Study Protocol
Collaborative European NeuroTrauma Effectiveness research in TBI: a prospective longitudinal observational study

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Collaborative European NeuroTrauma Effectiveness research in TBI: a prospective longitudinal observational study

Short study title:	CENTER-TBI study
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Contract Research Organization: ICON plc, (Dublin, Ireland)

Data entry tool developed by: QuesGen (Burlington, CA, USA)

Neuroimaging repository: Icometrix, Antwerp, Belgium

Database and data analysis platform: Coordinated by the International Neuroinformatics Coordinating Facility (INCF) with additional support from One Mind for Research

Study synopsis

Full study title	Collaborative European NeuroTrauma Effectiveness research in TBI: a prospective longitudinal observational study
Short study title	CENTER-TBI study
Study Design	Longitudinal prospective observational cohort
Study centers	Approximately 80 centers from 21 countries in Europe and Israel
Study population	Patients with traumatic brain injury
Funding source and international context	Funded by the European Union FP7 framework program (grant 602150) with additional national and local institutional support. CENTER-TBI is an InTBIR project (International Initiative for Traumatic Brain Injury Research: http://intbir.nih.gov/) Funding of additional elements has been provided by the Hannelore Kohl Foundation (Germany) and by the non-profit organization One Mind For Research (directly to INCF).

Study objectives

The global aims of the study are to:

- Improve characterization and classification of TBI in Europe, with inclusion of emerging technologies.
- To identify the most effective clinical care and to provide high quality evidence in support of treatment recommendations and guidelines.

Secondary objectives:

- To collect high quality clinical and epidemiological data with repositories for neuro-imaging, DNA, and serum from patients with TBI.
- To refine and improve outcome assessment and develop health utility indices for TBI.
- To develop multidimensional approaches to characterisation and prediction of TBI.
- To define patient profiles which characterise homogenous subgroups of patients and predict efficacy of specific interventions ("Precision Medicine").
- To develop performance indicators for quality assurance and quality improvement in TBI care.
- To validate the common data elements (CDEs) for broader use in international settings.
- To develop an open source database compatible with FITBIR.
- To intensify networking activities and international collaborations in TBI.
- To disseminate study results and management recommendations for TBI to health care professionals, policy makers and consumers, aiming to improve health care for TBI at individual and population levels.
- To develop a "knowledge commons" for TBI, integrating CENTER-TBI outputs with systematic reviews

Study design

Methodology	This study will be a multicentre longitudinal prospective observational, cohort study conducted in 21 countries across Europe and Israel. Data collection for CENTER-TBI will take place at 2 levels: CENTER-TBI registry (all patients) and CENTER-TBI Core data collection (patients meeting inclusion and exclusion criteria; detailed data collection).
Number of subjects	**CENTER-TBI core data study**: the planned total number of subjects will be 5400 equally distributed across three strata: - *ER stratum*: patients seen and discharged from the ER - *Admission stratum*: patients admitted to hospital but not to the ICU - *ICU stratum*: patients admitted directly to the ICU **CENTER-TBI registry**: 15.000-25,000
Inclusion criteria for observational study	1. Clinical diagnosis of TBI 2. Clinical indication for CT scan
Inclusion criteria for core data study **Exclusion criteria for core data study**	1. Presentation within 24 hours of injury 2. Informed consent obtained according to local and national requirements Severe pre-existing neurological disorder that would confound outcome assessments
Extended studies	Selected sites, meeting additional logistic requirements, will participate in extended data collection with regard to: - MR imaging - Extended coagulation and biomarker studies - Acquisition of high resolution ICU monitoring data
Study Interventions	
Therapeutic interventions	None
Diagnostic interventions	- Registry: none - Core study: blood sampling on presentation, in the ICU stratum during the clinical course and in all strata at follow up - Follow up assessments
Data collection	
Registry	Only observational data collected, without formal consent, in the context of routine clinical care
Core study	Prospective collection of clinical data with informed consent. Blood collection: - Hematology - Biochemistry - Genotyping - Biomarker analysis - Coagulation studies CT scan as part of routine clinical care Outcome assessments

Study endpoints

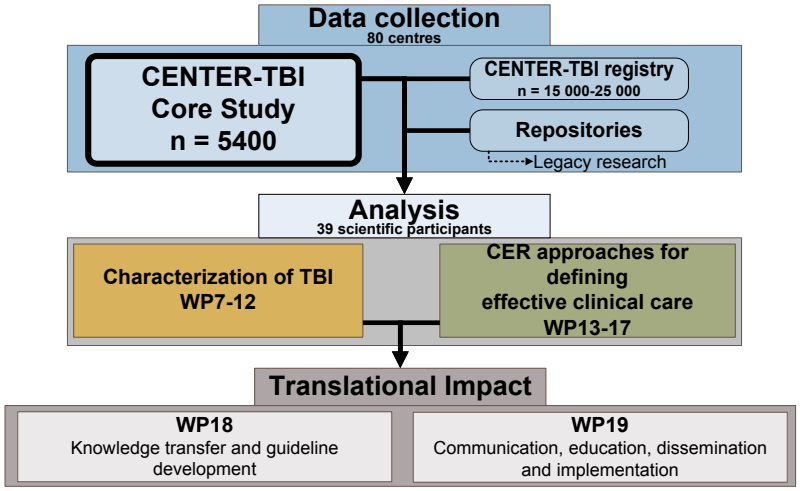
Registry: Vital status, injury severity indices, and discharge destination

Core data collection:
Cross sectional comprehensive outcome assessments across the three strata of recruitments in all subjects at 6 months; these assessments will include health related quality of life, psychological and neuropsychological testing (CANTAB).

Longitudinal assessments of outcome by telephone, postal questionnaire and/or face-to-face visits will be performed at various time points in the three strata up to 24 months after injury (focus on more early outcome assessments in ER stratum and later assessments in admission in ICU strata).

Analysis directions in the context of the CENTER-TBI project

The registry and core data study will form the basis of the scientific analysis described in the Description of Work of the CENTER-TBI project (funded by the European Union FP 7 program grant 602150).
Analysis of the CENTER-TBI core data and CENTER-TBI registry will be in two directions:
1. Improved characterization of disease
2. Identification of best practice, addressing both variations in process and in clinical care, and including the use of stratified/personalized approaches.
Results of the analyses will be integrated with results of ongoing living systematic reviews in a process of knowledge transfer aiming to provide practical evidence based recommendations.



Sample size justification

A total sample size of 5400 patients is planned for the Core Data Study with enrolment of approximately 1800 per stratum.

This sample size estimate was based on:

- Practical logistic considerations
- Power calculations for the different strata, targeting comparative effectiveness analyses, assuming a between-centre and between-countries differences as previously observed in TBI research
- Postulated odds ratios for intervention effects of approximately 5% improvement in outcome.

Overall, these calculations provided a statistical power to detect odds ratios of ~1.2 associated with differences in process or intervention variables across the core dataset with a power of 80%; and somewhat larger odds ratios in each of the 3 individual strata.
In the registry we expect to be able to detect differences (predominantly in organizational or system variables) with an odds ratio of 1.2 with a power of 82%.

Statistical analysis plan

Statistical analyses for the Comparative Effectiveness Research (CER) questions will primarily apply random effects modeling, in which center is included at the highest level, and patients are considered clusters within centers. Confounding factors as measured at the individual patient and/or center level, will be considered.
Statistical analyses for better characterization of TBI will be mainly exploratory. Standard statistical descriptive and inferential techniques, as well as machine learning techniques will be used. Prognostic analyses will consider a range of variables, including genetic, biomarker, neuro-imaging and additional outcome assessments. Previously and newly developed prediction models will be validated by measures for model fit, discrimination, and calibration.

Overall goals and impact of CENTER-TBI

The CENTER-TBI project will contribute towards the overall goals of InTBIR, by identifying more effective and efficient treatment provision, thus improving outcome and reducing costs. The science in the project will provide methodological advances (including novel, multilingual translations of key outcome instruments), novel information on disease processes, treatment, outcome, and prognosis in TBI, identifying new therapeutic targets and therapies; while the CENTER-TBI repositories will ensure opportunities for legacy research. Thus, the project has the potential to improve current health care and its delivery at both population and individual levels, deliver early scientific advances that could improve the care of patients with TBI, and provide a rich investment for future biomedical and clinical research.

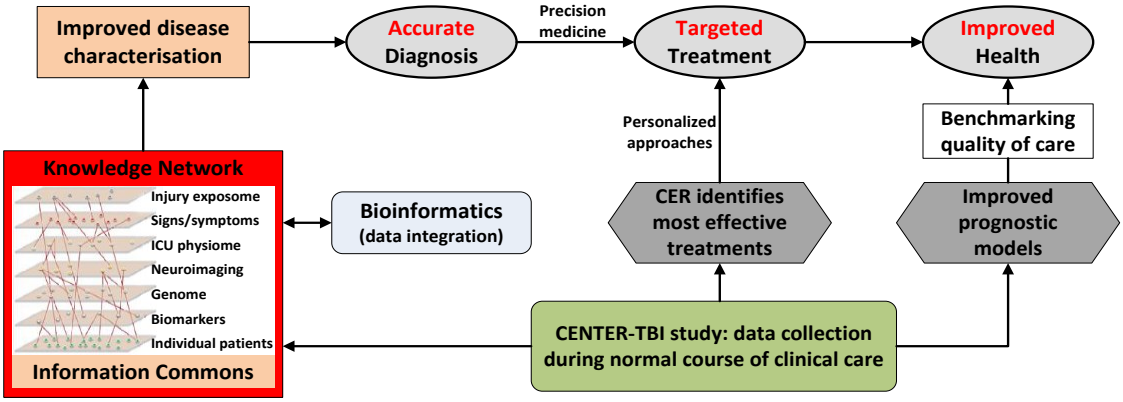


Figure 3.2: The CENTER-TBI participants represent a knowledge network that will analyze the clinical database and associated biorepositories. This highly granular "information commons", aided by novel bioinformatic approaches, will improve disease characterization, resulting in a new taxonomy of TBI (Precision Medicine). Clinical data will be subjected to CER analysis, both directly, and after refinement with precision medicine to identify more effective and targeted therapies. The increased data inputs will improve prognostic accuracy, allowing better benchmarking of care (Adapted from National Research Council).

Schedule of events

Schedule of Assessments - ER Stratum

Visit Name	Acute	≤ 72 hours from injury	2-3 weeks	3 month	6 month
Consent Subject/Consultee/Brief	x[a]				
Re-Consent		x[b]	x[b]	x[b]	x[b]
Emergency Room eCRF	x				
Post Discharge eCRF			x	X	x
Biomarker	X (1800)		X (600)	X (200)	
Genetics	X (1800)				
Routine Local Haemostasis	X[f] (1800)				
Extended Local Haemostasis	X[g] (600)				
Central Haemostasis					
Ultra Early MRI		X[c] (200)			
MRI			X (600)	X[e] (250)	
Neuropsychology Follow-Up			X[d] (600)	X (600)	X (1150)
Questionnaire Follow-Up			X (1400)	X (1300)	X (1250)

a	Consent procedure will depend on capacity assessment
b	Only if required
c	Only in sites participating in UE MR arm
d	Only in patients undergoing MR studies
e	Target patients with abnormalities on previous MR (patients who have a normal MR at 2-3 weeks will not be invited for repeat imaging)
f	Record routine clinical bloods if obtained in the eCRF
g	Only in sites participating in extended haemostatis arm

* Figures in brackets represent the number of subjects targeted for the procedure in that stratum (this accounts for funding constraints, mortality, loss to follow-up and feasibility)

Schedule of Assessments – Admission Stratum

Visit Name	Acute	Day 1-7	Day 10	Day 14	Day 21	Day 28	2-3 weeks	3 Month	6 month	12 month	24 month
Consent Subject/Consultee/Brief	x[a]										
Re-Consent		x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]
Admission eCRF	x	x[c]	x[c]	x[c]	x[c]	x[c]					
Post Discharge eCRF							x	x	x	x	x
Biomarker	X (1800)								X (1200)	X (300)	X (250)
Genetics	X (1800)										
Routine Local Haemostasis	X[i] (1800)										
Extended Local Haemostasis	X[j] (600)										
Central Haemostasis	X[j] (600)										
Ultra Early MRI	X[h] (200)										
MRI							X[e] (600)		X[f] (600)	X[g] (300)	X[g] (150)
Neuropsychology Follow-Up									X (1200)	X[d] (300)	X[d] (250)
Questionnaire Follow-Up								X (1450)	X (1300)	X[k] (1200)	X (250)

a	Consent procedure will depend on capacity assessment
b	Only if required
c	Only if an in-patient
d	Only in patients undergoing MR studies
e	Attempt to target patients who had UE MR at <72 hours
f	Attempt to target patients who had MR imaging at 2-3 weeks
g	Target patient who had MR imaging at 6 months
h	Only in site participating in UE MR arm
i	Record routine clinical bloods if obtained in the eCRF
j	Only in site participating in extended haemostatis studies
k	These patients will not have MR imaging

Schedule of Assessments – ICU Stratum

Visit Name	Acute	Post op	Day 1	Day 3	Day 4	Day 5	Day 6-7	Day 10	Day 14	Day 21	Day 28	2-3 wks	3 mth	6 mth	12 mth	24 mth
Consent Subject/Consultee/Brief	x[a]															
Re-Consent			x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]
ICU eCRF	x		x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]					
Post Discharge eCRF												x	x	x	x	x
Biomarker	X (1800)		X (1000)	X (250)	X (250)	X (250)						X (600)		X (1200)	X (300)	X (250)
Genetics	X (1800)															
Routine Local Haemostasis	X (1800)	X (300)														
Extended Local Haemostasis	X (600)	X (300)	X (600)													
Central Haemostasis	X (600)	X (300)	X (600)													
Ultra Early MRI	X[h] (200)															
MRI												X[e] (600)		X[f] (600)	X[g] (300)	X[g] (150)
HR-ICU	x[j]															
EcoG	x[j]															
EEG	x[j]															
Neuropsychology Follow-Up														X (1200)	X[d] (300)	X[d] (250)
Questionnaire Follow-Up													X (1450)	X (1300)	X[k] (1200)	X (250)

a	Consent procedure will depend on capacity assessment
b	Only if required
c	Only if an in-patient
d	Only in patients undergoing MR studies
e	Attempt to target patients who had UE MR at <72 hours
f	Attempt to target patients who had MR imaging at 2-3 weeks
g	Target patient who had MR imaging at 6 months
h	Only in site participating in UE MR arm
i	Only in site participating in extended haemostatis studies
j	Only in centres participating in these extended studies
k	These patients will not have MR imaging