divided in 7.2%, 52.9%, 31.4% and 8.5%, respectively.

Table S1. Distributions of the baseline model, DS model.

Activity duration	Distribution	Parameters	
Hospitalised vs. patients outside hospital	Discrete empirical	Value	Frequency
		Hospitalised	15
		Outside hospital	150

Time from stroke onset to CT (hospitalised patients)	Continuous empirical	Lower Bound	Upper Bound	Frequency
		0	30	7
		30	60	5
		227	227	1
Time from stroke onset to 911 call (patients outside hospital)	Continuous empirical	Lower Bound	Upper Bound	Frequency
		0	1	26
		1	5	22
		5	10	17
		10	15	10
		15	20	10
		20	30	11
		30	40	8
		40	50	7
		50	75	10
		75	100	6
		100	150	6
		150	200	3
EMS Response	Beta	Lower endpoint = 2.29; Upper endpoint = 30.53; $\alpha 1 = 2.56$; $\alpha 2 = 7.15$		
EMS on Scene	Gamma	Location = 1.70; $\alpha = 5.43$; $\beta = 2.73$		
EMS Transport: Divided in 3 subregion				
Western subregion (n=102)	Weibull	Location = 0.00 $\alpha = 2.03$; $\beta = 13.41$		
North-eastern subregion (n=42)	Beta	Lower endpoint = 3.41; Upper endpoint = 34.44; $\alpha 1 = 1.54$; $\alpha 2 = 3.87$		
Southern region (n=21)	Beta	Lower endpoint = 0.94; Upper endpoint = 15.16; $\alpha 1 = 1.05$; $\alpha 2 = 1.53$		
Time from hospital arrival to CT	Continuous empirical	Lower Bound	Upper Bound	Frequency
		0	5	8
		5	10	21
		10	15	39
		15	20	28
		20	25	14
		25	35	12
		35	55	3
ED routing (3Catergories)	Discrete empirical	Value		Frequency
		Route 1: CT to IVT to CTA		57
		Route 2: CT to CTA to IVT		63
		Route 3: CT to CTA		31
Time from CT to IVT (route 1)	Erlang	$\mu = 13.70$; $\sigma = 17.09$		

Time from IVT to CTA (route 1)	Erlang	$\mu = 14.54$; $\sigma = 13.73$		
Time from CTA to transfer call (route 1)	Gamma	Location = 0.00; $\alpha = 2.63$; $\beta = 13.66$		
Time from CT to CTA (route 2)	Gamma	Location = 0.00; $\alpha = 2.63$; $\beta = 3.53$		
Time from CTA to IVT (route 2)	Erlang	$\mu = 12.57$; $\sigma = 13.05$		
Time from IVT to transfer call (route 2)	Continuous empirical	Lower Bound	Upper Bound	Frequency
		0	5	12
		5	15	10
		15	25	14
		25	35	13
		35	60	9
		60	90	3
Time from CT to CTA (route 3)	Lognormal	$\mu = 23.06$; $\sigma = 21.72$		
Time from CTA to transfer call (route 3)	Continuous empirical	Lower Bound	Upper Bound	Frequency
		0	15	6
		15	30	5
		30	45	8
		45	60	9
		60	95	3
EMS response for transfer	Continuous empirical	Lower Bound	Upper Bound	Frequency
		0	2	12
		2	4	17
		4	6	18
		6	8	29
		8	10	39
		10	15	17
		15	30	8
EMS handover for transfer	Continuous empirical	Lower Bound	Upper Bound	Frequency
		0	5	5
		5	10	31
		10	15	59
		15	20	31
		20	30	11
		30	40	2
EMS transport (western subregion)	Beta	Lower endpoint = 17.92; Upper endpoint = 43.91; $\alpha 1 = 1.24$; $\alpha 2 = 1.85$		
EMS transport (southern subregion)	Log-logistic	Location = 25.02; $\alpha = 7.46$; $\beta = 3.80$		
EMS transport (north-east subregion)	Lognormal	$\mu = 10.97$; $\sigma = 7.03$		

Additional diagnostics vs. no additional diagnostics	Discrete empirical	Value	Frequency
		Additional diagnostics	18
		No additional diagnostics	147
Time from hospital arrival to last additional diagnostics	Gamma	Location = 10.39; $\alpha = 1.11$; $\beta = 17.41$	
Time from additional diagnostics to angiography suite	Beta	Lower endpoint = 4.82; Upper endpoint = 124.31; $\alpha1 = 0.67$; $\alpha2 = 1.60$	
Time from hospital arrival to angiography suite	Gamma	Location = 4.25; $\alpha = 2.23$; $\beta = 10.19$	
Time from angiography suite to groin puncture	Beta	Lower endpoint = 4.72; Upper endpoint = 65.69; $\alpha1 = 4.55$; $\alpha2 = 6.55$	
NIHSS(continuous)	Discrete empirical	Value	Frequency
		3	1
		4	5
		5	3
		6	3
		7	10
		8	7
		9	3
		10	2
		11	2
		12	7
		13	5
		14	10
		15	12
		16	10
		17	19
		18	17
		19	14
		20	9
		21	8
		22	7
		23	6
		24	3
		28	1
Age(Continuous)	Discrete empirical	Value	Frequency
		25	1
		34	1
		38	1
		40	1
		42	1
		45	2
		46	1
		48	1
		51	2
		52	2
		53	3
		54	2

		55	4
		56	1
		57	3
		58	2
		59	4
		60	4
		61	4
		62	4
		63	3
		64	4
		65	6
		66	5
		67	5
		68	5
		69	4
		70	5
		71	4
		72	5
		73	7
		74	5
		75	3
		76	2
		77	6
		78	5
		79	6
		80	5
		82	3
		83	7
		84	2
		85	4
		86	7
		87	1
		88	2
		89	2
		90	3
		91	1
		92	1
		93	1
		97	1
		99	1
Collaterals	Discrete empirical	Value	Frequency
		Absent (0)	11
		less than 50 % filling (1)	81
		> 50% or < 100% filling (2)	48
		100% filling (3)	13

DS, 'drip-and-ship' model; CT, Computed Tomography; EMS, Emergency Medical Services; SD, Standard deviation; IVT, intravenous thrombolysis; CTA, Computed Tomography angiography; ED, Emergency department; NIHSS, National Institutes of Health Stroke Scale.

Estimating patient outcomes

The efficacy of EVT is time dependent. For the simulation model the probability of each of the 7 scales belonging to the modified Rankin Scale (mRS) score, ranging from 0 (no symptoms) to 6 (death) is approximated by a ordinal regression model. Model fit was tested by the Likelihood Ratio chi-square test, which was significant (P=.000). This indicates that the full model represents an improvement in fit over the model with only the intercept. Pearson's chi-square test indicates that the model does not fit the data well [$\chi^2(906)=989.614$, p=.027], whereas Deviance chi-square test does indicate good fit to the data [$\chi^2(906)=489.881$, p=1.00]. Overall, this reflects an acceptable prediction of long-term outcomes for modelling purposes. For individual prognostication this may be another matter.

Regression models account for patient characteristics using the following variables;

- Stroke onset-to-groin puncture time (Total delay in minutes), continuous variable
- Age, continuous variable
- NIHSS score, continuous variable
- Collaterals in 4 categories, with dummy variables for absent of collaterals (yes or no, dummy 0), < 50 filling (yes or no, dummy 1), >50% filling, <100% filling (yes or no, dummy 2), 100% filling (yes or no, dummy 3, reference category).

The following formulas were obtained and used (n=154):

- Probability of mRS6 = 1/(1+exp(6.975-(Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017)))

- Probability of mRS5 = (1/(1+exp(6.841- (Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-

(NIHSS * 0.165)-(Age * 0.017))))-(1/(1+exp(6.975- (Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017))))

- Probability of mRS4 = (1/(1+exp(6.359- (Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017))))-(1/(1+exp(6.841- (Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017))))

- Probability of mRS3 = (1/(1+exp(5.549- (Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017))))-(1/(1+exp(6.359- (Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017))))

- Probability of mRS2 = (1/(1+exp(4.131- (Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017))))-(1/(1+exp(5.549- (Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017))))

- Probability of mRS1 = (1/(1+exp(2.366- (Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017))))-(1/(1+exp(4.131- (Collaterals_dummy_0 * 0.712)-

(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017))))

- Probability of mRS0 = 1-(1/(1+exp(2.366- (Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017))))

Adding CSC(s) – experiments

To evaluate the impact of adding one or more CSCs in our region, the baseline model was adapted. Table S2 shows the adapted steps in the acute pathway and the corresponding distributions for; 1) patients now routed directly to the new CSC, i.e. 'mothership' patients, and 2) patients still transferred from primary stroke centre (PSC) to the new CSC, i.e. 'drip-and-ship' patients.

Table S2; Distributions used for experiment 1 and 2 and 3; adding one or two CSC(s) in the region

Activity duration	Distribution	Parameters
'mothership' patients		
ED to call for transfer	None	0.00
EMS response (inter-hospital transfer)	None	0.00
EMS handover (inter-hospital transfer)	None	0.00
EMS transport (inter-hospital transfer)	None	0.00
Time from ED to angiography suite	Gamma	Location = 0.00; α = 3.49; β = 18.63
Time from angiography suite to groin puncture	Log-logistic	Location = 0.00; α = 28.36; β = 4.89
'drip-and-ship' patients		
EMS transport (inter-hospital transfer), western subregion, PSC 1	Log-logistic	Location = 13.71; α = 6.46; β = 7.93
EMS transport (inter-hospital transfer), western subregion, PSC 2	Log-logistic	Location = 0.00; α = 16.49; β = 18.21
EMS transport (inter-hospital transfer), western subregion, PSC 3	Weibull	Location = 5.95 α = 9.17; β = 11.24
EMS transport (inter-hospital transfer), southern subregion	Log-logistic	Location = 19.43; α = 3.68; β = 3.21

Table S2; Distributions used for experiment 'A'; Adding one or two CSC(s) in the region and adapt the pre-hospital routing to direct to the nearest CSC

Activity duration	Distribution	Parameters

Pre-hospital transport direct to CSC: add 1 CSC:		
Western subregion, PSC 1	Weibull	Location = 0.71 α = 2.26; β = 14.76
Western subregion, PSC 2	Weibull	Location = 0.00 α = 4.86; β = 24.55
Western subregion, PSC 3	Log-logistic	Location = 0.00; α =18.94; β =7.34
Western subregion, PSC 4	Beta	Lower endpoint = 16.87; Upper endpoint = 34.99; α1 = 0.87; α2 = 1.49
North-eastern subregion	Beta	Lower endpoint = 5.79; Upper endpoint = 28.79; α1 = 0.98; α2 = 1.23
Southern subregion	Gamma	Location = 0.00; α = 0.66; β = 58.27
Pre-hospital transport direct to CSC: add 2 CSCs:		
Western subregion, PSC 1	Weibull	Location = 0.71 α = 2.26; β = 14.76
Western subregion, PSC 2	Weibull	Location = 0.00 α = 4.86; β = 24.55
Western subregion, PSC 3	Log-logistic	Location = 0.00; α =18.94; β =7.34
Western subregion, PSC 4	Beta	Lower endpoint = 16.87; Upper endpoint = 34.99; α1 = 0.87; α2 = 1.49
North-eastern subregion	Beta	Lower endpoint = 5.79; Upper endpoint = 28.79; α1 = 0.98; α2 = 1.23
Southern subregion, PSC 1	Beta	Lower endpoint = 0.05; Upper endpoint = 15.07; α1 = 1.82; α2 = 0.85
Southern subregion, PSC 2	Discrete empirical	Value 19 22 24 / Frequency 1 3 1

Results – extended table

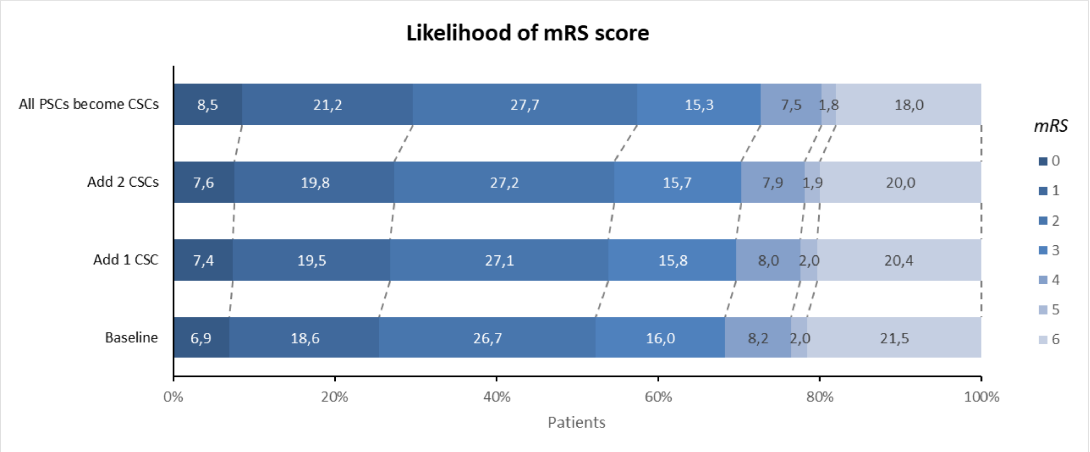
Table S3; Results of modelling the addition of CSC(s) and its effect on OTG, PPFO, and mortality.

Scenario	OTG (95%CI)	FI (95%CI)	Mortality (95%CI)
	All patients		
0. Baseline	240.9 (240.5 - 241.3)	52.4 (52.3 - 52.5)	21.4 (21.3 - 21.5)

a. 25% *slower* CSC workflow, original CSC	255.4 (255.1 - 255.8)	50.6 (50.5 - 50.7)	22.8 (22.7 - 22.9)
b. 25% *faster* CSC workflow, original CSC	226.4 (226.0 - 226.7)	54.2 (54.0 -54.3)	20.1 (20.1 - 20.2)
1. Adding a second CSC in northern Netherlands	227.4 (227.0 - 227.7)	54.0 (53.9 - 54.2)	20.3 (20.2 - 20.4)
a. 25% *slower* CSC workflow, compared to the original CSC	238.1 (237.7 - 238.5)	52.7 (52.6 - 52.9)	21.2 (21.1 - 21.3)
b. 25% *faster* CSC workflow, compared to the original CSC	216.6 (216.3 - 217.0)	55.4 (55.2 - 55.5)	19.4 (19.3 - 19.5)
2. Adding a second and third CSC in northern Netherlands	222.3 (221.9 - 222.7)	54.7 (54.5 - 54.8)	19.8 (19.8 - 19.9)
a. 25% *slower* CSC workflow, compared to the original CSC	235.7 (235.4 - 236.1)	53.0 (52.9 - 53.2)	21.0 (20.9 - 21.1)
b. 25% *faster* CSC workflow, compared to the original CSC	208.9 (210.0 - 210.7)	56.3 (56.2 - 56.4)	18.7 (18.7 - 18.8)
3. All PSCs upgraded to a CSC	197.9 (197.5 - 198.2)	57.6 (57.5 - 57.8)	17.9 (17.8 - 17.9)
a. 25% *slower* CSC workflow, compared to the original CSC	221.7 (221.3 - 222.1)	54.7 (54.6 - 54.9)	19.9 (19.8 - 20.0)
b. 25% *faster* CSC workflow, compared to the original CSC	174.0 (173.7 - 174.4)	60.5 (60.4 - 60.7)	16.0 (15.9 - 16.1)
All patients routed according to the DS model (to the new CSC and the original CSC)			
0. Baseline	240.9 (240.5 - 241.3)	52.4 (52.3 - 52.5)	21.4 (21.3 - 21.5)
1. Adding a second CSC in northern Netherlands	234.1 (233.8 - 234.5)	53.2 (53.1 - 53.4)	20.8 (20.7 - 20.9)
a. 25% *slower* CSC workflow, compared to the original CSC	244.8 (241.4 - 242.2)	52.3 (52.2 - 52.4)	21.5 (21.4 - 21.6)
b. 25% *faster* CSC workflow, compared to the original CSC	226.5 (226.1 - 226.8)	54.2 (54.0 - 54.3)	20.2 (20.1 - 20.2)
2. Adding a second and third CSC in northern Netherlands	231.7 (231.3 - 232.0)	53.5 (53.4 - 53.7)	20.6 (20.5 - 20.7)
a. 25% *slower* CSC workflow, compared to the original CSC	241.0 (240.7 - 241.4)	52.4 (52.3 - 52.5)	21.4 (21.4 - 21.5)
b. 25% *faster* CSC workflow, compared to the original CSC	222.3 (221.9 - 222.6)	54.7 (54.6 - 54.8)	19.8 (19.7 - 19.9)
3. All PSCs upgraded to a CSC	NA	NA	NA
Patients routed according to the modified MS model			
0. Baseline	NA	NA	NA
1. Adding a second CSC in northern Netherlands	198.1 (197.7 - 198.4)	57.6 (57.5 - 57.7)	17.8 (17.8 - 17.9)
a. 25% *slower* CSC workflow, compared to the original CSC	222.0 (221.6 - 222.4)	54.7 (54.5 - 54.8)	19.9 (19.8 - 20.0)
b. 25% *faster* CSC workflow, compared to the original CSC	174.1 (173.8 - 174.5)	60.5 (60.4 - 60.6)	16.0 (15.9 - 16.0)
2. Adding a second and third CSC in northern Netherlands	198.2 (197.8 - 198.6)	57.6 (57.4 - 57.7)	17.9 (17.8 - 18.0)
a. 25% *slower* CSC workflow, compared to the original CSC	222.1 (221.7 - 222.5)	54.6 (54.5 - 54.8)	19.9 (19.8 - 20.0)
b. 25% *faster* CSC workflow, compared to the original CSC	174.3 (173.9 - 174.6)	60.5 (60.3 - 60.6)	16.0 (16.0 - 16.1)
3. All PSCs upgraded to a CSC	197.9 (197.5 - 198.2)	57.6 (57.5 - 57.8)	17.9 (17.8 - 17.9)
a. 25% *slower* CSC workflow, compared to the original CSC	221.7 (221.3 - 222.1)	54.7 (54.6 - 54.9)	19.9 (19.8 - 20.0)
b. 25% *faster* CSC workflow, compared to the original CSC	174.0 (173.7 - 174.4)	60.5 (60.4 - 60.7)	16.0 (15.9 - 16.1)

OTG, onset to groin puncture; PPFO predicted probability of favorable outcome (mRS 0-2); CSC, comprehensive stroke centre; PSC, primary stroke centre; DS, drip and ship; NA, Not applicable; MS, mothership.

Figure S1; Distribution of predicted modified Rankin Scale (mRS) score for the baseline and the three scenarios.



PSC, primary stroke centre; CSC, comprehensive stroke centre; mRS, modified Rankin Scale.

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