Abstract: Re-orientation of clinical research in TBI
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None of the randomized controlled trials (RCTs) conducted with neuro-protective agents have convincingly shown beneficial treatment effects. Reasons for the failure of these trials include low robustness of pre-clinical and phase II studies, the lack of early mechanistic endpoints, the insensitivity of outcome measures and the inherent heterogeneity of the patient population. The IMPACT studies (International Mission on Prognosis and Analysis of RCTs in TBI) have addressed methodological issues of trial design in TBI with an emphasis on approaches for dealing with the heterogeneity.
Recommendations for improved trial design were developed:

- Inclusion criteria should be as broad as is compatible with the current understanding of the mechanisms of action of the intervention being evaluated
- The statistical analysis should incorporate pre-specified covariate adjustment to mitigate the effects of heterogeneity
- The statistical analysis should use an ordinal approach, based on either sliding dichotomy or proportional odds methodology.

Applying these recommendations yields the potential to increase statistical power by up to 50%. These potential benefits were proven when applying them to the real life situation in a re-analysis of the MRC CRASH study, confirming a substantial increase in power.
The IMPACT project has yielded important advances in trial design, but did not address the problem of heterogeneity related to mechanism. Early mechanistic endpoints which can serve as intermediate outcome markers in TBI trials are still lacking. We further recognize that it will be impossible to mount a sufficient number of trials to address all existing uncertainties in the management of TBI.

RCTs are not the only source of evidence to underpin treatment recommendations. A great potential is seen for employing comparative effectiveness research (CER). In these approaches the inherent heterogeneity of TBI populations is exploited. Such approaches are particularly applicable to TBI because of the inherent heterogeneity of the population and the availability of robust risk adjustment models to deal with differences in case mix and the availability of advanced statistical approaches.

The application of CER in TBI is now also advocated by funding agencies as evidenced by the recent publications of calls for CER in TBI by both the European Commission and NIH-NINDS. The CENTER-TBI consortium (Collaborative European NeuroTrauma Effectiveness Research in TBI) has successfully submitted an application in response to the FP7 call and negotiations are currently under way to formalize funding of this project. In brief, this project will include an observational study recruiting over 5000 patients with TBI of all severities across Europe and establishment of a registry on all patients seen with TBI in participating centers. These data will be subjected to analysis in 2 directions: first, improved characterization and second, identification of best practices. This project may be considered generationally unique and will be embedded in international collaborative efforts. A well characterized clinical dataset will be established together with repositories on neuro-imaging, biomarkers and outcome assessments offering opportunities for implementation of further collaborative research and legacy research in the future. The project has the potential to improve current health care for TBI and its delivery at both population and individual levels, deliver early scientific advances that could improve the care of patients with TBI and provide rich investment for future biomedical research.