National Institute for Health and Care Excellence

Final

Head injury: assessment and early management

[B] Evidence reviews for transport to a distant specialist neuroscience centre

NICE guideline NG232

Evidence reviews underpinning recommendations 1.3.13 and 1.3.14 a research recommendation in the NICE guideline

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Final

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1.1 Review question

What is the clinical and cost effectiveness of pre-hospital strategies to convey people with head injury to a distant specialist neuroscience centre instead of a closer non-specialist unit?

1.1.1 Introduction

Currently people with severe head injury are transported by ambulance to the nearest hospital, regardless of whether that hospital has specialist neurosurgeons. A decision is then made to see if they need to be transported on to a specialist centre. This approach has the advantage of getting patients to a hospital quickly so they can be treated for any immediately life-threatening injuries, but has the disadvantage of increasing the time before they receive specialist care. An alternative approach is for patients with severe head injuries and no other obvious life-threatening injuries to bypass the nearest hospital and go straight to a specialist neurosurgical centre. This has the advantage of getting the patient to specialist care quicker, but may delay treatment of other serious injuries. Since the last update of the guideline new evidence has been identified comparing outcomes in people who were either be transferred to the nearest hospital or transferred directly to a specialist neurosurgical centre.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	All adults, young people and children (including babies under 1 year) with a suspected head injury.
Intervention	Clinical decision rules (CDRs) or triage tools for direct transport to neuroscience centre or major trauma centre with neuroscience.
Comparison	Nearest emergency department (if nearest hospital is not an major trauma centre (MTC) with neuroscience care) – with option for secondary transfer
Outcomes	• All-cause Mortality – at ≤30 days • Quality of life - 3 months or more • Objectively applied score of disability e.g. Glasgow Outcome Score (GOS) or extended GOS (GOS-E) - at 3 months or more • Length of stay in acute care (until discharged home or to rehabilitation) • Serious adverse event – i.e. deterioration of ABC (airway, breathing, and circulation) at ≤30 days • Neurosurgery at ≤30 days • Other surgery at ≤30 days • Secondary transfer to specialist centre (for those initially transferred MTC) at ≤30 days
Study design	• Systematic reviews of RCTs (randomised controlled trials)

	• RCTs • If no RCT evidence is available for any of the identified strata, non-randomised studies will be considered for those strata if they adjust for key confounders, starting with prospective cohort studies

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A search was conducted for randomised trials and non-randomised comparative studies comparing clinical decision rules or triage tools for direct transport to neuroscience centre or major trauma centre with neuroscience with nearest emergency department with option for secondary transfer in people with suspected head injury. No evidence was identified specifically assessing clinical decision rules or triage tools. Two studies (3 papers) comparing specialist neuroscience centre (SNC) to the nearest non-specialist acute general hospital (NSAH) were identified for inclusion in this review. These included one cluster randomised controlled trial[9, 10] and one retrospective cohort study.[17] Evidence from these studies is summarised in the clinical evidence summary below (Table 2).

Population

All evidence was in adults and young people, no evidence was available for children (aged ≥1 to <16 years) and babies (aged <1 year).

Intervention

All papers compared specialist neuroscience centre (SNC) to the nearest non-specialist acute general hospital (NSAH). No evidence was available for direct transfer to a trauma centre.

Outcomes

No evidence was available for the outcomes quality of life (3 months or more) (data available was not in analysable format) and length of stay in acute care.

Key confounders

Included cohort study adjusted for all key confounders (age, GCS score at presentation/pupillary responses at presentation and severity of injury).

Several additional observational studies were identified and screened for inclusion, however most of these did not adjust for all of the key confounders outlined in the review protocol and so were excluded from this review.

Evidence from these studies are summarised in the clinical evidence summary below (Table 3).

Meta-analysis

Outcome data from new studies could not be meta-analysed with corresponding data included in CG 176 (see below) as the studies were heterogenous in terms of interventions. No meta-analysis was conducted in the old version of the guideline for this review question.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix A.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
RCT evidence				
Lecky 2016/2017[9, 10] Head Injury Transportation Straight to Neurosurgery (HITS-NS) UK Cluster RCT	**Intervention clusters:** Head-injured adult patients were transported with direct transport from scene of injury to the nearest specialist neuroscience centre (SNC), bypassing the nearest an acute general hospital (NSAH). n=169 **Control clusters:** Head-injured adult patients were transported to that closest non-specialist acute hospital (NSAH) with selected patients subsequently undergoing secondary transfer to a SNC n=124 Eligible clusters were ambulance stations (AS) within the North East Ambulance Service (NEAS) or the Lancashire and South Cumbria division of the North West Ambulance Service (NWAS). There were 74 eligible clusters in	Patients injured nearest an acute general hospital Emergency Department but not more than one hour land ambulance journey from a neuroscience centre (SNC) thought to be aged > 15yrs, when assessed at scene by ambulance personnel with both i) signs of significant traumatic brain injury (TBI) such as a reduced conscious level and external signs of head injury, and ii) no overt signs of airway, breathing and circulation (ABC) compromise. The GCS score cut-off for study inclusion in NWAS was one point lower (< 13 vs. < 14) than in NEAS. Scene GCS (Glasgow Coma Scale score): Intervention – 12 Control – 12	• Mortality • Quality of life • Degree of disability (GOSE) • Patients with TBI requiring neurosurgery • ABC intervention within 6 hours of leaving scene • Secondary transfer for further care	Less than a quarter of recruited patients had TBI on CT brain scan (70 out of 293, 24%). The proportion was similar to this in NEAS, at 21% (n = 52; 95% CI 16% to 26%) but significantly higher in NWAS at 55% (n = 18; 95% CI 40% to 70%). Adherence to treatment allocation (complied): Intervention 83/169, control 100/124

Study	Intervention and comparison	Population	Outcomes	Comments
	total within the two participating ASs.			
Observational evidence				
Prosser 2020[17] UK Retrospective cohort study	**Specialist neuroscience centre:** Patients bypassing a nearer non-specialist acute hospital. n=89 **Non-specialist centre:** Patients received primary care at a nearest non-specialist acute hospital, with or without secondary transfer to the specialist neuroscience centre. n=266	Adults with significant TBI injured closest to a NSAH with abbreviated injury score (AIS) of ≥3. Median scene GCS score: Bypass – 11 Secondary transfer – 14 NSAH alone – 15	• Survival	Outcome adjusted for age, gender, pre-existing health, abbreviated injury score (AIS), Glasgow coma scale (GCS score) and pupillary response.

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 3: Clinical evidence summary: Transport to specialist neuroscience centre (SNC) compared to transport to nearest non-specialist acute general hospital (NSAH) Emergency Department for head injury (RCT evidence)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with transport to NSAH	Risk difference with transport to SNC
All-cause mortality (30 days)	272 (1 RCT) Lecky 2017	⨁◯◯◯ VERY LOW[a,b]	RR 1.07 (0.50 to 2.29)	88 per 1,000	6 more per 1,000 (44 fewer to 114 more)
Patients with TBI requiring neurosurgery	70 (1 RCT) Lecky 2017	⨁⨁◯◯ LOW [a,b]	RR 0.36 (0.13 to 1.03)	314 per 1,000	201 fewer per 1,000 (273 fewer to 9 more)
ABC intervention within 6 hours of leaving scene	275 (1 RCT) Lecky 2017	⨁◯◯◯ VERY LOW[a,b]	RR 0.77 (0.44 to 1.34)	177 per 1,000	41 fewer per 1,000 (99 fewer to 60 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with transport to NSAH	Risk difference with transport to SNC
Secondary transfer for further care	276 (1 RCT) Lecky 2017	⨁⨁⨁◯ MODERATE [a]	RR 0.31 (0.14 to 0.69)	158 per 1,000	109 fewer per 1,000 (136 fewer to 49 fewer)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes)

Table 4: Clinical evidence summary –Transport to specialist neuroscience centre (SNC) compared to transport to non-specialist acute general hospital (NSAH) emergency department for head injury (RCT and observational evidence)[c]

Outcome	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Intervention (transport to SNC)	Comparison (transport to NSAH)	*P* value
Quality of life – EQ-5D VAS 6-month follow-up scale 0-100; high score represents good outcome	57 (1 RCT) Lecky 2017	⨁◯◯◯ VERY LOW[a]	Median (IQR): 0 (0-80)	Median (IQR): 25 (0-60)	*NS*
Degree of disability – extended Glasgow Outcome Score (GOSE) 6-month follow-up scale 1-8; high score represents poor outcome	57 (1 RCT) Lecky 2017	⨁◯◯◯ VERY LOW[a]	Median (IQR): 1 (1-4)	Median (IQR): 3 (1-5)	*NS*
Survival (vs expected – standardised survival rate expressed as W score)	356 (1 cohort study) Prosser 2020	⨁⨁⨁◯ MODERATE [b]	W score (95% CI): +6.15% (-1.24% to +13.55%) ~ 6.15 excess survivors per 100 patients	W score (95% CI): -1.13% (-4.51% to +2.25%) ~ 1.13 fewer survivors per 100 patients	0.08

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. High risk of bias due to concerns around intervention adherence and high rate of attrition.

Outcome	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Intervention (transport to SNC)	Comparison (transport to NSAH)	*P* value

Study authors note the low response rate – biased heavily towards those known to be deceased (n = 29) or with severe injury (n = 11)

b. Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at serious risk of bias based on ROBINS-I checklist

c. Data not suitable for analysis as no raw data was available. Data as reported in the papers.

See Appendix A for full GRADE tables.

Evidence from CG 176 (NICE 2014)

The benefits of direct transport from the scene to a specialist neurosciences centre compared to transport to the nearest district general hospital (2007)

Clinical evidence

The first study[7] was a retrospective observational cohort study (evidence level 2+), that obtained data from the New York State Trauma Registry from 1996-1998. This study examined patients who were transported to a regional/area trauma centre compared with patients transferred to non trauma centre. The patients in the latter group were assessed via the American Triage system (pre hospital care) and referred directly to a non trauma centre. The population were adults (over 13 years) with a GCS score less than 14. Sub group data of 2763 head injured patients from a data set of 5419 trauma patients were analysed. Group 1 (n=2272 (82.2%)) patients were transported to regional/area trauma centre. These patients were assessed via American Triage system (pre hospital care) and referred directly to the emergency department of either a regional or area trauma centre. Group 2 (n=491 (17.8%)) patients were assessed via American Triage system (pre hospital care) and referred directly to a non trauma centre. The limitations of this study were that patients were categorised as head injured from data reported in trauma registry however the extent of head injury was unknown, because the GCS score was classified as less than14. The results of this study[7] showed that the mortality rate of immediate transfer to a neurosciences centre versus transfer to a non trauma centre were in favour of transfer to neuroscience centre with an odds ratio 0.88, CI (0.64-1.22) which did not reach statistical significance.

The second study[6] (evidence level 2+) described a cohort of paediatric patients aged under 20 years old using a large national US paediatric trauma registry, admitted to one of ninety paediatric hospitals or trauma centres. The cohort compared 3 sub-groups defined by the site of intubation; in the field, in the trauma centre (n=1874) or in a non-trauma centre (n=1647). Taking the data from the latter two branches, risk stratification was performed in patients whose degree of head injury was measured using the New Injury Severity Score (NISS), and the Relative Head Injury Severity Scale (RHISS). The main outcomes were unadjusted mortality rates and functional outcomes. Patients who were assessed using the different scales had no significant differences in outcome or the place of intubation. Mortality (observed vs. expected) rate in group 1 was 16.5% and in group 2 was 13.3%.

Stratification of injury by NISS or degree of head injury showed that higher mortality rates were not only observed in the severely head injured patients who were intubated in a non trauma but also the mild and moderate head injured patients. Some doubt remains over the definition of head injured patients as it is unclear if these were isolated injury or part of a multiple trauma. This affects the conclusions one can draw from this study.

Summary of evidence from 2007 update (from CG 176)

With one study[6] it is difficult to draw rational conclusions as to the benefits of direct transport of patients from the scene to either a neurosciences unit or a DGH (district general hospital) as there is doubt over the definition of head injured patients. The other study[7] showed that the mortality rate of immediate transfer to a neurosciences centre versus DGH were in favour of transport to a neuroscience centre. From this evidence review there is limited evidence for direct transport of head injured patients from the scene to a neurosciences unit being beneficial.

1.1.7 Economic evidence

1.1.7.1 Included studies

One health economic study, an NHS health technology assessment, was included in this review.[9] This is summarised in the health economic evidence profile below (Table 5), where it is compared to the 2007 guideline model, and the health economic evidence table in Appendix H.

1.1.7.2 Excluded studies

Another NHS assessment was excluded due to limited applicability to the question.[15] This paper is listed in Appendix J, with reason for exclusion given.

See also the health economic study selection flow chart in Appendix G.

1.1.8 Summary of included economic evidence

Table 5: Health economic evidence profile: Bypass non-specialist acute hospital versus secondary transfer

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Lecky 2016[9] UK	Directly applicable	Potentially serious limitations[(a)]	• Probabilistic Markov model • Population: Adult with suspected significant head injury closer to non-specialist acute hospital (GCS score <13 and stable) • Comparators: 1) No transfer 2) Selective transfer[(d)] 3) Routine transfer[(e)] 4) Bypass • Time horizon: Lifetime	2 vs 1: £239 3 vs 2: £139 4 vs 3: £2,623	2 vs 1: 0.27 QALYs 3 vs 2: 0.06 QALYs 4vs 3: 0.07 QALYs	2 vs 1: £885 per QALY 3 vs 2: £2,317 per QALY 4vs 3: £37,471 per QALY	Probability Intervention most cost effective (£20k/30k threshold): 1): 1% / 1% 2): 10% / 7% 3): 46% / 44% 4): 42% / 48% Bypass became cost effective in several scenarios[(b)]
NICE 2007 See Appendix I (Model B) UK	Directly applicable	Potentially serious limitations[(c)]	• Probabilistic decision tree • Population: Adults with head injury and AIS>2 • Bypass vs secondary transfer if required	Far: £7,058 Near: £9393	QALYs Far: 0.41 Near: 0.54	Far: £17,228 Near: £17,323 per QALY	In the case that the NSH is far from the accident scene (53 minutes), the strategy of taking all the patients directly to the NSH is cost effective as long as the positive predictive value is more than 28%. If the NSH is near the accident scene (20 minutes), the direct transport to the NSH is marginally cost-effective strategy even if the positive

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
							predictive value is as low as 10%.

Abbreviations: AIS=Abbreviated Injury Scale; GCS=Glasgow Coma Scale; QALY= quality-adjusted life years; NSH=Neurosciences Hospital
(a) Relative treatment effects are based on expert opinion. Survival estimates are not described.
(b) Including those related to: neurosurgery costs, inpatient costs, life expectancy, compliance, discount rates. The expected net benefit of sampling to estimate relative treatment effects was maximised for a sample of 1040 patients but even much smaller trials would be beneficial in reducing uncertainty.
(c) Mortality treatment effects and some other parameters were based on expert opinion or from old studies. Not all incremental costs and cost savings were included. Health status was assumed to be constant beyond 6 months.
(d) The selective transfer strategy involved early secondary transfer of people requiring neurosurgical intervention.
(e) The routine transfer strategy involved early secondary transfer of people requiring neurosurgical intervention and people requiring critical care for their head injury.

1.1.9 Comparison of treatment effects used in economic models

Lecky 2016 - Adult patients with suspected significant head injury closer to non-specialist acute hospital (GCS score <13 and stable)

Relative effectiveness (vs. selective secondary transfer, proportional odds ratio for unfavourable outcome on Glasgow Outcome Scale)

- Bypass: acute neurosurgery 0.53 (Expert opinion)
- Bypass: traumatic brain injury requiring critical care 1.00 (Expert opinion)
- Bypass: traumatic brain injury requiring ward care 0.98 (Expert opinion)
- Bypass: major extracranial injury 0.80 (Mullins 1998[11])
- Routine transfer: traumatic brain injury requiring critical care 0.86 (Expert opinion)
- No transfer: traumatic brain injury requiring critical care 2.14 (Expert opinion)

Proportions in each patient subgroup and compliance with bypass were taken from the HITS-NS randomised controlled trial.

[16]NICE 2007 Adults with head injury abbreviated Injury Scale (AIS) >2

Based on the simulation study Stevenson 2001[23] where, directly transporting all serious head injury patients to the NSH led to an estimated increase in survival of

- 4.5% for injury scenes near to the specialist neurosciences hospital and
- 3.4% for more distant injury scenes.

The health loss associated with false positives was estimated:

- In the case of a distant specialist neurosciences hospital (53 minutes, as reported in Stevenson's model[23]), the mortality increases by 0.05%,
- while it increases by 0.03% if the specialist neurosciences hospital is near (20 minutes).

All of these effects were based on expert opinion. Assumed to be a survival benefit but no health status benefit.

There was a second model in the 2007 guideline (Model A). This was considered to be not applicable for the current update, as costs and benefits were estimated solely for patients requiring neurosurgery rather than all patients transported. This model is not reported here but details can be found in Appendix J.

1.1.10 Economic model

A model was developed for the 2007 guideline update. The treatment effect inputs are summarised in 1.1.9 and the results are reported in 1.1.8. For full details see Appendix I. The guideline development committee concluded:

"A simulation model[23] showed improved survival from directly transporting patients to a neurosciences hospital. However, a number of parameters were based on expert judgement rather than strong evidence. A cost-effectiveness analysis based on this model showed that direct transport is likely to be cost-effective."

1.1.11 Evidence statements

Economic

- One cost–utility analysis found that in adults with suspected significant head injury closer to a non-specialist acute hospital (GCS score <13 and stable), bypassing the local non-specialist acute hospital was not cost effective compared with early secondary transfer (ICER: £37,471 per QALY gained). This analysis was assessed as directly applicable with potentially serious limitations.
- A cost–utility analysis, conducted for the 2007 NICE Head Injury guideline, found that in adults with head injury and AIS>2, bypassing the local non-specialist acute hospital was cost effective compared with secondary transfer when the neurosciences hospital was either far or near the accident scene (ICERs: £17,228 and £17,323 per QALY gained). This analysis was assessed as directly applicable with potentially serious limitations.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The committee considered all outcomes as equally important for decision making and therefore have all been rated as critical: all-cause mortality at ≤30 days, quality of life at 3 months or more, objectively applied score of disability e.g. Glasgow Outcome Score (GOS) or extended GOS at 3 months or more, length of stay in acute care (until discharged home or to rehabilitation) , serious adverse event – i.e. deterioration of ABC at ≤30 days, neurosurgery at ≤30 days, other surgery at ≤30 days and secondary transfer to specialist centre (for those initially transferred MTC) at ≤30 days.

No evidence was identified for the outcomes of other surgery at ≤30 days and length of stay in acute care.

1.1.12.2 The quality of the evidence

Evidence from one randomised controlled trial and one retrospective cohort study was identified for this review. The studies compared transport to specialist neuroscience centre (SNC) to transport to nearest non-specialist acute hospital (SNAHS) emergency department for head injury.

All evidence was in adults and young people, no evidence was available for children (aged ≥1 to <16 years) and babies (aged <1 year).

The quality of the evidence ranged from moderate to very low. The main reasons for downgrading were risk of bias and imprecision. Th RCT was downgraded for risk of bias due to high rate of non-adherence in both the arms of the study. The committee noted that the low adherence in the studies could be due to difference in paramedic training (online and face-to-face) in the ambulance services and paramedic judgement at the site of injury. Adherence was found to be lower in services with online training. The retrospective cohort study was downgraded for risk of bias for selection bias and missing data. The studies were of small sample size, which increased the uncertainty around the point estimates. There were only dichotomous outcomes, and the minimally important differences were taken to be RRs of 0.8 and 1.25. The committee took into account the quality in their interpretation of the evidence.

1.1.12.3 Benefits and harms

Transport to specialist neuroscience centre (SNC) compared to transport to nearest non-specialist acute general hospital (NSAHS) emergency department for head injury (RCT evidence)

The evidence from one RCT suggested that there was some benefit for transfer to non-specialist acute general hospital (NSAHS) for the outcome mortality, but there was uncertainty around the evidence. The evidence suggested that for there was benefit of transport to specialist neuroscience centre for the outcomes of patients with TBI requiring neurosurgery and secondary transfer to further care. The committee noted the low proportion of people confirmed with traumatic brain injury (70 out of 293, 24%) and hence a very small percentage of those needing neurosurgery. Transfer to secondary care as expected was higher in the non-specialist acute general hospital group (NSAHS), transfers for further care occurred in the specialist neuroscience centre (SNC) group owing to repatriation to NSAH (n = 4) when no TBI was present or to a SNC in three cases of non-compliance in patients with TBI.

No difference was observed between SNC and NSAH for the outcome ABC intervention within 6 hours, QOL (EQ-5D) and degree of disability (GOSE).

Transport to specialist neuroscience centre compared to transport to nearest non-specialist general hospital Emergency Department for head injury (observational evidence)

The evidence from one retrospective cohort study suggested that there was no difference between the two groups for the outcome survival benefit.

Overall

The committee agreed that there was limited evidence with suggested benefit of transfer to specialist neuroscience centre for some outcomes but given the uncertainty in evidence the committee did not make any new recommendations. The committee noted that people with a mild/moderate TBI (GCS score 13 or more) should not be transferred to specialist centres due to the very low probability of any neurosurgical intervention being required. Transferring these people puts a burden on the ED department and on the ambulance service. The committee agreed to keep the existing recommendations in CG 176 and NG 40 as there was no compelling evidence to change practice.

The committee discussed that the decision to transfer to specialist care is generally done by ambulance crews/paramedic personnel at the site of injury and they are sometimes assisted by the paramedics in the control room/medical colleagues to check their decision. Patients should be stabilised before transport to specialist care to reduce the risk of deterioration during transfer.

Transfer to specialist care for older people should be based on clinical needs but the committee noted that there is no delay in neurosurgical opinion even if they are transferred to a non-specialist general hospital. The committee did not make any specific recommendation for this group due to lack of evidence.

The committee noted that the data collection for the RCT evidence was in 2012 when trauma care was re-organised in the UK to enable rapid and safe transfer of patients to Major Trauma Centres (MTCs). Hence the evidence is not entirely reflective of the recent trauma care system which now include more consultants, quicker CT scans and rehabilitation of

patients. The committee therefore agreed that further research should be undertaken in this area to determine the effectiveness of transport to specialist neuroscience centres in people with head injury. They developed a research recommendation to inform future guidance.

Rationale behind recommendation in NICE 2014 (CG 176)

There is no strong evidence to suggest a change in the previous recommendation (see bullet 5 within section 5.1). The guideline development group (GDG) recognises that the transported patients with head injury directly to a neuroscience unit rather than a district general hospital (DGH) would require a major shift of resources of between an additional 84,000 and 105,000 bed days to neurosurgery from the existing general surgical, orthopaedic, emergency department, paediatric and geriatric services that currently care for these patients. The Committee recognize that further research is needed in this area in order to identify benefits in transporting patients with head injury to a neuroscience unit or a district general hospital. Therefore, the Committee propose a research recommendation for this question (see Appendix K).

1.1.12.4 Cost effectiveness and resource use

A strategy that bypasses the nearest acute hospital for people with isolated moderate or severe head injury would increase ambulance transport time. A greater number of patients being transported to a neurosciences centre would impose an opportunity cost to that centre, because hospital beds, especially critical care beds, would not be available for other patients, both elective and non-elective. In the longer term this could be addressed by moving some resources from the local acute hospitals to the neurosciences centre. However, a bed-day at a neuroscience centre might be more costly if the staff-mix or staffing levels are more intense. And these costs would apply to all those patients who were bypassed but then found to have only a minor head injury.

All these additional costs of a bypass strategy would be partly offset by a reduced incidence of secondary transfer.

The impact on the cost of rehabilitation is unclear and will depend on the impact on health status. Some people might require less rehabilitation and care in the long-term if they have better outcomes. But if mortality is reduced then the extra survivors represent an increased need for rehabilitation.

The committee considered a published cost-utility analysis (conducted as part of an NHS health technology assessment) and another that was developed for the 2007 NICE head injury guideline (CG56). Both models found that bypassing the local acute hospital would be more costly. The 2007 model suggested that it would be cost effective, whereas the published study, which utilised some data from the HITS-NS trial, had a cost per QALY gained of £37,000 compared with routine early transfer of people requiring neurosurgery or critical care, so it would not be considered cost effective. There was greater uncertainty around this estimate, reflected in the wide confidence intervals.

In both models the treatment effects were based on expert opinion rather than hard evidence. The published model conducted a value of information analysis. It found that further research would be cost-effective.

Given the uncertainty in the clinical review and the results of the value of information analysis, the committee concluded that the cost effectiveness is uncertain. Therefore, they decided not to change practice and so did not recommend bypassing the nearest acute hospital. However, they made a recommendation for further research.

1.1.12.5 Other factors the committee took into account

The committee are aware of ongoing trials such as Major trauma Triage Tool Study (MATTS) on developing an accurate, acceptable and usable prehospital triage tool to identify patients with major trauma benefiting from major trauma centre (MTC) care but these triage tools are used in ED, not at the site of injury. They also noted that there is a published study based on The Trauma Audit and Research Network (TARN) data but will need to be expanded to have a longer follow-up.

The committee highlighted the importance of ensuring people in all settings including custodial settings receive appropriate assessment and can transfer to the most appropriate place of care. The committee were aware of the recommendations on how to manage health emergencies and support people with rapidly deteriorating health in the NICE guideline on physical health of people in prison (NG57).

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Appendices

Appendix A – Review protocols

Review protocol for pre-hospital strategies to convey people with head injury to a distant specialist neuroscience centre instead of a closer non-specialist unit

ID	Field	Content
0.	PROSPERO registration number	CRD42021273439
1.	Review title	What is the clinical and cost effectiveness of pre-hospital strategies to convey people with head injury to a distant specialist neuroscience centre instead of a closer non-specialist unit?
2.	Review question	What is the clinical and cost effectiveness of pre-hospital strategies to convey people with head injury to a distant specialist neuroscience centre instead of a closer non-specialist unit?
3.	Objective	To identify where to transport patients with head injury.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by:

		• English language studies • Human studies • Letters and comments are excluded Other searches: Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Head Injury
6.	Population	Inclusion: All adults, young people and children (including babies under 1 year) with a suspected head injury. Stratified by: • Adults (aged ≥16 years) • Children (aged ≥1 to <16 years) • Babies (aged <1 year)

		Exclusion: Adults, young people and children (including babies under 1 year) with superficial injuries to the eye or face without suspected or confirmed head or brain injury.
7.	Intervention	Clinical decision rules or triage tools for direct transport to neuroscience centre or major trauma centre with neuroscience.
8.	Comparator/Reference standard/Confounding factors	Nearest emergency department (if nearest hospital is not an MTC with neuroscience care) – with option for secondary transfer Confounders: • Age • GCS score at presentation/Pupillary responses at presentation • Severity of injury (intra/extracranial)
9.	Types of study to be included	• Systematic reviews of RCTs • RCTs • If no RCT evidence is available for any of the identified strata, non-randomised studies will be considered for those strata if they adjust for key confounders, starting with prospective cohort studies
10.	Other exclusion criteria	Non-English language studies. Non comparative NRS Before and after studies Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.

		Patients whose nearest centre is a specialist centre. Studies only including crew who have capacity to intubate patients at the scene.
11.	Context	Early identification and management of TBI could potentially improve patient outcomes for people with suspected or confirmed head injury. Direct transport of TBI patients to neuroscience centres, bypassing non-specialist acute hospitals, could potentially facilitate this. However, delays in stabilisation of airway, breathing and circulation and the difficulties in reliably identifying TBI at scene may make this practice harmful compared with selective secondary transfer from nearest non-specialist hospital to neuroscience centres and lead to over-triage to specialist centres. Current guidance: Transport patients who have sustained a head injury directly to a hospital that has the resources to further resuscitate them and to investigate and initially manage multiple injuries. All acute hospitals receiving patients with head injury directly from an incident should have these resources, which should be appropriate for a patient's age.
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • All-cause Mortality – at ≤30 days • Quality of life - 3 months or more • Objectively applied score of disability e.g. Glasgow Outcome Score (GOS) or extended GOS - at 3 months or more • Length of stay in acute care (until discharged home or to rehabilitation) • Serious adverse event – i.e. deterioration of ABC at ≤30 days • Neurosurgery at ≤30 days • Other surgery at ≤30 days • Secondary transfer to specialist centre (for those initially transferred MTC) at ≤30 days

14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. This review will make use of the priority screening functionality within the EPPI-reviewer software. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0)

		• Non randomised study, including cohort studies: Cochrane ROBINS-I
16.	Strategy for data synthesis	For clinical effectiveness evidence: • Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. • Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. • The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.
17.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity in clinical effectiveness outcome data is present: • Clinical decision tool used • Time to destination ○ ≤17 minutes

		○ >17 minutes • Seniority of staff making the decision on where to transfer ○ Senior healthcare professional ○ Non-senior healthcare professional • ABC status ○ Any of A,B or C impaired ○ None of ABC impaired	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date		
22.	Anticipated completion date		
23.	Stage of review at time of this submission	Review stage	Started / Completed
		Preliminary searches	☐ / ☑
		Piloting of the study selection process	☐ / ☑

		Formal screening of search results against eligibility criteria	☐	☑
		Data extraction	☐	☑
		Risk of bias (quality) assessment	☐	☑
		Data analysis	☐	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail headinjury@nice.org.uk [5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
25.	Review team members	 From the National Guideline Centre: Guideline lead: Sharon Swain Senior systematic reviewer: Sharangini Rajesh Senior systematic reviewer: Julie Neilson Health economist: David Wonderling Information specialist: Joseph Runicles		

		Project manager: Giulia Zuodar
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: 1 (nice.org.uk) .
29.	Other registration details	
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=273439
S31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Head injury

33.	Details of existing review of same topic by same authors	[Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible. NOTE: most NICE reviews will not constitute an update in PROSPERO language. To be an update it needs to be the same review question/search/methodology. If anything has changed it is a new review]	
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	

Table 6: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. The search covered all years
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published in 2006 or later that were included in the previous guidelines will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[12] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will decide based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded based on applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2006 or later (including any such studies included in the previous guidelines) but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as 'Not applicable'.
- Studies published before 2006 (including any such studies included in the previous guidelines) will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[12]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve.

Table 7: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 22 June 2022	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 22 June 2022	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Reviews to 2022 Issue 6 of 12 CENTRAL to 2022 Issue 6 of 12	
Epistemonikos (The Epistemonikos Foundation)	Inception to 22 June 2022	Exclusions (Cochrane reviews)

Medline (Ovid) search terms

1.	(trauma or (traumatic adj3 injur*)).ti,ab.

2.	craniocerebral trauma/ or exp brain injuries/ or coma, post-head injury/ or exp head injuries, closed/ or head injuries, penetrating/ or exp intracranial hemorrhage, traumatic/ or exp skull fractures/
3.	((skull or cranial) adj3 fracture*).ti,ab.
4.	((head or brain or craniocerebral or cranial or cerebral or skull) adj4 (injur* or trauma*)).ti,ab.
5.	or/1-4
6.	letter/
7.	editorial/
8.	news/
9.	exp historical article/
10.	Anecdotes as Topic/
11.	comment/
12.	case report/
13.	(letter or comment*).ti.
14.	or/6-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animals/ not humans/
18.	exp Animals, Laboratory/
19.	exp Animal Experimentation/
20.	exp Models, Animal/
21.	exp Rodentia/
22.	(rat or rats or mouse or mice or rodent*).ti.
23.	or/16-22
24.	5 not 23
25.	limit 24 to English language
26.	emergency service, hospital/ or trauma centers/
27.	Neurosurgery/
28.	(neuroscien* or neurosurg* or neurol* or emergenc* or accident* or "A and E" or "A & E" or A&E or ICU).ti,ab.
29.	((special* or tertiary or critical care or intensive care or regional or district general or acute) adj2 (cent* or unit* or hospital* or facilit*)).ti,ab.
30.	(trauma adj2 (centre* or center* or network* or service*)).ti,ab.
31.	or/26-30
32.	"transportation of patients"/ or exp ambulances/ or ambulance diversion/
33.	ambulance*.ti,ab.
34.	(transport* or transfer* or bypass or by pass or direct).ti,ab.
35.	or/32-34
36.	triage/
37.	(triage* or overtriage* or triaging).ti,ab.
38.	((pre-hospital or prehospital) adj3 (protocol* or guideline* or strateg* or tool* or index* or indices or score* or scoring or scale* or model* or rule* or criteria or calculat*)).ti,ab.

39.	((clinical or decision*) adj4 (tool or strateg*)).ti,ab.
40.	Decision support techniques/
41.	or/36-40
42.	35 or 41
43.	25 and 31 and 42
44.	randomized controlled trial.pt.
45.	controlled clinical trial.pt.
46.	randomi#ed.ti,ab.
47.	placebo.ab.
48.	randomly.ti,ab.
49.	Clinical Trials as topic.sh.
50.	trial.ti.
51.	or/44-50
52.	Meta-Analysis/
53.	exp Meta-Analysis as Topic/
54.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
55.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
56.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
57.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
58.	(search* adj4 literature).ab.
59.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
60.	cochrane.jw.
61.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
62.	or/52-61
63.	Epidemiologic studies/
64.	Observational study/
65.	exp Cohort studies/
66.	(cohort adj (study or studies or analys* or data)).ti,ab.
67.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
68.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
69.	Controlled Before-After Studies/
70.	Historically Controlled Study/
71.	Interrupted Time Series Analysis/
72.	(before adj2 after adj2 (study or studies or data)).ti,ab.
73.	exp case control study/
74.	case control*.ti,ab.
75.	Cross-sectional studies/
76.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.

77.	or/63-76
78.	43 and (51 or 62 or 77)

Embase (Ovid) search terms

1.	(trauma or (traumatic adj3 injur*)).ti,ab.
2.	head injury/
3.	exp brain injury/
4.	skull injury/ or exp skull fracture/
5.	((head or brain or craniocerebral or cranial or cerebral or skull) adj4 (injur* or trauma*)).ti,ab.
6.	((skull or cranial) adj3 fracture*).ti,ab.
7.	(trauma* and ((subdural or intracranial) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.
8.	or/1-7
9.	letter.pt. or letter/
10.	note.pt.
11.	editorial.pt.
12.	(conference abstract or conference paper).pt.
13.	case report/ or case study/
14.	(letter or comment*).ti.
15.	or/9-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animal/ not human/
19.	nonhuman/
20.	exp Animal Experiment/
21.	exp Experimental Animal/
22.	animal model/
23.	exp Rodent/
24.	(rat or rats or mouse or mice or rodent*).ti.
25.	or/17-24
26.	8 not 25
27.	limit 26 to English language
28.	exp hospital emergency service/
29.	neurosurgery/
30.	(neuroscien* or neurosurg* or neurol* or emergenc* or accident* or "A and E" or "A & E" or A&E or ICU).ti,ab.
31.	((special* or tertiary or critical care or intensive care or regional or district general or acute) adj2 (cent* or unit* or hospital* or facilit*)).ti,ab.
32.	(trauma adj2 (centre* or center* or network* or service*)).ti,ab.
33.	or/28-32
34.	patient transport/ or ambulance/ or emergency medical dispatch/
35.	"traffic and transport"/

36.	ambulance transportation/
37.	ambulance*.ti,ab.
38.	(transport* or transfer* or bypass or by pass or direct).ti,ab.
39.	or/34-38
40.	emergency health service/
41.	(triage* or overtriage* or triaging).ti,ab.
42.	((pre-hospital or prehospital) adj3 (protocol* or guideline* or strateg* or tool* or index* or indices or score* or scoring or scale* or model* or rule* or criteria or calculat*)).ti,ab.
43.	((clinical or decision*) adj4 (tool or strateg*)).ti,ab.
44.	exp clinical decision making/ or exp decision making/ or clinical decision rule/
45.	or/40-44
46.	39 or 45
47.	27 and 33 and 46
48.	random*.ti,ab.
49.	factorial*.ti,ab.
50.	(crossover* or cross over*).ti,ab.
51.	((doubl* or singl*) adj blind*).ti,ab.
52.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
53.	crossover procedure/
54.	single blind procedure/
55.	randomized controlled trial/
56.	double blind procedure/
57.	or/48-56
58.	systematic review/
59.	Meta-Analysis/
60.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
61.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
62.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
63.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
64.	(search* adj4 literature).ab.
65.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
66.	cochrane.jw.
67.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
68.	or/58-67
69.	Clinical study/
70.	Observational study/
71.	Family study/
72.	Longitudinal study/
73.	Retrospective study/

74.	Prospective study/
75.	Cohort analysis/
76.	Follow-up/
77.	cohort*.ti,ab.
78.	76 and 77
79.	(cohort adj (study or studies or analys* or data)).ti,ab.
80.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
81.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
82.	(before adj2 after adj2 (study or studies or data)).ti,ab.
83.	exp case control study/
84.	case control*.ti,ab.
85.	cross-sectional study/
86.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
87.	or/69-75,78-86
88.	47 and (57 or 68 or 87)

Cochrane Library (Wiley) search terms

#1.	(trauma or (traumatic near/3 injur*)):ti,ab
#2.	MeSH descriptor: [Craniocerebral Trauma] this term only
#3.	MeSH descriptor: [Brain Injuries] explode all trees
#4.	MeSH descriptor: [Coma, Post-Head Injury] this term only
#5.	MeSH descriptor: [Head Injuries, Closed] explode all trees
#6.	MeSH descriptor: [Head Injuries, Penetrating] this term only
#7.	MeSH descriptor: [Intracranial Hemorrhage, Traumatic] explode all trees
#8.	MeSH descriptor: [Skull Fractures] explode all trees
#9.	((skull or cranial) near/3 fracture*):ti,ab
#10.	((head or brain or craniocerebral or cranial or skull) near/3 (injur* or trauma*)):ti,ab
#11.	(trauma* and ((subdural or intracranial) near/2 (h?ematoma* or h?emorrhage* or bleed*))):ti,ab
#12.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13.	MeSH descriptor: [Emergency Service, Hospital] this term only
#14.	MeSH descriptor: [Trauma Centers] this term only
#15.	MeSH descriptor: [Neurosurgery] this term only
#16.	(neuroscien* or neurosurg* or neurol* or emergenc* or accident* or "A and E" or "A & E" or A&E or ICU):ti,ab
#17.	((special* or tertiary or critical care or intensive care or regional or district general or acute) near/2 (cent* or unit* or hospital* or facilit*)):ti,ab
#18.	(trauma near/2 (centre* or center* or network* or service*)):ti,ab
#19.	#13 or #14 or #15 or #16 or #17 or #18
#20.	MeSH descriptor: [Transportation of Patients] this term only
#21.	MeSH descriptor: [Ambulance Diversion] this term only

#22.	MeSH descriptor: [Ambulances] explode all trees
#23.	ambulance*:ti,ab
#24.	(transport* or transfer* or bypass or by pass or direct):ti,ab
#25.	#20 or #21 or #22 or #23 or #24
#26.	MeSH descriptor: [Triage] this term only
#27.	(triage* or overtriage* or triaging):ti,ab
#28.	((pre-hospital or prehospital) near/3 (protocol* or guideline* or strateg* or tool* or index* or indices or score* or scoring or scale* or model* or rule* or criteria or calculat*))ti,ab
#29.	((clinical or decision*) near/4 (tool or strateg*)):ti,ab
#30.	MeSH descriptor: [Decision Support Techniques] this term only
#31.	#26 or #27 or #28 or #29 or #30
#32.	#25 or #31
#33.	#12 and #19 and #32

Epistemonikos search terms

1.	(advanced_title_en:((advanced_title_en:(((trauma OR traumatic) AND (injury OR injuries))) OR advanced_abstract_en:(((trauma OR traumatic) AND (injury OR injuries)))) OR (advanced_title_en:(((skull OR cranial) AND fracture*)) OR advanced_abstract_en:(((skull OR cranial) AND fracture*))) OR (advanced_title_en:(((head OR brain OR craniocerebral OR cranial OR cerebral OR skull) AND (injur* OR trauma*))) OR advanced_abstract_en:(((head OR brain OR craniocerebral OR cranial OR cerebral OR skull) AND (injur* OR trauma*))))) OR advanced_abstract_en:((advanced_title_en:(((trauma OR traumatic) AND (injury OR injuries))) OR advanced_abstract_en:(((trauma OR traumatic) AND (injury OR injuries)))) OR (advanced_title_en:(((skull OR cranial) AND fracture*)) OR advanced_abstract_en:(((skull OR cranial) AND fracture*))) OR (advanced_title_en:(((head OR brain OR craniocerebral OR cranial OR cerebral OR skull) AND (injur* OR trauma*))) OR advanced_abstract_en:(((head OR brain OR craniocerebral OR cranial OR cerebral OR skull) AND (injur* OR trauma*)))))) AND (advanced_title_en:((neuroscien* OR neurosurg* OR neurol* OR emergenc* OR accident* OR "A AND E" OR "A & E" OR A&E OR ICU)) OR advanced_abstract_en:((neuroscien* OR neurosurg* OR neurol* OR emergenc* OR accident* OR "A AND E" OR "A & E" OR A&E OR ICU))) OR (advanced_title_en:(((special* OR tertiary OR critical care OR intensive care OR regional OR district general OR acute) adj2 (cent* OR unit* OR hospital* OR facilit*))) OR advanced_abstract_en:(((special* OR tertiary OR critical care OR intensive care OR regional OR district general OR acute) adj2 (cent* OR unit* OR hospital* OR facilit*)))) OR (advanced_title_en:((trauma AND (centre* OR center* OR network* OR service*))) OR advanced_abstract_en:((trauma AND (centre* OR center* OR network* OR service*)))) AND (advanced_title_en:((ambulance* OR transport* OR transfer* OR bypass OR by pass OR direct OR triage* OR overtriage* OR triaging)) OR advanced_abstract_en:((ambulance* OR transport* OR transfer* OR bypass OR by pass OR direct OR triage* OR overtriage* OR triaging))) OR (advanced_title_en:(((pre-hospital OR prehospital) AND (protocol* OR guideline* OR strateg* OR tool* OR index* OR indices OR score* OR scoring OR scale* OR model* OR rule* OR criteria OR calculat*))) OR advanced_abstract_en:(((pre-hospital OR prehospital) AND (protocol* OR guideline* OR strateg* OR tool* OR index* OR indices OR score* OR scoring OR scale* OR model* OR rule* OR criteria OR calculat*)))) OR (advanced_title_en:(((clinical OR decision*) AND (tool OR strateg* OR rule*))) OR advanced_abstract_en:(((clinical OR decision*) AND (tool OR strateg*))))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Head Injury population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies.

Table 8: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 22 June 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
	Quality of Life 1946 – 22 June 2022	
Embase (OVID)	Health Economics 1 January 2014 – 22 June 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 22 June 2022	
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception – 22 June 2022	English language

Medline (Ovid) search terms

1.	craniocerebral trauma/ or exp brain injuries/ or coma, post-head injury/ or exp head injuries, closed/ or head injuries, penetrating/ or exp intracranial hemorrhage, traumatic/ or exp skull fractures/
2.	((skull or cranial) adj3 fracture*).ti,ab.

3.	((head or brain or craniocerebral or intracranial or cranial or skull) adj3 (injur* or trauma*)).ti,ab.
4.	(trauma* and ((subdural or intracranial or brain) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.
5.	or/1-4
6.	letter/
7.	editorial/
8.	news/
9.	exp historical article/
10.	Anecdotes as Topic/
11.	comment/
12.	case report/
13.	(letter or comment*).ti.
14.	or/6-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animals/ not humans/
18.	exp Animals, Laboratory/
19.	exp Animal Experimentation/
20.	exp Models, Animal/
21.	exp Rodentia/
22.	(rat or rats or mouse or mice or rodent*).ti.
23.	or/16-22
24.	5 not 23
25.	limit 24 to English language
26.	economics/
27.	value of life/
28.	exp "costs and cost analysis"/
29.	exp Economics, Hospital/
30.	exp Economics, medical/
31.	Economics, nursing/
32.	economics, pharmaceutical/
33.	exp "Fees and Charges"/
34.	exp budgets/
35.	budget*.ti,ab.
36.	cost*.ti.
37.	(economic* or pharmaco?economic*).ti.
38.	(price* or pricing*).ti,ab.

39.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
40.	(financ* or fee or fees).ti,ab.
41.	(value adj2 (money or monetary)).ti,ab.
42.	or/26-41
43.	quality-adjusted life years/
44.	sickness impact profile/
45.	(quality adj2 (wellbeing or well being)).ti,ab.
46.	sickness impact profile.ti,ab.
47.	disability adjusted life.ti,ab.
48.	(qal* or qtime* or qwb* or daly*).ti,ab.
49.	(euroqol* or eq5d* or eq 5*).ti,ab.
50.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/43-61
63.	25 and (42 or 62)

Embase (Ovid) search terms

1.	head injury/
2.	exp brain injury/
3.	skull injury/ or exp skull fracture/
4.	((head or brain or craniocerebral or intracranial or cranial or skull) adj3 (injur* or trauma*)).ti,ab.
5.	((skull or cranial) adj3 fracture*).ti,ab.
6.	(trauma* and ((subdural or intracranial or brain) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.

11.	(conference abstract or conference paper).pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.
14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/16-23
25.	7 not 24
26.	limit 25 to English language
27.	health economics/
28.	exp economic evaluation/
29.	exp health care cost/
30.	exp fee/
31.	budget/
32.	funding/
33.	budget*.ti,ab.
34.	cost*.ti.
35.	(economic* or pharmaco?economic*).ti.
36.	(price* or pricing*).ti,ab.
37.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
38.	(financ* or fee or fees).ti,ab.
39.	(value adj2 (money or monetary)).ti,ab.
40.	or/27-39
41.	quality-adjusted life years/
42.	"quality of life index"/
43.	short form 12/ or short form 20/ or short form 36/ or short form 8/
44.	sickness impact profile/
45.	(quality adj2 (wellbeing or well being)).ti,ab.
46.	sickness impact profile.ti,ab.
47.	disability adjusted life.ti,ab.
48.	(qal* or qtime* or qwb* or daly*).ti,ab.

49.	(euroqol* or eq5d* or eq 5*).ti,ab.
50.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/41-61
63.	26 and (40 or 62)

NHS EED and HTA (CRD) search terms

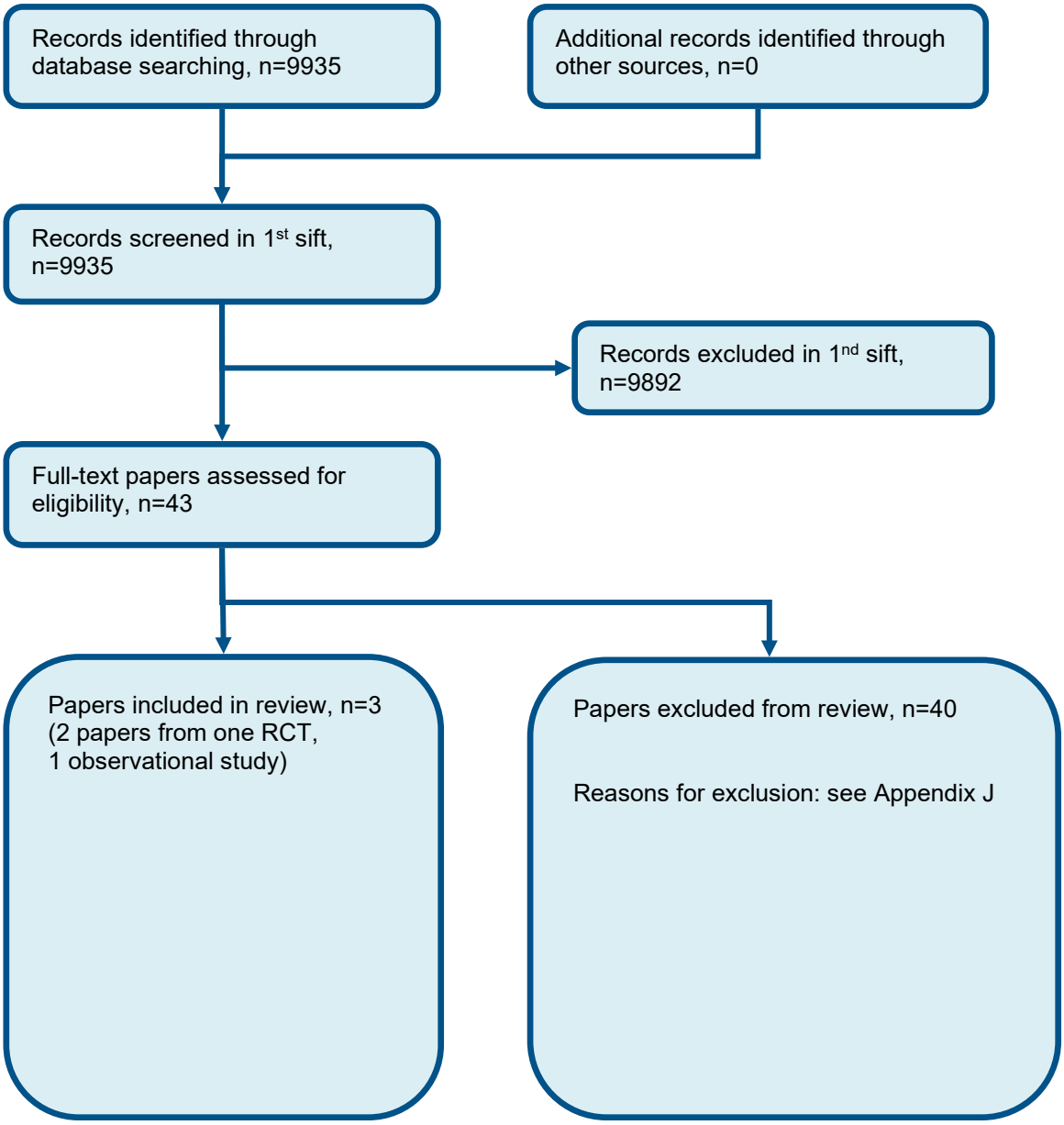
#1.	MeSH DESCRIPTOR Brain Injuries EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Craniocerebral Trauma
#3.	MeSH DESCRIPTOR Coma, Post-Head Injury
#4.	MeSH DESCRIPTOR Head Injuries, Closed EXPLODE ALL TREES
#5.	MeSH DESCRIPTOR Head Injuries, Penetrating
#6.	MeSH DESCRIPTOR Intracranial Hemorrhage, Traumatic EXPLODE ALL TREES
#7.	MeSH DESCRIPTOR Skull Fractures EXPLODE ALL TREES
#8.	(((skull or cranial) adj3 fracture*))
#9.	(((head or brain or craniocerebral or intracranial or cranial or skull) adj3 (injur* or trauma*)))
#10.	((trauma* and ((subdural or intracranial or brain) adj2 (h?ematoma* or h?emorrhage* or bleed*))))
#11.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

INAHTA search terms

1.	((((trauma* and ((subdural or intracranial or brain) and (haematoma* or hematoma* or haemorrhage* or hemorrhage* or bleed*)))))[Title]) AND (((trauma* and ((subdural or intracranial or brain) and (haematoma* or hematoma* or haemorrhage* or hemorrhage* or bleed*)))))[Title])) OR ((((skull or cranial) and fracture*))[Title] OR (((skull or cranial) and fracture*))[abs]) OR ((((head or brain or craniocerebral or intracranial or cranial or skull) and (injur* or trauma*)))[Title] OR (((head or brain or craniocerebral or intracranial or cranial or skull) and (injur* or trauma*)))[abs]) OR ("Skull Fractures"[mhe]) OR ("Intracranial Hemorrhage, Traumatic"[mhe]) OR ("Head Injuries, Penetrating"[mh]) OR ("Head Injuries, Closed"[mhe]) OR ("Coma, Post-Head Injury"[mh]) OR ("Brain Injuries"[mhe]) OR ("Craniocerebral Trauma"[mh])

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of transport to a distant specialist neuroscience centre



Appendix D – Effectiveness evidence

Lecky, 2017 and Lecky 2016

Bibliographic Reference	Lecky, F. E.; Russell, W.; McClelland, G.; Pennington, E.; Fuller, G.; Goodacre, S.; Han, K.; Curran, A.; Holliman, D.; Chapman, N.; Freeman, J.; Byers, S.; Mason, S.; Potter, H.; Coats, T.; Mackway-Jones, K.; Peters, M.; Shewan, J.; Bypassing nearest hospital for more distant neuroscience care in head-injured adults with suspected traumatic brain injury: findings of the head injury transportation straight to neurosurgery (HITS-NS) pilot cluster randomised trial; BMJ Open; 2017; vol. 7 (no. 10); e016355 Lecky, F., Russell, W., Fuller, G. et al. (2016) The Head Injury Transportation Straight to Neurosurgery (HITS-NS) randomised trial: a feasibility study. Health Technology Assessment (Winchester, England) 20(1): 1-198

Study details

Secondary publication of another included study- see primary study for details	Pilot cluster randomised controlled trial
Other publications associated with this study included in review	Lecky F, Russell W, Fuller G, et al. The Head Injury Transportation Straight to Neurosurgery (HITS-NS) randomised trial: a feasibility study. *Health Technol Assess*. 2016;20(1):1-198. doi:10.3310/hta20010
Trial name / registration number	HITS-NS. ISRCTN68087745
Study type	Cluster randomised controlled trial
Study location	United Kingdom
Study setting	Two English Ambulance Services. Lancashire/Cumbria in the North West Ambulance Service (NWAS) and the North East Ambulance Service (NEAS).
Study dates	The study was conducted between January 2012 and September 2013 with the majority of recruitment occurring from April 2012 to March 2013.

Sources of funding	The study was funded by the National Institute of Health Research Health Technology Assessment Programme HTA08/116/85.
Inclusion criteria	Patients injured nearest an acute general hospital Emergency Department (NSAH) but not more than one hour land ambulance journey from a neuroscience centre (SNC) thought to be aged > 15yrs, when assessed at scene by ambulance personnel with both In NWAS: i) Signs of significant TBI such as a reduced conscious level (GCS score < 13) and external signs of head injury AND ii) No overt signs of airway, breathing and circulation compromise. In NEAS: i) Signs of significant TBI such as a reduced conscious level (GCS score < 14) and external signs of head injury AND ii) No overt signs of airway, breathing and circulation compromise.
Exclusion criteria	Patients who fulfil ANY of the following criteria will be excluded: i) thought to be aged <16 years ii) who have been found by the treating paramedic in NWAS, or by the treating paramedic / Level 2 Emergency Medical Technician in NEAS, to not have signs of traumatic brain injury at the scene (i.e. full or only mildly impaired consciousness GCS score > 12 in NWAS; or full or only mildly impaired consciousness GCS score > 13 in NEAS) iii) Who have obvious life threatening injuries affecting the airway, breathing or circulation: A - Partial or complete airway obstruction / contamination present after simple manoeuvres, or any patient who has been intubated or had a supraglottic device inserted at the scene of injury B - Respiratory rate < 10 or > 30 in NWAS, or Respiratory rate < 12 or > 30 in NEAS, OR sucking chest wound OR signs of tension pneumothorax such as absent air entry into a hemithorax with contralateral tracheal deviation C - Significant external haemorrhage not easily controlled by pressure, OR amputation above the wrist or ankle OR absence of radial pulse on

	palpation (Paramedics recognise these signs as part of their current scope of practice) iv) Who are injured more than an hour's travelling time from a neuroscience centre. Eligible patients attended by Helicopter Emergency Medical Services or transported by other Ambulances Services into study hospitals were excluded as were patients injured more than 1hour from the nearest SNC by land ambulance.
Recruitment / selection of participants	The unit of cluster for the trial was the ambulance station (AS) of which there were 30 within each of the ambulance services (60 in total). 30 AS were intervention stations and took patients meeting the inclusion criteria (past the nearest Emergency Department) straight to the nearest neuroscience centre for the duration of the trial. The 30 control AS practiced usual care by taking patients to the nearest Emergency Department. Patient identification was confirmed by the research paramedics the following day. Patients were formally recruited and consented during their hospital stay.
Intervention(s)	Head-injured adult patients were transported with direct transport from scene of injury to the nearest SNC (intervention clusters), bypassing the nearest an acute general hospital.
Population subgroups	n/a
Comparator	Head-injured adult patients were transported to that closest hospital (control clusters) with selected patients subsequently undergoing secondary transfer to a SNC
Number of participants	293
Duration of follow-up	6 months
Indirectness	Less than a quarter of recruited patients had TBI on CT brain scan (70 out of 293, 24%)

Study arms

Direct transport from scene of injury to the nearest SNC (N = 169)
Head-injured adult patients were transported with direct transport from scene of injury to the nearest specialist neuroscience centre (SNC), bypassing the nearest an acute general hospital.

Transport to nearest acute general hospital (N = 124)
Head-injured adult patients were transported to that closest general hospital with selected patients subsequently undergoing secondary transfer to a SNC.

Characteristics

Study-level characteristics

Characteristic	Study (N = 293)
% Female Nominal	93

Arm-level characteristics

Characteristic	Direct transport from scene of injury to the nearest SNC (N = 169)	Transport to nearest acute general hospital (N = 124)
Mean age (SD) Custom value	Mean (IQR): 44.6 (29.6 to 70.1)	Mean (IQR): 48.8 (29.8 to 65.3)
GCS score Median (IQR)	12 (8 to 13)	12 (8 to 13)

Outcomes

Study timepoints
- 30 day (Occurring within 30 days of head injury)
- 6 month (Follow-up at 6 months. Data includes patients who consented and were available for the 6-month follow-up interviews (13 control patients, 15 intervention patients) and those known to have died (18 intervention patients and 11 control patients were known to be deceased).)

Direct transport from scene of injury to the nearest SNC versus Transport to nearest acute general hospital

Outcome	Direct transport from scene of injury to the nearest SNC, 30 day, N = 169	Direct transport from scene of injury to the nearest SNC, 6 month, N = 33	Transport to nearest acute general hospital, 30 day, N = 124	Transport to nearest acute general hospital, 6 month, N = 24
Mortality No of events	n = 15 ; % = 9.4		n = 10 ; % = 8.8	

Outcome	Direct transport from scene of injury to the nearest SNC, 30 day, N = 169	Direct transport from scene of injury to the nearest SNC, 6 month, N = 33	Transport to nearest acute general hospital, 30 day, N = 124	Transport to nearest acute general hospital, 6 month, N = 24
Patients with TBI requiring neurosurgery No of events	n = 4 ; % = 11.4		n = 11 ; % = 31.4	
ABC intervention within 6 hours of leaving scene No of events	n = 22 ; % = 13.6		n = 20 ; % = 17.7	
Transferred for further care No of events	n = 8 ; % = 4.9		n = 18 ; % = 15.8	
Quality of life - EQ-5D (EQ-5D) 6 month follow-up Median (IQR)		0 (0 to 80)		25 (0 to 60)
Degree of disability (GOSE) Median (IQR)		1 (1 to 4)		3 (1 to 5)

Mortality - Polarity - Lower values are better
Patients with TBI requiring neurosurgery - Polarity - Lower values are better
ABC intervention within 6 hours of leaving scene - Polarity - Lower values are better
Transferred for further care - Polarity - Lower values are better
Quality of life - EQ-5D - Polarity - Higher values are better
Degree of disability (GOSE) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

DirecttransportfromsceneofinjurytothenearestSNCversusTransporttonearestacutegeneralhospital-Mortality-NoOfEvents-Direct transport from scene of injury to the nearest SNC-Transport to nearest acute general hospital-t30

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High *(High-rate of non-adherence in intervention arm)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Concerns over allocation adherence.)*
Overall bias and Directness	Overall Directness	Directly applicable

DirecttransportfromsceneofinjurytothenearestSNCversusTransporttonearestacutegeneralhospital-PatientswithTBIrequringneurosurgery-NoOfEvents-Direct transport from scene of injury to the nearest SNC-Transport to nearest acute general hospital-t30

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High *(High-rate of non-adherence in intervention arm)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Concerns over allocation adherence.)*
Overall bias and Directness	Overall Directness	Directly applicable

DirecttransportfromsceneofinjurytothenearestSNCversusTransporttonearestacutegeneralhospital-ABCinterventionwithin6hoursofleavingscene-NoOfEvents-Direct transport from scene of injury to the nearest SNC-Transport to nearest acute general hospital-t30

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High *(High-rate of non-adherence in intervention arm)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Concerns over allocation adherence.)*
Overall bias and Directness	Overall Directness	Directly applicable

DirecttransportfromsceneofinjurytothenearestSNCversusTransporttonearestacutegeneralhospital-TransferredforfurthercareNoOfEvents-Direct transport from scene of injury to the nearest SNC-Transport to nearest acute general hospital-t30

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High *(High-rate of non-adherence in intervention arm)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Concerns over allocation adherence.)*
Overall bias and Directness	Overall Directness	Directly applicable

DirecttransportfromsceneofinjurytothenearestSNCversusTransporttonearestacutegeneralhospital-Degreeofdiability(GOSE)-MedianIQR-Direct transport from scene of injury to the nearest SNC-Transport to nearest acute general hospital-t6

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High *(High-rate of non-adherence in intervention arm)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns *(High risk of bias due to concerns around intervention adherence and high rate of attrition)*
Overall bias and Directness	Overall Directness	Directly applicable

DirecttransportfromsceneofinjurytothenearestSNCversusTransporttonearestacutegeneralhospital-Qualityoflife-EQ-5D-MedianIQR-Direct transport from scene of injury to the nearest SNC-Transport to nearest acute general hospital-t6

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High *(High-rate of non-adherence in intervention arm)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns *(High risk of bias due to concerns around intervention adherence and high rate of attrition)*
Overall bias and Directness	Overall Directness	Directly applicable

Prosser, 2020

Bibliographic Reference	Prosser, Callum J.; Edwards, David; Boumara, Omar; Fuller, Gordon; Holliman, Damian; Lecky, Fiona; Bypassing the nearest emergency department for a more distant neurosurgical centre in traumatic brain injury patients; British Journal of Neurosurgery; 2020; 1-7

Study details

Study location	UK
Study setting	SNCs or non-specialist acute hospitals in the North of England.
Study dates	June 2015 to February 2016
Sources of funding	None reported
Inclusion criteria	Adults with significant TBI injured closest to a NSAH with abbreviated injury score (AIS) of ≥3.

Exclusion criteria	Injured nearest to an SNC or were not transported to hospital by land ambulance.
Recruitment / selection of participants	Patients receiving care within the participating trauma network
Intervention(s)	**Specialist neuroscience centre:** Patients bypassing a nearer non-specialist acute hospital.
Population subgroups	n/a
Comparator	**Non-specialist centre:** Patients received primary care at a nearest non-specialist acute hospital, with or without secondary transfer to the specialist neuroscience centre.
Number of participants	356
Duration of follow-up	6 months
Indirectness	n/a
Additional comments	

Study arms

Specialist neuroscience centre (N = 89)
Patients bypassing a nearer non-specialist acute hospital.

Non-specialist centre: (N = 266)
Patients received primary care at a nearest non-specialist acute hospital, with or without secondary transfer to the specialist neuroscience centre.

Characteristics

Study-level characteristics

Characteristic	Study (N = 356)
% Female Nominal	162
Mean age (SD) Custom value	Median: 57.7/64.5/83.6

Outcomes

Study timepoints

- 30 day

Specialist neuroscience centre vs Non-specialist centre

Outcome	Specialist neuroscience centre, 30 day, N = 89	Non-specialist centre: , 30 day, N = 265
Survival Survival (vs expected – standardised survival rate expressed as W score) Custom value	W score (95% CI): +6.15% (-1.24% to +13.55%) ~ 6.15 excess survivors per 100 patients	W score (95% CI): -1.13% (-4.51% to +2.25%) ~ 1.13 fewer survivors per 100 patients

Survival - Polarity - Higher values are better

Critical appraisal - ROBINS-I checklist

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Serious
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Appendix E – Forest plots

E.1 Transport to specialist neuroscience centre (SNC) vs transport to nearest non-specialist acute general hospital (NSAH) emergency department for head injury (RCT evidence)

Figure 2: All-cause mortality (30 days)

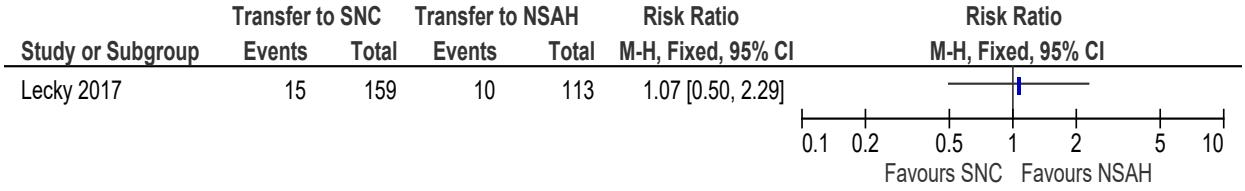


Figure 3: Patients with TBI requiring neurosurgery

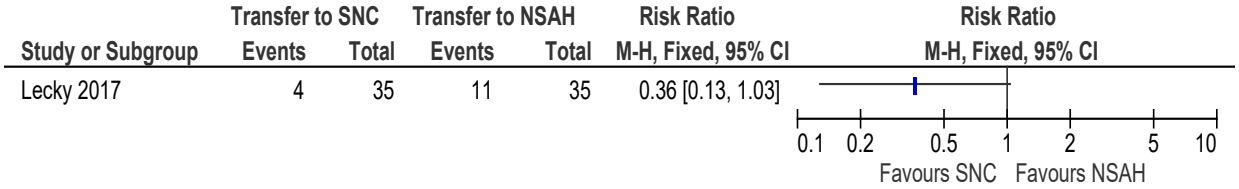


Figure 4: ABC intervention within 6 hours of leaving scene

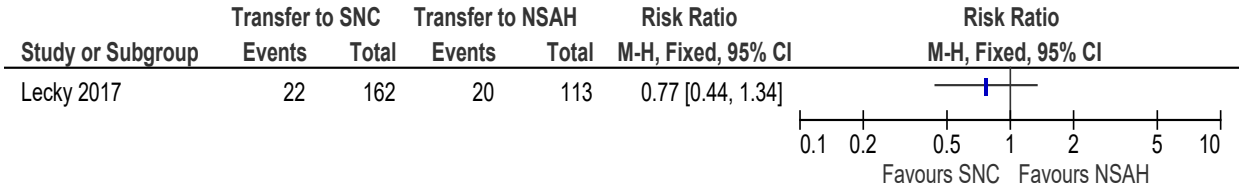
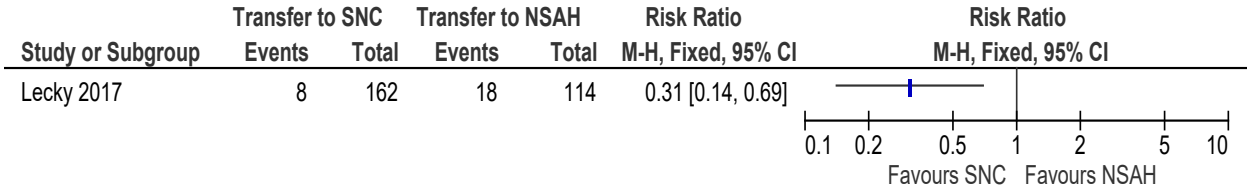


Figure 5: Secondary transfer for further care



Appendix F – GRADE tables

Table 8: Clinical evidence profile: Transport to specialist neuroscience centre (SNC) compared to transport to nearest non-specialist acute general hospital (NSAH) Emergency Department for head injury (RCT evidence)

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With transport to nearest general hospital Emergency Department	With transport to specialist neuroscience centre	Relative effect (95% CI)	Risk with transport to nearest general hospital Emergency Department	Risk difference with transport to specialist neuroscience centre
All-cause mortality (30 days)											
272 (1 RCT)	serious [a]	not serious	not serious	very serious [b]	none	⨁◯◯◯ VERY LOW	10/113 (8.8%)	15/159 (9.4%)	**RR 1.07** (0.50 to 2.29)	88 per 1,000	**6 more per 1,000** (from 44 fewer to 114 more)
Patients with TBI requiring neurosurgery											
70 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	11/35 (31.4%)	4/35 (11.4%)	**RR 0.36** (0.13 to 1.03)	314 per 1,000	**201 fewer per 1,000** (from 273 fewer to 9 more)
ABC intervention within 6 hours of leaving scene											
275 (1 RCT)	serious [a]	not serious	not serious	very serious [b]	none	⨁◯◯◯ VERY LOW	20/113 (17.7%)	22/162 (13.6%)	**RR 0.77** (0.44 to 1.34)	177 per 1,000	**41 fewer per 1,000** (from 99 fewer to 60 more)

Certainty assessment							Summary of findings				
Transferred for further care											
276 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	18/114 (15.8%)	8/162 (4.9%)	**RR 0.31** (0.14 to 0.69)	158 per 1,000	**109 fewer per 1,000** (from 136 fewer to 49 fewer)

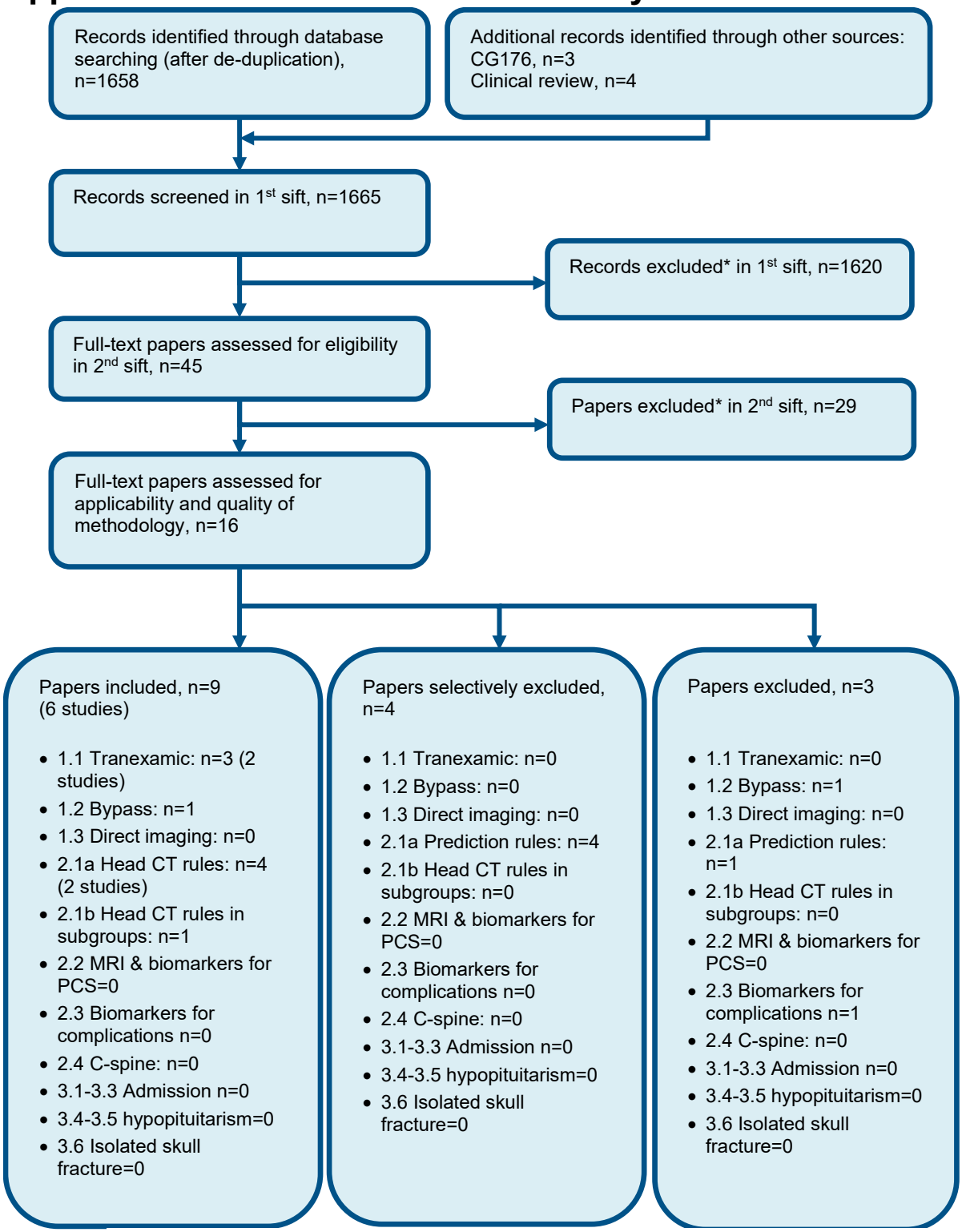
CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes)

Appendix G – Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H – Economic evidence tables

Study	Lecky 2016[9]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness (pa)**
Economic analysis: Cost-utility analysis (health outcome: QALYs) **Study design:** Decision tree and long-term Markov model **Approach to analysis:** Patients were sub-grouped according to care needs (Neurosurgery, critical care, ward care and major extra-cranial care) each has a probability of entering a GOS state, which is modified by the intervention. **Perspective:** UK NHS and PSS **Time horizon/Follow-up:** Lifetime **Treatment effect duration:**[(a)] Discharge **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Population:** Adult patients with suspected significant head injury closest to non-specialist acute hospital (GCS score <13 and stable cardiorespiratory physiology) **Cohort settings:** Start age: NR % Male: NR **Intervention 1:** No transfer **Intervention 2:** Selective secondary transfer: "Any patient with an acute neurosurgical lesion undergoes early secondary transfer.Selected patients requiring critical care also undergo early secondary transfer." **Intervention 3:** Routine secondary transfer: "All patients with an acute neurosurgical lesion or head injury requiring critical care undergo routine early secondary transfer" **Intervention 4:** Bypass	**Total costs (mean per patient) (pa):** Int'n 1: £26,805 Int'n 2: £27,044 Int'n 3: £27,183 Int'n 4: £29,086 **Currency & cost year:** 2012 UK pounds **Cost components incorporated:** Patient transport, inpatient management, and post-discharge care	**QALYs (mean per patient) (pa):** Int'n 1: 12.66 Int'n 2: 12.93 Int'n 3: 12.99 Int'n 4: 13.06	2 vs 1: £885 per QALY gained 3 vs 2: £2,317 per QALY gained 4vs 3: £37,471 per QALY gained Probability Intervention most cost effective (£20K/30K threshold): Int'n 1: 1% / 1% Int'n 2: 10% / 7% Int'n 3: 46% / 44% Int'n 4: 42% / 48% **Analysis of uncertainty:** Extensive scenario and one-way sensitivity analyses were conducted. So was expected value of information analysis. Bypass became cost effective in several scenarios including those related to: neurosurgery costs, inpatient costs, life expectancy, compliance, discount rates. The expected net benefit of sampling to estimate relative treatment effects was maximised for a sample of 1040 patients but even much smaller trials would be beneficial in reducing uncertainty.

Data sources				
Health outcomes: Relative treatment effects are based on expert opinion, except for major extracranial injury, which was based on Mullins 1998[11]. HITS-NS pilot data for population subgroups and compliance with bypass. HALO study was used for various parameters relating to extracranial injuries. Baseline parameters from various sources. Survival hazard ratios not reported. **Quality-of-life weights:** EQ-5D weights from Smits 2010[22] adjusted for age. **Cost sources:** HITS-NS pilot data for inpatient costs. Short-term costs from Beecham 2009[2]. Long-term costs based on expert opinion.				
Comments				
Source of funding: UK NIHR **Limitations:** Relative treatment effects are based on expert opinion. Survival estimates are not described. **Other:** There was a significant benefit from direct transfer for the subgroup with extra-cranial injury and mild TBI – might be because neuroscience centres are often major trauma centres.				
Overall applicability:(b) Directly applicable		**Overall quality:**(c) Potentially serious limitations		

Abbreviations: 95% CI= 95% confidence interval; EQ-5D= EuroQol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years; TBI=traumatic brain injury

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations.

Appendix I – Health economic model (2007 guideline update)

I.1 Literature review

We did not find any cost-effectiveness evidence for this question but we did find two simulation models, which we will refer to as the London and Staffordshire models. We have reviewed these models in some detail, as follows.

I.1.1 London model

The report[21] summarises the findings of a review conducted by the London Severe Injury Working Group focusing on the Trauma services provided in London, including care, treatment and transfer of severely injured patients. Severe injury was defined as the need for Intensive Care.

The analysis of the current service highlights some key issues:

- high secondary referral rate (two thirds of the severely injured patients group),
- evidence of problems associated with such transfers (adverse clinical events during transfer, delay to definitive intervention, low level of staff and standard of care), and
- difficulties for hospitals in transferring patients for specialist care, especially for neurosurgery (stabilisation of patient first, co-ordination between the first hospital and the specialist hospital and consequent long delays).

Methods

A modelling of the flow of trauma patients was carried out to determine the best trauma service configuration for adult trauma patients with severe injury in the London area. The model was designed to estimate the time from injury to:

- Critical Intervention (urgent lifesaving interventions such as intubation); these interventions are crucial for all trauma patients
- Definitive Intervention (specialist interventions such as neurosurgery); these interventions vary according to the site of the trauma

The specific aims of the modelling exercise were to evaluate the effect on time to intervention of:

1. different bypass strategies
2. improving the current system by reducing time taken in pre-hospital and in-hospital trauma management.
3. a doctor in the pre-hospital phase provided by the London Helicopter Emergency Medical Service (HEMS).

The model simulated results based on about 10,000 actual severe injuries from the London region. Of these 33% had isolated head injury and a further 18% had non-isolated head injury.

The model estimates time to intervention using flow charts. Figure 1 shows the flowchart for an isolated head injury patient with the average times based on current practice. Similar

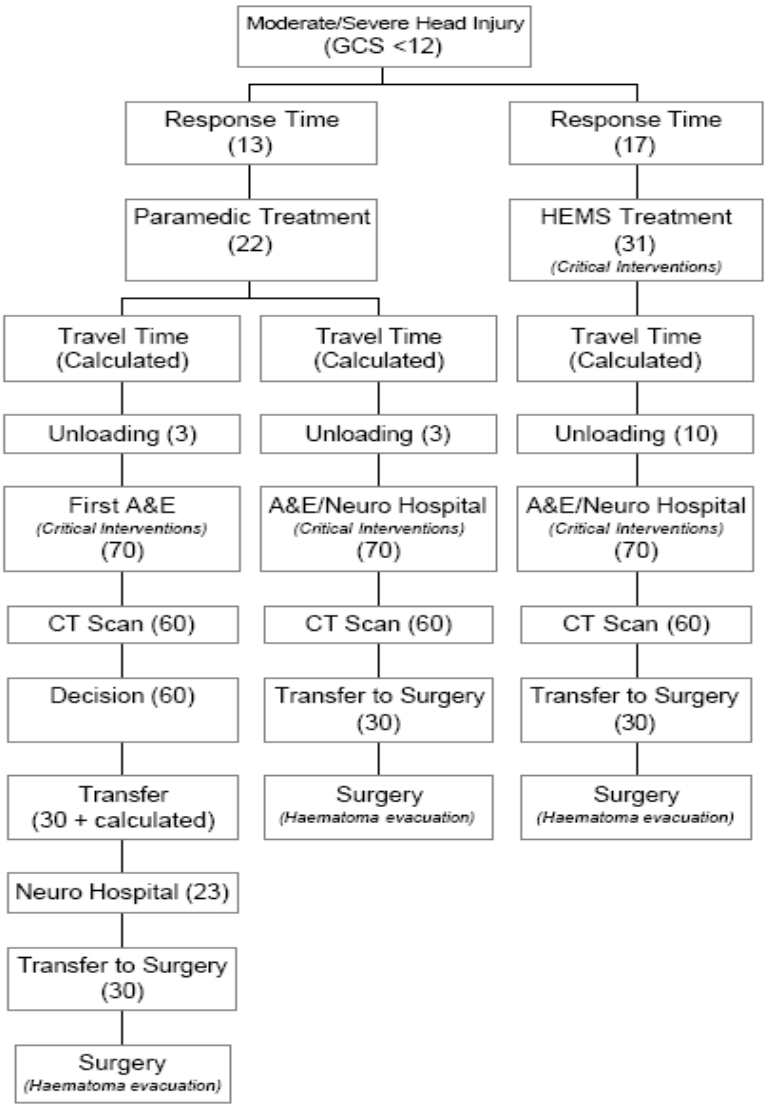
flowcharts were devised for the different types of trauma. The timings were based on ambulance service records and expert opinion.

For each type of injury, a group of clinical experts decided on a target time for intervention. For head injury, it was considered that it was crucial to carry out neurosurgery within 4 hours of the injury, based on some evidence.[18] For each service configuration scenario, the primary outcomes were:

- the median times to critical and definitive interventions.
- the proportion of patients receiving critical and definitive interventions within the relevant time target.

Figure 6: London Model flowchart for isolated head injury patients (figures in parentheses are average time in minutes)

1. Head Injury Needing Neurosurgery (33.2%)



Notes:
a. The 'Decision' box includes decision, communication, obtaining specialist opinion, finding a bed and arranging the transfer.

Table 9: London Model: Median time (hours) to critical/definitive interventions, by bypass strategy

	Current timings			Timings improved at LAS* & hospitals		
Bypass strategy	none	15	20	none	15	20
critical intervention (minutes)	41	43	45	32	34	36
head injury	4.8	3.7	3.4	3.8	2.9	2.7
head and chest injury	4.9	3.8	3.5	3.9	3.0	2.7
head, chest and orthopaedic injury	6.9	5.9	5.6	6.0	5.2	4.9
chest injury	4.6	3.8	3.4	3.7	3.0	2.7
orthopaedic injury	2.2	2.3	2.3	1.7	1.7	1.7
head and orthopaedic injury	6.8	5.8	5.5	5.8	5.1	4.8
chest and orthopaedic injury	6.7	5.9	5.5	5.7	5.1	4.8
head, chest and abdominal injury	7.0	5.9	5.6	6.0	5.2	4.9
chest and abdominal injury	6.6	5.9	5.5	5.7	5.1	4.8
orthopaedic and abdominal injury	3.2	3.2	3.2	2.5	2.5	2.6
abdominal injury	3.2	3.2	3.2	2.5	2.5	2.6
facial injury	3.8	3.8	3.5	3.0	3.0	2.7
head and facial injury	4.8	3.8	3.5	3.8	3.0	2.7
spinal injury	5.7	4.8	4.4	4.6	4.0	3.6
head and spinal injury	4.8	3.8	3.4	3.8	3.0	2.7
head, orthopaedic and abdominal injury	6.8	5.8	5.5	5.8	5.1	44.8
orthopaedic and vascular injury	6.9	5.9	5.6	5.9	5.2	4.9
traumatic amputation	4.7	3.8	3.5	3.7	3.0	2.7

Note: LAS=London Ambulance Service

Table 10: London Model: Proportion of patients receiving critical/definitive interventions within target time, by bypass strategy

	Current timings			Timings improved at LAS* & hospitals		
Bypass strategy	none	15	20	none	15	20
critical intervention (within 60 minutes)	91%	88%	84%	98%	97%	96%
head injury (within 4hs)	23%	60%	74%	63%	81%	90%
head and chest injury (within 2hs)	0%	0%	0%	2%	4%	5%
head, chest and orthopaedic injury (within 2hs)	0%	0%	0%	0%	0%	0%
chest injury (within 2hs)	0%	0%	1%	3%	6%	8%
orthopaedic injury (within 2hs)	30%	27%	25%	84%	82%	79%
head and orthopaedic injury (within 4hs)	0%	1%	1%	3%	8%	10%

	Current timings			Timings improved at LAS* & hospitals		
chest and orthopaedic injury (within 2hs)	0%	0%	0%	0%	0%	0%
head, chest and abdominal injury (within 2hs)	0%	0%	0%	0%	0%	0%
chest and abdominal injury (within 2hs)	0%	0%	0%	0%	0%	0%
orthopaedic and abdominal injury (within 2hs)	1%	0%	0%	9%	8%	7%
abdominal injury (within 2hs)	1%	0%	0%	9%	8%	7%
facial injury (within 3hs)	23%	22%	27%	49%	50%	63%
head and facial injury (within 3hs)	9%	22%	27%	19%	50%	63%
spinal injury (within 6hs)	62%	79%	88%	93%	96%	97%
head and spinal injury (within 4hs)	21%	55%	70%	61%	78%	88%
head, orthopaedic and abdominal injury (within 2hs)	0%	0%	0%	0%	0%	0%
orthopaedic and vascular injury (within 4hs)	0%	1%	1%	3%	7%	9%
traumatic amputation (within 4 hs)	30%	55%	70%	66%	78%	87%

Note: LAS=London Ambulance Service

Model Results

Table 9 shows the median time to critical/definitive intervention by type of injury and by bypass strategy used. On the left side of the table the results are based on current timings. On the right hand side the results are based on improved timings. In the case of the isolated head injury patient the median time to neurosurgery is 4.8 hours currently but would fall to 3.4 hours when bypassing patients who are less than 20 minutes from a specialist centre.

Table 10 shows the proportion of patients that receive interventions within the target time. In the case of the isolated head injury patient the number receiving neurosurgery within 4 hours would increase from 23% with no bypass to 74% with bypassing patients who are less than 20 minutes from a specialist centre. However, on the negative side with this bypass strategy only 84% (compared with 91%) would receive critical intervention within 60 minutes. The group that is made worse off by bypass is those patients with isolated orthopaedic injury: only 25% would receive their definitive intervention within their 2 hour target (compared with 30% without bypass).

For the injuries that can be treated in every hospital the most rapid movement to Definitive Intervention was achieved by the models without bypass, and with improvement in hospital times.

For injuries requiring specialist management the best models for providing early Definitive Intervention included 20 minutes bypass, improvement in hospital times and use of the London HEMS.

Report conclusions

The bypass protocol proposed is based on the 20 minutes of distance from a Multi-Specialty Centre, as this time gives the best trade off between longer time to Critical Interventions, and shorter time to Definitive Intervention. However, the best balance between these opposing effects had to be struck by clinical judgement, as little evidence was available.

The report recommended that within a 20 minute drive time of an appropriate specialist unit, a patient should be driven directly to the specialist unit rather than to the local hospital, and that a triage system for London should be gradually introduced, allowing training of pre-hospital personnel and evaluation of the effectiveness of each of the triage criteria. For head injury the initial criterion could be based on GCS and additional criteria could then be added. This would avoid the flooding of Multi-Specialty Centres.

Review

The report has a number of limitations:

- The model, especially the target times, was based more on expert judgement than hard evidence of clinical effectiveness.
- In reality there will be a continuum of risk rather than a time cut-off.
- The model assumes that the specialist hospital has a range of different specialist services in addition to neurosciences.
- The trade off between the need for immediate access to critical interventions (e.g. intubation) and the need for faster access to definitive interventions (e.g. surgery) was made on the basis of expert judgement rather than health outcomes.

I.1.2 Staffordshire model

The link between time and health outcomes missed by the London model was captured to some extent in the Staffordshire model[23].

It evaluated the impact of 10 different transport strategies on survival of patients with serious or worse HI (AIS more than 2). In the model, survival was determined by a number of variables including: a) head AIS score, b) non-head AIS score, c) time to surgery, d) grade of staff during transfer, e) incidence of hypoxia and hypotension, g) distance from hospitals. Some of these variables are patient-specific (a,b,g), some are service-specific (d) and some are determined by the transport strategy (c,e). The data used in the model came from a variety of sources including a large trauma database, the published literature and expert opinion. Monte Carlo simulation (that is repeatedly generating new results by simultaneously drawing at random from the distribution of each model parameter) was used to simulate 10,000 head injury patients and their outcomes under each strategy.

Table 11 shows the results for each strategy. All direct transport strategies had higher expected survival than a strategy of sending all patients to the nearest emergency department but strategies 2-6 were the most effective. Among these strategies, strategy 4 (direct transport of patients with critical head injury, AIS=5) required the least number of patients being diverted to specialist centres. The results were not sensitive to the parameters that were determined by expert opinion.

An important limitation that was acknowledged by the authors was that AIS score is determined after treatment and therefore assessment of patients at the scene of the injury is less accurate. The implication is that the survival gain observed in this model is probably larger than can be achieved in reality, although the pattern should be the same. There are different costs associated with each strategy and therefore a cost-effectiveness analysis is needed to assess which of the 10 strategies is the most cost effective.

In conclusion, the simulation study shows that survival of severe head injury patients could be substantially improved by transporting patients directly from the injury scene to a hospital with a specialist neurosciences centre. Cost effectiveness of these strategies was determined as described in I.1.3.

I.1.3 Comparison with the London model

The Staffordshire model went a step further than the London model by estimating the impact of different strategies on survival (as well as time) in order to trade off the different outcomes.

Both models rely on evidence combined with expert opinion to estimate the time to intervention. For the Staffordshire model, expert opinion is also used to estimate the survival rates. For the London model, expert opinion is also used to estimate the target times. Thus there must still be uncertainty around the results of both studies as they are not based on hard evidence.

Both research teams recommend bypass if the specialist hospital is ≤20 minutes from the injury scene. The Staffordshire model estimated substantial survival gains from bypass even if the specialist hospital is much further away (53 minutes). There are no obvious contradictions between the two models but the authors of the London report have been more cautious in recommending bypass over longer distances.

Table 11: Stevenson's Transport model - results

Criteria for transporting patients directly to Neurosciences Hospital	Percentage of patients bypassing DGH	Survival gain vs 1) (Neurosciences Hospital far)	Survival gain vs 1) (Neurosciences Hospital near)
1) None	0%	0.00%	0.00%
2) HI AIS>2	100%	3.40%	4.50%
3) HI AIS>3	78%	3.50%	4.60%
4) HI AIS=5	44%	3.40%	4.30%
5) Non-HI AIS<4	89%	3.30%	4.00%
6) Non-HI AIS<5	95%	3.40%	4.50%
7) Isolated head injury	75%	2.80%	3.60%
8) Intubated pre-hospital	20%	1.70%	1.90%
9): 7) and 8)	5%	1.30%	1.50%
10) Out of hours	40%	1.50%	2.00%

I.1.4 Cost-effectiveness model – Direct transport

We conducted a cost-effectiveness analysis of transporting patients with serious head injury directly from the injury scene to a specialist neurosciences hospital (NSH). This was compared to initially transporting such patients to the nearest emergency department and then later transferring them to the NSH after stabilising the patient.

The following general principles were adhered to:

- The GDG was consulted during the construction and interpretation of the models.
- The sources of data are published studies and expert opinion.
- Model assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- We followed the methods of the NICE reference case. Therefore, costs were calculated from a health services perspective. Health gain was measured in terms of quality-adjusted life-years (QALYs) gained.

I.1.4.1 General method

The model is represented by a decision tree (Fig.2): once the ambulance crews arrive at the accident scene, the patient can be transported either to the nearest District General Hospital (DGH) or to a Neurosciences Hospital (NSH). Severe head injury patients initially admitted to the DGH will be subsequently referred to the NSH. Patients that survive will require rehabilitation and frequently some kind of long term care. The number of survivors is different in the different strategies.

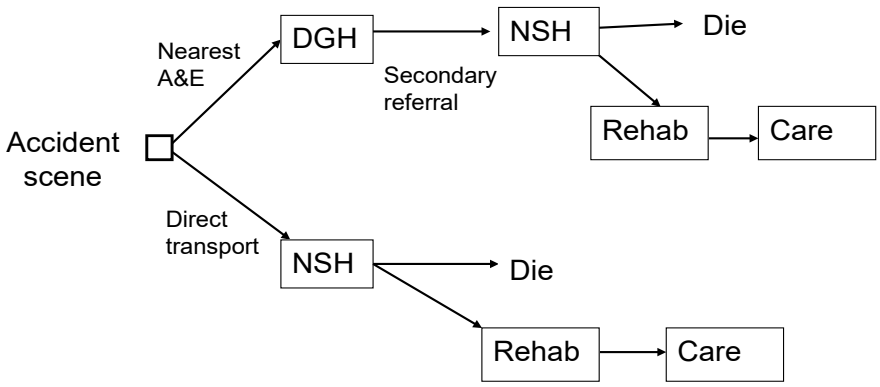
To assess the cost effectiveness of direct transport we need to assess not just changes to ambulance and emergency department costs associated with each strategy but also any changes in rehabilitation and long term care costs arising from the different strategies. These have to be balanced against the health gain.

We could not find evidence of effectiveness that perfectly suits this question. We therefore constructed two similar models based on different empirical studies:

Model A: We based this model on the only study in the clinical literature review that reported both mortality and health status (Glasgow Outcome Scale, GOS) in head injury patients– Poon et al 1991[16]. This study compared a cohort of patients that had been directly transported to NSH to another cohort that were transferred from DGH. This study allows us to estimate both the QALYs gained and the cost savings attributable to improved care status in patients being directly transported. However, there was concern that this study was biased, since case-mix was not properly controlled for. For this reason we developed a more conservative model.

Model B, a conservative model, calculates only the health gain attributable to those patients who survive with direct transport but would not survive with a secondary transfer strategy. The number of these extra survivors is estimated using the results of a decision model that was explicitly answering our question – Stevenson 2001[23] (see I.1.2). Model B does not take into account health gain for patients who survive under both strategies but have an improved health status with the direct transport strategy.

Figure 7: Transport model decision tree



Each model has advantages and limitations (Table 12).

Table 12: Summary of the models

	Description	Advantages	Limitations
Model A	Mortality & GOS: Cohort study - NSH direct vs NSH secondary referral (Poon1991[16]).	Both mortality and health state outcomes considered. Data coming from the same study.	Poon data seems overly optimistic and did not control for case-mix.
Model B	Mortality: Simulation study – NSH direct vs DGH (Stevenson 2001[23]) GOS: retrospective cohort study (Patel 2002[14]).	More conservative and hopefully less biased than Poon data.	Outcomes include only mortality, not differences in health status.

For each strategy in both models, the expected healthcare costs and the expected QALYs were calculated by estimating the costs and QALYs for each GOS state and then multiplying them by the proportion of patients that would be in that state as determined by the strategy taken. Health state defined by the GOS state was assumed to be fixed over the lifetime.

The base case models assume that only patients with serious head injury would be transported. A concern is the ability of ambulance crews to determine the severity of the head injury at the scene. There might be a risk of overestimating the number of severely injured patients and therefore of sending too many patients to the NSH, which would mean that cost-effectiveness is reduced and would be risky for patients with multiple trauma. For this purpose, we conducted a sensitivity analysis on the number of false positives (patients erroneously deemed having a serious head injury) that would be transported to the specialist centre without requiring neurosurgical care.

I.1.4.2 Methods: Effectiveness

In Model A, the mortality rate together with the outcomes were derived from a study by Poon at al[16] in which a group of patients having an extradural haematoma was directly transported to the NSH while another group was only secondarily transferred there (Table 13). The mortality and the outcomes were assessed six months after the injury.

Table 13: GOS score and death rate after neurosurgical care in a NSH (Model A)

GOS	% DGH then NSH patients 6 months after injury Poon 1991[16]	% NSH patients 6 months after injury Poon 1991[16]
Good Recovery	49%	86%
Moderate Disability/Severe Disability	27%	10%
Death	24%	4%

The survival gain in Model B was derived from the results of a simulation model by Stevenson et al[23], where the target patient population were adults with a serious head injury (AIS of 3 or more) – see I.1.2.

The model evaluated 10 different strategies of transporting patients directly to the NSH, which selected patients by different criteria (relating to level of AIS score, presence of multiple injuries, possibility of pre-hospital intubation, out of hours). Directly transporting all

serious head injury patients to the NSH led to an estimated increase in survival of 4.5% for injury scenes near to the NSH and 3.4% for more distant injury scenes.

Stevenson 2001[23] estimated only mortality and not health status. We assumed that health status in the additional survivors would be similar to the general population of patients with serious head injury treated in the NSH. We used 6-month GOS data from the surviving patients in a UK study, Patel 2002[14] (Table 14). The study population had all had a severe head injury (GCS score 8 or less) and had been treated in a Neurosciences Critical Care Unit.

Table 14: GOS score after neurosurgical care in a NSH (Model B)

GOS	% NSH patients 6 months after injury Patel 2002[14]
Good Recovery	49.6%
Moderate Disability	27.1%
Severe Disability	20.3%
Vegetative State	3.0%

We estimated the health loss associated with false positives. In fact, for these patients the longer the journey from the accident scene to the hospital, the higher is the risk of death from hypotension. In the case of a distant NSH (53 minutes, as reported in Stevenson's model[23]), the mortality increases by 0.05%, while it increases by 0.03% if the NSH is near (20 minutes). These figures derived from the calculation of the probability of death based on clinical estimates (see I.1.5.4).

I.1.5 Methods: Estimating QALYs

For each health state we estimated QALYs (Quality-Adjusted Life Years) by multiplying the discounted life expectancy by the utility score associated with each state. The expected QALYs for each strategy are then estimated by summing up the QALYs for each state weighted by the proportion of patients in that state.

In order to calculate the QALYs we combined data on life expectancy with data on quality of life.

Life expectancy

The life expectancy of patients in a vegetative state (VS) was assumed to be 10 years.[20, 24] In the case of a 60 year old patient in a VS, the life expectancy would be shorter and was assumed to be the same as for a patient in the severe disability state (see below).

To calculate the life expectancy for health states other than VS, we applied the standardised mortality rate (SMR), reported for 2,320 traumatic brain injured patients in Shavelle 2001[19], to the general population of England and Wales, using the Life Tables. According to Shavelle, the SMR decreases during the first 4 years post-injury but remains constant afterwards. In Shavelle 2001 the SMR was distinguished according to three levels of ambulation: a) none, b) some, c) stairs, which we matched approximately to the levels of disability of the GOS (a=SD, b=MD and c=GR).

Life expectancy was discounted at a rate of 3.5% per year, as required by NICE.

For our base case analysis we estimated life expectancy for men aged 40 (the average age of a patient in the Stevenson study[23]). For our sensitivity analysis, we also calculated life-years for patients aged 20 and 60.

Quality of life

The utility scores in Table 15 are a measure of the quality of life associated with each of the health states on a scale from 0 (death) to 1 (perfect health). For the good recovery (GR) outcome, we used the EQ-5D score of 0.83 reported for the United Kingdom population.[8] The other utility scores were taken from a decision analysis, Aoki 1998.[1] The mean utilities for each GOS score were elicited from a sample of 140 subjects with a clinical background using the standard-gamble method. The GOS states in this study were expressed as the degree of disability due to brain damage caused by subarachnoid haemorrhage.

The Poon 1991[16] study (Model A) did not distinguish between patients that were severely disabled (SD) and those that were moderately disabled (MD). For these patients we used the simple average of the two SMRs and the simple average of the two utilities.

Another study was found, Tsauo 1999,[25] which reported the utility scores associated with each GOS score obtained from health professionals in the UK using the standard gamble method. We did not use this study in our base case model for the following reasons:

- scores were presented for a number of time points and there seemed to be inconsistency between the estimates
- the figures were skewed towards high values (i.e. the utility associated with a moderate disability was higher than the average EQ5D utility score for the general population in the UK[8])
- the value for the vegetative state was missing
- the number of the health professionals interviewed for the elicitation of the utility scores was not reported.

Therefore, we used this study only for the purpose of sensitivity analysis.

Table 15: Health Utilities by Glasgow Outcome Scale (GOS) state

GOS	Utility score (base case analysis)	Source	Utility score (sensitivity analysis) Tsauo 1999
Model A			
Good Recovery	0.83	,Kind 1998 (UK general population)	0.931
Moderate Disability/Severe Disability	0.45	Aoki 1998 (mean of two states)	0.788
Death	0		0
Model B			
Good Recovery	0.83	Kind 1998 (average utility in the UK)	0.931
Moderate Disability	0.63	Aoki 1998	0.908
Severe Disability	0.26	Aoki 1998	0.668

GOS	Utility score (base case analysis)	Source	Utility score (sensitivity analysis) Tsauo 1999
Vegetative State	0.08	Aoki 1998	0.08
Death	0		0

In the sensitivity analysis on the assessment at the scene, we assumed that the false positives, if they survive the longer transport, would have had the same expected QALYs as the good recovery (GR) patient.

Calculating QALYs gained

For Model A, the QALYs gained are calculated as follows:

QALYs gained= Q1-Q0

Qi = (PiGR x LEGR x UGR) + (PiD x LED x UD)

where

Qi =the expected QALYs per patient (i=1: with bypass, i=0: without bypass)

PiGR, PiD, = proportion of patients in each of the GOS states at 6 months by strategy (where D is both mild disability and severe disability combined).

LEGR, LED, = the discounted life expectancy of patients by GOS states at 6 months

UGR, UD, = the utility score for each GOS state.

For Model B, the QALYs gained are calculated as follows:

QALYs gained=Qi-Q0= ESi x ((PGR x LEGR x UGR) + (PMD x LEMD x UMD) + (PSD x LESD x USD) + (PVS x LEvs x Uvs))

where

Qi =the expected QALYs per patient associated with bypass strategy i,

Q0 = the expected QALYs per patient associated with no bypass,

ESi = extra survivors=the proportion of patients surviving under strategy i that would not have survived under the no bypass strategy

PGR, PMD, PSD, PVS, = the proportion of extra survivors in each of the GOS states at 6 months

LEGR, LEMD, LESD, LEVS, = the discounted life expectancy of patients by GOS states at 6 months

UGR, UMD, USD, UVS, = the utility score for each GOS state.

I.1.5.1 Methods: Ambulance and emergency department costs

Emergency department costs in our models are the staff costs associated with secondary referral. While the cost of the primary transport to the DGH or to the NSH is similar, an inter-hospital transfer would be more costly than transport from the injury scene because it

requires additional staff and tasks. In fact, an anaesthetist and a nurse would always accompany a patient who required urgent transfer, which constitutes 90% of the transfers for head injury. The GDG experts estimated the total cost of the transfer as equal to three-hour time of a nurse and an anaesthetist, given the time necessary to activate a secondary transfer team at the DGH, the time spent in stabilising the patient, and the actual transfer time. Moreover, on arrival at the NSH the patient would need other treatment for complications due to the transfer. With the average cost of a nurse at £19 per hour, and the cost of an anaesthetist (specialist registrar) of £34 per hour;[3] the total cost per patient transferred was estimated to be £159.

The cost of patient management at the emergency department in the two hospitals was not expected to be different, according to the GDG experts' estimates, since the staff grades would not be different.

All the cost figures are expressed in 2006 Pound Sterling. Costs related to previous years were inflated using the Hospital and Community Health Services Prices Index.[3]

We have not calculated transportation and emergency department costs in much detail but would argue that this is not a major flaw since these costs are small compared with the additional rehabilitation and care costs incurred by survivors.

We calculated the increased transport cost associated with false positives, as they will be transported to a more distant hospital. The cost was obtained from the unit cost of an ambulance per minute, £6.50,[3] multiplied by the distance of the accident scene to the hospital, which was 20 minutes (near) or 53 minutes (far) in the simulation study.[23]

I.1.5.2 Methods: Rehabilitation and care costs

We derived the cost of rehabilitation from two UK studies: one, Wood 1999,[26] applicable to the severely disable patients and the other one, Nyein 1999,[13] applicable to the moderately disabled patients (Table 16). The length of rehabilitation for the severely disabled group was 14 months, while it was 75 days for the moderately disabled group. We assumed patients who had a good recovery to undergo the same intensity of rehabilitation as the moderately disabled group, given the fact that the good outcome was assessed six months post-injury. Patients in a vegetative state were assumed not to receive any specific rehabilitative therapy. If any rehabilitation service was provided to them, its cost was assumed to be incorporated in to the cost of long term care.

The same two UK studies were used to calculate the annual care costs (Table 16); in the case of severely disabled patients, the long term care was the community care support required after rehabilitation and it was based on the cost of a support worker. Similarly, the long term annual cost for the moderate disability group was calculated from the weekly cost of care three months after discharge from the rehabilitation. Patients having a good recovery were assumed not to incur any long term costs. Patients in a vegetative state were assumed to have the same annual care costs as those who are in the severe disability state.

Care costs were discounted at a rate of 3.5% per year, as required by NICE.

Table 16: Cost of rehabilitation and long term care

	total cost of rehabilitation	annual care costs
GR	19,575	0
MD	19,575	7,472

	total cost of rehabilitation	annual care costs
SD	108,874	45,450
VS	0	45,450

Thus, the model takes into account the increased costs of rehabilitation and care due to people surviving under direct transport, who would not survive under the current system. It could be that costs of neurosurgery and intensive care are also increased if patients are now making it to the NSH who would have died in transit. Since we do not have data on the timing of deaths, we have not included such costs in the base case. However, for a sensitivity analysis we added on the cost of 3 days of level 3 neurosurgical intensive care for each additional survivor. The costs of care in an ICU were calculated from the NHS Reference Costs 2005-2006[5] at £1,338 per day.

Calculating incremental cost

For Model A the incremental cost is calculated as follows:

Incremental cost = CostNSU - CostDGH

CostNSU = (PNSUGR x (RHGR + LEGR x ACCGR))

+ (PNSUD x (RHD + LED x ACCD))

CostDGH = (PDGHGR x (RHGR + (LEGR x ACCGR)))

+(PDGHD x (RHD + (LED x ACCD)))

+ TC

where

CostNSU = the expected cost per patient associated with direct transport to the NSU

CostDGH = the expected cost per patient associated with a secondary referral to the NSU from a DGH

PNSUGR, PNSUD = the proportion of survivors in good recovery or mild/severe disability at 6 months with direct transport to the NSU

PDGHGR, PDGHD = the proportion of survivors in good recovery or mild/severe disability at 6 months with a secondary referral

RHGR, RHD = the cost of rehabilitation by GOS state at 6 months (where D is both mild disability and severe disability combined)

LEGR, LED = the discounted life expectancy of patients by GOS state at 6 months

ACCGR, ACCD = annual care cost by GOS state at 6 months

TC = cost of transport in secondary referral

For Model B the incremental cost is calculated as follows:

Incremental cost = Cost i - Cost 0

= ESi x ((PGR x (RHGR + (LEGR x ACCGR))) + (PMD x (RHMD + (LEMD x ACCMD)))

+(PSD x (RHSD + (LESD x ACCSD))) + (PVS x (RHVS + (LEVS x ACCVS))))

– (TC x PDT)

where

Costi = the expected cost per patient associated with bypass strategy i

Cost0 = the expected cost per patient associated with secondary referral

ESi = the proportion of patients surviving under strategy i that would not have survived under the no bypass strategy

PGR, PMD, PSD, PVS, = the proportion of extra survivors in each of the GOS states at 6 months

RHGD, RHMD, RHSD, RHVS = the cost of rehabilitation by GOS states at 6 months

LEGR, LEMD, LESD, LEVS, = the discounted life expectancy of patients by GOS states at 6 months

ACCGR, ACCMD, ACCSD, ACCVS = annual care cost by GOS states at 6 months

TC = cost of transport in secondary referral

PDT = proportion of patients directly transported to the NSU

I.1.5.3 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was performed to assess the robustness of the model results to plausible variations in the model parameters.

This analysis was applied exclusively to the strategy of transporting all patients to the NSU (strategy 2) compared no bypass in the conservative model B.

Probability distributions were assigned to each model parameter, where there was some measure of parameter variability (Table 17). We then re-estimated the main results 5000 times, each time each of the model parameters were set simultaneously selecting from the respective parameter distribution at random.

Table 17: Parameters used in the probabilistic sensitivity analysis

Description of variable	Mean value	Probability distribution	Parameters	Source
Percentage of patients with good recovery at 6months	49.6%	Dirichlet	44, 24, 18,3 where each parameter refers to the number of people in each category	Patel 2002[14]
Percentage of patients with mild disability at 6 months	27.1%	Dirichlet		Patel 2002[14]
Percentage of patients with severe disability at 6 months	20.3%	Dirichlet		Patel 2002[14]

Description of variable	Mean value	Probability distribution	Parameters	Source
Percentage of patients in a vegetative state at 6 months	3.0%	Dirichlet		Patel 2002[14]
SMR up to 4 years post-injury (GR)	1.5	Lognormal	SE = 0.402	Shavelle 2001[19]
SMR up to 4 years post-injury (MD)	4.5	Lognormal	SE= 0.254	Shavelle 2001[19]
SMR up to 4 years post-injury (SD)	16.4	Lognormal	SE= 0.249	Shavelle 2001[19]
SMR up to 4 years post-injury (VS)	16.4	Lognormal	SE= 0.249	Shavelle 2001[19]
SMR after 4 years (GR)	1.3	Lognormal	SE= 0.245	Shavelle 2001[19]
SMR after 4 years (MD)	2.4	Lognormal	SE= 0.178	Shavelle 2001[19]
SMR after 4 years (SD)	6.4	Lognormal	SE= 0.168	Shavelle 2001[19]
SMR after 4 years (VS)	6.4	Lognormal	SE= 0.168	Shavelle 2001[19]
Utility value of GR	0.83	none		Aoki1999[1]
Utility value of MD	0.63	Gamma of 1-U	SE= 0.27, α= 1.878 , β=0.197	Aoki1999[1]
Utility value of SD	0.26	Gamma of 1-U	SE= 0.25, α= 8.762, β= 0.084	Aoki1999[1]
Utility value of VS	0.08	Gamma of 1-U	SE= 0.16, α= 33.063, β= 0.028	Aoki1999[1]
Cost of rehabilitation (GR)	19,575	Gamma	SE= 7986, α= 6.01, β= 3258	Nyein 1999[13]
Cost of rehabilitation (MD)	19,575	Gamma	SE= 7986, α= 6.01, β= 3258	Nyein 1999[13]
Cost of rehabilitation (SD)	108,874	none		Wood 1999[26]
Cost of rehabilitation (VS)	0	none		
Annual care costs (GR)	-	none		
Annual care costs (MD)	7,472	Gamma	SE= 12347, α= 0.37, β= 20402	Nyein 1999[13]
Annual care costs (SD)	45,450	none		Wood 1999[26]
Annual care costs (VS)	45,450	none		Wood 1999[26]

Description of variable	Mean value	Probability distribution	Parameters	Source
Survival gain (all patients taken to the NSU if within 20minutes)	4.50%	Gamma	SE= 0.32%, α= 198, β= 0.0002	Stevenson's model[23]

I.1.5.4 Results of the cost-effectiveness analysis

According to Model A there are large QALY gains and large cost savings associated with direct transport to the NSH – direct transport is dominant (Table 18). With Model B – the conservative model - the QALYs gained are smaller and costs are not decreased overall (Table 19 and Table 20). However, even with this conservative model, direct transport is cost effective (below £20,000 per QALY gained).

We chose the group of patients who were 40 years old at the time of injury to represent the results (Table 18, Table 19 and Table 20). In the tables we report the results for the groups of patients of 20 and 60 of age as well. In these cases, direct transport was the dominant strategy in Model A and the incremental cost-effectiveness ratio was still below the threshold of £ 20,000 per QALY in Model B.

After running the Model B 5,000 times, the probability that directly transporting all the patients to the NSU is cost effective (i.e. probability that the cost-effectiveness ratio is below £20,000 per QALY gained) is 73% when the NSU near the incident scene (within 20 minutes). In the cases of a patient aged 20 or 60, the probability falls to 66%.

For Model B, we performed a sensitivity analysis on the length of stay in the ICU: assuming that the most costly level 3 of care applies to all the outcome grades, the analysis shows that the direct transport would still be cost effective as long as the increased length of stay does not exceed 3 days per additional survivor. Furthermore, even if the LOS were longer than this, these costs could be counteracted by additional complications in those patients who are secondarily transported to the NSH and had delayed surgery.

Table 18: Results - Model A.

	Mean cost	QALYs	Incremental cost per QALY gained vs 1)
Base case – Age 40			
1) First to DGH	225,109	9.99	-
2) Direct to NSH	93,422	14.99	NSH dominates DGH
Age 20			
1) First to DGH	297,236	13.06	-
2) Direct to NSH	120,136	18.35	NSH dominates DGH
Age 60			
1) First to DGH	76,069	3.02	-
2) Direct to NSH	38,222	4.76	NSH dominates DGH

Table 19: Results - Model B – Far from NSU

	Incremental cost	QALYs gained	Incremental cost per QALY gained
Direct to NSH vs First to DGH (base case age 40)	7,058	0.41	17,228
Direct to NSH vs First to DGH (age 20)	9,382	0.51	18,343
Direct to NSH vs First to DGH (age 60)	2,259	0.12	18,367

Table 20: Results - Model B – Near from NSU

	Incremental cost	QALYs gained	Incremental cost per QALY gained
Direct to NSH vs First to DGH (base case age 40)	9,393	0.54	17,323
Direct to NSH vs First to DGH (age 20)	12,469	0.68	18,419
Direct to NSH vs First to DGH (age 60)	3,041	0.16	18,683

Using model B, we conducted a threshold sensitivity analysis to take into account the negative effects of overestimating the number of patients to be taken to the NSH. We define the positive predictive value as the proportion of patients transported directly to the NSH who are correctly diagnosed with a severe head injury. It is the number of true positives divided by the sum of both the true positives and false positives. In the case that the NSH is far from the accident scene (53 minutes), the strategy of taking all the patients directly to the NSH is cost effective as long as the positive predictive value is more than 28%. If the NSH is near the accident scene (20 minutes), the direct transport to the NSH is marginally cost-effective strategy even if the positive predictive value is as low as 10%.

Using model B we performed a sensitivity analysis by using an alternative set of utility scores. The result was that direct transport strategy proved to be even more cost effective than in the original model (Table 21).

Table 21: Results of the sensitivity analysis on the utility – Model B

	Incremental cost	QALYs gained	Incremental cost per QALY gained
Far NSU – Direct to NSH vs First to DGH (base case age 40)	7,058	0.53	13,369
Near NSU – Direct to NSH vs First to DGH (base case age 40)	9,393	0.70	13,442

I.1.5.5 Discussion

We found that direct transport is potentially cost saving if the health status of patients are substantially improved as was indicated by the Poon study. Even in our conservative model we find that direct transport is cost effective. But our analysis is limited for a number of reasons.

First, some of our assumptions regarding cost and survival were based on proxies or were extrapolated into the long term.

Our conservative model, Model B, was based on the mortality results of a previous simulation model. Some of the parameters in the simulation model were based on expert judgement (those listed in Table 22). The main clinical outcomes from which the probability of death derives were estimated by experts. In particular, experts were asked to estimate the number of patients that would have survived assuming they received the appropriate care (critical intervention or neurosurgery) at time zero. The actual time elapsed since the accident and its related probability of death was taken from the database. Having these two points on the probability of death graph, a straight line was drawn. The authors found that the results were not sensitive to the slope of the line. However, the curve representing the real relationship between time to intervention and probability of death could have a different shape.

Table 22: Parameters for which the value was estimated by clinicians.

Deaths from injuries in areas excluding the head if medical intervention could be given immediately
Deaths from a head injury that required neurosurgery if neurosurgical intervention could be given immediately
Deaths from a head injury that did not require neurosurgery if medical intervention could be given immediately
Reduction in transfer deterioration due to staff expertise
Delays administering intubation and delay before making a neurosurgical decision (according to the level of staff expertise)
Increased mortality risk due to a secondary referral
Extra risk of mortality if the patient suffers hypotension or full hypoxia

For simplicity, neither model considers the change in health status during the patient's lifetime - they assume that the GOS score (assessed six months after the head injury) remains constant. If instead patients continue to improve after 6 months then our conservative model is underestimating the health gain and cost effectiveness associated with direct transport. Likewise, our assumption that mortality is increased compared with the general population for survivors over their entire lifetime is a conservative one.

We have probably underestimated the cost savings attributable to direct transport because we included only hospital personnel (one anaesthetist and a nurse), omitting for the costs of drugs, equipment and ambulance. However, we have also omitted additional acute costs associated with direct transport in the treatment of complications such as hypoxia and hypotension, which are less likely if the patient has been stabilised earlier. This would require additional treatments such as volume replacement, blood transfusion, and in some extreme cases they would require surgery or ventilatory support for weeks.

A strategy of direct transport from the injury scene to an NSH will inevitably mean that the unit sees more patients than previously, even though many patients currently being taken to

the nearest emergency department are subsequently transferred to the NSH. From the viewpoint of the NSH there will be a substantial cost impact in particular in terms of ITU beds.

In the long-term, this should not represent an increase in cost to the NHS since patients and their treatment costs are merely being shifted from one hospital to another. Furthermore we have no reason to believe that ITU costs are higher at the NSH; indeed according to the 2006 Reference Costs,[5] the cost of a bed in a neurosurgical ITU is lower than the cost of a bed in a general ITU . Hence, we did not include ITU costs in our base case analysis.

In the short-term, the resource impact is less clear and will depend on local circumstances. A DGH might not achieve the full cost savings from seeing fewer patients as typically it would be losing only ¼ of an ITU bed. However, staff costs and consumables would be re-deployed almost immediately. The bed could also be re-deployed if there is currently under-capacity. If so more patients would be treated in ITU as a result of the increased capacity at DGHs but this would not necessarily see a reduction in costs to the Trust. However, this increase in ITU capacity could lead to cost savings from reduced transfers.

To implement a direct transport strategy, NSH units will need to invest in extra ITU beds. This will be offset by cost savings at DGHs. However, the cost savings will not necessarily offset the cost fully in the short-term. The implementation costs associated with shifting patients will have to be taken into account in any cost impact analysis conducted for the purposes of implementation.

A US study[4] reports a successful rate of GCS assessment (410/412 patients) by ambulance crews at the incident site, after an 8-hour training course. Hence, training for ambulance staff in the assessment of head injury patients would be necessary to safeguard the effectiveness and cost effectiveness of the direct transport strategy.

Since we do not have survival outcomes for the other simulation model based in London (see I.1.1) we could not use it to estimate cost effectiveness. However, there is no reason to believe that it would affect our conclusions for near hospitals: if the specialist hospital is ≤20 minutes from the injury scene then direct transport is likely to be cost effective. For distances greater than 20 minutes, the authors of the London model have erred on the side of caution by not recommending bypass. It seems logical that the further away is the specialist hospital the riskier is direct transport. Given the uncertainty of the evidence in this area, if we are to recommend direct transport at all then it probably is better to use some kind of cut-off but it is unclear how the authors of the London model made this decision since analyses based on transport times longer than 20 minutes are not present in the report.

The London model assumed that not just neurosciences but also other specialist services were available at the specialist centres. If specialist centres contain the whole range of services then the issue of whether ambulance crews can diagnose isolated head injury becomes less of an issue (this problem had been raised by several stakeholders), as long as specialist hospitals have adequate provision of beds, etc. Perhaps we should be recommending that bypass strategies are developed at a regional level to take into account local service configurations.

I.1.5.6 Direct transport model: Conclusions

- A simulation model and some empirical studies have shown reduced mortality associated with directly transporting patients with serious head injury to an NHS specialist neuroscience centre.

- If ambulance crews can assess patients accurately then a policy of direct transport to an NHS specialist neuroscience centre is likely to produce a net cost saving to emergency department services (because of the resources involved with stabilising and transferring patients).
- Long term care costs might increase or decrease depending on the extent that health status (quality of life) is improved by direct transport.
- We found that even with conservative estimates about long term care costs, direct transport is likely to be cost effective in spite of the very high costs of caring for patients with severe disability.
- If ambulance crews (unintentionally) overestimate the number of patients to be treated in the Neurosciences Centre, some patients will experience journeys that are longer than necessary and may incur complications– in which case health gain might be decreased and costs increased for these patients. Nevertheless, a sensitivity analysis showed that the number of overestimated patients would have to be quite high for the direct transport strategy to be no longer cost effective.

Appendix J – Excluded studies

Clinical studies

Table 23: Studies excluded from the clinical review

Study	Reason
Boschini, L. P., Lu-Myers, Y., Msiska, N. et al. (2016) Effect of direct and indirect transfer status on trauma mortality in sub Saharan Africa. Injury 47(5): 1118-22	- Population not relevant to this review protocol
Brown, E., Tohira, H., Bailey, P. et al. (2020) A comparison of major trauma patient transport destination in metropolitan Perth, Western Australia. Australasian Emergency Care 23(2): 90-96	- Population not relevant to this review protocol
Brown, J. B., Gestring, M. L., Guyette, F. X. et al. (2016) Development and Validation of the Air Medical Prehospital Triage Score for Helicopter Transport of Trauma Patients. Annals of Surgery 264(2): 378-385	- Population not relevant to this review protocol
Curtis, K., Kennedy, B., Lam, M. K. et al. (2022) Pathways and factors that influence time to definitive trauma care for injured children in New South Wales, Australia. Injury 53(1): 61-68	- Population not relevant to this review protocol *all children with major injury*
Fayeye, O., Ushewokunze, S., Stickley, J. et al. (2013) Does direct admission from an emergency department with on-site neurosurgical services facilitate time critical surgical intervention following a traumatic brain injury in children?. British Journal of Neurosurgery 27(3): 326-9	- No relevant outcome
Ford, D., Mills, B., Ciccone, N. et al. (2020) Does Direct Helicopter Retrieval Improve Survival of Severely Injured Trauma Patients From Rural Western Australia?. Air Medical Journal 39(3): 183-188	- Population not relevant to this review protocol
Granstrom, A., Strommer, L., Schandl, A. et al. (2018) A criteria-directed protocol for in-hospital triage of trauma patients. European Journal of Emergency Medicine 25(1): 25-31	- Population not relevant to this review protocol
Hamada, S. R., Delhaye, N., Degoul, S. et al. (2019) Direct transport vs secondary transfer to level I trauma centers in a French exclusive trauma system: Impact on mortality and determinants of	- Population not relevant to this review protocol

Study	Reason
triage on road-traffic victims. PLoS ONE [Electronic Resource] 14(11): e0223809	
Hsiao, Kuang-Yu, Chen, I-Chuan, Yang, Chia-Jung et al. (2012) Is direct transport to a trauma centre best for patients with severe traumatic brain injury? A study in south-central Taiwan. Emergency Medicine Journal 29(2): 156-159	- non-randomised trial - evidence not adjusted for all key confounders
Härtl, Roger, Gerber, Linda M, Iacono, Laura et al. (2006) Direct transport within an organized state trauma system reduces mortality in patients with severe traumatic brain injury. Journal of Trauma and Acute Care Surgery 60(6): 1250-1256	- non-randomised trial - evidence not adjusted for all key confounders
Joosse, Pieter, Saltzherr, Teun-Peter, van Lieshout, Willem AM et al. (2012) Impact of secondary transfer on patients with severe traumatic brain injury. Journal of Trauma and aCuTe Care surgery 72(2): 487-490	- Non-randomised trial - evidence unadjusted for key confounders
Kejriwal, Ritwik and Civil, Ian (2009) Time to definitive care for patients with moderate and severe traumatic brain injury--does a trauma system matter?. The New Zealand Medical Journal (Online) 122(1302)	- Non-randomised trial - evidence unadjusted for key confounders
Lin, Guy, Teplitsky, Alla, Hymas, Gila et al. (2012) Evacuation of wounded with intracranial injury to a hospital without neurosurgical service versus primary evacuation to a level I trauma centre. Injury 43(12): 2136-2140	- Non-randomised trial - evidence unadjusted for key confounders
Mallah, K., Zibara, K., Kerbaj, C. et al. (2021) Neurotrauma investigation through spatial omics guided by mass spectrometry imaging: Target identification and clinical applications. Mass Spectrometry Reviews 29: 29	- Study does not contain an intervention relevant to this review protocol
Mans, S., Reinders Folmer, E., de Jongh, M. A. et al. (2016) Direct transport versus inter hospital transfer of severely injured trauma patients. Injury 47(1): 26-31	- Population not relevant to this review protocol
Moen, Kent Gran, Skandsen, Toril, Karlsen, Beate Holmqvist et al. (2009) Patients with severe head injury in Norway-transfer and outcome. Journal of Neurotrauma 26 (A35)(8): 132-	- Conference abstract

Study	Reason
Moen, Kent Gøran, Klepstad, Pål, Skandsen, Toril et al. (2008) Direct transport versus interhospital transfer of patients with severe head injury in Norway. European Journal of Emergency Medicine 15(5): 249-255	- non-randomised trial - evidence not adjusted for all key confounders. Mortality reported for 6 months only
Neeki, M. M., Dong, F., Avera, L. et al. (2016) Alternative destination transport? the role of paramedics in optimal use of the emergency department. Western Journal of Emergency Medicine 17(6): 690-697	- Population not relevant to this review protocol
Nishijima, D. K., Gaona, S. D., Faul, M. et al. (2020) The Association of Trauma Center Transport and Long-term Functional Outcomes in Head-injured Older Adults Transported by Emergency Medical Services. Academic Emergency Medicine 27(3): 207-216	- non-randomised trial - evidence not adjusted for all key confounders
Pickering, A., Cooper, K., Harnan, S. et al. (2015) Impact of prehospital transfer strategies in major trauma and head injury: Systematic review, meta-analysis, and recommendations for study design. The journal of trauma and acute care surgery 78(1): 164-77	- Systematic review used as source of primary studies
Prabhakaran, K., Petrone, P., Lombardo, G. et al. (2017) Mortality rates of severe traumatic brain injury patients: impact of direct versus nondirect transfers. Journal of Surgical Research 219: 66-71	- Non-randomised trial - evidence unadjusted for key confounders
Ratliff, H., Korst, G., Moth, J. et al. (2021) Geographical Variation in Traumatic Brain Injury Mortality by Proximity to the Nearest Neurosurgeon. Journal of Surgical Research 259: 480-486	- Study design not relevant to this review protocol
Rubenson Wahlin, R., Ponzer, S., Skrifvars, M. B. et al. (2016) Effect of an organizational change in a prehospital trauma care protocol and trauma transport directive in a large urban city: a before and after study. Scandinavian Journal of Trauma, Resuscitation & Emergency Medicine 24: 26	- Population not relevant to this review protocol
Safavi, K. C., Gaitanidis, A., Breen, K. et al. (2020) Direct admission to improve timely access to care for patients requiring transfer to a level 1 trauma center. Trauma Surgery & Acute Care Open 5(1): e000607	- Population not relevant to this review protocol

Study	Reason
Sampalis, John S, Denis, Ronald, Frechette, Pierre et al. (1997) Direct transport to tertiary trauma centers versus transfer from lower level facilities: impact on mortality and morbidity among patients with major trauma. Journal of Trauma and Acute Care Surgery 43(2): 288-296	- Non-randomised trial - evidence unadjusted for key confounders
Scerbo, M., Radhakrishnan, H., Cotton, B. et al. (2014) Prehospital triage of trauma patients using the Random Forest computer algorithm. Journal of Surgical Research 187(2): 371-376	- Population not relevant to this review protocol
Sewalt, C. A., Gravesteijn, B. Y., Nieboer, D. et al. (2021) Identifying trauma patients with benefit from direct transportation to Level-1 trauma centers. BMC Emergency Medicine 21(1): 93	- Population not relevant to this review protocol *All trauma patients*
Simons, Richard, Brasher, Penelope, Taulu, Tracey et al. (2010) A population-based analysis of injury-related deaths and access to trauma care in rural-remote Northwest British Columbia. Journal of Trauma and Acute Care Surgery 69(1): 11-19	- Non-randomised trial - evidence unadjusted for key confounders
Sinclair, N., Swinton, P. A., Donald, M. et al. (2018) Clinician tasking in ambulance control improves the identification of major trauma patients and pre-hospital critical care team tasking. Injury 49(5): 897-902	- Study design not relevant to this review protocol
Singhal, E., Xu, T., Dhanasekara, C. S. et al. (2022) Comparing outcomes between patients transferred from a critical access hospital versus directly from scene to a level 1 trauma center. American Journal of Surgery 01: 01	- Population not relevant to this review protocol *All trauma patients*
Sollid, Snorre, Munch-Ellingsen, Jens, Gilbert, Mads et al. (2003) Pre-and inter-hospital transport of severely head-injured patients in rural Northern Norway. Journal of neurotrauma 20(3): 309-314	- Non-randomised trial - evidence unadjusted for key confounders
Tansley, G., Schuurman, N., Bowes, M. et al. (2019) Effect of predicted travel time to trauma care on mortality in major trauma patients in Nova Scotia. Canadian journal of surgery journalcanadiendechirurgie62(2): 123-130	- Study design not relevant to this review protocol
Tiesman, Hope, Young, Tracy, Torner, James C et al. (2007) Effects of a rural trauma system on traumatic brain injuries. Journal of neurotrauma 24(7): 1189-1197	- Non-randomised trial - evidence unadjusted for key confounders

Study	Reason
Tran, A., Taljaard, M., Abdulaziz, K. E. et al. (2020) Early identification of the need for major intervention in patients with traumatic hemorrhage: development and internal validation of a simple bleeding score. Canadian journal of surgery. Journal canadien de chirurgie 63(5): E422-E430	- Study does not contain an intervention relevant to this review protocol
Trivedi, D. J., Bass, G. A., Forssten, M. P. et al. (2022) The significance of direct transportation to a trauma center on survival for severe traumatic brain injury. European Journal of Trauma & Emergency Surgery 28: 28	- Comparator in study does not match that specified in this review protocol *regional trauma centre with neuroscience vs non-trauma centre*
van Rein, E. A. J., Houwert, R. M., Gunning, A. C. et al. (2017) Accuracy of prehospital triage protocols in selecting severely injured patients: A systematic review. The Journal of Trauma and Acute Care Surgery 83(2): 328-339	- Population not relevant to this review protocol
van Rein, E. A. J., van der Sluijs, R., Houwert, R. M. et al. (2018) Effectiveness of prehospital trauma triage systems in selecting severely injured patients: Is comparative analysis possible?. The American journal of emergency medicine 36(6): 1060-1069	- Population not relevant to this review protocol
Vats, A.; Roy, D.; Prasad, M. K. (2021) Direct versus indirect transfer for traumatic brain injury to James Cook University Hospital: a retrospective study. Annals of the Royal College of Surgeons of England 103(1): 23-28	- No relevant outcome (GOS reported at discharge only – PICO sets to include at >3 months)
Windorski, J., Reyes, J., Helmer, S. D. et al. (2019) Differences in hospital outcomes following traumatic injury for patients experiencing immediate transfer to a level I trauma facility versus resuscitation at a critical access hospital (CAH). American Journal of Surgery 217(4): 643-647	- Population not relevant to this review protocol
Zhu, T. H., Hollister, L., Opoku, D. et al. (2018) Improved Survival for Rural Trauma Patients Transported by Helicopter to a Verified Trauma Center: A Propensity Score Analysis. Academic Emergency Medicine 25(1): 44-53	- Population not relevant to this review protocol

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2006 or later and not from non-OECD country or

USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 24: Studies excluded from the health economic review

Reference	Reason for exclusion
Pickering 2014[15]	This was an NIHR report where cost effectiveness modelling was attempted unsuccessfully due to lack of data to populate the model.

Appendix K – Research recommendations – full details

K.1 Research recommendation

K.1.1 What is the clinical and cost effectiveness of pre-hospital strategies to take people with head injury to a distant specialist neuroscience centre instead of a closer non-specialist unit?

K.1.2 Why this is important

K.1.3 People with head injury are transferred to major trauma centres (MTCs) in the basis of Triage Tools. However, there is evidence that certain populations are not well assessed by these tools e.g. the elderly. There are also questions about whether all types of injury do need care in MTCs. Answering this is important to ensure people get the care they need in the correct place with appropriate use of resources.

K.1.4 Rationale for research recommendation

Importance to 'patients' or the population	People with head injury are transferred to MTCs in the basis of Triage Tools. However, there is evidence that certain populations are not well assessed by these tools e.g. the elderly. There are also questions about whether all types of injury do need care in MTCs. Answering this is important to ensure people get the care they need in the correct place with appropriate use of resources.
Relevance to NICE guidance	Evidence would inform the recommendations of an update of this guideline
Relevance to the NHS	It would potentially enable more refined decisions about who, when and why people with head injury would or would not benefit from transfer to a specialist centre. If guidance was altered it may need further planning to ensure that major trauma centres and trauma units have the resources required to deliver the care needed.
National priorities	Urgent and emergency care is an NHS England priority.
Current evidence base	Evidence from one randomised controlled trial and one retrospective cohort study was identified. The studies compared transport to specialist neuroscience centre compared to transport to nearest non-specialist acute hospital/general hospital emergency department for head injury. All evidence was in adults and young people, no evidence was available for children (aged ≥1 to <16 years) and babies (aged <1 year). The quality of the evidence ranged from moderate to very low. There was limited evidence with suggested benefit of transfer to specialist neuroscience centre for some outcomes but given the uncertainty in evidence the committee did not make any new

	recommendations. The committee noted that the data collection for the RCT evidence was in 2012 when trauma care was re-organised in the UK to enable rapid and safe transfer of patients to Major Trauma Centres (MTCs). Hence the evidence is not entirely reflective of the recent trauma care system which now include more consultants, quicker CT scans and rehabilitation of patients. The committee therefore agreed that further research should be undertaken in this area to determine the effectiveness of transport to specialist neuroscience centres in people with head injury.
Equality considerations	Particular areas to consider may include older adults.

K.1.5 Modified PICO table

Population	All adults, young people and children (including babies under 1 year) with a suspected head injury.
Intervention	Clinical decision rules or triage tools for direct transport to neuroscience centre or major trauma centre with neuroscience.
Comparison	Nearest emergency department (if nearest hospital is not a major trauma centre (MTC) with neuroscience care) – with option for secondary transfer
Outcome	• All-cause mortality – at ≤30 days or days alive and out of hospital (DAOOH) • Quality of life - 3 months or more • Objectively applied score of disability e.g. Glasgow Outcome Score (GOS) or extended GOS - at 3 months or more • Length of stay in acute care (until discharged home or to rehabilitation) • discharge back to admission residence • Serious adverse event – i.e. deterioration of ABC at ≤30 days • Neurosurgery at ≤30 days • Other surgery at ≤30 days • Secondary transfer to specialist centre (for those initially transferred MTC) at ≤30 days
Study design	RCT
Timeframe	Medium term – to inform any update of this guidance
Additional information	None