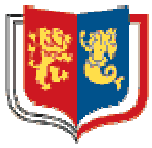

THE UNIVERSITY
OF BIRMINGHAM

The risk of post-traumatic seizures in non-surgically treated patients with evidence of brain injury on CT or MRI scan – a literature review

Aggressive Research Intelligence Facility

West Midlands Health Technology Assessment Collaboration

July 2007

For the Drivers Medical Group

DVLA

Swansea

ARIF

About ARIF and the West Midlands Health Technology Assessment Collaboration

The West Midlands Health Technology Assessment Collaboration (WMHTAC) is an organisation involving several universities and academic groups who collaboratively produce health technology assessments and systematic reviews. The majority of staff are based in the Department of Public Health and Epidemiology at the University of Birmingham. Other collaborators are drawn from a wide field of expertise including economists and mathematical modellers from the Health Economics Facility at the University of Birmingham, pharmacists and methodologists from the Department of Medicines Management at Keele University and clinicians from hospitals and general practices across the West Midlands and wider.

WMHTAC produces systematic reviews, technology assessment reports and economic evaluations for the UK National Health Service's Health Technology Assessment (HTA) programme, the National Institute for Health and Clinical Excellence (NICE). Regional customers include Strategic Health Authorities, Primary Care Trusts and regional specialist units. WMHTAC also undertakes methodological research on evidence synthesis and provides training in systematic reviewing and health technology assessment.

The two core teams within WMHTAC are the Aggressive Research Intelligence Facility (ARIF) and the Birmingham Technology Assessment Group (BTAG)

ARIF provides a rapid on-demand evidence identification and appraisal service primarily to commissioners of health care. Its mission is to advance the use of evidence on the effects of health care and so improve public health. The rapid response is achieved by primarily relying on existing systematic reviews of research, such as those produced by the Cochrane Collaboration, the National Institute for Health and Clinical Excellence (NICE), the NHS Centre for Reviews and Dissemination, and the NHS Health Technology Assessment (HTA) programme. In some instances, longer answers to questions are required in which case mini rapid reviews of existing systematic reviews and key primary studies are compiled, typically taking 1-2 months to complete.

Occasionally a full systematic review is required and then topics are referred to BTAG who coordinate the production of systematic reviews for several customers under a number of contracts. ARIF is intrinsically involved in the production of these systematic reviews.

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1 Introduction

The following questions were initially submitted by the Driver Medical Group to ARIF for literature review:

(a) What is the risk of seizure, black-out or sudden and disabling events if there is evidence on MRI or CT scanning of soft tissue damage?

(b) What is the risk associated with contusions, bi-lateral contusions and blood in the ventricles, particularly if such conditions are treated conservatively?

After discussion, these questions were refined and reformulated into the primary and secondary questions below.

2 Aim

The aim of this study was to review the scientific literature to look for answers to the following questions:

2.1 Primary Question

What is the lifetime risk of post-traumatic seizures in patients with evidence of brain damage following a traumatic brain injury?

2.2 Secondary questions

(a) What are the prognostic factors for long-term seizures in non-surgically treated patients with traumatic brain injury?

(b) How long are non-surgically treated patients with traumatic brain injury at risk of developing seizures?

3 Background

Traumatic brain injury (TBI) is a frequent occurrence that causes disability in young people under the age of 35.[1] In the UK, approximately 1 in 300 people will suffer from TBI each year[2]. In some areas of England as many as 1 in 240 people require hospitalisation following TBI each year[3] TBI is an accepted cause of post-traumatic seizures (PTS) or epilepsy and accounts for up to 20% of symptomatic epilepsy in the general population.[4]

The significant socioeconomic, clinical, public health and safety dimensions of PTS have frequently been highlighted and the need for consistent advice and a protocol for assessing fitness to drive after TBI have been commented on in two reviews (Hawley[5] and Tamietto[1]).

Although TBI and its sequelae may seriously limit driving ability, in Britain drivers do not appear to be routinely assessed or advised regarding returning to driving after recovering from TBI.[6] Tamietto[1] reported that 50% of TBI survivors resume driving and nearly two-thirds of these may do so without specific medico-legal examination or formal evaluation.

In order to be able to develop appropriate policies regarding returning to driving and for clinicians to be able to apply these consistently it is helpful:

a) To have a clear definition or definitions of TBI
b) To be able to make an informed estimation of risks of seizures following TBI.

The use of neuroimaging techniques, such as CT and MRI, provides visual evidence of brain damage in injured patients. This gives more information than the clinical picture alone and holds out the possibility of enabling more precise definitions of condition and estimations of risk.

This report therefore evaluates and summarises the relevant scientific evidence so that guidance regarding return to driving among non-surgically treated TBI patients with CT or MRI scan evidence of brain injury can be appropriately informed.

Further background information is given in the documentation supplied by the Drivers Medical Group contained in Appendix 1 – Details of Request.

4 Methods

4.1 Introduction

Outline methods were agreed in advance with the Drivers Medical Group (see Appendix 2 – Outline methods).

The focus was on studies looking at the risk of developing late post-traumatic seizures (LPTS)[i] rather than early post-traumatic seizures (EPTS)[ii] after a head injury. Late post-traumatic seizures are defined as an unprovoked seizure(s) occurring any time after one week following TBI (based on definitions suggested by Jennett and Lewin[7] and Annegers & colleagues[8]).

It was anticipated that there would be few studies directly addressing the question of interest, therefore studies with no documented CT or MRI scan evidence of brain damage were included in order to maximise the information we were able to obtain. It was agreed that searches for outcomes such as syncope and other cardiovascular events were not appropriate for answering the questions addressed.

Background research suggested that studies of post-traumatic seizures in military personnel were unlikely to be useful for estimating risk of seizures in civilians because

- Military subjects in these studies are often recruited from pension databases and are therefore more likely to be severely injured soldiers claiming early pension
- Most civilian injuries are thought to be of lesser severity than those seen among soldiers
- The injured soldiers studied are usually homogenous group of young men often with penetrating injuries different to most civilian injuries[9,10]

[i] Late Post-traumatic seizures (**LPTS**) refer to unprovoked seizures occurring after the first week of injury

[ii] Early Post-traumatic seizures (**EPTS**) refer to seizures occurring from immediately after injury up to a week

The emphasis in this report is on estimating the lifetime (cumulative) risk of developing late post-traumatic seizures among non-surgically treated civilians with closed head injuries where there is evidence of brain damage but no dural tears. The focus on lifetime risk allows the data about risks in children to be included where available.

4.2 Searches

4.2.1 Existing Reviews

Searches to identify existing systematic reviews on this topic were performed utilising the well-established ARIF search protocol (Appendix 3 – Search strategies).

4.2.2 Primary Studies

Searches for primary studies were undertaken in Ovid MEDLINE and EMBASE. The search strategy employed MeSH terms for seizures, risk, brain injury, and head injury combined with study design terms to filter prospective cohort studies. It was developed iteratively. MEDLINE searches covered the period 1950-2007 and EMBASE searches covered 1980-2007. Other sources of background information include TRL, Monash University Accident Research Centre, and Hospital Episode Statistics Online. The detailed search strategies are shown in Appendix 3 – Search strategies.

Articles were selected for review using the following criteria:

- **Inclusion**

  Study design:

  (i) Review Articles
  (ii) Cohort or longitudinal studies with follow up of a defined cohort of patients
  (iii) Cross-sectional surveys
  (iv) Studies with CT and/or MRI scan reports irrespective of study design

  Population: All head injured patients; no age limit was set
  Studies looking at civilian and non-civilian populations were initially included

  Outcome: Incidence of late PTS/post-traumatic epilepsy (PTE), prognostic factors for late PTS/PTE

- **Exclusion:**

  a) Studies focused on very early post-traumatic period with no follow-up beyond initial treatment period.
  b) Studies focused solely on animal experiments
  c) Studies with no patient-related outcomes
  d) Articles requiring translation (due to the timeframe available for this report)

Full text articles were assessed to see whether they matched the primary questions being addressed (external validity). Data from the most informative articles were extracted and are presented below. The reference lists of the most relevant articles were checked to identify further relevant papers. General

overviews and non-systematic reviews were utilised as background information and as a potential source of further data and/or further studies.

5 Results

5.1 Articles Identified

Searches for primary studies from MEDLINE (1950-2007) and EMBASE (1980-2007) identified over 400 articles. The titles and abstracts of these articles were assessed for general relevance and potential to meet the stated inclusion criteria. Initially, this resulted in a selection of 47 articles which were obtained in full for further scrutiny. The reference lists of these 47 articles were also scanned for potentially relevant articles and these yielded a further 26 articles which were also obtained in full for scrutiny.

5.1.1 Constraints

Most of the articles had no data specific to non-surgically treated TBI patients with CT or MRI scan evidence of brain damage. Many of the studies on PTS pre-date the introduction of CT and/or MRI scans. There are also other issues with the validity and utility of the results from these studies. Identified studies followed very different protocols, had different definitions of PTS and did not always stratify reported outcome data by type of treatment, severity of injury and/or type of PTS.

Precise definition of PTS is often difficult to obtain as the term is used interchangeably with post-traumatic epilepsy (PTE). In very recent literature, the use of the term PTE is increasingly restricted to two or more unprovoked seizures following head trauma,[12] but many of the studies identified in this review used PTS and PTE to mean the same thing, an unprovoked seizure after head injury. Therefore, PTS will be used in this report to refer to both PTS and PTE unless a distinction is necessary to clarify reported data.

An example of the overall complexity is review of 9 prospective studies,[10] where only 2 studies had a comparison group which is necessary to be able to fully estimate increased risk. The length of follow-up in these studies ranged from 2 to 15 years and 5 of the studies had different definitions of early seizures. Three of the studies did not specify how seizures were ascertained and more than half (5 studies) did not categorise patients by type of trauma preceding the seizure. Only three of the studies stated whether seizures arose from other cerebral insults apart from trauma and whether those patients were excluded in the overall result or not.

The data obtained from identified studies could not always be generalised to the wider population of TBI patients as subjects often came from highly selective groups such as from specialised units or rehabilitation centres for severely injured patients. Furthermore, the criteria by which head trauma and consequent brain injury in patients were ascertained were not always clearly stated or standardised across the studies. These factors threaten the validity of results obtained from these studies and make the pooling of results impossible. The methodological challenges outlined have contributed to the persistent confusion and uncertainty about risk of seizures following TBI.[1,11,12,13]

5.2 Choice of studies reviewed for this report

5.2.1 Relevant Study Types

Historical cohorts[iii] have been suggested as the best study design to unravel the relationship between seizures and CNS insults[4] but such studies are difficult to conduct and are therefore scarce.[14] There is continued call for well-designed multi-centre longitudinal studies of post-traumatic seizures in order to help clarify the risks, latency and chronicity of PTS and facilitate the development of better guidance regarding anticonvulsant prophylaxis, rehabilitation, and return to driving.[14,15,16,17,18,19]

Pohlmann-Eden and Bruckmeir[17] has however argued that retrospective case-control[iv] studies could be immediately useful based on observation that 12.3% of patients in their retrospective study reported their first seizure 10 to 30 years after TBI, a finding similar to Annegers' large population study[8] where risk of seizures in severely injured patients persisted over a similar period.

With these issues in mind, the main selection criterion for studies reviewed in this report is the availability of data on late post-traumatic seizure. Selected studies ranged from very small case series to large population studies of different designs. Civilian studies with large study population size, with ≥2-year follow-up, and data on neuroradiological (CT/MRI scan) evidence of brain damage are the most relevant. Seminal studies identified as such in general overview articles and by several authors of primary studies were also chosen for review, for example, Jennett & Lewin,[7] Annegers and colleagues,[8] and D'Alessandro & colleagues.[19]

Overall, in addition to the general overview articles, 14 primary studies were reviewed in detail for this report. Seven of these had data on patients with neuroradiological evidence of brain injury. Details regarding study design, methodological limitations, and relevant results from these studies are presented below.

5.3 Summary of obtained outcome data

It should be noted at the outset that due to the methodological issues outlined above, it is difficult to pool the results from the different studies identified in this review. A summary of the best available evidence from three categories of identified studies and a cautionary note based on their quality is all that is possible.

5.3.1 Risk of LPTS following TBI: Studies with no documented CT/MRI scan evidence

Many studies on the risk of LPTS pre-date widespread clinical use of CT and/or MRI scanning. Two large civilian studies with limited or no documented neuroradiological evidence of brain injury provided the best overview of the risk of LPTS in general. These two cohort studies are widely cited in the PTS literature but have notable limitations and methodological flaws as highlighted by previously published reviews.[10,12]

[iii] Cohort studies start with people without the outcome of interest followed-up over a suitable length of time until they develop the outcome of interest and have their risks of developing the outcome compared to a comparison group.

[iv] Case-control studies start with cases with outcome of interest and compare these with a control group without the outcome and attempt to analyse risk factors. These study types usually suffer from several methodological flaws especially case-control studies.

Study 1 - Jennett and Lewin[7]

Design

This is a 4[+]year prospective cohort study by Jennett and Lewin[7] of 1000 consecutive head-injured patients admitted via the accident service at Radcliffe Infirmary, Oxford, England between November 1948 and February 1952.

Main Findings

- 10% of patients (a selected series of head-injured patients in hospital setting) developed LPTS. In a later publication reporting the same series of patients,[20] Jennett suggested that this could be extrapolated to a 5% incidence among unselected cases of TBI.

- Mild, uncomplicated cases of TBI without EPTS had very low risk (1%) of developing LPTS. The presence of EPTS in patients with mild TBI increased overall incidence to 4.5%. The mildly injured patients with EPTS who later developed LPTS were entirely made up of children under the age of eight.

- Overall, there is a striking four-fold increase in the risk of LPTS in patients with EPTS after TBI compared to those without; 28.5% compared to 7.5%. Post-traumatic amnesia also appears to be a major risk factor for LPTS, particularly when combined with intracranial haematoma or depressed skull fracture. In the series, there were no cases with LPTS when post-traumatic amnesia was experienced for less than 24 hours.

Comments & Conclusions

This study was highly selective in the types of patients followed-up for occurrence of LPTS. Among the recruited 1000 patients, the authors chose to follow-up 175 subjects considered to be at high risk of developing LPTS i.e. those with early seizures, depressed skull fractures, intracranial haematoma, and post-traumatic amnesia of >24 hours and another 100 with uncomplicated injuries. Furthermore, there was no external comparison group to compute the relative risk of LPTS. Information about the proportion of the 275 patients chosen for follow-up that were completely followed-up was not available. Without information about the length and completeness of follow-up it is not possible to determine the validity of data reported.

The methods used to ascertain seizures and whether seizures following cerebral complications other than trauma were excluded from the outcome data, were not stated. Previously diagnosed epileptics were excluded. Patients in this study received the anticonvulsant – phenobarbitone for a variable length of time, which may or may not have had an effect on the development of LPTS. The lack of standardisation in the length of medication between patients may have changed their risk profiles for developing LPTS.

Relevant outcome data from this study is summarised in table 1 below. Overall, the significant selection bias in this study limits the representativeness of the results and thus their generalisability to all cases of head injury. The study mainly provides useful information about potential clinical risk factors for LPTS but does not offer comparative information about surgically vs. non-surgically treated cases.

Table 1: Summary of relevant results from Jennett & Lewin (1960)

Reference #	Jennett & Lewin 1960[7]			
Study Type	Prospective Cohort Study			
Study Population	British Population – 1000 consecutive admissions with none missile head injuries, Oxford, England (821 admitted directly from accident scene and 179 transferred in from other hospitals) (175 with complications[a] and 100 without complications and post-traumatic amnesia (PTA) <1hr selected for follow-up and reported in the study)			
Follow-up period	1948-1952 (≥4 years)			
Overall incidence of LPTS	*28/275 = 10%* *Jennett used this figure to estimate an overall incidence of 5%* *for an unselected population but did not provide any details of the calculation.[20].*			
No Early PTS	Depressed Skull Fracture	PTA <1hr (uncomplicated)	PTA >24hours or hematoma but no depressed fracture	Total
	16%	***1%***	***10.4%***	***7.5%***
	No confidence interval or statistical tests reported			
With Early PTS (seizure within 1 week of TBI)	Depressed Skull Fracture	PTA <1hr (uncomplicated)	PTA >24hours or hematoma but no depressed fracture	Total
	Not reported	**Not reported**	**Not reported**	**28.5%**
	No confidence interval or statistical tests reported			
Time elapsed since injury to first seizure	50% of cases developed LPTS by the end of the first year and 70% by the end of the second year. There were sporadic cases developing among the followed-up patients up to seven years after TBI.			
Seizure frequency	75% of LPTS patients in this series developed multiple seizures; 25% had only a single fit (cf. Annegers & colleagues below)			
Prognostic Factors	1. Early post-traumatic seizure 2. Intracranial haematomas 3. Depressed skull fracture 4. Post-traumatic amnesia >24 hours The development of LPTS after mild injuries appears to be confined to children.			
Clinical features	Generalised attacks were more common than focal attacks (10:6 ratio)			

a – inclusion criteria for 175 cases with complications: early PTS, depressed fracture, haematomas, and PTA >24hours

Study 2 – Annegers et al[8,16]

Design

This is a large population-based retrospective cohort study by Annegers and colleagues of all episodes of head injury (5984 injury episodes included) from 1935 to 1974[8] and then to 1984[16] in Olmsted County, Minnesota, USA using the Mayo Clinic record-linkage system. Only TBI cases with brain involvement were included in the study.

Main Findings

Annegers and colleagues presented outcome data categorised by injury severity. The diagnosis of brain involvement after TBI and the categorisation injury severity is entirely clinical as summarised below.

- **Mild TBI**
    - Loss of consciousness and/or post-traumatic amnesia ≤30 minutes
    - Absence of skull fracture
- **Moderate TBI** (at least one of the following)
    - Loss of consciousness ≥30minutes but ≤24 hours
    - Post-traumatic amnesia ≥30minutes but ≤24 hours
    - ± skull fracture
- **Severe TBI** (at least one of the following)
    - brain contusion diagnosed by focal neurological symptoms or seen at surgery
    - Intracranial haematoma
    - Loss of consciousness ≥24 hours
    - Post-traumatic amnesia ≥24 hours

In the final ten years of follow-up (1975-1985), 34 patients with mild or moderate head injury in the study had documented CT scan evidence of brain contusion but none of these were observed to develop seizures at the point at which follow-up was terminated.

- Overall, the study reported 2% incidence rate of LPTS among all TBI patients with an estimated 3.6 fold increase in the risk of seizures among all TBI patients. This overall figure masks the dependence of the increased risk on time since injury and severity of the injury.

- After the first 30-year follow-up period, available data showed that overall, the increased risk of LPTS is time dependent and peaks at a 12.7 fold rise in the first year following the injury, dropping to 4.4 fold rise for the next four years and by the fifth the risk would have dropped to the same level as that of an unaffected population.

- When further data became available after a 50-year follow-up from a larger cohort of TBI patients of the same study, Annegers and colleagues were able to refine the estimation of increased risk over time and by injury severity, it was shown that the increased risk of LPTS can persist for up to 20 years in severely injured patients.[16] A breakdown of increased risk of LPTS by time since injury and severity of injury is as follows:

Table 2: Standardised incidence ratio by time and severity of injury

Time since TBI/Severity	Mild TBI	Moderate TBI	Severe TBI
<1year	3.1 (1.0-7.2)	6.7 (2.4-4.1)	95.0 (58.4-151.2)
1-4years	2.1 (1.1-3.8)	3.1 (1.4-6.0)	16.7 (8.4-32.0)
5-9years	0.9 (0.3-2.6)	3.0 (1.2-6.2)	12.0 (4.5-26.6)
≥10years	1.1 (0.5-2.1)	1.8 (0.8-3.6)	4.0 (1.1-10.2)

(confidence interval in parentheses)

- Generally, the risk of LPTS after mild injuries is marginally increased to 1.5 times that of the unaffected population but this increased risk varies with time. It peaks in the first year when it could be as high as 3.1 times (*possible range 1-7 times*) that of the general population. The increased risk then tails off and comes down to the level of the general population by the fifth year.

- For moderate injuries, the increased risk is 6.7 times that of the general population in the first year, the increase is maintained at 3 times (*possible range 1.2-6.2 times*) that of the general population until the 10th year when it drops to near that of the general population.

- In severe cases, the increased risk is very high, about 95-fold increase compared to the general population in the first year, and up to 12 times that of the general population until the 9th year. The risk persists for more than ten years where the increased risk is 4 times that of the general population (*range from 1.1-10.2 times*).

Several prognostic factors, similar to those reported by Jennett & Lewin for LPTS were identified. However, the prognostic effect of EPTS was eliminated by adjusting for the other factors listed in table 2. In children while there is a higher risk of EPTS, the risk of LPTS is low compared to adults irrespective of severity of injury. There is some evidence that EPTS is a risk factor after moderate or severe TBI in adults. The authors commented about the crude nature of the analysis and the small numbers involved in this result.

Comments & Conclusions

Overall, this is a well-designed study. It was unselective and included all patients whether hospitalised or not. All patients with no exception were followed-up until one of the following occurred – had first intracranial surgery, had first late seizure, emigrated from Minnesota or died. The study excluded cases with known confounders i.e. previous epilepsy, >1 episode of head trauma, suffering from sequelae of head trauma (these types of cases are likely to have been admitted because of seizures as shown by Jennett & Lewin[7] in their study where directly admitted cases had lower rates of seizures compared to referred cases).

The risk of LPTS in the study population was compared to the risks of seizures in the general population of Rochester, USA. All patients in this study received antiepileptic drugs for 6 months and not more. The main limitations of the study arise from the fact that it is retrospective and relied solely on medical records which may not be complete or accurate.

Furthermore, the rural population of Olmsted County may not be representative of multi-ethnic and diverse populations of the UK or even the USA.[14] The authors mentioned that a more rigorous assessment of brain involvement is required for better analysis of the relationship between severity of TBI and the risks of developing LPTS. It has also been argued by other authors that clinical classification of brain injury may not be adequate when attempting to estimate the relationship between TBI and LPTS.[19,21]

The results from this study (table 3 below) provide comprehensive data on non-surgically managed TBI cases and categorised the outcomes by age and well-defined clinical criteria of severity but offers limited information about conservatively managed cases with CT or MRI scan evidence of brain injury.

Table 3: Summary of relevant results from Annegers & Colleagues (1980, 1998)

Reference #	**Annegers & Colleagues 1980[8]**		**Annegers & Colleagues 1998[16]**	
Study Type	**Retrospective Cohort Study**			
Study Population	**US Population – Olmsted County, Minnesota (Total of 4541 head injury episodes included in the study; 2747 episodes in the first period 1935-1974)**			
Follow-up period	**1935-1974**		**1934-1985**	
Overall incidence of LPTS	**51/2747 = ~2%**		**97/4541 = 2%**	
Incidence Mild	**<1yr post injury**	**0-5y post injury**	**5yr post injury**	**30yr post injury**
Children	***0.0%***	***0.2%***	***Not reported***	
Adults	***0.1%***	***0.8%***		
All age groups	***0.1%***	***0.6%***	***0.7%***	***2.1%***
Incidence Moderate	**<1yr post injury**	**0-5y post injury**	**5yr post injury**	**30yr post injury**
Children	**0.5%**	**1.6%**	**Not reported**	
Adults	**1.0%**	**1.6%**		
All age groups	**0.7%**	**1.6%**	**1.2%**	**4.2%**
Incidence Severe	**<1yr post injury**	**0-5y post injury**	**5yr post injury**	**30yr post injury**
Children	**5.6%**	**7.4%**	**Not reported**	
Adults	**7.7%**	**13.3%**		
All age groups	**7.1%**	**11.6%**	**10%**	**16.7%**
Period of increased risk for LPTS	There is a **3.6 fold** increase in the risk of LPTS following head trauma compared to unaffected population. The increased risk is however time dependent: **<u>Relative Risk</u>** **1 yr** = 12.7 fold rise (CI 7.7-20.0) **1-4y** = 4.4 fold rise (CI 2.7-6.9) **5+ year** = 1.4 (CI 0.7-2.5 - not statistically significant) **<u>Prognostic Factors</u>**		Overall, standardised incidence ratio (SIR) **for** 1st year post TBI = 3.1 and 2.1 for the next four years. No further increase in SIR after 5yrs. This aggregate figure however hides the effects of injury severity on risk of LPTS over time. Increased risk of LPTS following TBI as well as being time limited is also dependent on severity of injury. **Standardised incidence ratio by severity of injury:** • Mild = 1.5 (CI 1.0-2.2) • Moderate = 2.9 (CI 1.9-4.1) • Severe = 17 (CI 12.3-23.6) **Standardised incidence ratio by time**	

<table>
<tr><td></td><td>1. Brain contusion and/or subdural haematomas
2. Skull fracture including linear fracture (depressed fracture especially in children)
3. Loss of consciousness and/or post-traumatic amnesia >24 hours
4. Age less than 65y+
5. Alcohol withdrawal and/or alcoholism
6. Early post-traumatic seizures</td><td>and severity of injury
<table><tr><td></td><td>Mild</td><td>Mod.</td><td>Severe</td></tr><tr><td><1y</td><td>3.1 (1.0-7.2)</td><td>6.7 (2.4-4.1)</td><td>95.0 (58.4-151.2)</td></tr><tr><td>1-4y</td><td>2.1 (1.1-3.8)</td><td>3.1 (1.4-6.0)</td><td>16.7 (8.4-32.0)</td></tr><tr><td>5-9y</td><td>0.9 (0.3-2.6)</td><td>3.0 (1.2-6.2)</td><td>12.0 (4.5-26.6)</td></tr><tr><td>≥10y</td><td>1.1 (0.5-2.1)</td><td>1.8 (0.8-3.6)</td><td>4.0 (1.1-10.2)</td></tr></table></td></tr>
<tr><td>Time elapsed since injury to first seizure</td><td colspan="2">Incidence of first seizure after five years was not greater than in the general population but the numbers are too small to robustly determine the level of risk. Among 109 cases there were 2 seizures in the sixth year and 1 in the 7th year.</td></tr>
<tr><td>Seizure frequency</td><td colspan="2">75% of patients in this series developed multiple seizures</td></tr>
<tr><td>CT/MRI scan risk factors</td><td colspan="2">In the last ten years of this 50-year study, CT scan evidence and records of abnormalities and diagnosis of brain contusion were available for 34 patients with mild or moderate TBI and none of these patients were observed to develop seizures.</td></tr>
</table>

5.3.2 Risk of LPTS following TBI: Studies with documented CT/MRI scan evidence but no data on surgical intervention status

More recent studies of post-traumatic seizures include patients with documented neuroradiological (CT and/or MRI scan) evidence of brain injury. Three early studies were identified but unfortunately these studies also share the methodological weaknesses and potential selection bias of the older observational studies described above. In general, the results from these studies are not widely generalisable.

Study 1 - D'Alessandro et al[19]

Design

This retrospective follow-up study after excluding known epileptics, patients discharged home on antiepileptic drugs and patients who have suffered other possible causes of seizures before or after their injuries recruited 233 patients admitted with head trauma to a tertiary centre in Italy between 1977 and 1978.

Main Findings

- Published in 1982, this was the first study to show that only patients with CT scan evidence of a focal brain lesion developed PTS and that the risk of PTS appears to be particularly high when intracerebral haemorrhage and extracerebral haematoma co-exist.[19]

Comments & Conclusions

The study divided head-injured patients into two categories, severe TBI (similar to the definition used by Annegers and colleagues above) and mild-moderate for all other patients. Early CT scan (within 48 hours) had been performed on 40% (93/233) of the patients and the results presented are for these 93 patients only. The proportion of patients scanned differed between the severe and mild-moderate groups (66% compared to 24%) thus making the reported incidence of PTS in this study less relevant for the purpose of this report. The selection of severely injured patients, the potential non-comparability of the two categories of head-injured patients and the lack of a comparison group limit the utility of the incidence data.

Study 2 - Pohlmann-Eden and Bruckmeir[17]

Design

This study by Pohlmann-Eden and Bruckmeir[17] is a case-control study of head injured patients attending a special epilepsy clinic. Excluded from cases in this study were known epileptics, patients with repeated head trauma, mild TBI patients with no evidence of contusional lesions and those with insufficient documentation of primary trauma or clinical outcomes. 57 cases were compared to 50 age-sex matched controls.

Main Findings

- The most useful information from this study centres on the latency of LPTS. Among the patients observed with PTS in this study, 68% developed recurrent seizures within 2 years of their injury. 12.3% of these patients had their first seizure between 10 and 30 years after the brain injury. The results of this study also support the finding in study 1 (D'Alessandro et al[19]) above that documented evidence of focal lesions on CT scan is a better predictor of LPTS compared to clinical risk factors. The specific combination of extended cortical lesions, prolonged post-traumatic amnesia and depressed fracture is the high-risk profile for LPTS.

Comments & Conclusions

The high susceptibility of this study to confounding, case selection of more severely injured patients and special referrals limit the utility and the ability to generalise incidence data from this study. However, the long follow-period in this study, up to 30 years provides some useful information about latency of LPTS.

Study 3 - Asikainen et al[22]

Design

This retrospective study by Asikainen and colleagues[22] studied 490 TBI patients referred because of educational or social needs into a rehabilitation centre in Finland and followed them up for ≥5 years. All patients in this study had a CT scan done either during the acute phase or at the first follow-up examination (between 6 months and 2 years of the injury).

Main Findings

- The study found the highest risk of LPTS among children ≤7 years, they also had a higher risk of EPTS; 32.7% of these children developed LPTS compared to 31.45% in 8-16-years age group and 18.9% among subjects older than 16 years.
- The authors suggested that injury severity measured by Glasgow Coma Scale, prolonged loss of consciousness and/or post-traumatic amnesia without local brain lesion should not be considered risk factor for LPTS. This was the only study in the series reviewed to report that the increased risk of LPTS when there is an evidence of brain lesion on CT scan did not reach statistical significance OR = 1.2 (CI 0.75-2.07).

Comments & Conclusions

This retrospective cohort study excluded known epileptics, fatal and severely disabled patients but included patients with other CNS conditions which may cause seizures e.g. post-traumatic bacterial meningitis and liquorrhea. This, in combination with the systematic exclusion of all TBI patients who recovered and were not referred for rehabilitation, makes the results not generalisable.

5.3.3 Risk of LPTS following TBI: Studies with documented CT/MRI scan evidence and data on surgical intervention status

From this category, four studies were identified. One of these studies with some MRI data had a short follow-up period and high drop-out rate. Three studies are therefore reviewed in detail here. These studies are significantly different from each other and the relevant data obtained from each study is summarised below.

Study 1 - Temkin[18]

Design

Temkin[18] prospectively followed-up patients at high risk of developing PTS recruited into two controlled trials of prophylactic antiepileptic drugs for a maximum of two years. This was not a full prospective cohort study but compared this cohort to the population of Rochester, Minnesota.

783 patients aged 14 years and above admitted to University of Washington, Seattle USA with at least one of the following inclusion criteria: cortical contusion, haematoma (subdural, epidural, or intracerebral), depressed skull fracture penetrating brain injury, early seizures and Glasgow Coma Scale (GCS) ≤10 were recruited into the study.

Main Findings

- Patients with surgically treated subdural haematoma are 2.3 times more likely to develop LPTS than non-surgically treated patients
- Patients with surgically treated subdural haematoma are 3 times more likely to develop LPTS than those with no subdural haematoma
  - 44% of high-risk patients with surgically evacuated subdural haematoma develop LPTS
  - 19% of high-risk patients with non-surgically treated subdural haematoma develop LPTS

- 15% of TBI patients with no subdural haematoma develop LPTS

  The difference in rates between these groups was statistically significant ($p < 0.001$).

- Other risk factors reported are at least one non-reactive pupil, depressed skull fracture that is not surgically elevated, dural penetration by injury but not by surgery and parietal contusion on CT scan which have seizure-incidence rate that is >400 times of that expected in the general population.

Comments & Conclusions

Recruited patients were part of a randomised controlled trial, therefore case and outcome ascertainment is assumed to be good. The major limitations to this study are that only high-risk patients were included and there is not enough demographic data from the trial reports[23,24] to judge whether the study population is representative of the UK population. The result is most useful for estimating the risk of LPTS in high-risk TBI patients with severe injuries who were conservatively managed.

Study 2 - DeSantis et al[21]

Design

DeSantis and colleagues[21] retrospectively followed up three groups of patients admitted to a tertiary neurosurgical centre in Italy.

Main Findings

Group 1: 4831 adult patients admitted to the neurosurgical unit of University of Milan between 1971 and 1981 were studied. None of these had CT scan done. 129 patients (2.7%) developed early seizures, 85 were discharged from hospital and 52 of these discharged patients with EPTS were followed up (mean follow-up period – 5.6 years). 17 of the 52 patients were surgically treated and 35 were conservatively treated. Based on the data from the 52 patients with early seizures;

- Overall incidence of LPTS = 23%
- Incidence of LPTS among surgically treated patients = 53%
- Incidence of LPTS among non-surgically treated patients = 8.5%
- 75% of patients with LPTS had focal brain lesion requiring surgery

Group 2: 1420 adult patients admitted to the same unit between 1984 and 1989 were studied. All these patients had CT scan performed on them. 41 patients (2.9%) developed early seizures, 36 were discharged from hospital and 32 of these discharged patients with early PTS were followed up (range 1-4years). Based on the data from these 32 patients with early seizures;

- Overall incidence of LPTS = 9.4% (3 of 32) and all three patients had a CT documented focal brain lesion

Group 3: 3302 head-injured children (age 2 months to 14 years) admitted to the same unit between 1965 and 1981 were studied. Some of these patients had CT scan performed on them. 165 patients (5%) developed early seizures, 85 of these were followed up (range 1-14years, mean = 5 years). Based on the data from these 85 patients with early seizures;

- Overall incidence of LPTS in children with early PTS =20%. Interestingly, only 40% of LPTS in children was associated with a documented focal brain lesion and 60% of children with early PTS who later developed LPTS had no definite brain lesion and in many of them the head injury had been trivial - a finding comparable to Jennett's.[7]

In a sub-analysis of the data from 98 patients in this study with CT documented focal intracranial lesions, there was an overall LPTS incidence of 12.2% (12 out of 98). Seizures developed in 28% of these patients with large brain contusions, only in 6% of patients with small brain contusions treated conservatively and in 4.7% of those with purely extracerebral collections.

Comments & Conclusions

The study is biased towards hospitalised patients, had no comparison group and the follow-up was selective. It is possible that the patients followed-up could be systematically different from those that were not and therefore the results cannot be generalised. It was also unclear whether known epileptics or patients with other CNS condition or sequelae which could predispose the patients to seizures were excluded or not. The result of this study supports the evidence that brain lesions that are managed conservatively carry a lower risk of LPTS compared to those requiring surgery.

Study 3 - Englander et al[14]

Design

This large multi-centre prospective cohort study by Englander and colleagues[14] followed 647 individuals (age ≥16 years) admitted into four urban trauma centres in the USA. Patients were followed up for 24 months or until death, first episode of LPTS (i.e. seizure ≥8 days post injury) or placement on antiepileptic drugs for more than one month.

Subjects included in the study must exhibit at least one of the following inclusion criteria on a CT scan done during the first 7 days of the injury: intracerebral contusions, punctate haemorrhages, subarachnoid, intraventricular, intraparenchymal, subdural or epidural haemorrhage, depressed skull fracture with dural penetration or dural penetration by metallic fragments.

Main Findings

- Over the 24-month follow-up period, the cumulative likelihood of developing LPTS is 28% among patients with subdural haematoma managed surgically compared to 15% in conservatively managed patients. Similarly, bilateral contusions carry twice the probability of developing LPTS as compared to unilateral contusions over the same period; 33% vs. 16%.
- The study also suggests that multiple contusions increase the risk of LPTS especially when located in the parietal region (a finding previously reported by Temkin above[18]). Patients with bilateral parietal contusions have the highest probability of developing LPTS; cumulative likelihood of 66% over the 2-year period.
- Within 18 months, 92.4% of patients developing LPTS in this study have had their first late seizure. A detailed summary of the results from this study is presented in table 4 below.

Other prognostic factors include EPTS, ventriculostomy, and surgical evacuation of subdural haematomas. It appears that non-contusional haemorrhages, evacuation of epidural haematomas, débridement of cortical contusions and surgical elevation of depressed skull fracture do not appear to increase the risk of LPTS.

Comments & Conclusions

Overall, this is a well-designed cohort study with standardised exposure and outcome ascertainment protocol across the four study sites. Subjects came from diverse ethnic backgrounds and suffered a wide range of TBI. For each risk factor studied, sub-groups without the risk factor among the study subjects were used for internal comparison. The findings from this study are probably most useful when considering short-term risks of LPTS among severely injured hospitalised patients. The major limitations of this study are high selectivity for severely injured and a relatively short follow-up period.

Table 4: Summary of relevant results from Englander & Colleagues (2003)

<table>
<tr><td>24-month cumulative likelihood of LPTS</td><td>Overall = 13.8%
<u>Ventriculostomy</u>
No ventriculostomy = 12.6%
Ventriculostomy = 24.6% (significant difference p = 0.0065)

<u>Subdural haematoma</u>
Surgically managed = 27.8%
Conservatively managed = 15.3% (significant difference p = 0.0008)

<u>Subcortical Contusions</u>
With unilateral subcortical contusion irrespective of location = 15.5%
With bilateral contusion irrespective of location = 33.4%

<u>Cortical Contusions</u>
With any multiple contusions = 25.2%
With any single contusion = 8.2%
With unilateral contusion irrespective of location = 13.6%
With bilateral contusion irrespective of location = 25.4%

<table><tr><th>LOCATION/TYPE</th><th>Unilateral</th><th>Bilateral</th></tr><tr><td>Frontal</td><td>20.1%</td><td>25.6%</td></tr><tr><td>Temporal</td><td>15.9%</td><td>31.2%</td></tr><tr><td>Parietal</td><td>19.1%</td><td>66%</td></tr></table></td></tr>
<tr><td>Time elapsed since injury to first seizure</td><td>92.4% of LPTS occurred between 8days and 18 months post-TBI</td></tr>
<tr><td>Clinical Features</td><td>79% had generalised seizures and 21% had focal seizures</td></tr>
<tr><td>Prognostic Factors</td><td>1. Early PTS (2.4 fold increase; p 0.0019)
2. Multiple contusion (4.97 fold increase compared to no contusion; p<0.001)
3. Single contusion (1.38 fold increase compared to no contusion; p<0.001)
4. Surgical management of subdural haematoma but the difference noted between surgically and conservatively managed epidural haematoma did not reach statistical significance</td></tr>
<tr><td>Other findings</td><td>1. Débridement of cortical contusions and surgical elevation of depressed skull fractures do not appear to increase risk of LPTS over the 24-month period
2. Presence of punctate, subarachnoid or intraventricular haemorrhages does not appear to increase the risk of LPTS over the 24-month period
3. Risk of LPTS with dural penetration is high but dural penetration by bone alone does not appear to increase the risk of LPTS</td></tr>
</table>

5.4 Overall summary of results

The estimates of the incidence and cumulative risk of LPTS summarised in this report should be interpreted with caution. The evidence is constrained by the significant differences in the quality and methodology of identified studies. From available literature it not possible to estimate with certainty the magnitude of the risk of developing LPTS after a head injury and the length of time during which the risk persists. Data specific to the risk of LPTS in patients with CT and/or MRI scan documented evidence of brain injury are limited and where available are often not useful for comparisons of risks between surgically and non-surgically treated patients.

Incidence of LPTS after TBI

TBI is an accepted cause of PTS and many studies have attempted to estimate the overall incidence of LPTS after TBI. Reported incidence ranges from 1% in mild uncomplicated injuries to 53% among surgically treated hospitalised TBI with a diagnosis of EPTS. A population-based prospective study of relatively good quality reported an overall incidence rate of 2% of LPTS.

It is possible to conclude that the incidence rate of LPTS among TBI patients is determined by injury severity and is affected by factors such as dural penetration, skull fracture, the presence of EPTS and prolonged post-traumatic amnesia. For example, in a selected case series, Jennett & Lewin reported an incidence of rate of ~29% in patients with EPTS compared to 8% in patients without. This increased risk associated with EPTS is reported by almost all of the other studies reviewed. However, Annegers and colleagues reported that after adjusting for other risk factors the effect of EPTS on increased risk seems to disappear.

The introduction of neuroimaging techniques – CT and MRI scans and the evidence from more recent studies of PTS have called into question the predictive value of clinical categorisation of TBI previously used to estimate the risk of LPTS. A recent prospective study[14] of relative good quality among hospitalised, severely injured patients reported that 24-months cumulative probability of LPTS is 28% for patients with surgically treated subdural haematoma and 15% for conservatively managed patients. Additionally, bilateral contusions carry a 33% probability compared to 16% for unilateral contusions. Parietal contusions especially bilateral ones carry the highest probability of LPTS at 66% cumulative likelihood over a 24-month period.

With the exception of the incidence rate reported from the large population study by Annegers & Colleagues, incidence data obtained in this report come from highly selective rehabilitation or hospitalised patients already considered at high risk of developing LPTS and is therefore not generally representative of all TBI patients with mild to moderate injuries.

Magnitude and duration of increased risk of LPTS after TBI compared to the general population

The best information about the magnitude of increase in the risk of LPTS following TBI comes from the large population cohort study by Annegers & colleagues. Risk of developing seizures can be multiplied from 3-fold to 95-fold in the first year following TBI depending on severity. It is possible that the increased risk of developing LPTS after TBI can persist for up to 30 years in severely injured patients as reported by

Annegers and colleagues[8] and another case-control study[17] with a long follow-up period which reported 12.3% of the study population having first LPTS between 10-30 years after TBI.

The large population-based study by Annegers which is of relatively good methodologically quality (limited mainly by total reliance on clinical categorisation of TBI), reports that the increased risk of LPTS in mildly injured patients is 3 times that of the general population in the first year following TBI and falls to the level of that of the general population by the 5th year.

For moderate injuries, risk of LPTS is increased by up to six-fold compared to the general population in the first year and remains at about three times that of the general population until the 10th year after TBI from when it begins to fall to the level of the general population. With severe injuries the risk is increased 95-fold in the first year and remains high at about 12-16 times that of the general population up to the 10th year. Even after 10 years the risk of LPTS developing in these patients is up to four times that of the general population.

Latency of LPTS after TBI

Despite the potential of persistent risk of LPTS over a 30-year period after severe TBI, it can be estimated that between 68% and 93% of patients with TBI prone to LPTS would have had their first late seizure within two years following the injury. The main problem is that it is difficult to know whether this two-year risk period is the same for mildly to moderately injured patients or not.

Clinical picture of LPTS following TBI

It appears that most cases of LPTS will develop generalised seizures and even when they have focal seizures still show some generalised involvement. Jennett & Lewin[7] reported a 10:6 ratio for generalised compared to focal seizures. Many of the studies report that 75% of patients with LPTS following TBI develop recurrent seizures.

Age and risk of LPTS following TBI

Most of the studies reviewed reported an increased risk of EPTS in children especially those younger than eight years, this elevated risk of EPTS predisposes children to LPTS. The study by Annegers and colleagues was the only one to report no discernible increased risk of LPTS in children despite the presence of EPTS. The authors did mention that their analysis and interpretation of data about the relationship between EPTS and risk of LPTS was rudimentary.

5.5 Limitations of this report

This is not an exhaustive systematic review but a rapid assessment for relevant literature. Although the search strategies were broad and comprehensive for both systematic reviews and primary studies, the searches for the latter were restricted to observational studies reporting outcomes related to post-traumatic seizures. To increase sensitivity, the reference lists of relevant articles were scanned for further studies.

A large cohort study with long-term follow-up and analyses adjusted for possible confounders is needed to reliably determine prognostic factors, increased risk of LPTS as compared to unaffected population and lifetime risk of LPTS. Such a study was not found, we have therefore reported on cohort studies of highly selective cases and other observational studies of inadequate quality with several confounders. These types of studies may not offer very reliable findings.

6 Conclusion

The evidence available from primary studies about the lifetime risk of post-traumatic seizures is poor and confusing. Most of the observational studies identified have significant methodological flaws and limited representativeness. Confounding, selection bias, and variable length of follow-up period make it impossible to determine reliably the incidence, lifetime risk, and prognostic factors of LPTS in head-injured patients.

The evidence found during this review shows that the risk of LPTS is associated with various prognostic factors including early seizures, focal brain lesions, extensive contusions especially bilateral ones and those located in the parietal region. Dural penetration and neurosurgical interventions especially repeated surgeries also increase the risk of late seizures. Most patients with the propensity to develop PTS would have had their first seizure within two years of being injured. These seizures can persist for a protracted period of time especially when the injury is severe.

It has been particularly difficult to estimate with certainty the risk of seizures in conservatively managed patients with evidence of brain damage on CT/MRI scan because of the limited number of studies specific to this group of patients. The need for well-designed multi-centre longitudinal studies has been reiterated by many authors. The significant socio-economic and public health implications of LPTS justify such a study.

7 References

1. Tamietto M, Torrini G, Adenzato M, et al. To drive or not to drive (after TBI)? A review of the literature and its implications for rehabilitation and future research. NeuroRehabilitation. 2006; 21: 81-92

2. British Society of Rehabilitation Medicine. Rehabilitation after traumatic brain injury. London: BSRM, 1998.

3. Tennant A. Admission to hospital following head injury in England: Incidence and socio-economic associations. BMC Public Health. 2005; 5:21

4. Annegers JF, Rocca WA, Hauser WA. Causes of epilepsy: Contributions of the Rochester Epidemiology Project. Mayo Clinic Proceedings. 1996; 71: 570-575

5. Hawley CA. Return to driving after head injury. J. Neurol. Neurosurg. Psychiatry. 2001; 70: 761-766

6. Brooks N, Hawley CA. Return to driving after traumatic brain injury: a British perspective. Brain Injury. 2005; 19: 165-175

7. Jennet WB, Lewin W. Traumatic Epliepsy After Closed Head Injuries. J. Neurol. Neurosurg. Psychiatry. 1960; 23: 295-301

8. Annegers JF, Grabow JD, Groover RV et al. Seizures after head trauma: A population study. Neurology. 1980; 30: 683-689

9. Caveness, WF: Onset and cessation of fits following cerebral trauma. J. Neurosurg. 1963; 20: 570-583

10. Deymeer F, Leviton A. Posttraumatic seizures: an assessment of the epidemiologic literature. Central Nervous System Trauma. 1985; 2:33-43

11. Kuhl DA, Boucher BA, Muhlbauer MS. Prophylaxis of posttraumatic seizures. DICP. 1990; 24: 277-285

12. Frey LC. Epidemiology of Posttraumatic Epilepsy. Epilepsia. 2003; 44(Suppl. 10): 11-17

13. Garga N, Lowenstein DH. Posttraumatic Epilepsy: A Major Problem in Desperate Need of Major Advances. Epilepsy Currents. 2006; 6:1-5

14. Englander J, Bushnik T, Duong TT, et al. Analyzing risk factors for late posttraumatic seizures: A prospective, multicenter investigation. Archives of Physical Medicine & Rehabilitation. 2003; 84(SUPPL. 1): 365-373

15. Clifton GL. Comment. Central Nervous System Trauma. 1985; 2:43. Deymeer F, Leviton A. Posttraumatic seizures: an assessment of the epidemiologic literature. Central Nervous System Trauma. 1985; 2:33-42

16. Annegers JF, Hauser AW, Coan SP et al. A population-based study of seizures after traumatic brain injuries. NEJM 1998; 338(1):20-24

17. Pohlmann-Eden B, Bruckmeir J. Predictors and dynamics of posttraumatic epilepsy. Acta Neurologica Scandinavica. 1997; 95: 257-262

18. Temkin NR. Risk Factors for Posttraumatic Seizures in Adults. Epilepsia. 2003; 44(s 10):18-20

19. D'Alessandro R, Tinuper P, Ferrara R, et al. CT scan prediction of late post-traumatic epilepsy Journal of Neurology, Neurosurgery, and Psychiatry, 1982; 45: 1153-1155

20. Jennet, W.B. (1973). Epilepsy after non-missile head injuries. Scot. Med. J. 18, 8-13

21. De Santis A. Sganzerla E. Spagnoli D. Bello L. Tiberio F. Risk factors for late posttraumatic epilepsy. Acta Neurochirurgica - Supplementum. 1992;55:64-7

22. Asikainen I, Kaste M, Sarna S. Early and late posttraumatic seizures in traumatic brain injury rehabilitation patients: Brain injury factors causing late seizures and influence of seizures on long-term outcome. Epilepsia. 1999; 40: 584-589

23. Temkin NR, Dikmen SS, Wilensky AJ et al. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. New England Journal of Medicine. 1990; 323: 497-502

24. Temkin NR. Dikmen SS. Anderson GD, et al. Valproate therapy for prevention of posttraumatic seizures: a randomized trial. Journal of Neurosurgery. 1991; 91: 593-600

8 Appendices

8.1 Appendix 1 – Details of Request

ARIF REQUEST FORM

Date of Request	4 / 4 / 2007
Lead Medical Adviser Issuing request	Name – Dr Judith Morgan Secretary to the Neurology Panel
Contact details	Drivers Medical Group DVLA Sandringham Park Swansea Vale Llansamlet Swansea SA7 OAA [redacted]

1. Without worrying about the structure of the question, state in full the nature and context of the problem.

We need to know the risk of seizure, blackout or sudden and disabling event(s) if there is evidence on MRI or CT scanning of soft tissue damage. We need to know the risk associated with contusions, bi-lateral contusions and blood in the ventricles, for example, particularly if such conditions are treated conservatively.

2. Please give a background to the question. Why has DMG raised this problem?

At present, most head injury advice is related to x-ray and operative procedures; e.g. in cases of fractured skull, trauma to dura or when brain surgery after an accident occurs. There is little guidance when such injuries are managed conservatively, but have been shown to have intra-cranial damage on CT or MRI scans.

3. Giving references where appropriate, briefly detail the sources you have used to obtain background information on the *options* and *issues*, which might be important for the problems, you describe.

At a Glance Guide to the current Medical Standards of Fitness to Drive, February 2007.
Chapter 1 Neurological Disorders.

4. Please give name and contact details of any expert or clinical contact e.g. relevant Panel Chairman/expert Panel member.

Mr R S C Kerr
BSc MS FRCS
Consultant Neurosurgeon
Department of Neurology
Level 3, West Wing
John Radcliffe Hospital
Headley Way
Headington
Oxford OX3 9DU

[redacted]

5. What is the nature of the target population of the issue detailed above? E.g. age, profile, vocational drivers, young drivers, other co-morbid features.

Group 1 and Group 2 drivers of all ages.

6. What are the outcomes you consider particularly important in relation to the question posed? What decisions rest on these outcomes?

We wish to determine whether a driving licence can be maintained or revoked based on the evidence of the risk of a sudden and disabling event such as seizure occurring, related to the MRI/CT findings.

What is the latest date that an ARIF response would be of value 29 / 06 / 07

Please either:

Fax this form to: 0121 414 7878 marking FAO ARIF

E-mail as a word document or pdf attachment to: [redacted]

Post to:-
Dr David Moore
Senior Research Reviewer and Analyst
Aggressive Research Intelligence Facility
West Midlands Health Technology Assessment Collaboration
Department of Public Health
University of Birmingham
Edgbaston
Birmingham
B15 2TT

Please ring 0121 414 3166 or 6767 if you have any queries, or you want to check the progress with your request.

8.2 Appendix 2 – Outline methods

1. The report will focus on evaluating the lifetime risk of posttraumatic seizures in people with evidence of brain damage following a traumatic brain injury.

    a. The literature review will include relevant studies on both the incidence and prevalence of all types of seizures (e.g. petit mal and grand mal) in populations with a history of all types of head injuries (closed and open injuries including skull fractures) and all types of brain injuries including dura tears, haematomas, & haemorrhages.
    b. No age limit will be set for the affected population (there will however be an emphasis on adults very near or within the age bracket of the driving population i.e. 14 years and above). It is likely that many of the studies available would have focussed on paediatric populations, such studies will be assessed for relevance based on the length of follow-up and reported outcomes.
    c. The review will **exclude** syncope, and other cardiovascular events following traumatic head injuries
    d. The review will **exclude** posttraumatic events consequent of ventriculo-peritoneal shunts (as these are generally covered under a different regulation)
    e. The review will **not** necessarily exclude studies where there is no confirmation of brain damage on MRI or CT scan

2. A comprehensive literature search will be conducted including the following databases MEDLINE (1950-2007) and EMBASE (1980-2007). Furthermore, sources of statistical information regarding head injuries in the UK will also be searched e.g. Hospital Episode Statistics (HES) and Transport Research Laboratory.

3. Cohort studies of relevant population from the literature search with reports of relevant outcomes will be selectively reviewed and critically appraised. Other study types including case series, cross-sectional studies, and case-control studies will be included as appropriate based on the volume of relevant and robustly designed studies focusing on inception cohorts (which would be an ideal study type to answer the question in the request).

4. Data on relevant outcomes will be extracted and interpreted wherever possible.

5. The volume of studies and their methodological quality will be commented upon. Comments regarding the need for long-term prospective studies and/or head injury database based on knowledge garnered from the literature review may be included in the report if appropriate.

8.3 Appendix 3 – Search strategies

8.3.1 ARIF Reviews Protocol

SEARCH PROTOCOL FOR ARIF ENQUIRIES

(June 2007)

In the first instance the focus of ARIF's response to requests is to identify systematic reviews of research. The following will generally be searched, with the addition of any specialist sources as appropriate to the request.

1. Cochrane Library

- Cochrane Reviews
- Database of Abstracts of Reviews of Effects (DARE)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Health Technology Assessment (HTA) database

2. ARIF Database

An in-house database of reviews compiled by scanning current journals and appropriate WWW sites. Many reviews produced by the organisations listed below are included.

3. NHS CRD

- DARE
- Health Technology Assessment Database
- Completed and ongoing CRD reviews

4. Health Technology Assessments

- NICE guidance (all programmes)
- Evidence Based Commissioning Collaboration (Trent R & D Support Unit). Links to Trent Purchasing Consortia reports and Wessex DEC reports (both no longer published)
- SBU – Swedish Council on Technology Assessment in Health Care
- NHS Coordinating Centre for Health Technology Assessments
- Canadian Agency for Drugs and Technologies in Health
- New Zealand Health Technology Assessment
- STEER Reports (no longer published)
- Agency for Healthcare Research and Quality (AHRQ)
- Alberta Heritage Foundation
- McGill Medicine Technology Assessment Unit of MUHC (McGill University Health Centre)
- Monash reports – Centre for Clinical Effectiveness, Monash University
- US Department of Veterans Affairs
- NHS QIS (Quality Improvement Scotland)
- SIGN (Scottish Intercollegiate Guidelines Network)

5. Clinical Evidence

6. Bandolier

7. National Horizon Scanning Centre

8. TRIP Database

9. Bibliographic Databases

- Medline – systematic reviews
- Embase – systematic reviews
- Other specialist databases

10. Contacts

- Cochrane Collaboration (via Cochrane Library)
- Regional experts, especially Pharmacy Prescribing Unit, Keele University (& MTRAC) and West Midlands Drug Information Service for any enquiry involving drug products.

8.3.2 Primary studies protocol

Database: Cochrane Library (Wiley) 2007 Issue 2
Search Strategy:

#1 soft next tissue
#2 contusion*
#3 blood near ventricle*
#4 head near injur*
#5 (#1 OR #2 OR #3 OR #4)
#6 seizure*
#7 blackout*
#8 disabling
#9 sudden
#10 syncope
#11 conscious*
#12 (#6 OR #7 OR #8 OR #9 OR #10 OR #11)
#13 (#5 AND #12)
#14 risk
#15 (#13 AND #14)

Database: Ovid MEDLINE(R) 1950 to May Week 1 2007
Search Strategy 1:

1 brain injur$.mp.
2 head injur$.mp.
3 exp Brain Injuries/
4 exp Craniocerebral Trauma/
5 soft tissue.mp.
6 (blood adj2 ventricle$).mp
7 exp Contusions/
8 (post adj concussive).mp.
9 (post adj traumatic).mp.
10 exp Seizures/ or seizure$.mp.
11 blackout$.mp.
12 disabling.mp.
13 exp Syncope/ or syncope.mp.
14 sudden.mp.
15 conscious$.mp.
16 faint$.mp.
17 or/10-16
18 exp Cohort Studies/ or cohort.mp.
19 exp Follow-Up Studies/ or follow-up.mp.
20 or/18-19

21 risk.mp. or exp Risk/
22 or/1-9
23 22 and 17
24 21 and 17 and 22 and 20
25 17 and 22 and 21
26 25 and 20

Database: Ovid MEDLINE(R) 1950 to May Week 1 2007
Search Strategy 2:

1 brain injur$.mp.
2 head injur$.mp.
3 exp Brain Injuries/
4 exp Craniocerebral Trauma/
5 soft tissue.mp.
6 (blood adj2 ventricle$).mp.
7 exp Contusions/
8 (post adj concussive).mp.
9 (post adj traumatic).mp.
10 exp Seizures/ or seizure$.mp.
11 blackout$.mp.
12 disabling.mp.
13 exp Syncope/ or syncope.mp.
14 sudden.mp.
15 conscious$.mp.
16 faint$.mp.
17 or/10-16
18 risk.mp. or exp Risk/
19 or/1-9
20 17 and 18 and 19

Database: Ovid MEDLINE(R) 1950 to May Week 1 2007
Search Strategy 3:

1 ct.mp.
2 mri.mp.
3 1 or 2
4 ((head or brain) adj injur$).mp.
5 3 and 4
6 exp Follow-Up Studies/ or follow-up.mp.
7 outcome$.mp.
8 exp Cohort Studies/ or cohort$.mp.
9 7 or 8
10 5 and 9
11 5 and 7
12 4 and 9
13 brain.ti.
14 head.ti.
15 13 or 14
16 follow.ti.
17 outcome$.ti.
18 16 or 17
19 15 and 17
20 3 and 19
21 seizure$.mp.
22 19 and 21
23 20 and 21
24 22 or 23

Database: EMBASE 1980 to 2007 Week 19
Search Strategy:

1 brain injur$.mp.

2 exp Brain Injury/
3 exp Head Injury/
4 head injur$.mp.
5 or/1-4
6 seizure$.mp. or exp SEIZURE/
7 syncope.mp. or exp SYNCOPE/
8 or/6-7
9 follow-up.mp. or exp Follow Up/
10 exp COHORT ANALYSIS/ or cohort$.mp.
11 or/9-10
12 risk.mp. or exp RISK/
13 likelihood.mp.
14 occurrence.mp.
15 or/12-14
16 5 and 8 and 11 and 15
17 limit 16 to human

Other databases/sites searched (9-10/5/2007):

AHRQ
CADTH
DACEHTA
HAS
NZHTA
SBU
Merck Manual
Clinical Evidence
NICE
NCCHTA
Attract
CRD
TRIP
National Guidelines ClearingHouse
HES Online

General internet searches:

TRIS Online (National Transportation Library)
TRL (Tranportation Research Laboratory)
UNESCO
Highways Agency
CARE Europe
DVLA
US Driving Assessment Symposia
Monash University Accident Research Centre
NHTSA (National Highway Traffic Safety Association)
LTSA NZ
Driving Assessment 2001, 2003 and 2005 International Driving Symposia on Human Factors in Driver Assessment, Training and Vehicle Design Various locations

Search terms used: brain injury, head injury, trauma, soft tissue, post traumatic; seizure, blackout , syncope, fainting, driving , drivers

[1] Tamietto 2006
[2] BSRM 1998
[3] Tennant 2005
[4] Annegers 1996 Mayo Clinic
[5] Hawley2001
[6] Brooks & Hawley 2005
[7] Jennett & Lewin 1960 JNNP
[8] Annegers, Grabow, Groover, et al. 1980 Neurology
[9] Caveness 1963 J Neurosurg.
[10] Deymeer 1985
[11] Kuhl 1990
[12] Frey 2003
[13] Garga 2006
[14] Englander, Bushnik, Duong et al. 2003
[15] Clifton 1985 CNS Trauma comment
[16] Annegers et al. 1998 NEJM
[17] Pohlmann-Eden & Bruckmeir 1997
[18] Temkin 2003 Epilepsia
[19] D'Alessandro, Tinuper, Ferrara, et al. 1982 JNNP
[20] Jennett 1973 Scot Med. Journal
[21] DeSantis et al. 1992 Acta Neurochir
[22] Asikainen et al
[23] Temkin et al. 1990 NEJM
[24] Temkin et al 1999 J. Neurosurg.