Medical Research Council

Workshop report – 15th June 2022

Traumatic Brain Injury across the life course: priorities, challenges, and opportunities

1. Context

In the world, 10 million people are affected annually by Traumatic Brain Injury (TBI) and it is an increasing cause of death and disability globally, particularly in lower-middle income countries. In the high-income countries, it is the commonest cause of death and disability in the under 40s and there are global costs of $400 billion a year (0.5% of annual global output)[1].

In the UK, annually there are 900,000 accident and emergency attendances with head injury with 160,000 people admitted to hospital each year. There are approximately 1.3 million people living with disabilities resulting from these injuries. The vast majority of head injuries are not admitted, and most people with head injuries do not attend hospitals[2]. The costs of traumatic brain injury in the UK is estimated at £15 billion[2] (0.8% of GDP) per year.

In June 2022, MRC convened a Workshop, with experts in the field, aiming to develop an overarching MRC strategy for traumatic brain injury research.

2. Key discussion points and Recommendations

There was a strong national and international research base from which to progress, however there were challenges which would need to be overcome to enhance this:

Clinical cohorts and longitudinal studies

- There were existing data repositories and epidemiological and observational studies to inform TBI outcomes and disease progression in different contexts (armed forces, sports, intimate partner violence, road traffic accident). Better linkage across these, whilst also increasing social and demographic data, would help to stratify patients and potentially predict disease outcomes and improve understanding of why some people were at increased risks of some conditions and others not. Similarly, it would be important to link the late outcomes post TBI to wider individual and societal outcomes to have a full picture of the conditions.
- There was agreed to be a knowledge gap between the acute phase of TBI and once long-term outcomes had become established. A better understanding of this middle phase was needed and would ideally be reflected in data collection in clinical cohorts/longitudinal studies, to increase the understanding of disease progression, resilience and risks of developing a neurological condition post a TBI across the life course.
- One of the UK strengths was the large amount of data available through the NHS and other national datasets (mortality, social, environmental, financial, educational, Hospital Episode Statistics), which could be leveraged and linked to the already existing TBI cohorts to inform disease progression post a TBI. In addition, linking existing TBI longitudinal studies with existing NHS data could help to form a platform for patient recruitment to interventional studies across the lifespan, to better understand the spectrum of outcomes and comorbidities, and to influence strategies for intervention. This would harness the power of

[1] Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research, The Lancet neurology - http://dx.doi.org/10.1016/S1474-4422(17)30371-X

[2] *Centre for Mental Health - Traumatic brain injury and offending: an economic analysis*

machine learning and AI to direct precision medicine approaches and patient stratification. There was also an opportunity to collect real world data at an earlier time point post-acute phase via the NHS which could provide an opportunity to assess and discover new biomarkers.

- It would be critical to also include neglected groups (e.g. children, prisoners, homeless people, victims of Intimate Partner Violence) which might be less represented within NHS and care datasets. In addition, there was a need for cohorts including children or young adolescents. There were many head injuries in young adults and adolescents which may predispose them to negative outcomes. Most of the biomarkers which have been found to track disease progression have been developed in older adults (aged over) and therefore might not be relevant for the younger population. It was agreed that there was a lack of knowledge around paediatric TBI and that observational studies would be needed, capitalising on recent technology development around imaging, molecular markers and wearables.
- A unified approach was needed on standardised data collection, guidelines, as well as open data sharing. This also needed to include unified approaches to defining what a traumatic brain injury was as well as how best to include comparator injuries, such as acquired brain injury.

Early phase clinical trials and experimental medicine interventions

- Given the heterogeneity of the patient population, there was a need for new and refined interventions and clinical trials which incorporated patient stratification.
- Progression of big data research would provide a new opportunity to innovate early phase clinical trials, although it was agreed that this would not be possible without stratification of patients and a better understanding of the mechanisms of disease progression.
- Experimental medicine studies in humans to generate first in human data and improved interventions to determine cause and effect were needed to better understand how groups could be targeted for better interventions and to help tackle the heterogeneity of post TBI patients. Additionally, early engagement with MHRA from the research community would help to move more quickly across the R&D pipeline.
- These Experimental Medicine studies and early clinical trials should take into account diversity of socio demographic data and consider currently under-researched populations (e.g., intimate partner violence victims, prisoners, homeless people, children/adolescent).

Mechanism – mechanistically linked biomarkers to clinical relevance

- Post TBI patients are heterogeneous due to the different contexts in which they acquire their brain injury and also through socio-economic and demographic aspects. It was noted that the current models used to study TBI in the laboratory currently do not optimally reflect human pathophysiology. More clinically relevant models were needed to more fully reflect the heterogeneity of the human condition. These models could be designed using reverse translation from observations of human patients which in turn would help to better understand the pathophysiology. In clinical settings, this could inform a more appropriate stratification of patients at the onset of the injury based on biology, pathology and molecular indices rather than using the Glasgow Coma Scale (injury severity).
- These new models would be key in helping discover new biomarkers of disease progression.

3. Strategy and Implementation

Focus would be best placed on areas where the UK is world leading and where existing capabilities can be leveraged to maximise impact and fully seize opportunities:

1. Longitudinal cohorts and analysis of real-world data: There were opportunities to leverage across existing investments (e.g. DPUK HDRUK, Our Future Health) to help establish a TBI national data resource focused on patient stratification to facilitate study recruitment. This would include under-researched population, social and demographic data as well as clinical data. Finally, the data generated would need to be open and shared to facilitate scientific breakthroughs.
2. National biomarkers platform: Development of a national platform to accelerate the discovery of clinically relevant biomarkers and harmonisation of guideline and practice. New biomarkers could be cross validated via the TBI national data resource and linked to disease outcomes (e.g. mental health, headache, neurological conditions etc). Improved models of disease will also be developed to further understanding of the pathophysiology of TBI.
3. Improve clinical trials and experimental medicine studies: Cross-linkage across the data and biomarker strands of the platform would help to increase proof of concept experimental medicine studies and patient stratification as well as link disease outcomes with mechanistic targets which would lay the foundation for larger clinical trials in the future and consensus on trial end-points. The major trauma centres within the UK could be leveraged to input into the new adaptive trial design.