Mechanical Thrombectomy in Patients with Acute Ischaemic Stroke: a Cost-effectiveness and Value of Implementation Analysis

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Abstract

Background: Recent clinical trials have demonstrated the efficacy of mechanical thrombectomy (MT) in acute ischaemic stroke.

Aims: To determine the cost-effectiveness, value of future research and value of implementation of MT.

Methods: Using UK clinical and cost data from the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) trial, we estimated the cost-effectiveness of MT over time horizons of 90-days and lifetime, based on a decision-analytic model, using all existing evidence. We performed a meta-analysis of seven clinical trials to estimate treatment effects. We used sensitivity analysis to address uncertainty. Value of implementation analysis was used to estimate the potential value of additional implementation activities to support routine delivery of MT.

Results: Over the trial period (90 days), compared with best medical care alone, MT incurred an incremental cost of £5,207 and 0.025 gain in QALY (incremental cost-effectiveness ratio (ICER) £205,279), which would not be considered cost-effective. However, MT was shown to be cost-effective over a lifetime horizon, with an ICER of £3,466 per QALY gained. The expected value of perfect information per patient eligible for MT in the UK is estimated at £3,178. The expected value of full implementation of MT is estimated at £1.3 billion over five years.

Conclusion: MT was cost-effective compared with best medical care alone over a patient's lifetime. On the assumption of 30% implementation being achieved throughout the UK healthcare system, we estimate that the population health benefits obtained from this treatment are greater than the cost of implementation.

Trial registration: NCT01745692

Background

In acute ischaemic stroke caused by large artery occlusion of the anterior circulation, mechanical thrombectomy (MT) significantly increases the proportion of patients achieving favourable outcomes at day 90 on the modified Rankin Scale (mRS) (3-10). In 2015, the European Stroke Organisation (ESO) updated guidelines for the treatment of acute ischaemic stroke to recommend the use of mechanical thrombectomy (11). In 2016, the National Institute for Health and Care Excellence (NICE) updated their guidelines to include the use of mechanical thrombectomy in the UK (12).

Mechanical thrombectomy is a highly skilled procedure undertaken predominantly in neuroscience centres. Several studies have assessed the cost-effectiveness of thrombectomy in combination with best medical care compared with best medical care alone, and concluded thrombectomy to be cost-effective (13-20) or potentially cost-saving (21-24). Best medical care includes intravenous thrombolysis with recombinant tissue plasminogen activator (IV rtPA) in the majority of cases, and in some clinical trials eligibility for IV rtPA was a mandatory inclusion criterion. Two model-based cost-utility analyses, from the perspective of the UK NHS have been carried out (16, 23). Based on meta-analysis of five RCTs, compared with best medical care alone, thrombectomy in combination with best medical care was associated with an additional £7,061 per quality adjusted life year gained (16). In the other study, based on data from an RCT conducted in the US and Europe (the SWIFT-PRIME trial), thrombectomy in combination with best medical care was reported to be associated with cost-savings of £33,190 per patient (23). However, the adoption and implementation of thrombectomy into routine practice requires additional investment in staff and capital equipment, and is also likely to require significant reorganisation of the healthcare system (25). Implementation in the UK has been limited due to combinations of staffing shortages in interventional and diagnostic neuroradiology, and the need for service reconfiguration. Most existing services currently cover only limited working hours (26-28). It is planned that the service should expand. Currently, one study has estimated the budget impact of adopting and implementing mechanical thrombectomy in Ireland (15). Based on treatment being delivered at two centres and treating 1,340 patients over five years, the cost of implementation was estimated to be 7.2 million euros over five years.

Aims

We conducted an economic evaluation to determine the cost-effectiveness of mechanical thrombectomy in combination best medical care compared with best medical care alone, in patients with acute ischaemic stroke. We undertook value of information analysis to estimate the monetary value of future research to reduce uncertainty in our estimate of cost-effectiveness. In adopting non-drug interventions into clinical practice, challenges to implementation may have an impact on cost-effectiveness. Value of implementation analysis was used to estimate the potential value of additional implementation activities to support the delivery of mechanical thrombectomy in routine practice.

Methods

We estimated the cost-effectiveness of mechanical thrombectomy plus best medical care, compared with best medical care alone, in patients who had acute ischaemic stroke with large artery occlusive anterior circulation. Our analysis was performed over two time horizons: (i) 90-days – alongside the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) trial (9) and (ii) lifetime – based on a decision-analytic model. The lifetime model was used to conduct one-way and probabilistic sensitivity analysis. We also estimated the potential value of future research and the value of implementation initiatives to support the introduction of thrombectomy in routine practice. The analysis was carried out from the perspective of the UK National Health Service (NHS) and Personal and Social Services (PSS). Costs and health benefits were discounted at 3.5% in line with national guidelines (29). Costs were expressed in UK pounds Sterling (2015/16 prices).

Within-trial analysis

The PISTE trial was a multicentre, randomised controlled clinical trial comparing mechanical thrombectomy plus best medical care including IV rtPA with best medical care including IV rtPA alone, in patients who had acute ischaemic stroke with large artery occlusive anterior circulation. Eligible patients were administered IV-tPA within 4.5 hours of stroke. Patients receiving additional mechanical thrombectomy were treated within a target time of <90 mins from IV-tPA start to arterial puncture. The primary outcome was the proportion of patients achieving functional independence mRS 0-2 at 90 days.

We conducted an economic evaluation using data from the PISTE trial. Clinical outcome at 90 days was measured by mRS score. The mRS scores were converted into health utilities using a conversion algorithm (30). Health utilities were used to calculate quality-adjusted life-years (QALYs) over 90 days. Resource use estimates collected during the trial included hospital bed days and cost of treatment with mechanical thrombectomy and best medical care. Unit costs were obtained from the literature (16, 31, 32) and applied to resource use.

Mean patient costs and QALYs were estimated by using a generalised linear model (GLM) and adjusting for potential confounding (33). We adjusted for the following covariates: age group, National Institutes of Health Stroke Scale (NIHSS) group, and baseline health utility (QALY estimates only). The appropriate family for the GLM was selected based on the results of the modified Park's test. Our final cost model was based on the log link and gamma family. Our final QALY model was based on the identity link and Gauss family. All analyses were conducted in Stata 12.1 (StataCorp).

Based on the estimation of the final statistical model, the total cost and QALY difference between groups is based on the marginal prediction.

Cost-effectiveness was expressed as the incremental cost-effectiveness ratio (ICER). We used nonparametric bootstrapping to calculate 95% confidence intervals for our estimate of the difference in mean cost and QALYs between treatment groups.

Lifetime economic model

The economic model was based on a previously published model (16) and is in line with the clinical pathway described for patients with acute ischaemic stroke who are eligible for treatment with both best medical care and mechanical thrombectomy, according to the guidance set out by NICE (National Institute for Clinical Excellence 2016) (figure 1).

[INSERT FIGURE 1]

The 90 days following stroke is represented by a decision tree. Although patients' mRS score can vary appreciably over 90 days, we assume that the mRS score recorded at 90 days represents the most appropriate measure of functional status following treatment. Hence, at 90 days, patients are assumed to enter into one of three possible mutually exclusive health states (mRS 0-2: functional independence; mRS 3-5: functional dependence; mRS 6: death). Subsequently, a four-state Markov model is used to estimate costs and outcomes beyond three months. The model runs for 80 cycles of three months (20 years).

We performed a meta-analysis to estimate the probabilities of patients resulting in the three mRS states using data from five RCT studies published in 2015 (3-7) and two recent trials – THRACE and PISTE trials (9, 10). Transition probabilities for the Markov model were sourced from the literature (34). Table 1 presents a list of parameters used in the lifetime model. Health utility estimates were obtained from published literature (35). Unit cost were obtained from the literature and applied to the recorded resource use associated with hospitalisation (procedure and stay costs), rehabilitation and community care costs (16, 32, 36). Non-UK currencies were converted to UK currency at the cost year reported in the literature and inflated to our reference year of 2015/16 prices using the Hospital & Community health services (HCHS) index (37, 38)

Table 1: Point estimates, probability distributions and source of parameter estimates used in the lifetime economic model

Parameter	Point estimate	Probability distribution	Source
Decision tree			
mRS 0-2 (Best medical care + MT)	0.57	Conditional beta distribution	Meta-analysis
mRS 3-5 (Best medical care + MT)	0.27	Conditional beta distribution	Meta-analysis
mRS 6 (Best medical care + MT)	0.16	Conditional beta distribution	Meta-analysis
mRS 0-2 (Best medical care only)	0.26	Conditional beta distribution	Meta-analysis
mRS 3-5 (Best medical care only)	0.55	Conditional beta distribution	Meta-analysis
mRS 6 (Best medical care only)	0.19	Conditional beta distribution	Meta-analysis
Markov model			
Year 1			
From independent (mRS 0-2) to:			
mRS 0-2	0.955	Conditional beta distribution	Davis (2012)
mRS 3-5	0.024	Conditional beta distribution	Davis (2012)
recurrent stroke	0.013	Conditional beta distribution	Davis (2012)
dead	0.008	Conditional beta distribution	Davis (2012)
From dependent (mRS 3-5) to:		Conditional beta distribution	Davis (2012)
mRS 0-2	0.029	Conditional beta distribution	Davis (2012)
mRS 3-5	0.919	Conditional beta distribution	Davis (2012)
recurrent stroke	0.013	Conditional beta distribution	Davis (2012)
dead	0.039	Conditional beta distribution	Davis (2012)
After year 1			Davis (2012)
From independent (mRS 0-2) to:			Davis (2012)
mRS 0-2	0.979	Conditional beta distribution	Davis (2012)
mRS 3-5	0	Conditional beta distribution	Davis (2012)

recurrent stroke	0.013	Conditional beta distribution	Davis (2012)
dead	0.008	Conditional beta distribution	Davis (2012)
From dependent (mRS 3-5) to:		Conditional beta distribution	Davis (2012)
mRS 0-2	0	Conditional beta distribution	Davis (2012)
mRS 3-5	0.948	Conditional beta distribution	Davis (2012)
recurrent stroke	0.013	Conditional beta distribution	Davis (2012)
dead	0.039	Conditional beta distribution	Davis (2012)
Recurrent stroke		Conditional beta distribution	Davis (2012)
(Best medical care + MT) mRS 0-2	0.867	Conditional beta distribution	Davis (2012)
(Best medical care + MT) mRS 3-5	0.104	Conditional beta distribution	Davis (2012)
(Best medical care + MT) recurrent stroke	0	Conditional beta distribution	Davis (2012)
(Best medical care + MT) dead	0.029	Conditional beta distribution	Davis (2012)
(Best medical care alone) mrs 0-2	0.834	Conditional beta distribution	Davis (2012)
(Best medical care alone) mrs 3-5	0.137	Conditional beta distribution	Davis (2012)
(Best medical care alone) recurrent stroke	0	Conditional beta distribution	Davis (2012)
(Best medical care alone) dead	0.029	Conditional beta distribution	Davis (2012)
Health utilities			
Independent	0.74	Beta distribution	Dorman (2000)
Dependent	0.38	Beta distribution	Dorman (2000)
Recurrent	0.34	Beta distribution	Dorman (2000)
Costs			
Best medical care	£1,919	Gamma distribution	British National Formulary
MT	£8,912	Gamma distribution	Ganesalinham (2015), Davis (2012)

first 3 months:			
Independent	£7,302.83	Gamma distribution	Ganesalinham (2015)
Dependent	£15,627.49	Gamma distribution	Ganesalinham (2015)
Fatal	£10,039.42	Gamma distribution	Ganesalingam (2015)
Recurrent	£380.46	Gamma distribution	Ganesalingam (2015)
Ongoing per 3 months:			
Independent	£498.42	Gamma distribution	Ganesalingam (2015)
Dependent	£1,339.64	Gamma distribution	Ganesalingam (2015)

Incremental analysis

Cost-effectiveness was expressed as the Incremental cost-effectiveness ratio (ICER) and the incremental Net Monetary Benefit (NMB). ICERs are calculated as follows:

Incremental cost-effectiveness ratio (ICER) = ΔCosts/ΔQALY

Where ΔCosts is the difference in total costs between: and ΔQALY is the difference in utility between interventions.

The NMB is a measure of the health benefit, expressed in monetary terms, which incorporates the cost of the new strategy, the health gain obtained, and the societal willingness to pay for health gains. The NMB is calculated using the following formula:

Incremental NMB = (ΔE*WTP) - ΔC

E = effectiveness: WTP = willingness-to-pay threshold (£20,000 in the UK); C = cost

Uncertainty

Uncertainty around the parameter estimates used in our model was fully characterised and propagated through to the model results by conducting probabilistic sensitivity analysis (PSA). This was done by defining parameter values using distributions rather than point estimates. The model was then run 5,000 times with a value randomly drawn from the assigned probability distribution. This produced a distribution of model outputs which was represented visually on the cost-effectiveness plane. Cost-effectiveness acceptability curves (CEAC) were used to represent the probability that an intervention would be cost-effective compared to the control group at a range of willingness-to-pay thresholds.

We conducted one-way sensitivity analysis on the key parameters driving the cost-effectiveness estimate of mechanical thrombectomy in our model. We tested: the cost of the mechanical thrombectomy procedure, the health utility associated with functional independence, dependence and death, the proportion of patients achieving functional independence, dependence and death, following treatment with mechanical thrombectomy or best medical care alone. We tested the impact on the model's estimate of cost-effectiveness (i.e. the ICER) of varying each of these parameters individually by +/- 20%. Further details are given in the appendix.

Value of information

Value of information analysis on the expected value of perfect information (EVPI) was carried out to quantify the potential value of further research based on the difference between the expected NMB with perfect information and with existing information. The EVPI represents the amount a decision maker should be willing to pay to eliminate uncertainty regarding which intervention is the best option. This uncertainty is characterised in the model in terms of parameter uncertainty and is addressed through the use of PSA which produces a distribution of outcomes, in terms of costs and QALYs, for each treatment. The difference between the NMB, based on a decision made with perfect information (i.e. no uncertainty) and with current information, represents the EVPI. We also estimated the expected value of perfect parameter information (EVPPI). This estimates the value of reducing the uncertainty relating to specific parameters in your model. For the purpose of this analysis, we grouped together groups of related model parameters as follows; i) parameters for mRS state at 90 days from clinical trial data; ii) utility parameters; iii) cost parameters; iv) lifetime transition parameters.

It has been estimated that approximately 11,000 patients with acute ischaemic stroke are eligible for mechanical thrombectomy per year in the UK (39-41). For the analysis, we assumed the "effective population" (discounted population) which stands to benefit from this treatment to be 51,404 patients over a five year period, and that the lifetime of the new technology to be five years.

Value of implementation

We calculated the value of implementation as the value of perfect implementation minus the cost of implementation (42), measured over a five-year time horizon. We estimate the maximum potential value of implementation as the net monetary benefit of achieving 100% implementation across the

UK (51,404 patients over five years). We then subtracted from this the cost of 27 comprehensive stroke centres across the UK necessary to perform this procedure. We included costs of ongoing staff salaries and initial set-up costs - such as training and equipment (full details are given in the appendix). We also estimated the "break-even" point at which the NMB obtained from the proportion of eligible patients treated is equal to the cost of implementation.

Results

Within-trial analysis

The results of the within-trial analysis found that mechanical thrombectomy plus best medical care, compared to best medical care alone, had a total cost of £17,157 compared with £11,949. Over the course of the trial (90 days), the QALYs gained in the intervention group were 0.142, compared with 0.117 in the control group. This equates to an incremental cost of £5,207 and 0.025 QALYs associated with the addition of mechanical thrombectomy to best medical care alone and an ICER of £205,279 per QALY gained. The bootstrapped mean cost difference between groups was £5,207 (95% CI: -£1,458, £11,873) and the mean QALY difference was 0.026 (95% CI: -0.008, 0.059).

Lifetime economic model

The results of the economic model found that mechanical thrombectomy plus best medical care, compared to best medical care alone, had a total cost of £46,684 compared with £39,035 (table 2). Over a lifetime horizon, the QALYs gained in the intervention group were 7.614, compared with 5.408 in the control group. This equates to an incremental cost of £7,649 and 2.207 QALYs associated with the addition of mechanical thrombectomy to best medical care alone and an incremental cost-effectiveness ratio of £3,466 per QALY gained and an incremental NMB of £36,484 per patient.

Table 2: Lifetime economic model results, in terms of lifetime costs and QALYs, for MT plus best medical therapy compared with best medical therapy alone (outcomes are presented per patient)

Treatment	Cost (£)	QALYs gained	Incremental cost (£)	Incremental QALYs gained	Incremental cost/QALY gained (ICER)	Incremental NMB
Best medical care	£39,035	5.408				
Best medical care + Mechanical thrombectomy	£46,684	7.614	£7,649	2.207	£3,466	£36,484

Probabilistic sensitivity analysis

The cost-effectiveness plane shows the results of running the model 5,000 times and recording the difference in cost and effectiveness between the mechanical thrombectomy and best medical care (figure 2). Although most data points are observed in the upper right quadrant of the plane (representing the scenario of 'more costly and more effective'), there is considerable uncertainty surrounding the extent and existence of the additional expected costs and the existence and extent of the additional expected QALYs.

The cost-effectiveness acceptability curve (CEAC) shows the probability of mechanical thrombectomy being cost-effective for different levels of willingness-to-pay thresholds, compared with best medical care alone (figure 3). The CEAC shows that, at a willingness-to-pay threshold of £20,000 per QALY gained, mechanical thrombectomy has a 76% probability of being cost-effective, compared with best medical care alone.

[INSERT FIGURE 2]

[INSERT FIGURE 3]

One-way sensitivity analysis

We conducted one-way sensitivity analysis on the key parameters driving the cost-effectiveness estimate of mechanical thrombectomy in our model. Our results showed that varying all of these key parameters within our model had no impact on the decision problem, i.e. all ICER estimates remain below £20,000 per QALY. The parameter which had the greatest negative impact on cost-effectiveness (i.e. increased the ICER) was the proportion of patients achieving functional independence (mRS 0-2) after receiving mechanical thrombectomy.

Value of information

The expected value of perfect information per patient affected by the decision to recommend treatment using mechanical thrombectomy is estimated at £3,178 per person. Based on our assumptions of 51,404 eligible patients over a five-year lifetime of this technology, at a willingness-to-pay of £20,000 per QALY gained, this equates to an expected value of perfect information of £163 million over a five-year period for the UK population (FIGURE 4).

[INSERT FIGURE 4]

The expected value of perfect parameter information suggests that all of the value of reducing parameter uncertainty in our model is generated from the lifetime transition probabilities for patients following the 90-day period after stroke.

Value of implementation

We estimate the value of perfect implementation as the NMB from mechanical thrombectomy (£36,484 per person) multiplied by the effective population (51,404). This implies that the expected value of perfect implementation in UK would be £1.7 billion. We estimate a cost of £16,404,911 per comprehensive stroke centre, over a five-year period. Hence, a total cost of £443 million to implement this procedure across the UK in 27 comprehensive stroke centres over five years (a full breakdown of the cost calculation is given in Table 3 and details of assumptions are given in supplementary material). This suggests an expected value of implementation of £1.3 billion over five years. We estimate the "break-even" value of implementation activity point at approximately 30% implementation (approx. 3,084 patients per year). Below this point, the cost of implementing mechanical thrombectomy into routine practice is expected to be greater than the benefit, in NMB terms.

Table 3: Breakdown of cost calculation for the set-up of a comprehensive stroke unit capable of performing MT, including capital costs, staff and training costs, over a five-year period.

Resource	Units required	Unit cost	Set-up costs	Year 1	Year 2	Year 3	Year 4	Year 5	Resource costs per stroke unit (5 years)
Ongoing costs									
Interventional neuroradiologist (year 1)	3	£116,451	£0	£349,352					
(year 2)	3	£119,455			£358,365				
(year 3)	3	£122,537				£367,611			
(year 4)	4	£125,699					£502,794		
(year 5)	5	£128,942						£644,708	£2,222,831
Anaesthetists (year 1)	3	£17,000	£0	£51,000					-
(year 2)	3	£17,439			£52,316				-
(year 3)	3	£17,889				£53,666			-
(year 4)	4	£18,350					£73,400		-
(year 5)	4	£18,823						£75,294	£305,675
Anaesthetist assistant (year 1)	3	£6,383	£0	£19,148					-
(year 2)	3	£6,547			£19,642				-
(year 3)	3	£6,716				£20,149			-

(year 4)	4	£6,890					£27,559		-
(year 5)	4	£7,067						£28,270	£114,769
Theatre nurse (year 1)	5	£6,383	£0	£31,914					-
(year 2)	5	£6,547			£32,737				-
(year 3)	5	£6,716				£33,582			-
(year 4)	5	£6,890					£34,448		-
(year 5)	5	£7,067						£35,337	£168,019
Recovery nurse (year 1)	1	£5,153	£0	£5,153					-
(year 2)	1	£5,286			£5,286				-
(year 3)	1	£5,422				£5,422			-
(year 4)	1	£5,562					£5,562		-
(year 5)	1	£5,706						£5,706	£27,128
Radiographer (year 1)	5	£4,983	£0	£24,914					-
(year 2)	5	£5,111			£25,557				-
(year 3)	5	£5,243				£26,216			-
(year 4)	5	£5,379					£26,893		-
(year 5)	5	£5,517						£27,586	£131,166
Radiologist (year 1)	2	£23,290	£0	£46,580					-
(year 2)	2	£23,891			£47,782				-
(year 3)	2	£24,507				£49,015			-
(year 4)	2	£25,140					£50,279		-
(year 5)	2	£25,788						£51,577	£245,233
Stroke physician (year 1)	1.4	£23,290	£0	£32,606					-
(year 2)	1.4	£23,891			£33,447				-
(year 3)	1.4	£24,507				£34,310			-
(year 4)	1.4	£25,140					£35,196		-
(year 5)	1.4	£25,788						£36,104	£171,663
Ambulance transfer per MT (year 1)	1	£231	£0	£12,833					-
(year 2)	1	£237			£26,329				-
(year 3)	1	£243				£54,016			-
(year 4)	1	£249					£83,115		-
(year 5)	1	£256						£104,206	£280,499
Helicopter transfer per MT (year 1)	0.17	£2,900	£0	£27,389					-
(year 2)	0.17	£2,975			£56,191				-
(year 3)	0.17	£3,052				£115,282			-
(year 4)	0.17	£3,130					£177,384		-
(year 5)	0.17	£3,211						£222,396	£598,641
MT device costs (stent retriever, catheter, procedure pack, drapes, gowns, gloves, sheath) (year 1)	1	£4,878	£0	£271,000					-
(year 2)	1	£5,004			£555,984				-

(year 3)	1	£5,133				£1,140,656			-
(year 4)	1	£5,265					£1,755,127		-
(year 5)	1	£5,401						£2,200,501	£5,923,267
CT angiography per MT (year 1)	1	£1,200	£0	£66,667					-
(year 2)	1	£1,231			£136,773				-
(year 3)	1	£1,263				£280,604			-
(year 4)	1	£1,295					£431,766		-
(year 5)	1	£1,329						£541,329	£1,457,138
CT perfusion per MT (year 1)	1	£60	£0	£3,333					-
(year 2)	1	£62			£6,839				-
(year 3)	1	£63				£14,030			-
(year 4)	1	£65					£21,588		-
(year 5)	1	£66						£27,066	£72,857
Nurse to accompany CT scan per MT (year 1)	1	£49	£0	£2,722					-
(year 2)	1	£50			£5,585				-
(year 3)	1	£52				£11,458			-
(year 4)	1	£53					£17,630		-
(year 5)	1	£54						£22,104	£59,500
Nurse assessment per MT (year 1)	1	£4	£0	£218					-
(year 2)	1	£4			£447				-
(year 3)	1	£4				£917			-
(year 4)	1	£4					£1,410		-
(year 5)	1	£4						£1,768	£4,760
Routine nurse observation per MT (year 1)	1	£16	£0	£898					-
(year 2)	1	£17			£1,843				-
(year 3)	1	£17				£3,781			-
(year 4)	1	£17					£5,818		-
(year 5)	1	£18						£7,294	£19,635
Junior staff review per MT (year 1)	1	£13	£0	£700					-
(year 2)	1	£13			£1,436				-
(year 3)	1	£13				£2,946			-
(year 4)	1	£14					£4,534		-
(year 5)	1	£14						£5,684	£15,300
Consultant review at 24 hours per MT (year 1)	1	£35	£0	£1,944					-
(year 2)	1	£36			£3,989				-
(year 3)	1	£37				£8,184			-
(year 4)	1	£38					£12,593		-
(year 5)	1	£39						£15,789	£42,500

Training and set-up costs		£40							-	
Angio suite	1	£1,800,000	£1,800,000	£160,000	£164,128	£168,363	£172,706	£177,162		£2,642,359
Interventional neuroradiologist (training)	5	£300,000	£1,500,000	£0						£1,500,000
Anaesthetists (training)	4	£35,798	£143,192	£0						£143,192
Anaesthetist assistant (training)	4	£97	£387	£0						£387
Theatre nurse (training)	5	£20,000	£100,000	£0						£100,000
Recovery nurse (training)	1	£97	£97	£0						£97
Radiologist (training for diagnostic CT)	2	£14,915	£29,830	£0						£29,830
Radiographer (training for diagnostic CT)	5	£10,937	£54,685	£0						£54,685
Stroke physician (training for diagnostic CT)	1.4	£52,700	£73,780	£0						£73,780
									-	
No. of patients treated in UK				1500	3000	6000	9000	11000	-	
No of patients treated per centre				56	111	222	333	407	-	
Annual costs			£3,701,971	£1,108,373	£1,534,677	£2,390,209	£3,439,803	£4,229,880	-	
Cost per MT				£19,951	£13,812	£10,756	£10,319	£10,382	-	
						Total cost per centre over five years:				£16,404,911

Discussion

Our results indicate that mechanical thrombectomy plus best medical care, compared with best medical care alone, meets standard criteria to be considered a cost-effective use of resources in a UK health service setting. The results of our study are consistent with other UK economic evaluations which suggest the cost-effectiveness of mechanical thrombectomy over a patient's lifetime perspective (16, 23). One UK study found mechanical thrombectomy to be cost-saving. This is partly driven by the assumption of higher long-term care costs associated with disability after stroke and the savings resulting from avoidance of disability due to treatment with mechanical thrombectomy. Furthermore, the proportion of patients achieving functional independence (mRS 0-2) following mechanical thrombectomy is 60% (obtained from SWIFT-PRIME trial), compared with our estimate of 57%.

Our results suggest that the use of mechanical thrombectomy is unlikely to be cost-effective over a 90-day time horizon, based on data from the UK-based PISTE trial. This is due to a very small difference in health benefits between the two treatments observed in the trial. The incremental cost of mechanical thrombectomy over a 90-day period was £5,207, compared with £7,649 over a lifetime horizon. However, the QALY gain over a 90-day horizon was 0.025 QALYs, compared with 2.207 QALYs over a lifetime horizon. This implies that, over a lifetime horizon, there is a proportionally greater increase in QALYs than costs. The premature termination of the PISTE trial, and hence reduced sample size and some treatment crossovers, may have had an impact on the QALY different between treatment groups. However, the estimated effect sizes were similar to those seen in other mechanical thrombectomy trials, and results were significant in the per protocol population despite small sample size (43). It should also be noted that best medical care in all patients in the PISTE trial included IV rtPA, in common with some other MT trials (EXTEND-IA, SWIFT-Prime), while other trials permitted inclusion of thrombolysis-ineligible patients (MR CLEAN, ESCAPE, REVASCAT). The effect of MT on very poor functional outcomes is greater among thrombolysis-ineligible patients (44), thus PISTE may have under-estimated the proportion of highly dependent outcomes. Further, PISTE also required good baseline function, as measured by estimated pre-stroke mRS score, which may have influenced the treatment effect observed in the trial.

Our value of information analysis suggests that further research costing less than £163 million has the potential to be considered a cost-effective use of resources. This is because the return on the investment from further research, in terms of the costs and/or health benefits gained from choosing an alternative strategy based on the new evidence, is expected to be no higher than the figure of £163 million. The expected value of perfect parameter information suggests that all of the value of reducing parameter uncertainty in our model is generated from the lifetime transition probabilities for patients following the 90-day period after stroke. Intuitively this makes sense. The recent clinical trials have demonstrated the efficacy of mechanical thrombectomy, compared with best medical care, over a 90-day time horizon. The results of our within-trial cost-effectiveness analysis of the PISTE trial suggests that over 90-days, the benefits associated with mechanical thrombectomy do not outweigh the costs. The result is reversed over the lifetime of a patient, as the cost and utility gain resulting from reduced disability from stroke have proportionally greater influence. Hence, the finding of cost-effectiveness of mechanical thrombectomy comes from our estimates of what happens to a patient over their lifetime, i.e. it comes from our lifetime model. Further research in this area could take the form of a follow-up study aimed at identifying the mRS states of patients following treatment with mechanical thrombectomy at future time points (i.e. 5 years, 10 years).

Our lifetime cost-effectiveness model used clinical evidence from seven RCTs of mechanical thrombectomy (using second generation stent retrievers), but did not consider subsequent trials indicating benefit from mechanical thrombectomy in patients presenting in later time windows (6-24 hours) based on additional imaging selection criteria (40, 41). In order to estimate the cost of routinely providing mechanical thrombectomy across the UK, it was necessary to make some assumptions (see appendix). In terms of staffing costs, our results are likely to be an overestimate. This is because we have chosen to provide the cost of a full-time equivalent for some staff (interventional neuroradiologist) to reflect the need to have these staff available on demand over a 24-hour service focussed on delivering MT. In practice, it is likely that a proportion of these staff will spend their time on activities unrelated to thrombectomy. Support staff (e.g. anaesthetist) are assumed to spend a portion of their time supporting MT delivery, and the remaining time delivering other services. However, precise numbers required to populate a rota capable of providing a 24-hour MT service is highly uncertain and will vary by region and stroke services available. In addition, we have included the full cost of an angiography suite required to undertake the procedure to reflect the initial set-up costs required, however, in practice, this equipment will be available for other activities and hence not all costs associated with the suite will be attributable to thrombectomy.

The ability to identify patients mostly likely to benefit from mechanical thrombectomy and to triage these patients from stroke onset to initiation of treatment within the required time period presents a challenge. To meet this challenge, significant system reorganisation will be required (25). The clinical trial evidence relates to patients who were predominantly able to receive treatment within 6 hours from stroke onset, a small minority being treated beyond 6 hours in the two trials with longer time windows (ESCAPE 12 hours and REVASCAT 8 hours). Patient level meta-analysis confirms steeply declining benefit with later treatment even within the first 6 hours (45). As such, strategies aimed at minimising door-to-needle times are recommended. The role of imaging in the selection of patients for mechanical thrombectomy, as undertaken in both trials of thrombectomy beyond the 6 hour time window (46, 47), remains uncertain for those treated within the first 6 hours, since only two trials mandated similar selection criteria (48, 49) . The role of regional hospitals ("primary stroke centres"), unable to deliver mechanical thrombectomy, in the early administration of IV-tPA prior to transfer to a comprehensive stroke centre - the so called "drip and ship" model vs. the "mothership" model - is likely to require local planning dependent on service characteristics and transport networks (50). The need to maintain a minimum institutional and individual workload to maintain skills would likely pose a challenge to regional hospitals. Further research in these areas will contribute to the discussion around optimal system organisation and will impact on the cost-effectiveness of mechanical thrombectomy that will be observed in routine practice. The results of our implementation analysis suggest that the cost-effectiveness of mechanical thrombectomy in practice is not contingent on achieving full implementation. Indeed, our results suggest that any level of implementation greater than 30% is likely to be a cost-effective use of resources.

Conclusion

Based on a lifetime horizon, our economic model suggests that mechanical thrombectomy is cost-effective compared with best medical care. The CEAC showed that, at a willingness-to-pay threshold of £20,000 per QALY gained, mechanical thrombectomy has a 76% probability of being cost-effective, compared with best medical care alone. Our value of information analysis suggests that there is value in future research aimed at reducing the uncertainty around transitions between mRS states in the longer term. On the assumption of full implementation being achieved throughout the UK healthcare system, we estimate that the value of implementation is greater than the cost of implementation. We find that this result holds for any level of implementation greater than approximately 30%.

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Conflict of interest

The PISTE Trial Steering Committee was chaired by GAF (Stroke Association funded phase) and by H Markus (HTA phase). JF was the lay representative on the Trial Steering Committee and participated in all trial design and management decisions. The Data Monitoring Committee was chaired by K R Lees (Stroke Association phase) and by T Robinson (HTA phase); and included S Lewis (Stroke Association phase), J Norrie (HTA phase) and A Molyneux (throughout).

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party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

Patient/public involvement

N/A

Contribution statement

RH undertook the analysis and drafted the paper. OW designed the study. KM was Principle Investigator on the PISTE trial. All co-authors reviewed and commented on the paper.

Summary statement

What is already known on the topic: the clinical effectiveness of mechanical thrombectomy (MT) has been established in multiple clinical trials. Clinical trials from non-UK data have been combined with UK cost data to estimate potential cost-effectiveness of MT in a UK setting.

What this study adds: This is the first study to utilise UK clinical trial data, resource use data and cost data to estimate the potential cost-effectiveness of MT in a UK setting. Due to the significant capital costs and systems reorganisation required to deliver MT, uncertainty remains over the potential cost-effectiveness of implementation of MT into routine practice throughout the UK. This is the first study which has estimated the cost of setting-up a 24 hour MT service in the UK capable of treating the eligible population over the required 4.5 hour time from stroke onset.

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