STATISTICAL ANALYSIS PLAN FOR

DEXCON-TBI trial

1. INTRODUCTION

1.1 Project title	***DEXAMETHASONE FOR THE TREATMENT OF TRAUMATIC BRAIN INJURED PATIENTS WITH BRAIN CONTUSIONS AND PERICONTUSIONAL EDEMA: STUDY PROTOCOL FOR A PROSPECTIVE, RANDOMIZED AND TRIPLE BLIND TRIAL. (DEXCON-TBI TRIAL)***
1.2 Trial protocol	*DEXCON-01-2019; Versión 1/October 2019* *approved by the IRB: November 27, 2019*
1.3 Trial registration	*ClinicalTrials.gov number: NCT04303065* *EUDRA number: 2019-004038-41*
1.4 Author(s) of statistical analysis plan	*Jon Pérez-Bárcena; PhD (1)* *Guillem Frontera Juan; PhD (2)* 1. *Neuro UCI. Servicio de Medicina Intensiva. Hospital Universitario Son Espases. Instituto de Investigación de las Islas Baleares (IDISBA). Palma. Spain* 2. *Unidad de Ensayos Clínicos. Hospital Universitario Son Espases. Instituto de Investigación de las Islas Baleares (IDISBA). Palma. Spain*

2. LOGIC MODEL

Has the project's logic model (setting out the underlying logic or theory of change and a set of assumptions about how an intervention works) changed since the trial protocol was completed?	*NO*

3. CONSTRUCTION OF KEY VARIABLES

Primary of secondary outcome?	**Description of variable**	**Detailed definition**	**Any significant changes made since the trial protocol**
Primary	Proportion of patients with good recovery (Glasgow Scale Outcome Extended 7 and 8) at 1 and 6 month after injury. The scale will be dichotomized in unfavorable outcome (GOSE 1-6) and favorable outcome (GOSE 7-8).	The GOSE is an ordinal scale on which each increment represents a better quality of recovery. A GOSE score of 1 indicates death, 2 a vegetative state, 3 or 4 severe disability, 5 or 6 moderate Disability, and 7 or 8 good recovery. Since the severity of the initial injury will significantly determine the final outcome of the	no

		patient, regardless of any treatment, the results of this study will be analyzed using the 'sliding dichotomy'. According to this analysis, patients with a less severe initial injury should have a better recovery than those with a severe initial injury. For example, a moderate disability in a patient for whom no more than death or severe disability could be expected is considered a good outcome, and vice versa, consider a moderate disability in a patient with excellent initial prognosis as poor outcome. Patients with a severe initial injury (GCS score of 4 to 5 or, or with a GCS motor score of 2 to 3) will be considered to have a favorable outcome if the 6-month GOS-E score is 3 or higher.	

		Patients with a moderate-to-severe initial injury (GCS score of 6 to 8 or, GCS motor score of 4 to 5) will be considered to have a favorable outcome if the 6-month GOS-E score is 5 or higher, and those with a less initial injury (GCS score of 9 to 12, GCS motor score of 6) will be considered to have a favorable outcome if the 6-month GOS-E score is 7 or higher.	
Secondary	Volume of pericontusional edema before and after 12 days of treatment in both groups of patients.	Semi-automated manual segmentation of all intracranial traumatic lesions (contusions including both hyperdense and hypondense areas, subdural hematoma, epidural hematoma, subarachnoid hemorrhage and intraventricular hemorrhage) wil be performed. The imaging data were pseudonymized and uploaded to the QUIBIM Precision® platform (version 3.0.3; Quibim, Valencia, Spain), which was specifically designated	no

		for this study	
Secondary	Presence of adverse events between the two groups during the 12 days of treatment. Adverse events of special interest included hyperglycemia, new-onset delirium and infections	Maximum value of capillary glycemia will be recorded daily. The amount of daily insulin that the patient needs to control de glucose level will also be collected. presence of psychotic symptoms using the Confusion Assessment Method (CAM). Presence of new infectious episodes. Infectious episode will be confirmed in accordance with the Centers for Disease Control (CDC) criteria and mainly based on microbiological criteria.	no
Secondary	Number of episodes of neurological deterioration in both groups of patients during the 12 days of treatment.	An episode of neurological impairment is defined as a worsening of at least 2 points on the Glasgow coma scale or the NIHSS scale, which lasts at least 2 hours, and which cannot be fully attributed to other causes other than that cerebral edema. In order to rule out other causes of neurological deterioration, complementary tests will be performed according to the protocol of action of each hospital	no
Secondary	Symptoms associated with TBI in both groups of patients during the 12 days of treatment.	The symptoms associated with TBI will be studied daily through the Rivermead Post Concussion Symptom (RPQ) scale.	no

		The RPQ is a questionnaire that measures the severity of symptoms associated with TBI. The questionnaire contains 16 symptoms and the patient is asked to quantify these symptoms during the past 24 hours.	
Secondary	Compare the results of the neuropsychological tests between the two groups of patients one month and 6 months after the TBI.	-The MOCA (Montreal Cognitive Assessment): originally designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. - Rey Auditory Verbal Learning Test (RAVLT) is one of the most widely used word learning tests in clinical research and practice. Five presentations of a 15-word list are given, each followed by attempted recall. This is followed by a second 15-word list (list B), followed by recall of list A, and delayed recall and recognition are also tested. - Coding (WAIS-IV Battery subtest): essentially aims to	no

		assess processing speed, associative memory, graphomotor speed. - Computerized Continuous Continued Test (CPT) The CSAT-II RESEARCH VERSION: this version is used to evaluate sustained attention, discrimination, types of errors made, motor response style and response speed during the task. - Stroop test: This is a psychological test linked especially to neuropsychology that measures measuring the level of interference generated by automatisms in the performance of a task. - Digit Span (WAIS-IV Battery subtest): essentially measures auditory working memory and your ability to record, maintain and manipulate auditory information consciously. - Test Tower of London-Drexel University version test (TOLDX): measures executive planning ability in subjects with frontal lobe injury. Traditionally used as a planning and problem-solving measure.	

		- Quality of Life after brain injury (QOLIBRI) Spanish version: to measure quality of life after TBI. Through these scales and questionnaires, what is intended is to obtain information obtained, preferably, from the patient himself and simultaneously from a family member or friend (proxy) in order to corroborate the information provided by the patient himself.	

4. DATA CLEANING

Describe any steps that you intend to take to prepare the data for analysis, including whether any observations will be excluded from the analysis and how you will deal with missing data.

Handling of missing data in outcome measures	missing values will be excluded from the analysis
Criteria to be used to exclude observations from the analysis	None
Any additional data cleaning	None

5. MAIN ANALYSIS

	Default approach	Primary approach to be used
Type of treatment effect to be estimated	Modified intention-to-treat	Modified intention-to-treat basis, which included all patients who were randomly assigned, except those who withdrew consent, those who were lost the follow up or had protocol violations. Protocol violations corresponded to those patients who did not complete the 12-day treatment duration
Treatment groups to be compared	Treatment group against control group.	Dexamathasone vs placebo
Type of statistical test	The primary analysis will compare the baseline variables between both groups. In the secondary analysis we will measure the effect of dexamethasone and placebo on the patient´s functional status measured with the GOSE at one month and at 6 months, including the sliding the sliding dichotomy approach.	Values will be expressed as number of patients and percentage or median and first-third quartile (Q1-Q3) Between group differences were calculated as the value of the dexamethasone group minus the value in the placebo grupo. ARR: Absolute Risk Reduction Unadjusted t-test (for continuous variables); Chi-squared test (for binary variables); Mann-Whitney U test to compare median values
Subgroup analysis	we will conduct a pre-specified subgroup analyses in those patients with baseline pericontusional edema greater than 10 ml in the pre-inclusion CT scan	As our hypothesis holds that dexamethasone could exert its beneficial effect by reducing the pericontusional edema, we conducted a pre-specified subgroup analyses in those

		patients with baseline pericontusional edema greater than 10 ml in the pre-inclusion CT scan