Institution: University of Cambridge		
Unit of Assessment: UoA 4		
Title of case study: Reshaping the treatment of traumatic brain injury		
Period when the underpinning research was undertaken: 2000 - present		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Professor Peter Hutchinson	Professor of Neurosurgery	Jan 2003 – present
Professor David Menon	Professor of Anaesthesia	Sep 2000 – present
Period when the claimed impact occurred: 2014 - present		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact (indicative maximum 100 words)

Resulting mainly from transport accidents, falls, assaults and sports-related injuries, traumatic brain injury (TBI) comprises a complex range of brain damage. Outcomes differ greatly between patients, and with the full heterogenous range of head injuries, it has been extremely difficult to improve outcomes by linking particular characteristics to optimum treatments. Multidisciplinary Cambridge University research has developed new therapies and combined novel monitoring and advanced imaging tools to guide patient care. The discoveries have also resulted in changes to clinical guidelines, routine practice, clinical training and public understanding of TBI. Ultimately, they have improved the management and health outcomes of patients with TBI, worldwide.

2. Underpinning research (indicative maximum 500 words)

As the most common cause of death under the age of 40 in high-income countries, TBI causes a million deaths each year globally [1]. The outcome from TBI is highly variable, but approximately 50% of patients who are admitted to an Intensive Care Unit (ICU) with TBI do not survive or are left severely disabled [1].

TBI combines the primary injury of the initial impact with secondary injuries including hypoxia (tissue oxygen deprivation) and hypotension (low blood pressure). The brain swells within the tight confines of the skull leading to a hitherto poorly-understood vicious cycle of raised intracranial pressure, reduced cerebral blood flow, compromised cerebral oxygenation, energy failure, cell death and further swelling. The interventions used to manage these physiological insults include hazardous medical therapies (induced coma) and operative interventions. The complexity of TBI has meant that it is difficult to determine the benefits of these treatments in populations of patients, or balance their risk and benefits in individual patients.

University of Cambridge researchers have led international, multidisciplinary efforts to characterise these problems and identify global strategies to address them. Under the leadership of Hutchinson and Menon, the researchers have developed innovative therapies [2-4] and identified novel monitoring tools [5-6]; all of which target the management of intracranial pressure, thus breaking the vicious cycle of brain swelling. Significantly, in 2017 Hutchinson and Menon established the NIHR Global Health Research Group on Neurotrauma which brings together researchers from 11 low and middle income countries (LMICs) and three high-income countries to improve the management and outcome of TBI in resource-limited settings [2, 4], in addition to a large study of outcome in over 50 countries.

New therapies: decompressive craniectomy

Cambridge University researchers have led international studies to assess novel treatments for TBI, and specifically, decompressive craniectomy (removal of a section of the skull to reduce intracranial pressure) [2]. Between 2004 and 2014 they led the **RESCUEicp** trial, involving 408 patients from 50 countries, to establish a robust evidence base on which to evaluate patient outcomes [3]. The trial determined the success of decompressive craniectomy when medical management measures had failed to control intracranial pressure. Decompressive craniectomy was shown to reduce mortality when compared against standard medical treatment, with a

spectrum of outcome in the survivors and an improvement in outcome between six months and 12 months.

New therapies: development of 3D titanium plates for skull reconstruction
Decompressive craniectomy requires subsequent repair with either the patient's bone or a synthetic plate. As hosts of the NIHR Medtech Brain Injury Co-operative, Hutchinson and the Cambridge team have continued to develop new technologies via collaboration with other academic institutions, industry, patients and the public. Through these collaborations, the team pioneered the development of individually-tailored 3D-printed titanium plates for skull reconstruction, and designed special software that uses CT data of the patient's skull to ensure a precise fit. The plates are made from 3D virtual models using an additive manufacturing (3D printing) process called laser sintering, then finished to a smooth texture. The team has obtained preliminary data showing that skull reconstruction can be performed safely within three months of the initial decompressive craniectomy surgery [4]. The technology offers the benefit of being lower cost, reduced operating time, a good aesthetic result, and good biocompatibility, especially for complex craniofacial reconstruction.

Novel monitoring tools: biochemical monitoring and advanced imaging
In parallel with the development of innovative therapies, the researchers have established protocols which integrate and display advanced monitoring technologies to predict outcomes and deliver individualised treatments. In 2004, the team launched intensive care monitoring software, ICM+. Since its launch, the researchers have continued to develop new applications for more precise monitoring of intracranial pressure and cerebrovascular reactivity (the change in cerebral blood flow in response to therapeutics designed to increase or decrease blood pressure and heart rate) [5]. In a study of 601 adult TBI patients, the combination of these dynamic monitoring variables and their time profile improved prediction of outcome [5]. These studies have been underpinned by data from high-field magnetic resonance imaging (MRI) and positron emission tomography (PET), [6] which have informed clinical protocol development.

The team has also pioneered cerebral microdialysis (continuous sampling of the brain's extracellular fluid for analysis of brain tissue biochemistry) to monitor cerebral metabolism and inflammation in real-time [7]. In a study of 223 adult TBI patients, the researchers demonstrated that extracellular metabolic biomarkers are independently associated with outcome following traumatic brain injury [7].

This research programme represents the efforts of numerous individuals, in particular: Dr Rowan Burnstein, Dr Keri Carpenter, Dr Jon Coles, Professor Marek Czosnyka, Dr Ari Ercole, Mr Adel Helmy, Mr Alexis Joannides, Mr Angelos Kolias, Dr Virginia Newcombe, Dr Peter Smielewski, Dr Emmauel Stamatakis, Mrs Carole Turner.

3. References to the research (indicative maximum of six references)

1. Lawrence T, Helmy A, Bouamra O, Woodford M, Lecky F, Hutchinson P. Traumatic brain injury in England and Wales: prospective audit of epidemiology, complications and standardised mortality. *BMJ Open*, 2016; 6(11): e012197. DOI: 10.1136/bmjopen-2016-012197 *
2. Maas AIR; Menon, DK, […], Czosnyka, M, Newcombe, V, […], Wilson, L., Yaffe, K., InTBIR Participants and Investigators. Traumatic brain injury: Integrated approaches to improve prevention, clinical care, and research. *The Lancet Neurology* 2017; 16(12): 987-1048. DOI: 10.1016/S1474-4422(17)30371-X *
3. Hutchinson PJ, Kolias AG, Timofeev IS, Corteen EA, Czosnyka M, […], Kirkpatrick PJ, RESCUEicp Trial Collaborators . Trial of decompressive craniectomy for traumatic intracranial hypertension. *The New England Journal of Medicine* 2016; 375(12): 1119-1130. DOI: 10.1056/NEJMoa1605215 *
4. Bjornson A , Tajsic T, Kolias AG, Adam Wells A, Naushahi MJ, 1 , Fahim Anwar, Helmy A, Timofeev I, Peter J Hutchinson PJ A case series of early and late cranioplasty-comparison of surgical outcomes. *Acta Neurochirurgica* 2019; 161(3): 467–472. DOI: 10.1007%2Fs00701-019-03820-9 *

5. Adams H, Donnelly J, Czosnyka M, Kolias AG, Helmy A, Menon DK, Smielewski P, Hutchinson PJ. Temporal profile of intracranial pressure and cerebrovascular reactivity in severe traumatic brain injury and association with fatal outcome: An observational study. *PLoS Med.* 2017;14(7):e1002353. DOI: 10.1371/journal.pmed.1002353. *
6. Launey Y, Fryer TD, Hong YT, Steiner LA, Nortje J, Veenith TV, Hutchinson PJ, Ercole A, Gupta AK, Aigbirhio FI, Pickard JD, Coles JP, Menon DK. Spatial and Temporal Pattern of Ischemia and Abnormal Vascular Function Following Traumatic Brain Injury. JAMA Neurol. 2020 Mar 1;77(3):339-349. DOI: 10.1001/jamaneurol.2019.3854.*
7. Timofeev I, Carpenter KL, Nortje J, Al-Rawi PG, O'Connell MT, Czosnyka M, Smielewski P, Pickard JD, Menon DK, Kirkpatrick PJ, Gupta AK, Hutchinson PJ. Cerebral extracellular chemistry and outcome following traumatic brain injury: a microdialysis study of 223 patients. *Brain.* 2011; 134(2):484–94. DOI: 10.1093/brain/awq353. *

Evidence of min 2* quality: *these publications have been peer reviewed; research underpinned by competitively awarded funding.

Competitive funding receivedEuropean Union-funded Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) Project, EUR30 million
NIHR Global Health Research Group on Neurotrauma, GBP1.78 million

4. Details of the impact (indicative maximum 750 words)

Impact on management and outcomes of patients with TBI worldwide

Hutchinson and Menon have led and participated in a number of collaborations, which have contributed to reducing the likelihood of dying from brain injury in the UK [A]. Specifically, decompressive craniectomy[3] is now used routinely in the UK and has saved 22 additional lives out of 100, with 60% of survivors independent at home [A]. The President of the World Federation of Neurosurgical Societies explained that "*decompressive craniectomy [which] is routinely performed and listed as a treatment in the guidelines […] leads to a marked reduction in mortality (from 52-30% at 12 months) and categorised the outcome in survivors (43% upper severe disability or better, 30% lower severe disability or worse)"* [B].

Through collaboration with colleagues and partners in LMICs, Cambridge University research has also improved TBI management in resource-limited settings. Professor of Neurosurgery at the University of Cape Town and past-President of the International Neurotrauma Society, stated that the NIHR Global Research Group "*has stood out as the one [neuro-trauma initiative] with the greatest impact across the widest economic and geographic range."* Furthermore, he noted that Cambridge research is "*helping us raise the profile of traumatic brain injury in Africa and implement policy change"* through collaborations on a number of research studies related to improving TBI management and outcome and through establishing global registries [C].

Impact on clinical guidelines

Cambridge research findings have contributed to new protocols for the management of patients in neuro-intensive care, especially the management of raised intracranial pressure. These have included multinational consensus statements and international guidelines as follows:

- Facilitated by the NIHR Global Health Research Group, Hutchinson led the 2019 '*Consensus statement from the International Consensus Meeting on the Role of Decompressive Craniectomy in the Management of Traumatic Brain Injury'* [D]. The Consensus Statement settled debate among the clinical and research communities through providing general guidance on decompressive craniectomy.
- Hutchinson led the 2015 '*Consensus statement from the 2014 International Microdialysis Forum'* [D], which paved the way for improved neurocritical care protocols for patients with raised intracranial pressure and for further individualised patient therapies [6].
- Menon co-chaired and Hutchinson contributed to the 2017 *Lancet Neurology Commission on Traumatic Brain Injury* [D] which has informed EU policy and research funding decisions on the basis of Cambridge-led research.
- Menon co-chaired and Hutchinson contributed to the 2014 US Neurocritical Care Society and the European Society of Intensive Care Medicine '*Consensus summary statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care'* [D]. This Consensus Statement provides healthcare professionals with best practice for monitoring patients with TBI.

- In 2020, following the publication of RESCUEicp, the US Brain Trauma Foundation amended its guideline, *Decompressive craniectomy is suggested to treat neurologic deterioration, herniation, or intracranial hypertension refractory to medical management'* [D] which included changes to its recommendations on intracranial pressure thresholds based on Cambridge University research.

Given their significant expertise and scientific leadership, the Cambridge University team has also contributed to key national and international guideline developments:

- Hutchinson and Menon were members of the 2014 NICE Guideline Development Group for Head Injury, with the respective specialities as neurosurgeon and neurointensivist [E].
- The Cambridge research team produced the 2019 *Intensive Care in Myanmar* report [E] which provides a series of recommendations and helps design and deliver courses training physicians and nurses to improve trauma patient care in the country.

Impact on clinical practice

Decompressive craniectomy is now a routine clinical procedure, improving outcomes for patients worldwide [B]. Additionally, Cambridge University's pioneering research into the development of 3D-printed titanium cranioplasty plates [4] emphasised the need for the routine collection of high-quality data about cranioplasties undertaken across the UK to improve outcomes for patients. Consequently in 2014 the researchers launched the UK Cranial Reconstruction Registry (UKCRR) [F]. Partly inspired by the UKCRR, the German Cranial Reconstruction Registry (GCRR) was established in 2015, providing further data to improve patient outcomes [F].

The UKCRR is hosted on the Outcome Registry Intervention and Operation Network (ORION) platform to document referral processes. The ORION web application, developed and hosted by the research team at Cambridge since 2012, enables secure submission, retrieval and sharing of healthcare information across multiple sites. It has been adopted by other neuroscience units in the UK and by 2015 over 30,000 patients had been captured by ORION [F].

ICM+ software provides clinicians with real-time multimodality monitoring, analysis and data storage. A neurointensivist at Maastricht University and Editor of Neurocritical Care has described the clinical utility of ICM+ as follows: *"the ICM+ platform, perhaps uniquely, provides metrics that better enable us to match treatments to patients, allowing us to use precision medicine approaches in clinical ICU care following traumatic brain injury"* [G]. Since 2014, 129 ICM+ licences have been issued to centres across Europe, North America, South America, Asia and Australia and New Zealand, facilitating improved management and treatment of TBI around the globe [G]. User group interviews have provided insight on how ICM+ can support clinical decision-making: *"ICM+ helps me to understand what has happened to patients over a long period of time. For example, if intracranial pressure has increased, clinicians can use ICM+ to understand how cerebral autoregulation has changed."* [G].

Impact on improvement training for healthcare professionals

Cambridge-led innovations have had a significant impact on training speciality clinicians. In addition to its clinical utility, the ICM+ software is a useful teaching tool. From the user group: *"ICM+ can help me to articulate and show my students how the patients' physiological conditions have changed over a long period of time using the visualisation function."* [G].

The Cambridge University research team is also dedicated to training healthcare professionals across the globe to ensure that there is sufficient clinical capacity and expertise in TBI. The NIHR Global Health Research Group on Neurotrauma has facilitated improvements in TBI care across a number of LMICs. For example, the Group established the University of Cambridge – Lusaka, Zambia Twinning Programme in 2017 as part of a teaching, capacity building and research endeavour. Since its establishment, the initiative has improved local ICU care through a programme of training courses for physicians and nurses [H]. In Myanmar, the Group has facilitated the development of a Yangon city-wide trauma network and accompanying training programme [E].

Impact on public policy, awareness and understanding

Through engaging with policy-makers and the public, the research team has contributed to public understanding of TBI and its prevention. Menon was Executive Editor of and Hutchinson was a contributor to the *Time for Change* report produced by the UK All-Party Parliamentary Group on Acquired Brain Injury (ABI; brain injury from any cause after birth) to which TBI is a major contributor [I].

As an expert in head injury, Hutchinson collaborated with the Sport and Recreation Alliance to develop and endorse its 2015 *Concussion Guidelines for the Education Sector*, which set out how to recognise concussion, how to respond to it and how to ensure the individual returns safely to their education and sport. [J]; these Guidelines have been adopted by the English Rugby Football Union (Hutchinson is also a member of its Concussion Panel) for all those taking part in the sport in schools and colleges [J]. The President of the Faculty of Sport and Exercise Medicine states: *"We are now delighted to see the launch of concussion guidelines to help teachers, school staff, coaches, parents and carers to be aware of the danger signs and how a suspected concussion should be managed in the absence of a trained medical professional"* [J].

Impact on commerce and the economy

ICM+ software was commercialised by Cambridge Enterprise in 2011 and since 2014, 129 licenses have been sold [text removed for publication] [G].

5. Sources to corroborate the impact (indicative maximum of 10 references)

A. Testimonial from Research Director & Execuitve Director of Trauma Audit Research Network
B. Testimonial from the President of the World Federation of Neurosurgical Societies
C. Testimonial from Professor of Neurosurgery at the University of Cape Town and past-President of the International Neurotrauma Society
D. Multinational consensus statements and guidelines: (i) US Neurocritical Care Society and the European Society of Intensive Care Medicine *Consensus summary statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care* (ii) *Consensus statement from the 2014 International Microdialysis Forum*; (iii) *The Role of Decompressive Craniectomy in the Management of Traumatic Brain Injury*; (iv) *Lancet Neurology Commission on Traumatic Brain Injury*; (v) US Brain Trauma Foundation guideline, *Decompressive craniectomy is suggested to treat neurologic deterioration, herniation, or intracranial hypertension refractory to medical management*
E. National and international guidelines: (i) NICE Head Injury Guideline Development Group membership; (ii) Intensive Care in Myanmar: Review of the current Intensive Care capacity in Myanmar and consensus recommendations for the development of the service over the next 10 years, Feb 2019
F. Registries: (i) UKCRR; (ii) GCRR; (iii) ORION
G. ICM+: i) Testimonial from neurointensivist at Maastricht University and Editor of Neurocritical Care [text removed for publication]
H. International training: University of Cambridge – Lusaka, Zambia Twinning Programme
I. Time for Change: Report of the All Party Parliamentary Group on Acquired Brain Injury
J. Concussion in educational settings: (i) *Concussion Guidelines for the Education Sector*; (ii) English Rugby Union concussion guidelines; (iii) Faculty of Sports and Exercise Medicine Supports Concussion Guidelines for the Education Sector