Health Research Authority

Multimodality Monitoring Directed Management of Patients Suffering from Traumatic Brain Injury

Directed management in brain injury

- **This protocol has regard for the HRA guidance and order of content**

Consultation in use Version 1.0 June 2015

RESEARCH REFERENCE NUMBERS

R&D: A094233

PROTOCOL VERSION NUMBER AND DATE

V1.0 31/10/2016

OTHER RESEARCH REFERENCE NUMBERS

IRAS: 214040

SPONSOR / CO-SPONSORS / JOINT-SPONSORS

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University of Cambridge

FULL TITLE:

Multimodality Monitoring Directed Management of Patients Suffering from Traumatic Brain Injury

SHORT TITLE:

Directed management in brain injury

PROTOCOL VERSION NUMBER AND DATE:

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IRAS Number:	*214040*
SPONSORS Number:	*A094233*
FUNDERS Number:	*N/A*

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

..../...../.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature: Date:

..../...../.....

Name: (please print):

.....

KEY STUDY CONTACTS

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Joint-sponsor(s)/co-sponsor(s)	University of Cambridge, Cambridge, United Kingdom
Funder(s)	Swedish Society of Medicine
Key Protocol Contributors	N/A
Committees	N/A

STUDY SUMMARY

Study Title	Multimodality Monitoring Directed Management of Patients Suffering from Traumatic Brain Injury
Internal ref. no. (or short title)	Directed management in brain injury
Study Design	Controlled trial without randomisation
Study Participants	Patients with traumatic brain injury and need for intracranial monitoring.
Planned Size of Sample (if applicable)	100
Follow up duration (if applicable)	6 months
Planned Study Period	5 years
Research Question/Aim(s)	*Primary aim:* Establish and validate a clinical protocol for microdialysis derived chemistry driven therapy in TBI and see if it improves lactate:pyruvate ratio (<25). *Secondary aims:* Determine the optimal strategies for correcting abnormalities in microdialysis derived parameters. Determine the inflammatory, tissue and functional outcome for patients suffering from different defined pathological conditions

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
Swedish Society of Medicine	214.000 SEK (Swedish Krona ~ 20.000£)

ROLE OF STUDY SPONSOR AND FUNDER

The study sponsor will guarantee that the study will be performed according to rules and regulations, and will assume overall responsibility for the initiation and management of the study.

The Funder will guarantee salary for Eric P Thelin. The funder will have no role in study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

Neither sponsors nor funder will have control over the final decision regarding any of these aspects of the study.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Study Steering Groups

The study has been drafted solely by the research team. No other committee or group has been involved.

Patient & Public Involvement Group

We have a longstanding interest in traumatic brain injury research and patients. As well as dealing with patients and their families in their acute stay, we have a multi-disciplinary neurotrauma clinic that combines healthcare professionals from neurosurgery, neurorehabilitation, neuropsychology as well as the Headway Brain Injury Charity.

The details of a project such as this require specialist knowledge to fully appreciate the clinical need and scientific design of the study, however, our commitment to head injury extends to improving every aspect of patient care as demonstrated by our long track record in this field.

Protocol contributors

Mr. Adel Helmy

Dr. Eric P Thelin

Dr. Tamara Tajsic

Dr. Keri LH Carpenter

Dr Susan van der Heide
Dr Ari Ercole
Prof David K Menon
Mr. Ivan Timofeev
Prof Peter JA Hutchinson

Neither sponsors nor funder will have control over the final decision regarding any of these aspects of the study.

KEY WORDS: Microdialysis; Traumatic Brain Injury; Multimodal Monitoring; Metabolism; Oxygenation; Intracranial pressure;

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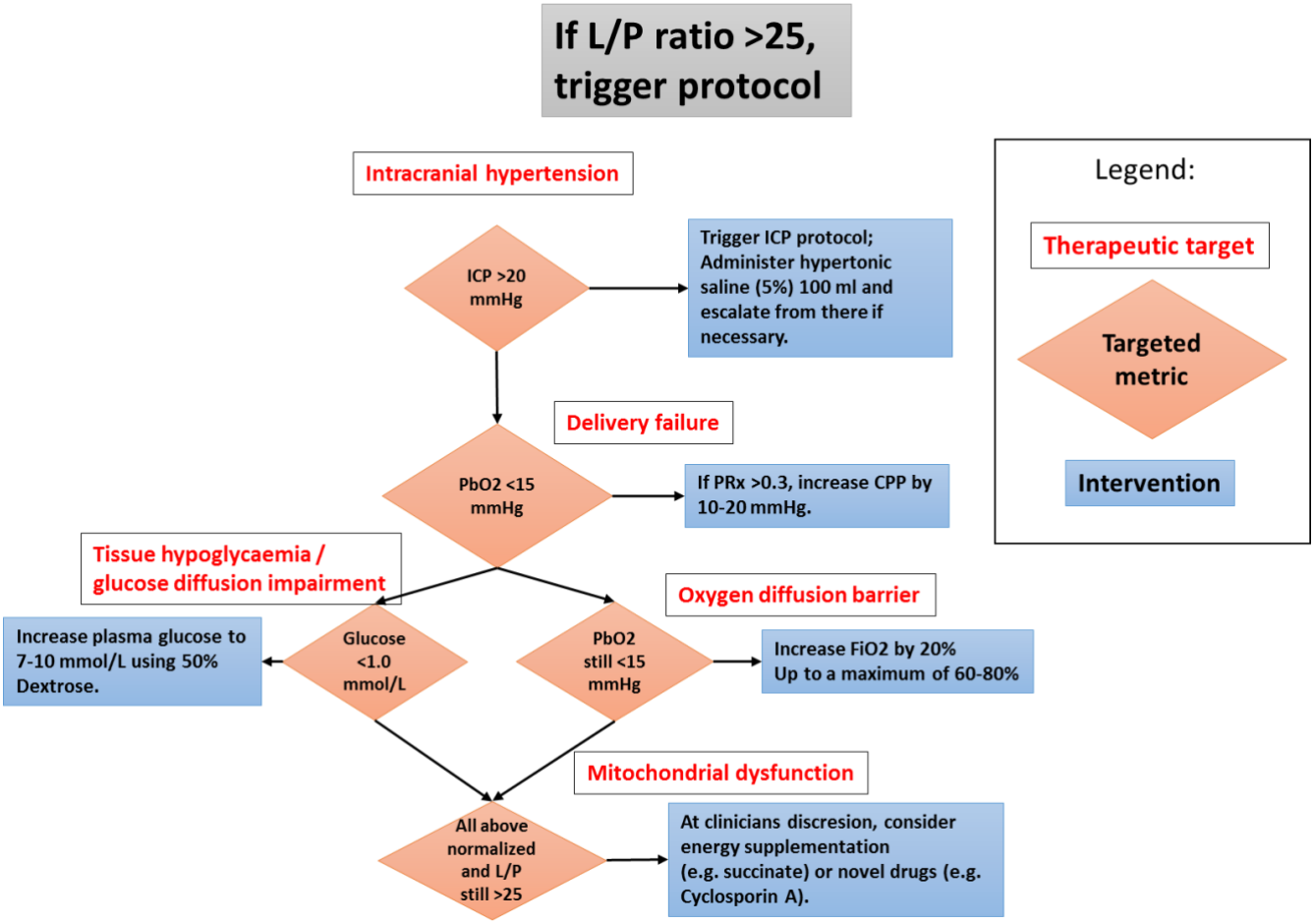
STUDY FLOW CHART



If a patient presents with a L/P ratio >25 we will include the patient in the study. As the different monitoring thresholds are reached, it will trigger different treatment strategies in order to treat a specific pathological substrate.

Excess serum, CSF and microdialysis samples will be stored for analyses of inflammatory markers and tissue damage markers.

Follow-up at 6 months following trauma will be done through outpatient clinic.

STUDY PROTOCOL

Multimodality Monitoring Directed Management of Patients Suffering from Traumatic Brain Injury

1 BACKGROUND

Traumatic brain injury (TBI) is a major cause of morbidity and mortality worldwide especially in population under 40 years of age and has a significant socioeconomic impact. TBI results from the head impacting with an object or from acceleration/deceleration forces that produce vigorous movement of the brain within the skull, with the resultant mechanical forces potentially damaging glia, neurones, axons and blood vessels. The nature of the initiating force, as well as its site, direction and magnitude, determine the type and the severity of the injury[1]. Contact trauma usually results in focal injuries such as skull fractures, extradural or subdural haemorrhages and contusions. Unrestrained head movement which generates acceleration/deceleration forces usually results in diffuse axonal injury[1,2].

The major determinant of outcome from TBI is the severity of the primary injury, which is irreversible. However, all neurological damage does not occur at the moment of initial injury, but evolves over the ensuing hours and days. Primary injury invariably leads to the activation of cellular and molecular responses which mediate secondary injury. These include an increase in extracellular levels of glutamate leading to excitotoxicity, the onset of oxidative stress, inflammation, disruption to the blood-brain barrier (BBB) and cerebral oedema formation, all of which exacerbate injury and tissue damage[3-11]. Ultimately, all this leads to brain swelling within the confines of a fixed intracranial compartment, leading to increased intracranial pressure (ICP) and compromising cerebral perfusion pressure (CPP). Current ICU protocols for the treatment of TBI focus on the treatment of secondary injury and ensuring optimal cerebral perfusion[12-18].

Most specialized neurocritical care units now use multimodality monitoring which involves placing intraparenchymal probes/catheters to measure the ICP (thus enabling the calculation of cerebral perfusion pressure), brain tissue oxygen tension (PbO2) and microdialysis, in order to minimize secondary injury. However, all current clinical protocols are ICP based, i.e. a certain ICP threshold triggers a step wise treatment approach. At present, although there is evidence base to suggest their usefulness and potential for early detection of secondary, information that microdialysis or PbO2 monitors provide has not been implemented in clinical protocols yet.

Microdialysis is invasive monitoring which uses a semi-permeable membrane inserted into brain parenchyma to monitor the biochemistry and metabolic status of the surrounding brain tissue[20]. The use of this technique increased our understanding of the pathophysiology of several neurological conditions. Microdialysis provides information about the energy and metabolic status of the focal area examined measuring lactate, pyruvate (and the lactate/pyruvate ratio LPR), glucose, glycerol and glutamate. After traumatic brain injury, due to ischemic/hypoxic conditions, energy production will decrease while lactate levels, and the LPR, will increase as a sign of tissue ischemia[38]. In contrast, if pyruvate levels remain normal and lactate levels increase, ongoing mitochondrial dysfunction has been suggested[39]. A growing body of evidence shows that microdialysis parameters (principally the lactate/pyruvate ratio) correlate with outcomes after TBI[24,25,26], and can be used for: early detection of secondary insults[30,31], monitoring and treatment of low cerebral glucose guiding systemic glucose and insulin management[32,33,34], monitoring during CPP augmentation/reduction and derivation of optimal CPP (CPP opt)[35,36,37], evaluating the effect on body temperature on cerebral chemistry[24]. The recent International Consensus Statement from the 2014 International Microdialysis Forum [23]summarises

data on the utility and prognostic power of microdialysis derived parameters and strongly supports its use in TBI treatment, but no microdialysis parameter guided clinical protocols exist to date.

2 RATIONALE

Microdialysis parameters are recognized to correlate with outcome in population studies, however they have not yet been rationalised into treatment strategies for individual patients. Further research is needed to determine which interventions may be used to modify or improve microdialysis parameters towards a goal directed target.
Given the failure to demonstrate the benefits of ICP monitoring in a large randomised trial (Chestnut *et al*, 2012) and given the number of possible neuromonitoring technique, how can an evidence base be developed for second line monitoring techniques for early detection and minimization of secondary brain injury.

3 THEORETICAL FRAMEWORK

We aim to include all traumatic brain injured patients admitted to the neuro-critical care unit that are being monitored and have multi-modality monitoring already in place. As all patients will follow the same protocol, we will minimize the risk of selection and researcher bias. As the patient will be unconscious during this process, next of kin will be asked for consent. As mentioned, this is a structured form of the standard treatments already provided in intensive care.

We will specifically identify patients in whom the microdialysis lactate:pyruvate ratio (LPR) increase above 25. This threshold has been proven to relate to a worse outcome after head injury. This will trigger our protocol which will consist of the following steps:

1. If ICP >20 mmHg, we will aim to escalate intracranial pressure decreasing measures by administering hypertonic saline (5%) 100 ml and if necessary continue on with further ICP decreasing measures.

2. If the brain oxygen pressure falls <15 mmHg, and the pressure reactivity index is >0.3 (an indication that the normal auto-regulation of the brain blood flow is not functioning properly), will increase the cerebral perfusion pressure by 10-20 mmHg.

3. If this still does not improve the brain oxygen pressure, we will increase the flow of inspired oxygen up to a maximum of 60-80%.

4. These steps do not adjust the LPR and if there is a decrease in glucose in the affected brain tissue (<1 mmol/l), we will increase the plasma glucose levels to a maximum 10 mmol/l in order to ensure that the correct amount of nutrients is being delivered, using 50% dextrose (sugar) solution.

5. If all the above steps fail to improve the LPR, it could be due to mitochondrial failure, the powerhouse of the cell. There are currently no approved therapies for this condition. However, at the treating physicians discretion, energy supplementation (e.g. succinate) or neuro-protective drugs (e.g. cyclosporine A) could be provided.

Following a 6 month period, we will see the patients in our outpatient clinic to assess functional outcome. This is part of the patient's standard clinical care as all our patients are offered clinical follow up in this way.

We will collect any biological samples that are available as part of the standard clinical care of the patient and will not subject the patients to any additional procedures. This would consist of:

-left over microdialysate samples that are not used for the standard clinical care of the patient
-blood samples if the patient has an arterial line
-cerebrospinal fluid samples if the patient has an external ventricular drain inserted into the ventricles.

4 RESEARCH QUESTION/AIM(S)

Primary aim:

Establish and validate a clinical protocol for microdialysis derived chemistry driven therapy in TBI and see if it improves lactate:pyruvate ratio (<25).

Secondary aims:

Determine the optimal strategies for correcting abnormalities in microdialysis derived parameters.

Determine the inflammatory, tissue and functional outcome for patients suffering from different defined pathological conditions

4.1 Objectives

1. We wish to determine which of the provided therapies that was superior to others in improving the deranged brain metabolism.

2. We also wish to determine the inter-relationships between parameters detected using the microdialysis and other monitoring techniques, such as brain oxygen saturation and perfusion pressure in the damaged brain, and how microdialysis may complement these techniques.

3. How the protocol will alter cytokine, chemokine and markers of brain damage markers (S100B) in serum and microdialysate for patients suffering from different pathological states?

4. How will the functional outcome distribution be for patients suffering from different pathological states?

4.2 Outcome

Improvement of lactate/pyruvate ratio <25 (by different treatment strategies).

5 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYIS

Multimodality monitoring parameters that will be included:

a) Standard monitoring
Intracranial pressure
Cerebral perfusion pressure (mean arterial pressure – intracranial pressure)
Brain tissue oxygen tension
Pressure reactivity index (PRx)
Therapy intensity levels

b) Microdialysis parameters
Metabolic intermediaries (lactate, pyruvate, glucose, glutamate, glycerol)
Cytokine analysis
Nitric oxide

c) CSF parameters
Cytokines and chemokines

d) Serum
Circulating cytokines, chemokines, tissue damage markers (S100B)

The monitoring data will be stored automatically. The chemokine, cytokine and tissue damage marker samples will be analysed using commercially available LUMINEX kits by members of the research team.

Standardized questionnaires to assess extended Glasgow Outcome Score (eGOS) as well and Short Form 36 (SF-36) will be used during the follow-up appointment in the outpatient clinic by members of the research team.

Data will be analysed by members of the research team using comparative statistics between patients with different pathological targets. The statistical program R will be used.

6 STUDY SETTING

This will be a single-center (Addenbrooke's Hospital) prospective study utilising a new treatment algorithm using lactate/pyruvate ratio to direct management following traumatic brain injury. We will assess patients admitted to the neuro-critical care unit to see if they are eligible for inclusion.

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

We will include patients with traumatic brain injury in need of intracranial monitoring admitted to the in the neuro-critical care unit, fulfilling the inclusion criteria.

7.1.1 Inclusion criteria

a) Patients with head injury requiring ICP monitoring

b) Age 18-65 years

c) Abnormal CT scan

7.1.2 Exclusion criteria

a) Bilateral fixed and dilated pupils
b) Bleeding diathesis
c) Thrombocytopenia (platelets < 100)
d) Devastating injuries; patient not expected to survive > 24 hours
e) Brainstem damage
f) Pregnancy
g) Involvement in other studies non-observational studies
h) MD catheter located in haemorrhagic lesion

7.2 Sampling

All patients will have a full medical history taken and a clinical examination.
The following are to be recorded:

a) Weight and BMI
b) Sex
c) Age and date of birth
d) Any significant past medical history
e) Full blood count (including platelets and differential white cell count)
f) Biochemical series (including urea, creatinine, uric acid, electrolytes, calcium, alkaline phosphatase, AST, CRP and serum glucose)
g) Initial Glasgow Coma Scale score
h) Focal neurological deficit
h) CT diagnosis, Marshall and Rotterdam score
i) Drug dosages of paralysing and sedating agents
j) Drug doses of vasoactive agents
k) Fraction of inspired oxygen (FiO2), partial pressure of oxygen in arterial bloods (PaO2) partial pressure of carbon-dioxide in arterial blood (PaCO2)

Study Assessments

Dynamic	Multi-modality monitoring (ICP, CPP, PbtO2), MAP, FiO2
Every 30 minutes	Microdialysis Parameters
Hourly	GCS, Clinical examination,
	PaO2, PaCO2, serum sodium, serum glucose
2xDaily	Serum and if possible CSF sampling.

Brain imaging will be performed when clinically indicated.

All monitored parameters will be extracted automatically and stored on hospital computers as part of conventional care. Microdialysis sampling, as part of the standard routine, will be done twice hourly where 20 µl will be extracted. If the patient has an extra-ventricular drain, it will be used to sample cerebrospinal fluid as part of standard routine in the department (200 µl per sample, if available). Blood samples will be drawn twice daily, and we will use discarded samples for analysis (200µlx2 per day).

7.2.1 Size of sample

The aim is to reach a sample size where there is a statistical difference between patients with different pathological targets. It is difficult to assess what this sample size is considering this has never been done before, but we estimate that a n=100 will suffice.

7.2.2 Sampling technique

All monitored samples will be digitally stored automatically. All bodily fluids will be sampled at convenience, as these samples would have been otherwise discarded.

7.3 Recruitment

Members of the research team will daily approach the staff in the neuro-critical care unit to determine if any of the newly admitted patients are eligible for inclusion in the study.

7.3.1 Sample identification

Members of the research team, together with the staff in the NCCU at Addenbrooke's Hospital, will identify patients eligible for inclusion.

7.2.2 Consent

The next-of-kin, or consultee, will be informed about the study and will have to provide written assent as patients who require multimodality monitoring are unconscious and not able to give consent. Patients will, after regaining consciousness, be given the option to consent into the study, or withdraw if they choose, without prejudice for future care.

8 ETHICAL AND REGULATORY CONSIDERATIONS

The main ethical issue is that the eligible patients will be unconscious at admission to the hospital and the neuro-critical care unit and therefore not be able to provide an informed consent. In these cases, family and next of kin will be asked if the will allow the patient to take part in the study. The study will not specifically withhold treatments from any patient, we will be delivering treatments that would be considered anyway, but in a structured fashion.

Data collection and storage will be done in password protected computers, and blood/CSF samples will be stored in locked freezers, at the University of Cambridge.

The protocol is in line with relevant legislation and regulation.

8.1 Assessment and management of risk

The study is designed to closely follow the standard clinical management of traumatic brain injury. Patients with injuries severe enough to participate in this study are by definition unconscious, and will not suffer any discomfort from the study. We will work closely with the treating clinicians and ensure that they are happy with every aspect of the protocol in each individual patient and that the opinion of the treating clinician is respected.

As this protocol is a more structured version of the conventional therapy provided on a regular basis, we do not believe that there will be are any additional risks with this protocol.

8.2 Research Ethics Committee (REC) review & reports

Before the start of the study, approval will be sought from REC and IRAS, this include all protocols, informed consent forms and other relevant documents.

All correspondence with the REC will be retained.

The chief investigator will produce annual reports as required and will notify the REC at the end of the study.

8.3 Peer review

The protocol has been reviewed extensively within the research team and with staff from the neuro-critical care unit during several meetings and has been approved by the head the unit.

The protocol was discussed at the International Consensus Meeting on Microdialysis 2014 (external peer review). The results of this meeting are published as a scientific paper and outline the scientific rationale for the study.

8.4 Patient & Public Involvement

We have a longstanding interest in traumatic brain injury research and patients. As well as dealing with patients and their families in their acute stay, we have a multi-disciplinary neurotrauma clinic that combines healthcare professionals from neurosurgery, neurorehabilitation, neuropsychology as well as the Headway Brain Injury Charity.

The details of a project such as this require specialist knowledge to fully appreciate the clinical need and scientific design of the study, however, our commitment to head injury extends to improving every aspect of patient care as demonstrated by our long track record in this field.

8.5 Regulatory Compliance

Before patients will be enrolled in the current study, necessary regulatory measures will be taken through NHS R&D (the Sponsor). We will work in partnership with the study sponsor to ensure the study is conducted in a safe fashion and complies with all aspects of GCP. The sponsor has arrangements in place to monitor or audit the conduct of this study as part of the sponsor's obligations under the Department of Health's Research Governance Framework.

For any amendment that will potentially affect a site's NHS permission, the Principal Investigator or designee will confirm with that site's R&D department that NHS permission is ongoing

8.6 Protocol compliance

Any accidental protocol deviation will be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

8.7 Data protection and patient confidentiality

The Principal Investigator will be responsible for access to any source data. Only defined researchers will be delegated this responsibility.

It is expected that the data generated from the study will be kept on electronic media in the form of a database. This will be kept on computers which are password protected and under the care of the research team. Data from the study will be kept on digital media for a period of ten years to assist in the design and implementation of future studies.

Any stored tissue (blood and CSF) samples will be kept anonymized in a locked freezer.

8.8 Indemnity

As NHS will act as a sponsor, the standard NHS indemnity scheme will apply.

8.9 Amendments

Currently no amendments to the protocol

8.10 Access to the final study dataset

Only members of the study team will have access to the final dataset.

9 DISSEMINIATION POLICY

9.1 Dissemination policy

The authors will own the data following completion of the study. Upon completion of the study, the data will be analysed and tabulated and a Final Study Report prepared accessible via the University of Cambridge website. We aim to publish the study in an open-access peer-reviewed scientific journal, where the public will be able to access it. While the funding bodies will be acknowledged, they have no role in the assessment of data or preparation of the study.

The study participants will be informed by the results of the study, as mentioned in the Patient Information Sheet.

9.2 Authorship eligibility guidelines and any intended use of professional writers

The research team will be granted authorship in the upcoming publication. We have no plan to use any professional writers.

Mr. Adel Helmy
Dr. Eric P Thelin
Dr. Tamara Tajsic
Dr. Keri LH Carpenter
Dr Susan van der Heide
Dr Ari Ercole
Prof David K Menon
Mr. Ivan Timofeev
Prof Peter JA Hutchinson

10 REFERENCES

1. *Smith DH, Meaney DF, Shull WH (2003). Diffuse axonal injury in head trauma. J Head Trauma Rehabil 18: 307-316.*
2. *Blumbergs PC, Reilly PL, Vink R (2008). Trauma. In Love S, Louis DN, Ellison DW (eds). Greenfield's Neuropathology, 8th edn. London: Hodder Arnold Publishers. pp 733-832.*
3. *Block ML, Li G, Qin L, Wu X, Pei Z, Wang T, Wilson B, Yang J, Hong JS. (2006) Potent regulation of microglia-derived oxidative stress and dopaminergic neuron survival: substance P vs.dynorphin. FASEB J. 2092:251-8.*
4. *Brown GC, Neher JJ (2010). Inflammatory neurodegeneration and mechanisms of microglial killing of neurons. Mol Neurobiol 41: 242-247.*
5. *Donkin JJ, Nimmo AJ, Cernak I, Blumbergs PC, Vink R. (2009) Substance P is associated with the development of brain edema and functional deficit following traumatic brain injury. J Cereb Blood Flow Metab. 29(8):1388-98.*
6. *Fiebich BL, Schleicher S, Butcher RD, Craig A, Lieb K. (2000) The neuropeptide substance P activates p38 mitogen-activated protein kinase resulting in IL-6 expression independently from NF-kappa B. J Immunol.165(10):5606-11.*
7. *Gabrielian L, Helps SC, Thornton E, Turner RJ, Leonard AV, Vink R. (2013) Substance P antagonists as a novel intervention for brain edema and raised intracranial pressure. Acta Neurochir Suppl. 118:201-4.*
8. *Morganti-Kossmann MC, Rancan M, Stahel PF, Kossmann T (2002). Inflammatory response in acute traumatic brain injury: a double-edged sword. Curr Opin Crit Care 8:101-105.*
9. *Nimmo AJ, Cernak I, Heath DL, Hu X, Bennett CJ, Vink R. (2004) Neurogenic inflammation is associated with development of edema and functional deficits following traumatic brain injury in rats. Neuropeptides 38(1):40-7.*
10. *Saatman KE, Bozyczko-Coyne D, Marcy V, Siman R, McIntosh TK (1996). Prolonged calpain-mediated spectrin breakdown occurs regionally following experimental brain injury in the rat. J Neuropath Exp Neurol 55: 850-860.*
11. *Shohami E, Ginis I, Hallenbeck JM (1999). Dual role of tumor necrosis factor alpha in brain injury. Cytokine Growth Factor Rev 10: 119-130.*
12. *Bernard SA and Buist M (2003) induced hypothermia in critical care medicine: a review. Crit Care Med, 31(7): 2041-51*
13. *Bhardwaj A (2007) Osmotherapy in neurocritical care. Curr Neurol Neurosci Rep7:513-521.*
14. *Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, Manley GT, Nemecek A, Newell DW, Rosenthal G, Schouten J, Shutter L, Timmons SD, Ullman JS, Videtta W, Wilberger JE, Wright DW. (2007) Guidelines for the management of severe traumatic brain injury. Blood pressure and oxygenation. J Neurotrauma. 24(1):S7-13*

15. *Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, Manley GT, Nemecek A, Newell DW, Rosenthal G, Schouten J, Shutter L, Timmons SD, Ullman JS, Videtta W, Wilberger JE, Wright DW. (2007) Guidelines for the management of severe traumatic brain injury. Indications for intracranial pressure monitoring. J Neurotrauma. 24(1):S37-44.*
16. *Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, Manley GT, Nemecek A, Newell DW, Rosenthal G, Schouten J, Shutter L, Timmons SD, Ullman JS, Videtta W, Wilberger JE, Wright DW. (2007) Guidelines for the management of severe traumatic brain injury. Intracranial pressure thresholds. J Neurotrauma. 24(1):S55-58*
17. *Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, Manley GT, Nemecek A, Newell DW, Rosenthal G, Schouten J, Shutter L, Timmons SD, Ullman JS, Videtta W, Wilberger JE, Wright DW. (2007) Guidelines for the management of severe traumatic brain injury. Brain oxygen monitoring and thresholds. J Neurotrauma. 24(1):S65-70.*
18. *Helmy A, Vizcaychipi M, Gupta AK. (2007) Traumatic brain injury: intensive care management. Br J Anaesth. 99(1):32-42.*
19. *Chesnut, R. M., N. Temkin, et al. (2012). "A trial of intracranial-pressure monitoring in traumatic brain injury." N Engl J Med **367**(26): 2471-2481.*
20. *Tisdall MM, Smith M. (2006) Cerebral microdialysis: research technique or clinical tool. Br J Anaesth 97:18-25*
21. *Chamoun, R., D. Suki, et al. (2010). "Role of extracellular glutamate measured by cerebral microdialysis in severe traumatic brain injury." J Neurosurg **113**(3): 564-570.*
22. *Chesnut, R. M., N. Temkin, et al. (2012). "A trial of intracranial-pressure monitoring in traumatic brain injury." N Engl J Med **367**(26): 2471-2481.*
23. *Hutchinson, P. J., I. Jalloh, et al. (2015). "Consensus statement from the 2014 International Microdialysis Forum." Intensive Care Med **41**(9): 1517-1528.*
24. *Soukup, J., A. Zauner, et al. (2002). "Relationship between brain temperature, brain chemistry and oxygen delivery after severe human head injury: the effect of mild hypothermia." Neurol Res **24**(2): 161-168.*
25. *Stein, N. R., D. L. McArthur, et al. (2012). "Early cerebral metabolic crisis after TBI influences outcome despite adequate hemodynamic resuscitation." Neurocrit Care **17**(1): 49-57.*
26. *Timofeev, I., K. L. Carpenter, et al. (2011). "Cerebral extracellular chemistry and outcome following traumatic brain injury: a microdialysis study of 223 patients." Brain **134**(Pt 2): 484-494.*
27. *Unterberg, A. W., O. W. Sakowitz, et al. (2001). "Role of bedside microdialysis in the diagnosis of cerebral vasospasm following aneurysmal subarachnoid hemorrhage." J Neurosurg **94**(5): 740-749.*
28. *Vespa, P., R. Boonyaputthikul, et al. (2006). "Intensive insulin therapy reduces microdialysis glucose values without altering glucose utilization or improving the lactate/pyruvate ratio after traumatic brain injury." Crit Care Med **34**(3): 850-856.*
29. *Vespa, P., D. L. McArthur, et al. (2012). "Tight glycemic control increases metabolic distress in traumatic brain injury: a randomized controlled within-subjects trial." Crit Care Med **40**(6): 1923-1929.*
30. *Adamides, A. A., F. L. Rosenfeldt, et al. (2009). "Brain tissue lactate elevations predict episodes of intracranial hypertension in patients with traumatic brain injury." J Am Coll Surg **209**(4): 531-539.*
31. *Belli, A., J. Sen, et al. (2008). "Metabolic failure precedes intracranial pressure rises in traumatic brain injury: a microdialysis study." Acta Neurochir (Wien) **150**(5): 461-469; discussion 470.*
32. *Oddo, M., J. M. Schmidt, et al. (2008). "Impact of tight glycemic control on cerebral glucose metabolism after severe brain injury: a microdialysis study." Crit Care Med **36**(12): 3233-3238.*

33. *Vespa, P., R. Boonyaputthikul, et al. (2006). "Intensive insulin therapy reduces microdialysis glucose values without altering glucose utilization or improving the lactate/pyruvate ratio after traumatic brain injury." Crit Care Med **34**(3): 850-856.*
34. *Vespa, P., D. L. McArthur, et al. (2012). "Tight glycemic control increases metabolic distress in traumatic brain injury: a randomized controlled within-subjects trial." Crit Care Med **40**(6): 1923-1929.*
35. *Johnston, A. J., L. A. Steiner, et al. (2004). "Effect of cerebral perfusion pressure augmentation with dopamine and norepinephrine on global and focal brain oxygenation after traumatic brain injury." Intensive Care Med **30**(5): 791-797.*
36. *Johnston, A. J., L. A. Steiner, et al. (2005). "Effect of cerebral perfusion pressure augmentation on regional oxygenation and metabolism after head injury." Crit Care Med **33**(1): 189-195; discussion 255-187.*
37. *Nordstrom, C. H., P. Reinstrup, et al. (2003). "Assessment of the lower limit for cerebral perfusion pressure in severe head injuries by bedside monitoring of regional energy metabolism." Anesthesiology **98**(4): 809-814.*
38. *Persson L, Hillered L. (1992) Chemical monitoring of neurosurgical intensive care patients using intracerebral microdialysis. J Neurosurg 76:72–80*
39. *Nielsen TH, Bindslev TT, Pedersen SM, Toft P, Olsen NV, Nordstrom CH. Cerebral energy metabolism during induced mitochondrial dysfunction. Acta Anaesthesiol Scand (2013) 57:229–3510*

11. APPENDICIES

11.1 Appendix 1- Required documentation

- Short CV from Principal Investigator
- Patient consent form Version 1.0, Date 31/10/2016
- Patent information sheet Version 1.0, Date 31/10/2016
- Consultee declaration form Version 1.0, Date 31/10/2016
- Consultee information sheet Version 1.0, Date 31/10/2016

11.2 Appendix 2 – Schedule of Procedures

Procedures	**Visits (insert visit numbers as appropriate)**				
	Screening	**Baseline**	**Week 1-2**	**6 Months**	
Informed consent	x				
Demographics		x			
Medical history		x			
Observation of treatment		x	x		
Monitoring			x		
Follow-up interview				x	

13.3 Appendix 3 – Amendment History

Amendment No.	**Protocol version no.**	**Date issued**	**Author(s) of changes**	**Details of changes made**

Currently no existing amendments.