
# User Manual

User Manual and General Instructions for researchers finding CENTER-TBI data in Mica and Opal

| Version number | Purpose/Change | Author | Date |
|---|---|---|---|
| 1.0 | Initial draft, proof reading, extended draft, testing, finalization | Merijn Driessen, LUMC<br>Judith Manniën, LUMC<br>Eva Timmermans, LUMC<br>Véronique De Keyser, UZA | Between 24-08-2021 and 09-03-2022 |
| 1.1 | Revision by Mica/Opal test-users | Francesca Graziano, UNIMIB<br>Véronique De Keyser, UZA<br>Merijn Driessen, LUMC | Between 20-04-2022 and 20-06-2022 |
| 2.0 | Changes for update to Mica 5.0, use of R token added. | Merijn Driessen, LUMC, Kristel Schaap, LUMC | 13-10-2022 |
| 3.0 | Updated procedures for access to data files and imaging data; added info regarding exports and token expiration; creating views removed. | Richard Wissels, LUMC, Kristel Schaap, LUMC, Véronique De Keyser, UZA | 03-04-2025 |
| 4.0 | Changes for update to Mica 6.0.1 and Opal 5.1.2 | Richard Wissels, LUMC | 13-05-2025 |

# Table of Contents

# 1. Introduction

The CENTER-TBI study data were collected in 69 sites in Europe, Israel, India, and Australia.

- The **CENTER-TBI (Europe and Israel)** dataset is composed of two parts:
  - The CENTER-TBI Registry (n= 22 782)
  - The CENTER-TBI Core (n= 4509)

- The **OzENTER (Australia)** dataset is composed of one part:
  - The OzENTER Core (n= 198)

- The **CINTER-TBI India** dataset is composed of two parts:
  - The CINTER-TBI India Registry (n= 3 904)
  - The CINTER-TBI India Core (n= 1 046)

The *Registry dataset* serves to validate and generalize results of the Core dataset.

All datasets were collected using the same e-CRF and the same inclusion criteria. The Australian and Indian dataset are more limited than the European dataset. For logistic reasons, not all variables from CENTER-TBI have been captured in the dataset of Australia and India.

This is a non-exhaustive list of data that was not or less captured in Australia:

- only ICU stratum (no ER or ADM stratum)
- only CT scans in acute phase (no MRI substudy)
- no lab sampling performed
- only waiver of consent, no confirmation of consent
- no registration of other studies, other registries or associated trials
- no physician concern recorded in TIL
- only 6 and 12month outcome
- only GOSE and SF-12 performed as outcome assessments (at 6/12 month only)
  → this means: no capture of follow up surgical data, follow up medications, follow up rehab data, follow up socio-economic data, …

This is a non-exhaustive list of data that was not or less captured in CINTER (India):

- only CT scans in acute phase (no MRI substudy)
- no lab sampling performed
- no registration of ICD codes
- no brain monitoring
- only 3 and 6 month outcome
- only questionnaires performed as outcome assessments (at 3/6 month)
- Structured Reporting of CT scans not performed (yet)

For *the Core dataset*, sites were able to participate in one or more of the three strata that are differentiated according to care path:

- Patients seen in the Emergency Room and discharged [ER]
- Patients primarily admitted to the hospital ward (non-ICU) [Adm]
- Patients primarily admitted to the ICU [ICU]

Important remark: the stratum is allocated at presentation based on planned care paths. However, possibility exist that a patient allocated to for example the ER stratum, was still admitted to WARD or ICU in a later stage of his care path due to worsening.

In addition, a number of sub-studies were performed: some patients received extensive MRI imaging and some patients received High Resolution monitoring. Inclusion in these sub-studies was centre specific.

Patients in the Core dataset had extensive follow up assessments that could go up to 2 years after enrolment. The type and timepoints of follow up assessments depend on the strata and sub-studies (see below overview).

| **Type A: questionnaires only** | **Type B: questionnaires + neuropsychological assessment** |
|---|---|
| - Participant Q A<br>- GOSE questionnaire<br>- GOSE interview<br>- SF12<br>- SF36<br>- Qolibri<br>- PCL-5<br>- RPQ<br>- PHQ-9<br>- GAD-7 | - Participant Q A<br>- GOSE questionnaire<br>- GOSE interview<br>- SF12<br>- SF36<br>- Qolibri<br>- PCL-5<br>- RPQ<br>- PHQ-9<br>- GAD-7<br><br>- Participant Q B<br>- GOAT<br>- RAVLT<br>- TMT + RAVLT<br>- Mobility<br>- CRS-R |

| | **2-3 wks** | **3 months** | **6 months** | **12 months** | **24 months** |
|---|---|---|---|---|---|
| ER non MR* | A | A | B | | |
| ER MR* | B | B | B | | |
| Adm non MR* | | A | B | A | |
| Adm MR* | A | A | B | B | B |
| ICU non MR* | | A | B | A | |
| ICU MR* | | A | B | B | B |

*non MR: patient did not receive extensive MRI imaging / MR: patient did receive extensive MRI imaging
See previous table for A (type A) and B (type B) specifications

The overall time points of assessments and investigations differentiated by stratum and sub-studies is presented below. **You can find an interactive version of this table on the last page of this document**.

**CENTER-TBI Core Data Collection : Guide to timing of assessments and investigations differentiated by stratum + Early MR imaging + Ultra early MR + External completion studies**

| | | TIME POINT | Day 1 (Adm)* | Post-op | Day 2 | Day 3 | Day 4 | Day 5 | 2-3 Week | 3 Month | 6 Month | 12 Month | 24 Month |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CORE DATA | | **ER STRATUM: 1800** | | | | | | | | | | | |
| | | **Clinical data : on presentation/discharge ER and at time of follow-up** | | | | | | | | | | | |
| MR | Blood Sampling | Routine hospital | All | | | | | | | | | | |
| | | Biomarkers | All | | | | | | MR Sites | MR Sites[2] | | | |
| | | Genetics | All | | | | | | | | | | |
| | | ROTEM/TEG[3] | ROTEM/TEG[3] | | | | | | | | | | |
| | MRI (only MR sites) | | | Ultra early MR | | | | | MR Sites | MR Sites[2] | | | |
| | Outcome Measures | Neuropsych | | | | | | | MR Sites | MR Sites[2] | All | | |
| | | Questionnaires | | | | | | | All | All(F2F) | All | | |
| Ultra Early MR | | **ADMISSION STRATUM: 1800** | | | | | | | | | | | |
| | | **Clinical data : on presentation, day 1-7, day 10, day 14, day 21 and day 28 unless discharge earlier** | | | | | | | | | | | |
| | Blood Sampling | Routine hospital | All | | | | | | MR Sites | | | | |
| | | Biomarkers | All | | | | | | | | All | MR Sites | MR Sites |
| | | Genetics | All | | | | | | | | | | |
| | | Ext. Coag[3] | Ext. Coag[3] | | | | | | | | | | |
| | MRI (only MR sites) | | | Ultra early MR | | | | | MR Sites | | MR Sites | MR Sites | MR Sites |
| | Outcome Measures | Neuropsych | | | | | | | | | All | MR Sites | MR Sites |
| | | Questionnaires | | | | | | | MR Sites | All | All | All | MR Sites |
| HR ICU | | **ICU STRATUM: 1800** | | | | | | | | | | | |
| | | **Clinical data : on presentation, day 1-7, day 10, day 14, day 21 and day 28 unless discharge earlier** | | | | | | | | | | | |
| | Blood Sampling | Routine hospital | All | | All | All | All | All | | | | | |
| | | Biomarkers | All | | All | HR ICU | HR ICU | HR ICU | MR Sites | | All | MR Sites | MR Sites |
| | | Genetics | All | | | | | | | | | | |
| | | Ext. Coag[3] | Ext. Coag[3] | Ext. Coag[3] | Ext. Coag[3] | | | | | | | | |
| Extended Coagulation | MRI (only MR sites) | | | Ultra early MR | | | | | MR Sites | | MR Sites | MR Sites | MR Sites |
| | Outcome Measures | Neuropsych | | | | | | | | | All | MR Sites | MR Sites |
| | | Questionnaires | | | | | | | | All | All | All | MR Sites |

Day 1 = Defined as day of Admission; in most cases this will be the same as day of injury, but in some (those patients presenting in the evening) it may be the next day.
Day 2 = Day after Admission
HR ICU: only sites participating in the HR ICU sub-study
[2] Initially target all patients scanned at 2-3 weeks, may later be restricted to only those with an abnormal MR at 2-3 weeks
[3] only sites participating in the extended coagulation sub-study

## 2. Understanding e-CRF, forms and variables

As the CENTER-TBI data consists of a large number of variables (over 2500 clinical variables alone), it is important to have an understanding about the overall structure of the e-CRF, the different data collection forms, and the associated variables in order to identify the relevant variables and export them.

The main structure of the e-CRF consists of data related to:

- The patient type, injury, and enrolment
- The pre-hospital and presentation status
- Additional Ward or ICU data (depending on the type of patient)
- Additional MRI or HR ICU data (depending on the sub-studies performed)
- Transitions of care
- Treatment (labs, medication, surgery)
- Outcome assessments

More details can be found in the study protocol: Maas et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI), *Neurosurgery. 2015 Jan;76(1):67-80* doi: 10.1227/NEU.0000000000000575

The categories/domains used in the data collection regrouping variables are:

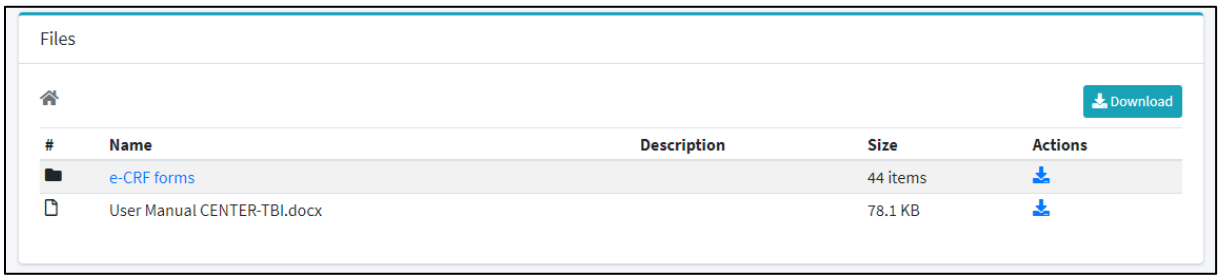
| **Domain/Dataset** | **Details** |
|---|---|
| AIS | Abbreviated Injury Scale details |
| Biomarkers | Metadata and results from biomarkers samples |
| Brainmonitoring | Metadata from ICU files |
| CTMRI | Imaging CT/MRI details, contains data in session/experiment level. We recommend however using “Imaging” domain. |
| CentralHaemostasis | Metadata and results from Central Haemostasis samples |
| DailyTIL | Daily Therapy Intensity Level |
| Genetics | Metadata from genetics samples |
| Imaging | Imaging details, CTMRI domain contains data in session/experiment level, whereas Imaging domain has data in scan level. This also contains metadata from scans including header and QC information and structured reporting |
| InjuryHx | Injury details including details coming from Cause of injury, ER therapy and discharge, ER arrival status, Second insults, Neurological assessments and Behavioral history |
| Labs | Lab values coming from ICU, ER and Admission labs. |
| LabSampling | Blood sampling data collection details |
| FollowUp | Patient follow up details coming from Unscheduled follow up, Follow up appointments, ER Therapy and discharge, Hospital discharge forms |
| Hospital | Hospital discharge and ICU monitoring details |

| | |
|---|---|
| HourlyValues | Vitals measured every second hour |
| HourlyMeasurements | Hourly values in long format with datetime |
| MedHx | Medical History prior to the accident |
| Medication | Therapies and medications during the hospital stay |
| Meds | Medication during the hospital stay |
| Outcomes | Outcomes details coming from Follow up appointments, Outcome Assessments, Rivermead RPQ, Rivermead Assessment RPQ, GOSE Structured Interview, GOSE Questionnaire, QoLIBRIOS, QoLIBRI, GAD-7 Anxiety, PCL5, PHQ9 Depression, SF12, SF36, TMT RAVLT, 10m Walk & Timed Up and Go, JFK CRSR |
| PriorMeds | Medical History prior to the accident |
| Subject | Patient details coming from Informed Consent, Demographics and Socioeconomic Status, ER therapy and discharge, Hospital Discharge, Vitals Target Dates, Neurological Assessments, Follow up appointments |
| Surgeries | Surgery details |
| SurgeriesCranial | Cranial surgery details |
| SurgeriesExtraCranial | Extracranial surgery details |
| TransitionsOfCare | Transition of care and ward admission details |
| Vitals | Daily Vitals, GCS, Four Score, Second Insults details |

Find here the overall tree structure of the eCRF with the link to each eCRF form: Annex 8

Or click on the following link or the image to access the individual e-CRF forms in MICA.

Access the e-CRF forms (at the bottom of the webpage; see screenshot below)




**Read the "_Annex_1:_Imaging" of this manual for more details on specifically the imaging data, outcome data, HR ICU data and biomarkers data.**

## 3. Data anonymization

The CENTER-TBI data is anonymized, the images are de-faced and the variables are associated with individual patients based on the Global Unique Personal Identifier (GUPI). As part of the anonymization, the following elements are modified or not available.

- Site identifier - Not available; however an anonymized site code is available.
- Country - Not available
- Dates - Date of Injury of all the subjects are made to 1st January 1970 and other dates are shifted relative to the date of injury
- Free text - all of the identifiable information were either modified or removed

## 4. Baseline derived variables

As baseline and for risk adjustment we recommend using the following variables:

- InjuryHx.PupilsBaselineDerived
- InjuryHx.GCSScoreBaselineDerived
- InjuryHx.GCSMotorBaselineDerived

For outcome, we recommend using:

- Subject.GOSE6monthEndpointDerived

For predictive modelling, the imputed variable might be preferred (see annex 3):

- Subject.DerivedImputed180DaysGOSE

## 5. Data access requests

For data access requests, submit a study plan proposal on the CENTER-TBI website: https://www.center-tbi.eu/data.

The following data access routes are available:

- **OPAL**: Access to data tables and variables in Opal . See chapters 6 to 9.
- **XNAT**: Imaging Nifti files in XNAT. See Annex 1 .
- **Personal file transfer**: Separate data files that are not stored in Opal or XNAT can be requested and will be transferred by the user in person. These files are listed in the table below

| Data files | file format(s) | number of files |
|---|---|---|
| **Imaging controls** | csv | 1 |
| **Imaging phantoms** | csv | 1 |
| **Metabolomics** | mzML | 25 |
| **Genotype data** | vcf, txt | 23 VCF files & 23 statistics files |
| **High resolution data of vital parameters** | hdf5 | 284 |
| **Imaging DICOM header files** | json | Available on request |
| **Imaging QC results** | json | Available on request |
| **Imaging Bval** | bval | Available on request |
| **Imaging Bvec** | bvec | Available on request |
| **Imaging CT Quantitative analysis (icobrain icometrix)** | csv, pdf | 2 |
| **Biomarker results ABCDx Cytokines** | csv | 2 |
| **Biomarker results ABCDx GFAP & IL10** | csv | 1 |

## 6. About Mica and Opal

Mica and Opal are part of the Obiba open source software suite.

**Mica** is an online data portal that includes the study catalogue and a searchable variable dictionary giving insight into the CENTER-TBI dataset. It also provides additional information on the study goals, design and participants.

The data dictionary, available in Mica and through the CENTER-TBI website, provides:

- A description of each variable, including measurement methods, unit type and entity type (i.e. level on which the variable was measured)
- The option groups / look-up values
- The location in the e-CRF
- A link to the e-CRF's.
- Any relevant remarks concerning the curation of variables
- Frequency tables giving some orientating insight into the availability and distributions of the data (see also annex 6)

**Opal** is the data warehouse where you can view datasets and export & download the data, or connect your local R session to the Opal server, using a special R package (OpalR). Because of its integration with R, complex statistical analysis and reports can be performed in R without having to access the Opal user interface and without having to store a dataset from Opal onto your local pc storage.

# 7. Mica

The Mica environment is an online data catalog and portal to provide insight into the CENTER-TBI dataset. It has a direct connection to the Opal data warehouse.
You can find the CENTER-TBI Mica portal at https://mica-ctbi.clinicalresearch.nl/.

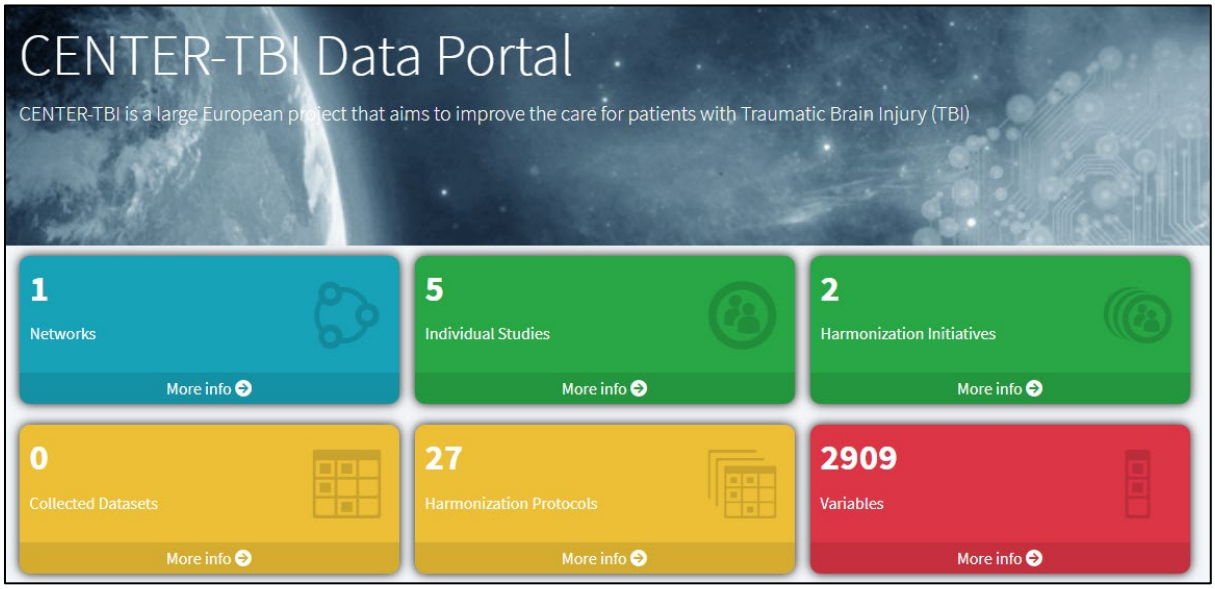
## 7.1 Login

Logging in is not necessary to enter the Mica portal or to request variables. You can log in in Mica with your CENTER-TBI account if you like to store your lists of requested variables.

## 7.2 The Mica environment

On the CENTER-TBI Mica homepage you can see the main building blocks of Mica:

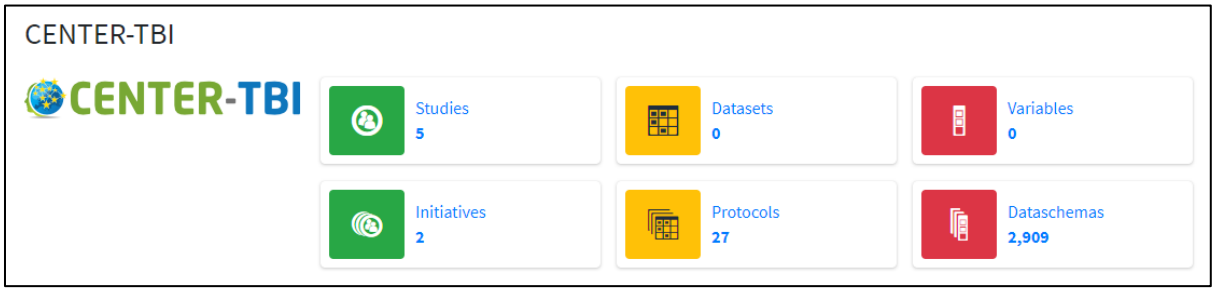
- Networks,
- Studies and Initiatives,
- Datasets and Protocols (=corresponding to the domains described in chapter 2) and
- Variables.



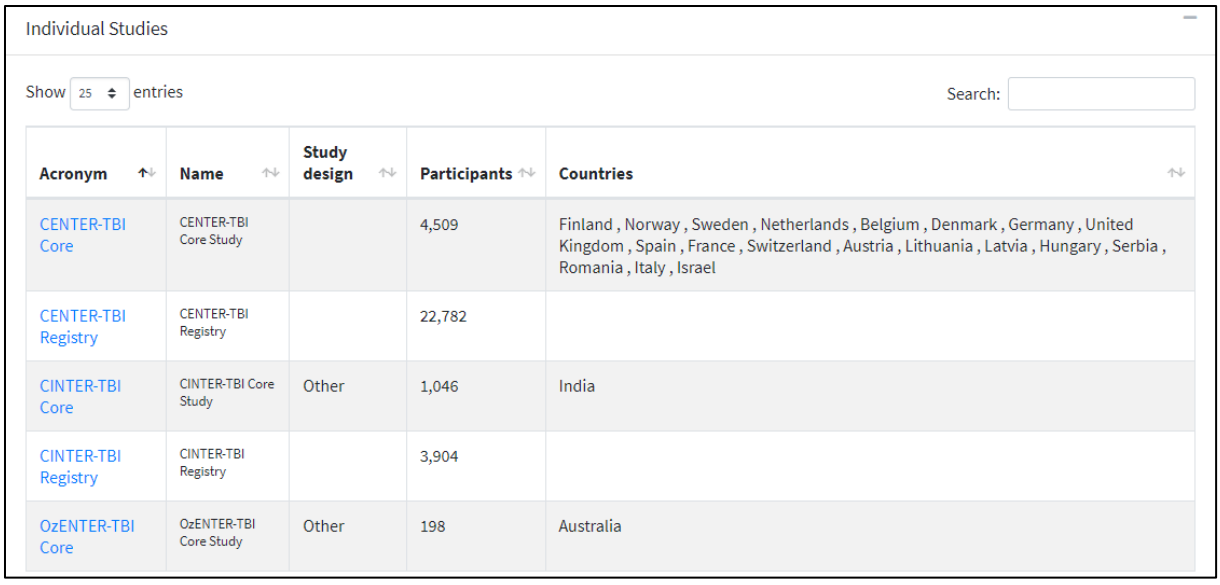

### 7.2.1 Networks, Studies, Initiatives, Protocols and Variables

The network is the overarching umbrella that houses the various studies. By clicking on networks, you can find the CENTER-TBI network. Click on ‘Read more’ to navigate to the network page.


The network page shows an overview of the number of studies, initiatives, datasets, protocols and variables within the CENTER-TBI network.

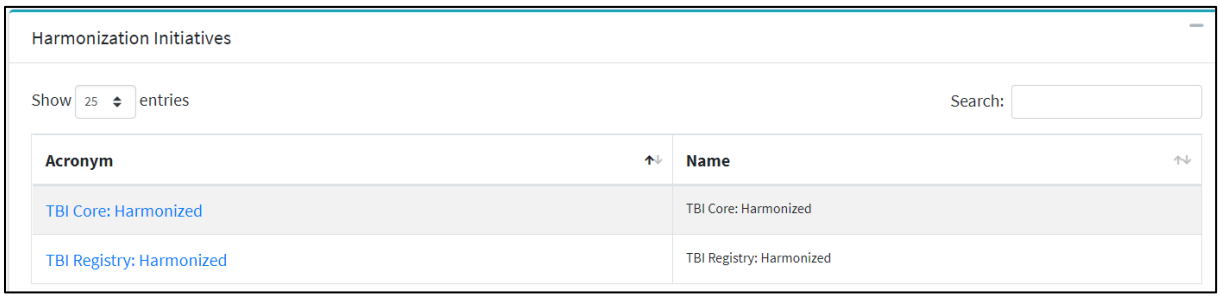



The network currently holds 5 individual studies: CENTER-TBI Core, CENTER-TBI Registry, OzENTER Core, CINTER Core and CINTER Registry. By clicking on one of these studies, you will be taken to the study-specific page.
The study pages of the individual studies show information on the study details, including study design, the timeline, the number of participants and availability of data.

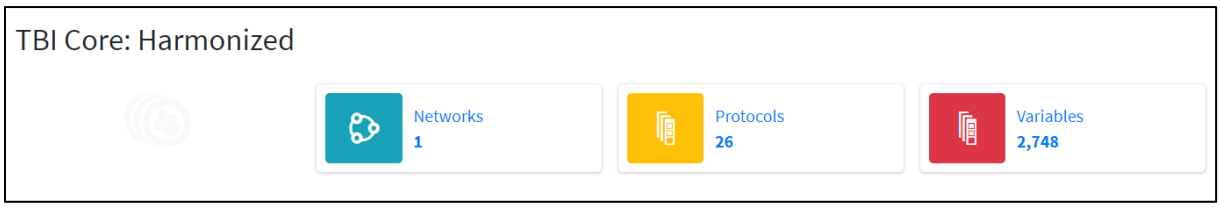



| Acronym | Name | Study design | Participants | Countries |
|---|---|---|---|---|
| CENTER-TBI Core | CENTER-TBI Core Study | | 4,509 | Finland , Norway , Sweden , Netherlands , Belgium , Denmark , Germany , United Kingdom , Spain , France , Switzerland , Austria , Lithuania , Latvia , Hungary , Serbia , Romania , Italy , Israel |
| CENTER-TBI Registry | CENTER-TBI Registry | | 22,782 | |
| CINTER-TBI Core | CINTER-TBI Core Study | Other | 1,046 | India |
| CINTER-TBI Registry | CINTER-TBI Registry | | 3,904 | |
| OzENTER-TBI Core | OzENTER-TBI Core Study | Other | 198 | Australia |

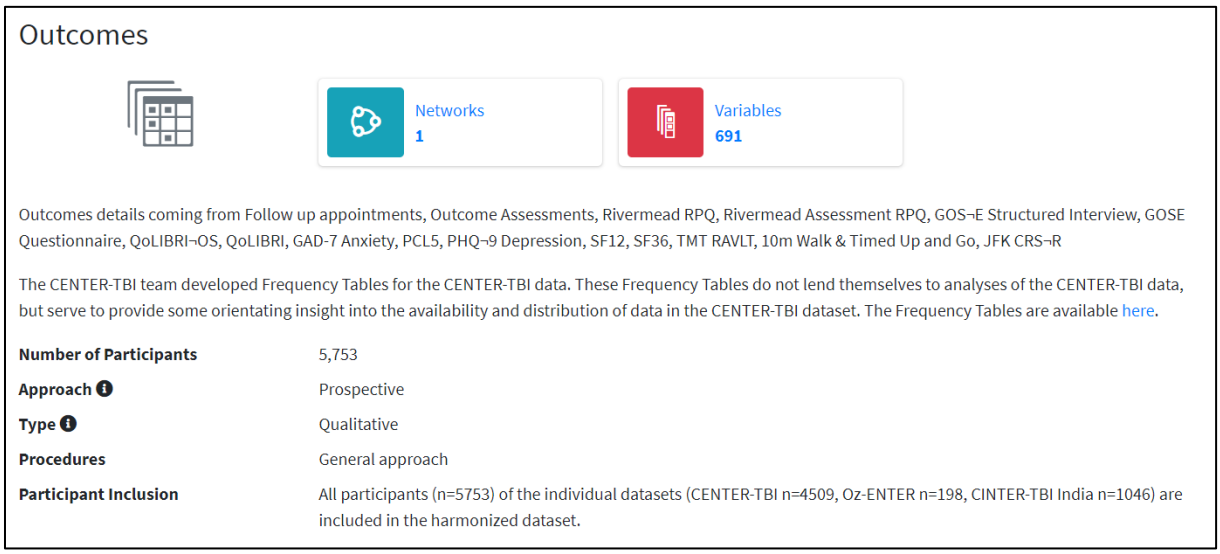
Note that the individual study pages do not include information about the actual datasets and collected variables; you can find these in the Harmonized Initiatives.
The Center-TBI network contains 2 overarching Harmonized Initiatives: 'TBI Core: Harmonized' and 'TBI Registry: Harmonized'. You can find these at the bottom of the Network page, under 'Harmonization Initiatives', or on the homepage behind the green box.




To see the specific datasets or variables that belong to the Center-TBI studies, select one of the Harmonization Initiatives and click on the icons for Protocols or Variables. This will guide you to the search environment, where all protocols and variables are listed.




The protocols are equal to the data tables that belong to each study (see also domains described in chapter 2). Clicking on a protocol shows information on the contents of the dataset and shows the number of variables that make up de dataset. An example of a dataset ('Outcomes') can be seen in the following figure:




The studies for which this dataset has been harmonized can be found under 'Studies Included' (under each "Dataset"). Here you can click on the study, population or data collection event for more information on the included studies.

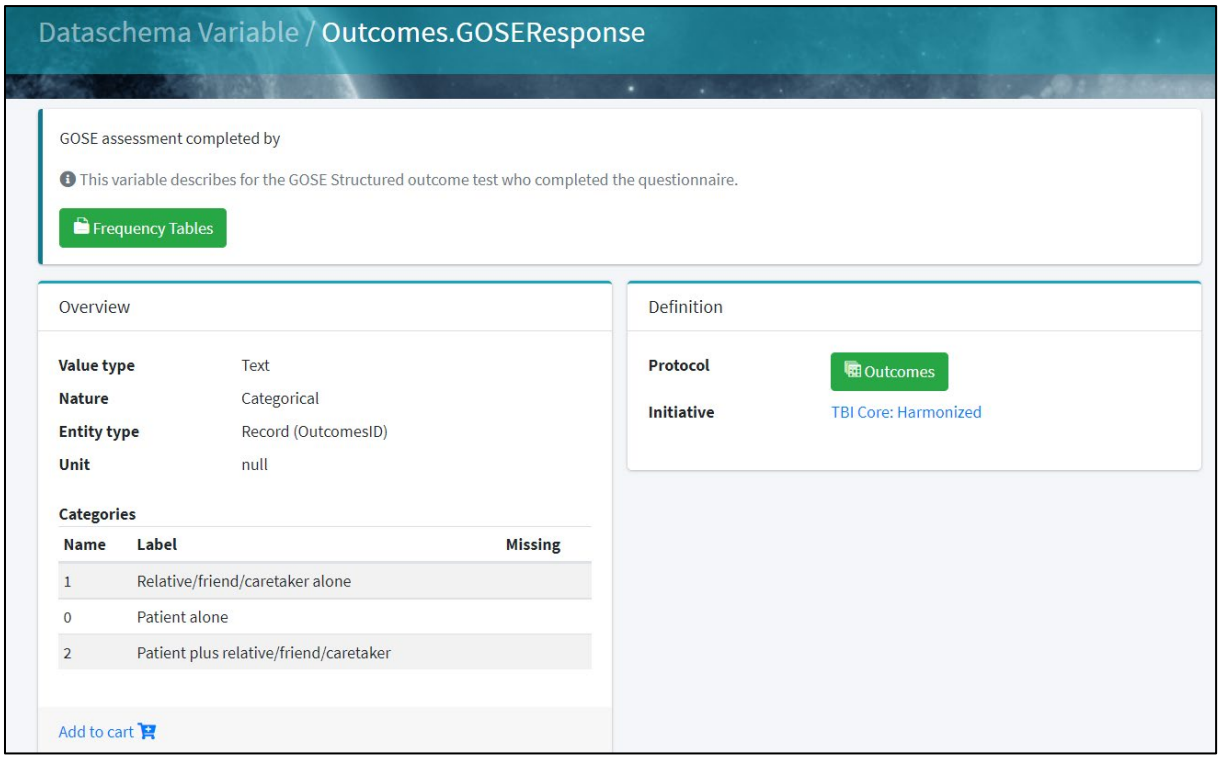
Studies Included

| Study | Population | Data Collection Event |
|---|---|---|
| CENTER-TBI Core | TBI patients CENTER-TBI Core | CENTER-TBI data collection |
| CINTER-TBI India Core | TBI patients CINTER-TBI | CINTER-TBI India data collection |
| OzENTER-TBI Core | TBI patients OzENTER-TBI | OzENTER-TBI data collection |

At the bottom of the protocol page you can find an overview of the harmonization. It shows which variables in this protocol are available from the different included studies. Some variables will only be available in the CENTER-TBI study, since they were not collected in CINTER-TBI India and OzENTER-TBI. This overview can also be downloaded by clicking the download button.

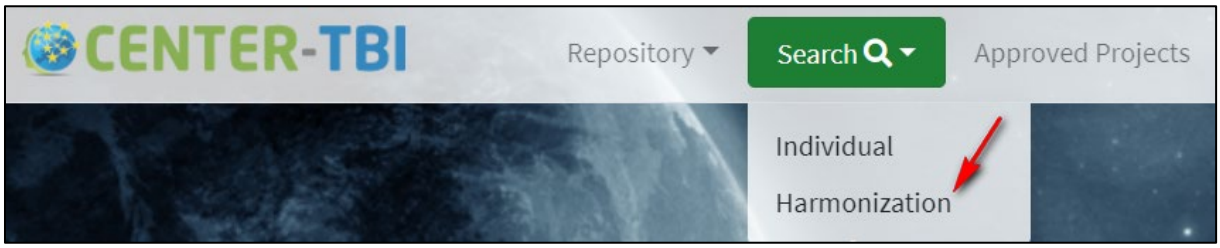
| Variable | CENTER-TBI Core CENTER-TBI Outcomes | CINTER-TBI India Core CINTER-TBI Outcomes | OzENTER-TBI Core OzENTER-TBI Outcomes |
|---|---|---|---|
| Outcomes.OutcomesID | ✓ | ✓ | ✓ |
| Outcomes.SubjectID | ✓ | ✓ | ✓ |
| Outcomes.Timepoint | ✓ | ✓ | ✓ |
| Outcomes.GOSEDate | ✓ | ✓ | ✓ |
| Outcomes.GOSEQuestionnaireMode | ✓ | ✓ | ✓ |
| Outcomes.GOSEResponse | ✓ | ✓ | ✓ |

The protocol page also includes a list the variables collected in this protocol. If you click on one of the variables in the list, you will be directed to an overview page for the selected variable, providing you with extra insight into its metadata, based on the CENTER_TBI data dictionary.

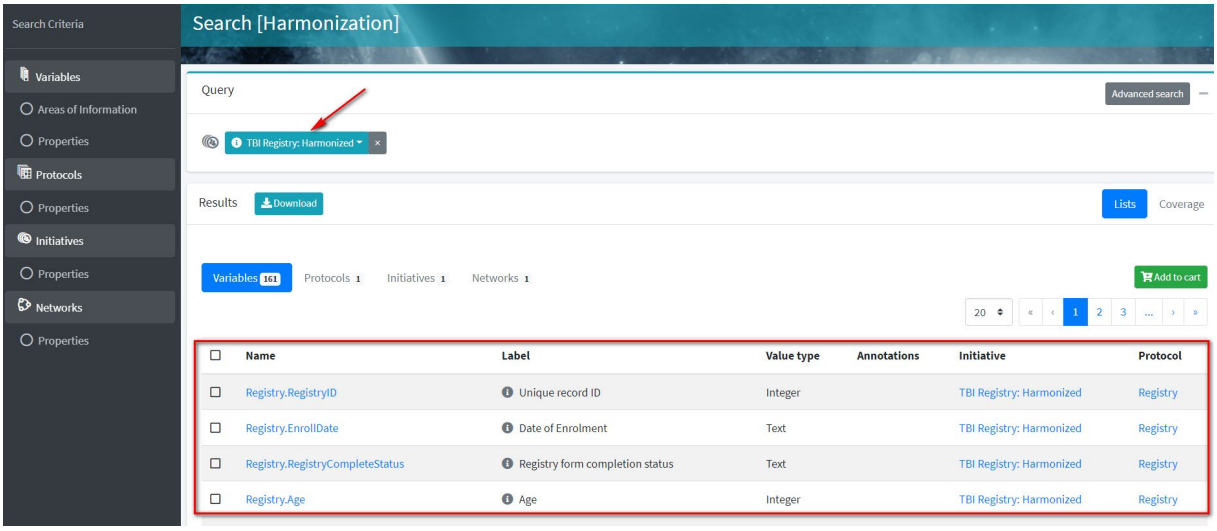


## 7.3 The MICA search environment

To search for variables or protocols, click on the green Search button on the top of the screen and select ‘Harmonization’.




You can also get to the search environment if you click on the red ‘Variables’ box on the Mica homepage or another page. Depending on where you do this, the search environment will automatically filter for that selection. For instance, when you are in the ‘TBI Registry: Harmonized’ project and click on the red ‘Variables’ box, the search environment will automatically list all variables within TBI Registry:

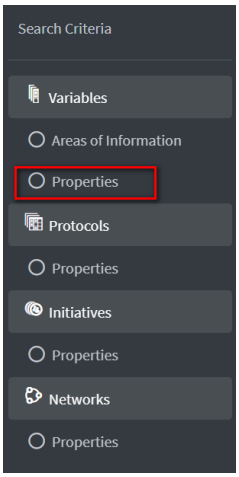



Clicking on any of the shown search results (highlighted in the red box above) will take you back out of the search environment and to the page of your selected variable, protocol or harmonization initiative.

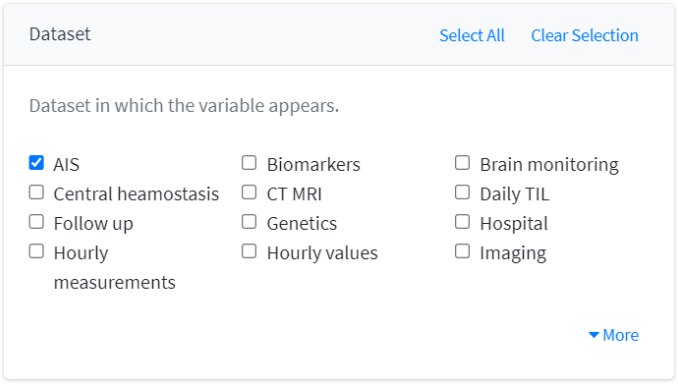
### 7.3.1 Searching within the search environment

The search environment gives you the ability to search for specific Harmonization Initiatives, datasets (here named Harmonization Protocols) or variables.
When searching within the search environment, make sure that you select the right level. For instance, when you want to search variables, you need to select the ‘Variables’ button :

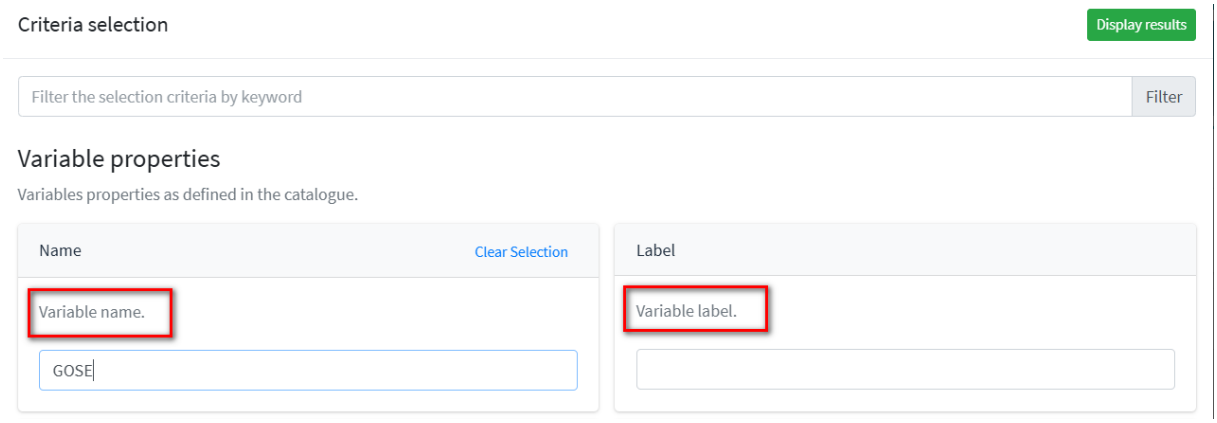
By making use of the properties buttons in the search criteria menu on the left, you can narrow down your search.




For instance, when you click on *Properties* under *Variables*, you can narrow down your selection by Study, Dataset or data type or search for parts of the variable name or variable label.
For example, by selecting the Dataset AIS, it will show only the available variables within the AIS table.

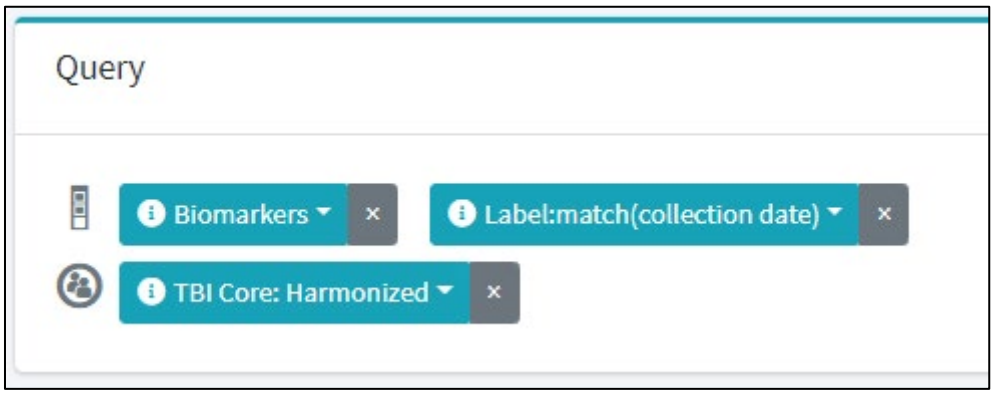



You can also search for specific variables, using (part of) the variable name or label.



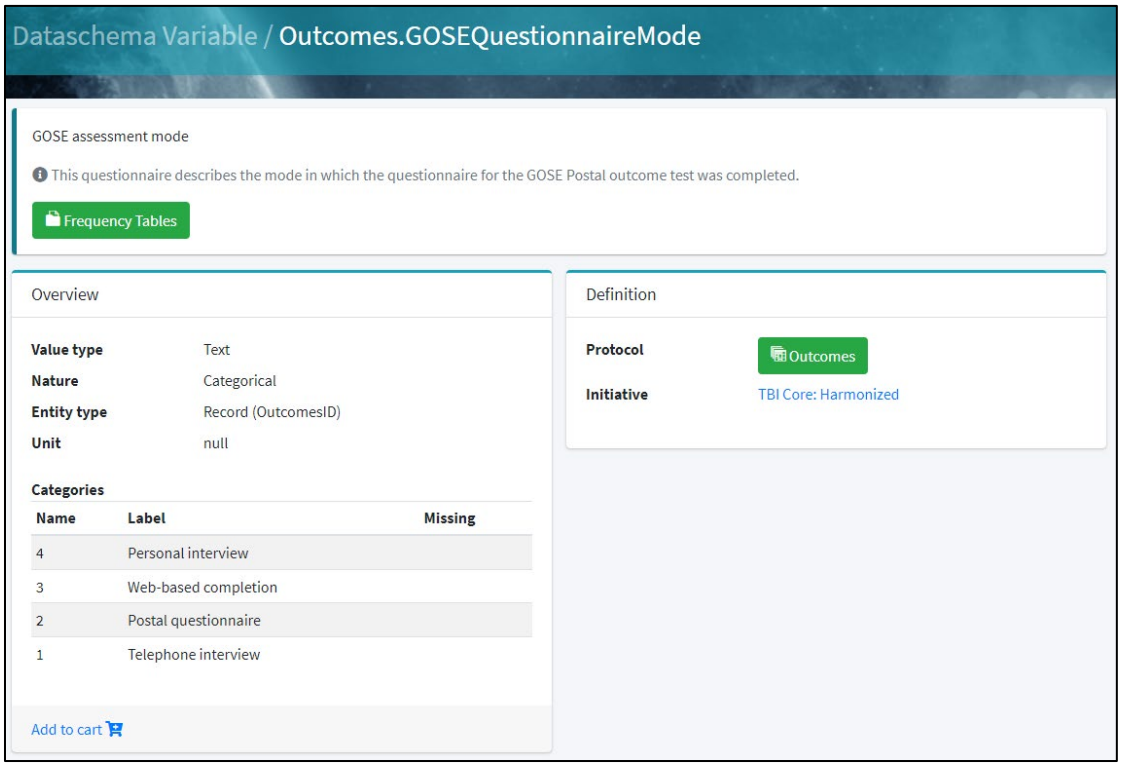
After specifying your selection, click ‘Display results’ on the top right of the window.


By using a combination of variable names/labels and studies or datasets, you will always be able to find the correct variable. The selection criteria that you chose will be shown at the top, under ‘Query’.




By clicking on the criteria, you open a small menu where you can always alter your criteria, and further specify the request. By clicking the crosses, you can quickly remove unwanted criteria.

Once you have found your chosen variable, you can click on the name to be directed to an overview page for the selected variable, providing you with extra insight into its metadata, based on the CENTER_TBI data dictionary.

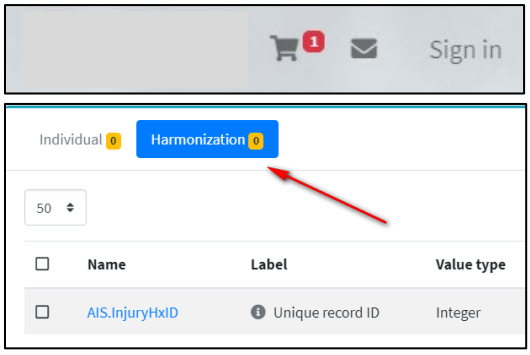


# 8. Data access requests and shopping cart in MICA

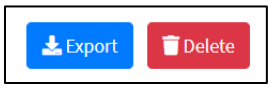
External researchers who are not part of the Center-TBI collaboration, can request access to variables in Opal required for their research proposal. In the MICA catalogue they can search for relevant variables (as described in the previous chapter) and select these for their data access request, as described below.

By clicking 'add to cart' in MICA, either on the variable page or within the search environment, you can add a variable to your shopping cart. You can also select multiple variables within the search environment, and then click on the green 'add to cart' icon in the top right:


You can see which variables are currently in your shopping cart by clicking the 'cart' icon in the top row and go to 'Harmonization' to see the items listed:




The variables in your shopping cart can be downloaded as a zip file, by clicking the 'Export' button on the shopping cart page. The zip file contains multiple csv files.




When you are logged in to Mica with your Agate account (see: 9.1 sign up), you can add the items in your shopping cart to lists that can be stored for later re-use or export. Creating and saving multiple lists is possible. Your lists can be found next to your cart on the top right.

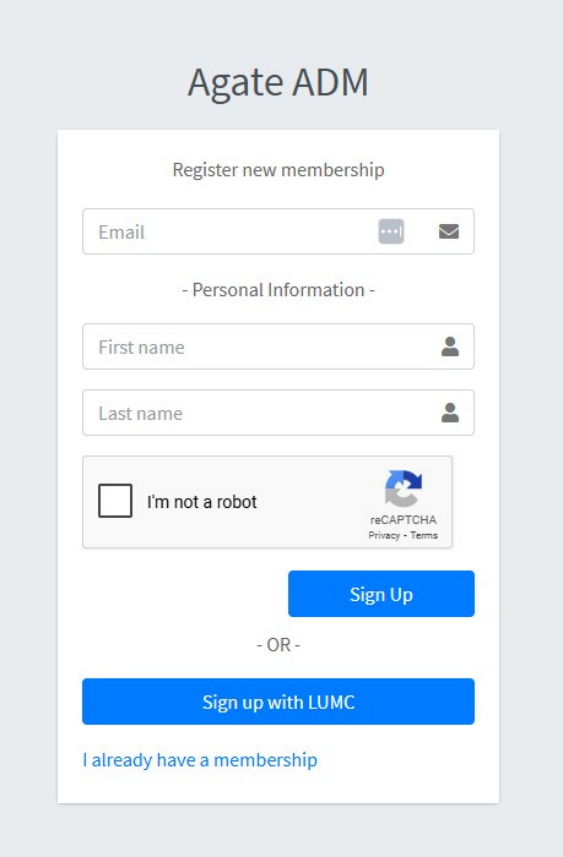

**Attach the original, unchanged zip file to your data access request, to clarify the variables that you would like to request.** For further information about data access requests, see **(https://www.center-tbi.eu/data)**.

# 9. Opal

Opal is the core data warehouse application of OBiBa software stacks that provides all the necessary tools to import, validate, derive, query, report, analyze and export data. Because of its integration with R, complex statistical analysis and reports can be performed within Opal as well.
Further user guides of Opal are available here.

## 9.1 sign up

All users that require access to Opal, will need an account in Agate first, to register in Agate go to https://agate.clinicalresearch.nl/signup. If you have a LUMC account there is a difference in the sign up method, which is explained below.




After registering in Agate, you will not yet have access to Opal. To get access, you have to inform the ADM project manager; who will be able to arrange you access to Opal and add you to relevant projects and tables.

### Regular sign-up for non LUMC users:

You are able to register yourself into Agate by filling in your work Email address, name and verifying that you are not a robot, and pressing the “Sign Up” button. You will then receive an email with the message your account is under review. An Agate administrator at ADM will approve your sing-up request (this might take some time). When your request has been approved, you receive another e-mail which lets you create an password. Note: Never share your password with other people and keep it safe.

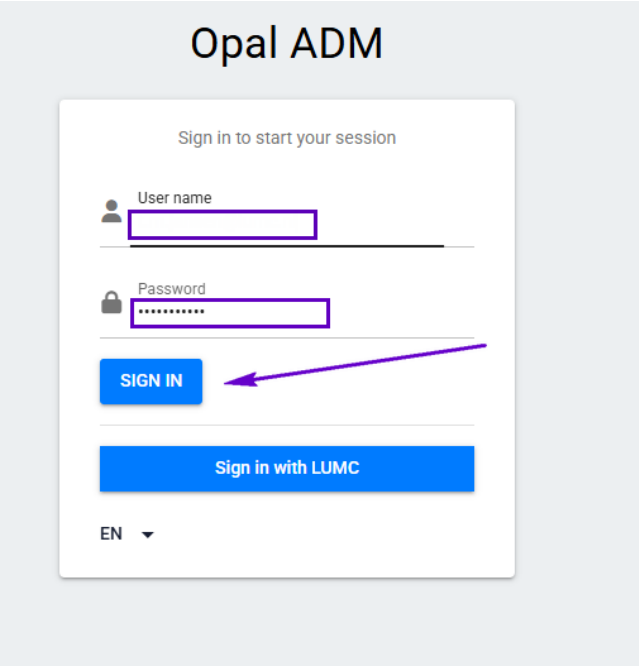
### For users with LUMC account:

If you got an LUMC account, it is possible to register yourself into Agate using the “Sign up with LUMC” button. After clicking on this button, you will receive a permissions requested popup for the Obiba production environment (Microsoft popup), which you have to accept. This will lead you into an already filled in screen from which you only have to press the Sign Up button at the bottom. After this you get the confirmation screen your membership registration has been completed.

### Login into Opal:

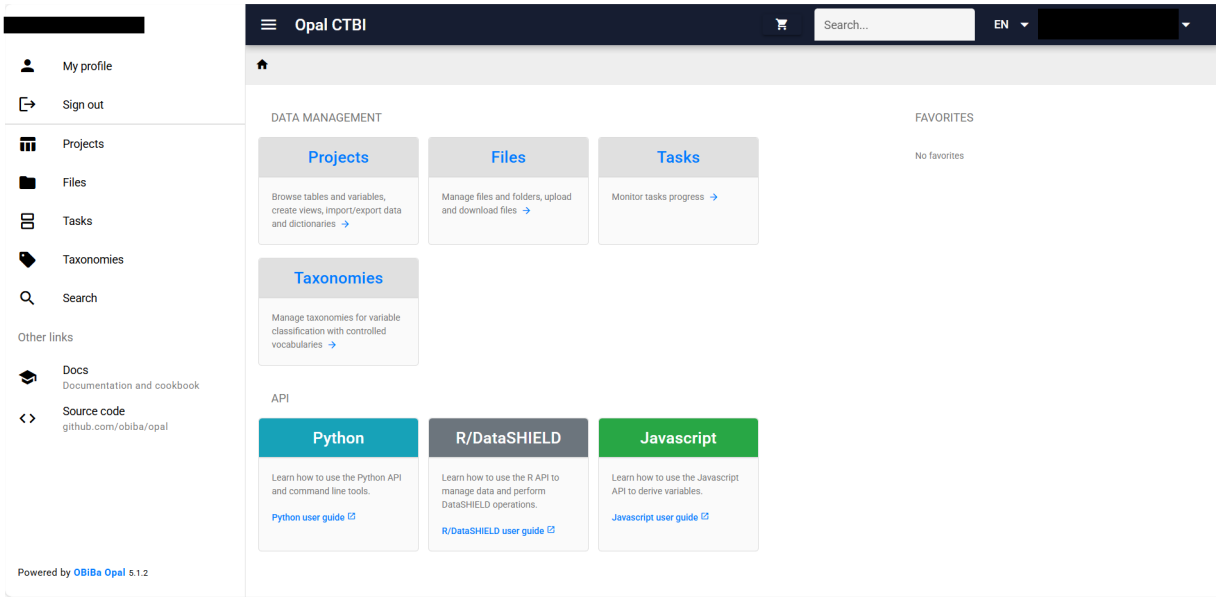
When your Agate account has been set up and approved, ADM will notify you that your account has been linked to your opal project. After this, you can login into opal via https://opal-ctbi.clinicalresearch.nl/ or Mica via https://mica-ctbi.clinicalresearch.nl/.

1. LUMC users that access have to sign in via the “Sign in with LUMC” button.
2. Users outside of the LUMC can fill in their username and password and press the "SIGN IN" button. When first logged in, you are asked to set up Two-factor authentication (2FA). It is mandatory you configure 2FA login before you are able to access projects and tables/data views within Opal. After setting this up, each time you login you will be asked to fill in your 2FA code from the authenticator app.



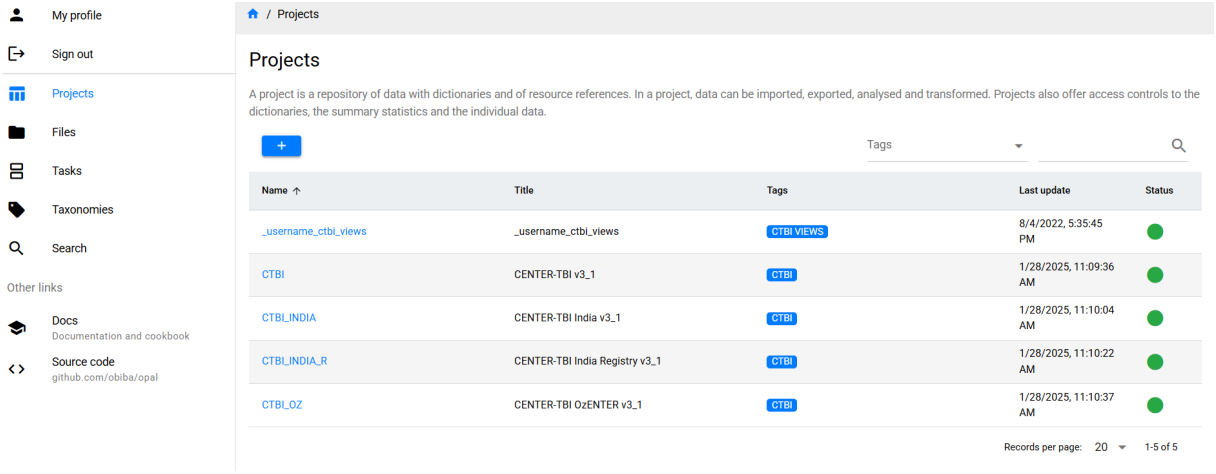

## 9.3 The Opal environment

Upon opening Opal, you start on the dashboard page. From the dashboard you can navigate to your datasets, search specific tables or variables, and manage files within the Opal environment.

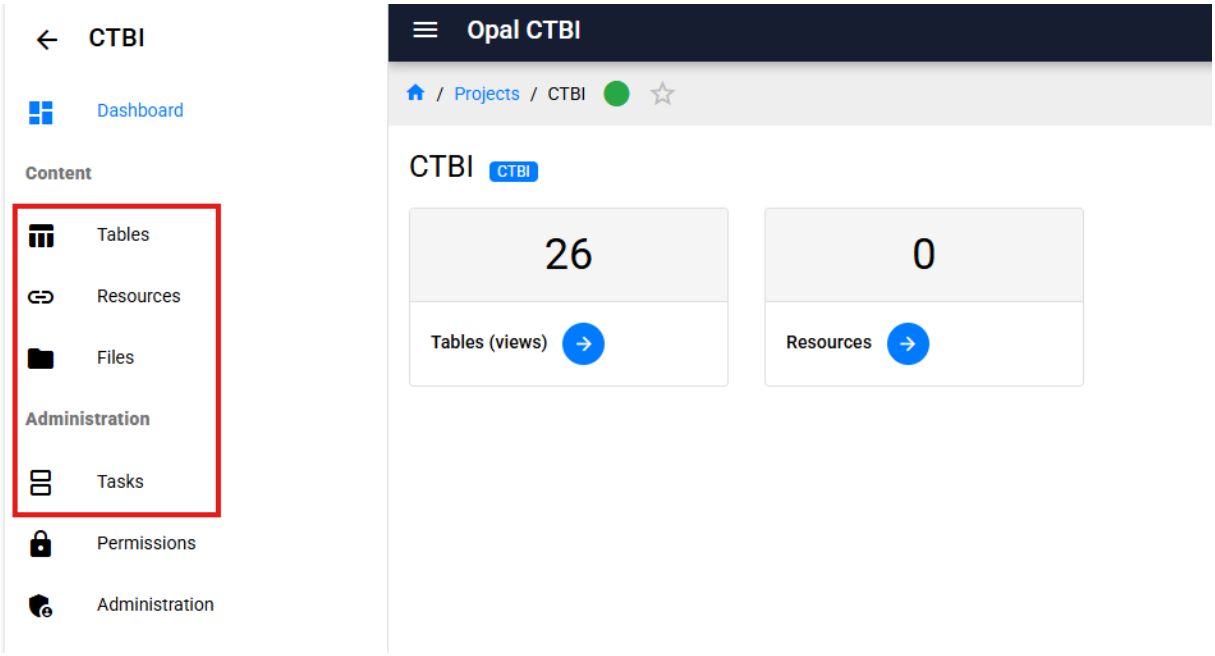



### 9.3.1 Exploring data in Opal

To get to the data, you can go to 'Projects' button, or click on 'Projects' in the side bar. This will guide you to the project section, where you can find the different datasets: CENTER-TBI Core, CENTER-TBI Registry, CINTER-TBI India Core, CINTER-TBI India Registry and OzENTER-TBI, or for external researchers: the views that have been created for your project.

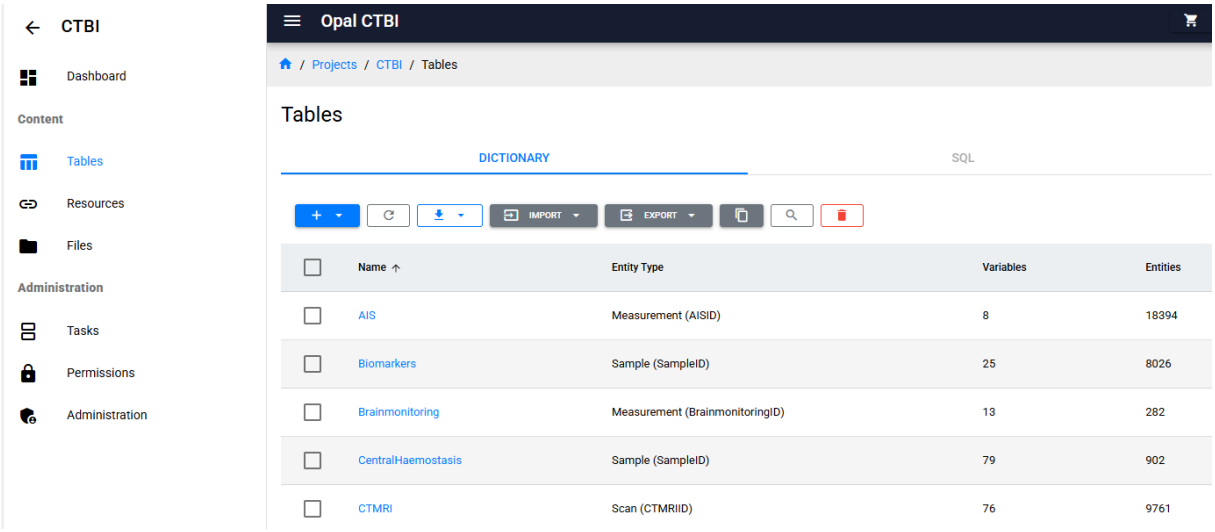



Clicking one of the projects will take you to the project Dashboard. The project dashboard gives an overview of the number of tables/views that are available within the project.




Using the options on the left side, you can navigate to different sections.

Tables directs you to the tables section within the project.

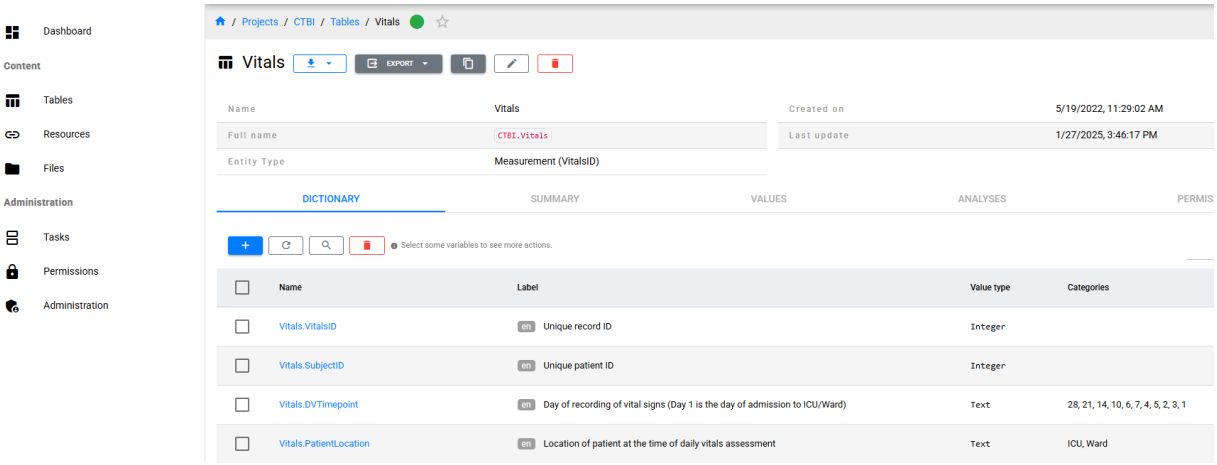



The overview also shows the number of variables and entities, which corresponds with the number of unique ID's. The column 'Entity Type' gives some insight into the nature of the ID's.

In the tables section you can click on the tables to navigate to a table. You can also select tables for export, or write SQL statements to make subsets of the data. More on how to use these options can be found in the export section of this manual.

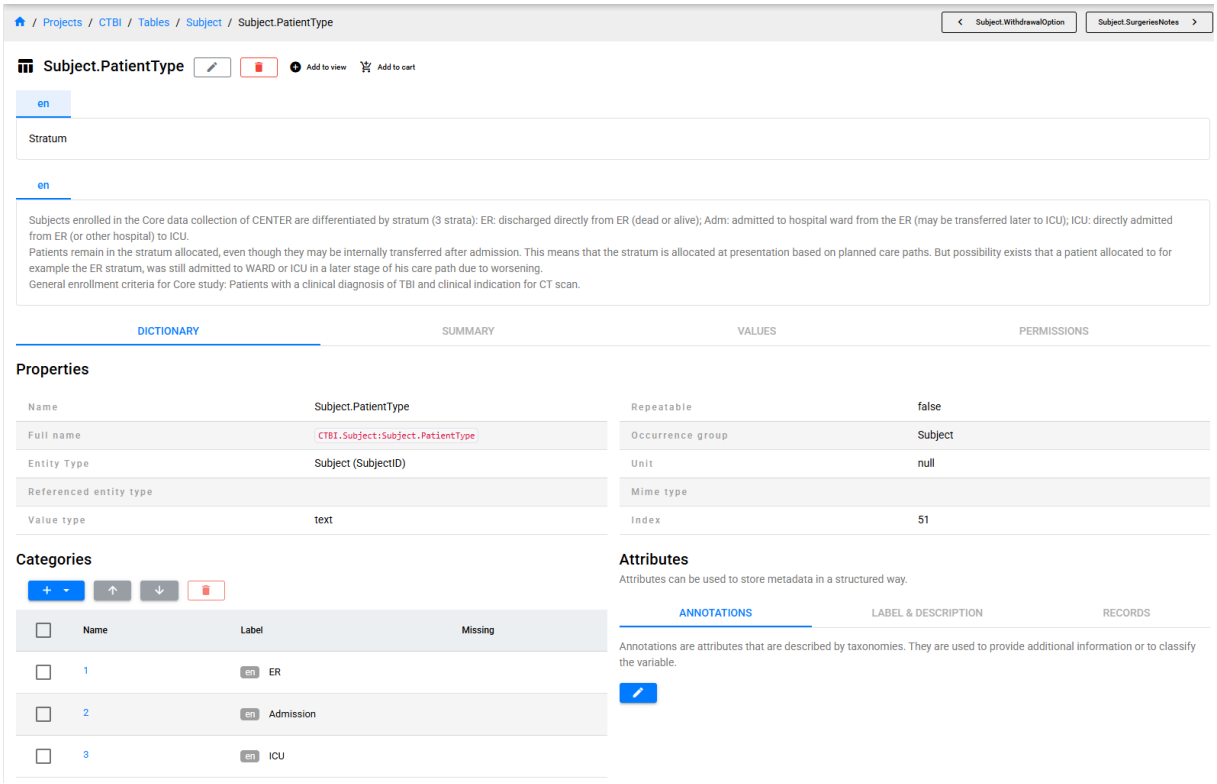
After clicking on a table, you will see an overview of all the variables in the table.

*Table 'Vitals' (in the study 'CTBI'):*

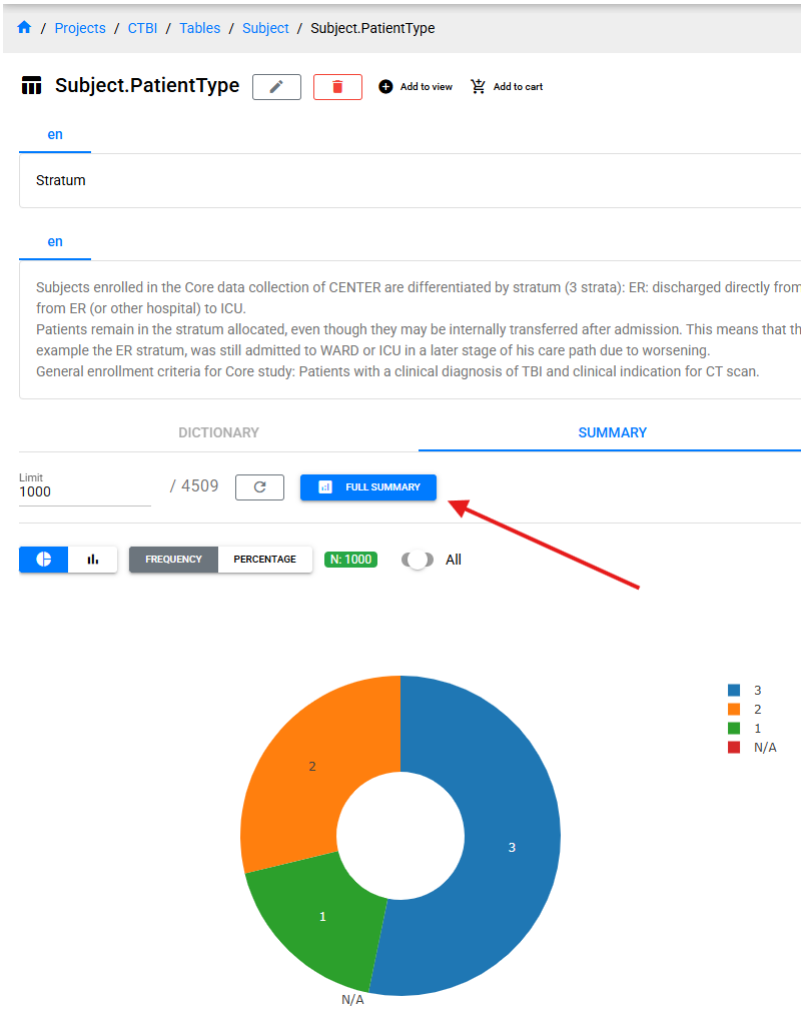



Here you can click on a variable to see more details, or select variables for creating views.

*Variable 'Subject.PatientType' (in the table 'Subject', in the study 'CTBI'):*

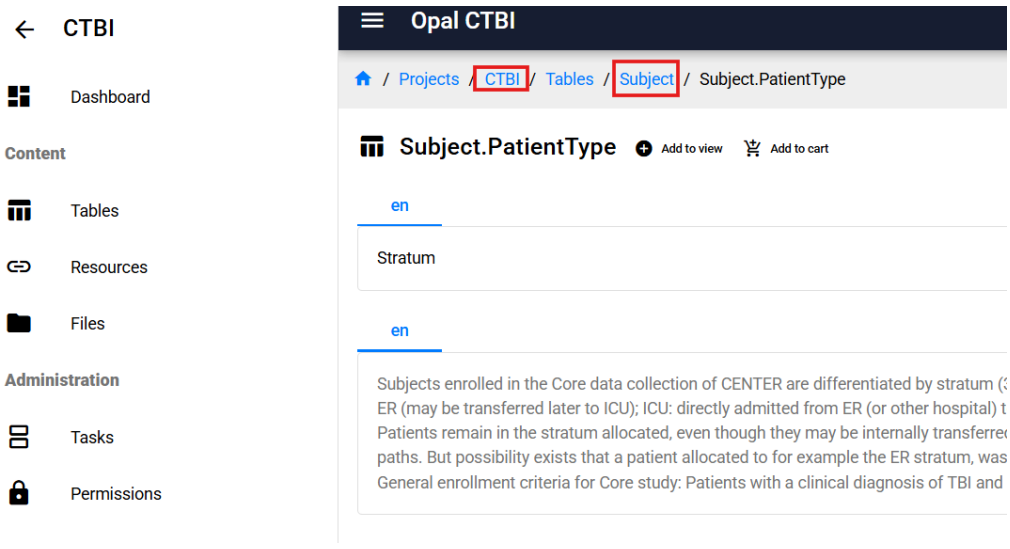



The 'Summary' tab gives an overview of the basis data descriptives, such as frequency diagrams and tables. !Note that by default Opal only shows the summary data based on the first 1000 records. Click on 'Full Summary' to see the summary of all records.




The 'Values' tab shows you a table of the data values for this specific variable.

When you are looking at a specific variable, and you want to go back to the table view, click on the table name, *e.g.* "Subject". You can also use the "back" option in the browser. When you want to go back to the list of all the tables in the Project, you can click on "CTBI" in this example:



| | | |
|---|---|---|
| | Files | directs you to the files system, where you can find your downloaded files and extract them to your computer. Also see 'Exporting your data'. |

## 9.4 Exporting your data

There are two ways of accessing the data in Opal for data analysis. The recommended method is to load data into R through a direct connection with Opal. You can run your analyses in R, without having to store the data outside Opal. In this way, the data don't leave the server and this prevents many copies of the data roaming around. Alternatively, exporting the data to data files for use within other programs is also possible.

### 9.4.1 Loading data into R

To analyze the data, you can load tables and views into R. R is widely used free statistical software that is available for Windows, MacOS and UNIX platforms. For more information on R, or to download the software, you can go to https://www.r-project.org/. It is recommended to also use the Rstudio software, which provides a more user-friendly graphical interface. Rstudio can be downloaded here.

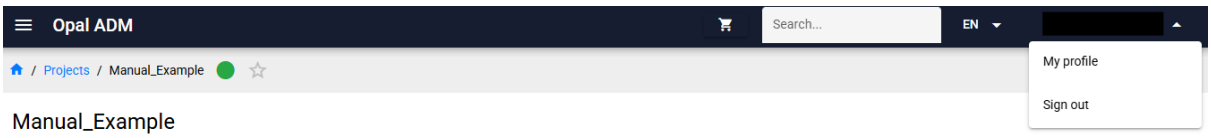
For loading data from Opal into R, you need the 'opalr' package. To install and use this package, you can run the following commands in R:

```
install.packages('opalr')
library(opalr)
```

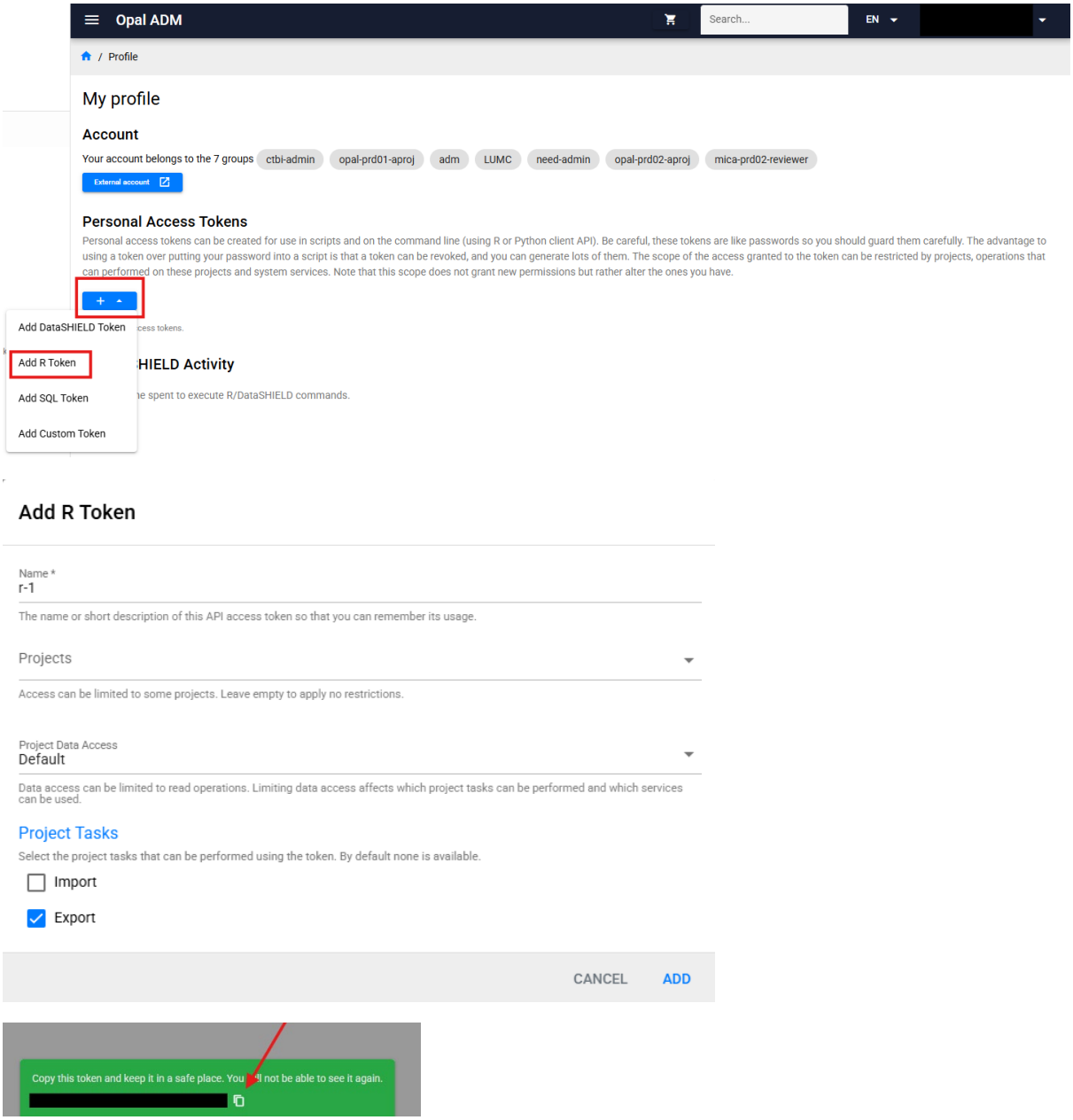
You use a personal Opal token to make a connection to the Opal database. Never type your token directly in your R scripts, since scripts might be shared with other people or stored on shared spaces. It is strongly recommended to save your token in a password manager, instead of directly in your scripts. The 'keyring' R package is recommended as a good way to safely store your token(s) in the password vault on your pc.

**Store your Opal token with the keyring package (this needs to be done only once):**

1. Navigate to Opal and login. Click on My Profile by clicking on your username




2. Click on the **Add Access Token** button followed by **Add R token**.
    a. A standard name is provided for your token. If you wish, you can change the name.
    b. Remember the token name you've entered and copy the token that has been created. Please note that the token will appear only once!
    c. Leave 'Projects' empty to get access with this token to all your Opal projects. If you wish to work with only one or two projects, you can select the names of those projects.
    d. At 'Project tasks', make sure that 'export' is selected.




3. Open R
4. Make sure you've installed the 'keyring' package in R:

```
install.packages('keyring')
library(keyring)
```

5. Set keyring by the following script: *keyring::key_set("name of your token").* You can give any name you wish to the key, but it would make sense to choose the same name as given to the R token in step 2. A pop-up will appear. Paste the token that has been created in step 2. You will not see a confirmation, but you can check whether the key has been stored correctly by typing: *keyring::key_get("name of your token").*
6. The keyring will be saved in the Windows Credential Store (or other system safe store) of your device.

**Use the keyring to access Opal**

To make a connection to the Opal database, run the following code in R:

```
opal_connection  <- opal.login(token = keyring::key_get("name of your token"), url ='https://opal-ctbi.clinicalresearch.nl/')
```

For loading your data into R, you can use the opal.table_get command as shown below, where you need to insert the name of your project and view or table in the appropriate place. After loading the data, it is ready to be used for data analysis within R.

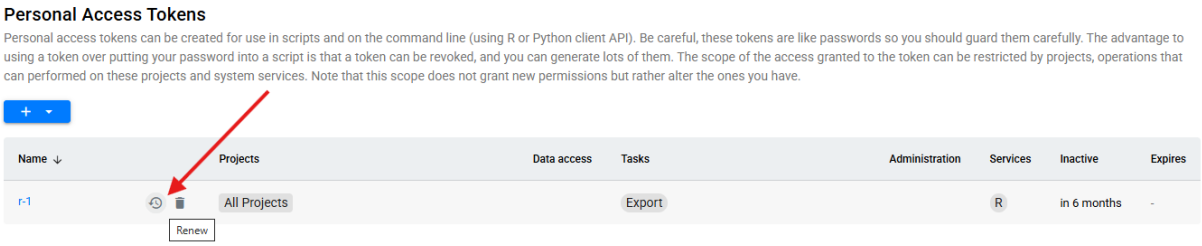
```
data_table1 <- opal.table_get(opal = opal_connection, project = 'insert name of project' , table = 'insert view or table name')
```

*e.g.*

```
data_table1 <- opal.table_get(opal = opal_connection, project = 'CTBI' , table = 'Surgeries')
```

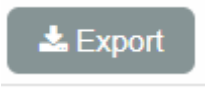
**Expiration of Opal tokens**

Please note that an Opal token expires 2 months after last use. When your token is expired, you can renew the token yourself by logging into Opal, going to your profile and under Personal Access tokens, click on the 'renew' symbol.



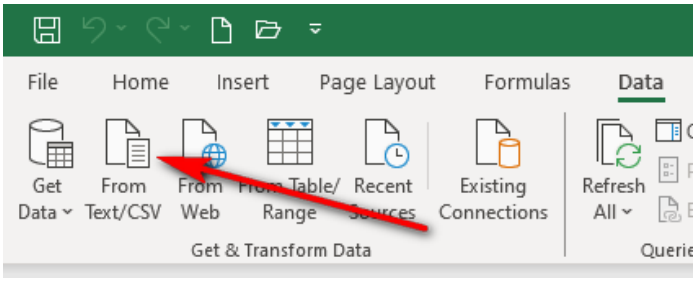

## 9.4.2 Exporting to a data file

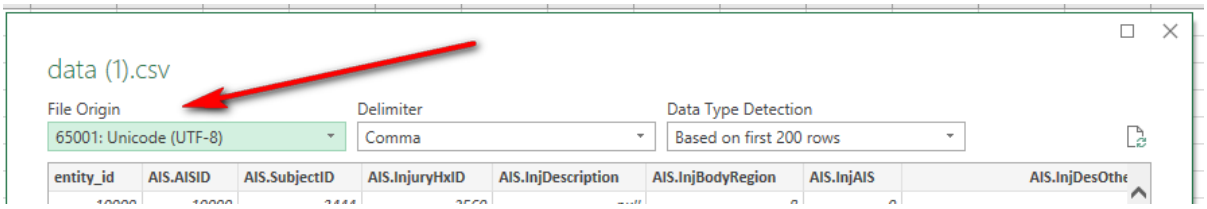
If you prefer not to work with R, it is also possible to export data from Opal into various formats, like CSV or SAV (SPSS). To do this, you have to navigate to the view, and then click on the export button. A window will pop up where you can specify the data format.




The export will be placed in your personal export folder within Opal, found in the files section. From there, you can download it to your personal computer. The file will stay available in your export folder for later use, until you delete it.

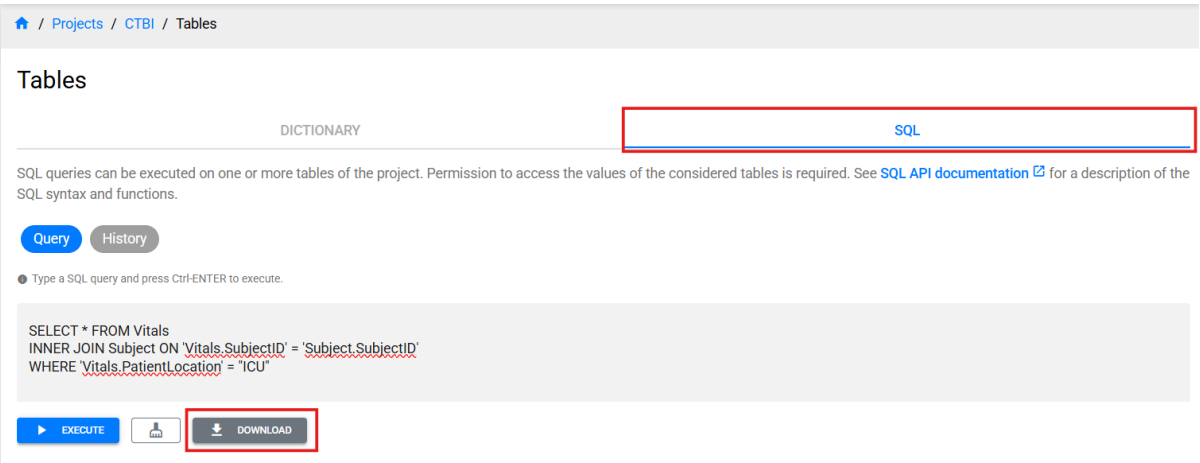
***Note**: Several text fields in Opal contain special characters, including Greek notations such as 'µ' to describe units of volume, size or weight. If you wish to use these fields in your analyses, please make sure to choose the correct encoding (UTF-8) when reading in the exported files. For example, when reading in a downloaded CSV file into Microsoft Excel, first open Excel and then read in the CSV file:*




### 9.4.3 SQL selections

When making manual exports from Opal, it is also possible to use SQL statements to make selections in variables and records, commonly known as queries. In the 'SQL' tab, users can use standard SQL commands like SELECT, FROM and WHERE to make selections for the specific use-case. It is important to use backticks (`) around the names of table and variables within these query statements. The selection can be downloaded using the download button below the query. Creating joins between tables is also possible. **Beware** that this should only be used if the user has experience with SQL, as it is easy to make mistakes leading to incorrect datasets.




## 9.5 Deletion of personal view projects

For external users outside the Center-TBI collaboration, a personal view project is created which contains views on the variables they requested for their research project.

Once a user account has been deactivated, their personal view project will be deleted 1yr after last login date.

# 10. Useful Links

CENTER-TBI website: https://www.center-tbi.eu/

Data Dictionary: https://datadictionary.center-tbi.eu/

GitLab Repository: https://git.center-tbi.eu

Data access & publication requests https://www.center-tbi.eu/data

Cantab manual: https://www.center-tbi.eu/manual/CANTAB-RS6-v20140728

# Annex 1: Imaging data

The domain 'Imaging' contains all the imaging-related variables in the Opal tables. These include (meta-)data concerning the imaging files, such as scanner settings and scan datetime, but also information extracted from interpretation of the images.

The actual imaging scans are stored as Nifti files in XNAT, hosted on a server at the Leiden University Medical Center. XNAT is an open-source imaging informatics software platform developed by the Neuroinformatics Research group at Washington University, enabling access and viewing of the available Nifti scans. Access to the imaging files in XNAT can be requested via the Center-TBI office (see chapter 5, 'Data access requests').

In addition, access to the following imaging metadata files can be requested trough the Center-TBI office:

| Data files | file format(s) |
|---|---|
| **Imaging controls** | csv |
| **Imaging phantoms** | csv |
| **Imaging DICOM header files** | json |
| **Imaging QC results** | json |
| **Imaging Bval** | bval |
| **Imaging Bvec** | bvec |
| **Imaging CT Quantitative analysis (icobrain icometrix)** | csv, pdf |

By searching the domain 'Imaging' in Opal, you can access all the imaging-related variables in the Opal tables.

| Variables in the Imaging table that contain the term 'URL' can be used to link the external files to the applicable data record: data file type | opal variable | variable content |
|---|---|---|
| **Nifti files** | Imaging.NiftiURL | XNAT URL per experiment (NB. multiple scans are possible per URL) |
| **Snapshots** | Imaging.SnapshotURL | "Can be found in XNAT under the specified scan session." |
| **Thumbnails** | Imaging.ThumbnailURL | "Can be found in XNAT under the specified scan session." |
| **Dicom headers** | Imaging.DicomHeaderURL | Filename |
| **QC results** | Imaging.QCResultsURL | Filename |
| **Bval** | Imaging.BvalURL | Filename incl folder structure (because file names are not unique) |

| | | |
|---|---|---|
| **Bvec** | Imaging.BvecURL | Filename incl folder structure (because file names are not unique) |

We recommend using the "**Imaging.**" domain primarily, since that domain combines all data from CTMRI and FollowUp together with the imaging Meta data.

The "Imaging.CRF…" variables combine imaging data extracted from the e-CRF.

e.g. Imaging.CRFTimepoint = CTMRI.Timepoint + FollowUp.Timepoint.

**Central Structured and Standardized Reporting** was performed using the NINDS CDEs on all interpretable CT images. By searching "StructuredReporting" you can access this data.

An R code has been developed to help you extract into comprehensive tables the detailed structured reporting information from the Imaging.LesionData variable (JSON files). The code is available in the CENTER-TBI Gitlab. You will also find an interactive diagram of the 25 CDEs and their possible attributes on the CENTER-TBI Gitlab.

CT early is considered "**first CT**". When a Central review is not available this can be due to:

- Scan uninterpretable (wrong scans, bad quality, etc.)
- Scan not available/performed/uploaded

  Reasons for scan not being available included:

  - Scan performed in referring hospital and images not available
  - Pediatric patient and MR performed instead of CT (reducing radiation risk)
  - Patient too uncooperative to undergo scan, and no indication for sedation.

In order to obtain the reports for the initial CT scan, follow the next steps:

1) in Opal download Subject.Gupi, Imaging.ExperimentId, Imaging.Timepoint and your variables of interest;

2) select for unique values of Imaging.ExperimentId;

3) select for timepoint = CT early;

4) you should get 4221 CT early reports of which 4088 were interpretable and interpreted

To measure the reproducibility of imaging data, in particular DTI data with the aim to enhance standardized analyses, both **phantom** and **healthy volunteer** data were collected in a selected number of sites. These files can be requested at the Center-TBI office.

For the following list of experiment IDs, Nifti scans are not available. This can be due to the uninterpretability, Dicom missing, preprocessing failed, too few slices, slice increment inconsistency, spine scans uploaded, etc..

| | | |
|---|---|---|
| CTBI_E00720 | CTBI_E01568 | CTBI_E06282 |
| CTBI_E00750 | CTBI_E02498 | CTBI_E06314 |
| CTBI_E00806 | CTBI_E02714 | CTBI_E06316 |
| CTBI_E01185 | CTBI_E04472 | CTBI_E06338 |

CTBI_E06358
CTBI_E07598
CTBI_E08970
CTBI_E10511
CTBI_E10515
CTBI_E10517
CTBI_E13350
CTBI_E13751
CTBI_E14440
CTBI_E15031
CTBI_E18183
CTBI_E18185
CTBI_E19049
CTBI_E19985
CTBI_E20029
CTBI_E20033
CTBI_E20035
CTBI_E20043
CTBI_E20497
CTBI_E21936
CTBI_E25935
CTBI_E27070
CTBI_E28374
CTBI_E29423
CTBI_E30197
CTBI_E32561
CTBI_E32569
CTBI_E41403
CTBI_E43223
CTBI_E43227
CTBI_E43231
CTBI_E43235
CTBI_E43239
CTBI_E43243
CTBI_E43247
CTBI_E43251
CTBI_E43255
CTBI_E43259
CTBI_E43263
CTBI_E43267
CTBI_E43271
CTBI_E43275
CTBI_E43279
CTBI_E43283
CTBI_E43287
CTBI_E43291
CTBI_E43295
CTBI_E43299
CTBI_E43303
CTBI_E43307
CTBI_E43311
CTBI_E43315
CTBI_E43319
CTBI_E43323
CTBI_E43327
CTBI_E43331
CTBI_E43335
CTBI_E43339
CTBI_E43343
CTBI_E43347
CTBI_E44845
CTBI_E45724
CTBI_E47528
CTBI_E54085
CTBI_E54687
CTBI_E56454
CTBI_E65876
CTBI_E65993
CTBI_E66128
CTBI_E66364
CTBI_E66384

For the following list of GUPI's there is no imaging data available because no images have been uploaded to the central repository:

| | | | | |
|---|---|---|---|---|
| 2aKg329 | 3Mxj242 | 5hqa779 | 7CGC395 | 8rWe275 |
| 2aZc954 | 3nxp645 | 5hSR652 | 7DkP965 | 8swy254 |
| 2CwE756 | 3QtP966 | 5iBD359 | 7dKx492 | 8Tvi853 |
| 2CYR995 | 3rqp487 | 5iLF374 | 7dMi577 | 8xyJ537 |
| 2DLL573 | 3rth894 | 5JHf259 | 7FEV334 | 8Ypg329 |
| 2EeT899 | 3tPx998 | 5kgp479 | 7fzL326 | 8YQm799 |
| 2enN423 | 3Vzc963 | 5kGq874 | 7GjL839 | 9bkT239 |
| 2FXu462 | 3xYA486 | 5kxA247 | 7hBd367 | 9bPn863 |
| 2GBu796 | 3zCu247 | 5LXx254 | 7hQS673 | 9BQE783 |
| 2GEY763 | 4aiT765 | 5QpW899 | 7keL575 | 9ceB526 |
| 2gSm989 | 4arN655 | 5qyM254 | 7Ndj855 | 9frd568 |
| 2Hqs463 | 4cNx999 | 5uEp795 | 7ryW383 | 9gzj428 |
| 2LSz237 | 4CRz375 | 5xfa852 | 7TAg459 | 9hYZ524 |
| 2nEF378 | 4FmV422 | 5Xrg353 | 7TFQ763 | 9Khz638 |
| 2Njt548 | 4fVB478 | 5yeX796 | 7tjT299 | 9LSS688 |
| 2pjV364 | 4GiQ982 | 5zEy356 | 7Uig748 | 9NAk452 |
| 2qbz679 | 4hJR542 | 6Amc624 | 7UiY495 | 9qCk363 |
| 2Qjc754 | 4hWG766 | 6AQD757 | 7uXt263 | 9qsP965 |
| 2rCM426 | 4JAW268 | 6bJy778 | 7VDS928 | 9QwR739 |
| 2SiV997 | 4Jbh597 | 6CSJ667 | 7vzi267 | 9SzG278 |
| 2tYg498 | 4mrf549 | 6eVk586 | 7Xrc556 | 9TAP374 |
| 2UFb788 | 4pUb945 | 6ezY353 | 7yAV286 | 9tfK563 |
| 2uKc322 | 4qeX427 | 6HuM739 | 7ydN775 | 9thB794 |
| 2VdG646 | 4Qzq727 | 6itq446 | 7YeE448 | 9umj552 |
| 2xPq786 | 4rde674 | 6iYc665 | 7Zmp573 | 9UUC848 |
| 2yuc942 | 4RST279 | 6KNy732 | 7ZqT564 | 9UYd464 |
| 2ZFf733 | 4SnU954 | 6RLt465 | 8ahU997 | 9VdG934 |
| 2zUX287 | 4vnx935 | 6sqR823 | 8aYp777 | 9Wcr656 |
| 2Zzf943 | 5bDR966 | 6teA862 | 8bcT775 | 9WXx422 |
| 3bwd673 | 5btz622 | 6VmM865 | 8cdZ428 | 9xNa427 |
| 3Cen349 | 5BwA829 | 6Xtv852 | 8cZU858 | 9XtN928 |
| 3dsY975 | 5DPs832 | 6yeM346 | 8dAj689 | 9yPZ753 |
| 3dyu657 | 5Dzy536 | 6Yvw547 | 8fgS499 | 9zQx843 |
| 3gAJ693 | 5fWB355 | 6ywi954 | 8iga477 | |
| 3HCR796 | 5GXU253 | 6ZQE735 | 8kCf765 | |
| 3iUs972 | 5hDc979 | 6ZTC457 | 8PTs464 | |
| 3MiC879 | 5hPD942 | 7AcU632 | 8qdZ537 | |

# Annex 2: High Resolution ICU data

By searching the domain 'Brainmonitoring', you can access all the High resolution ICU related variables.

To gain access to the HDF5 files themselves, a data access request can be made via the Center-TBI office. Once the request has been approved, a personal data transfer will be prepared and additional information will be provided on how to download the files.

Variable Brainmonitoring.HDF5URL in domain 'Brainmonitoring' contains the file names that could be used to link the data records in Opal and the HDF5 files belonging to each record.

# Annex 3: Outcome data: GOSE scoring

There are four main sources for GOSE ratings in CENTER-TBI, summarized as follows:

(1) Clinician overall GOSE rating (*Outcomes.GOSEScore)*. Structured interviews for the GOSE were conducted face to face or by telephone with either the patient or another informant. Interviewers then assigned an overall rating. Occasionally a clinician rating may have been recorded without an interview, if contact was not possible, and there was sufficient information from other sources.

(2) Centrally assigned GOSE based on structured interview responses. Completed GOSE questionnaires were assigned a rating centrally on the basis of the responses recorded, as described above.

(3) GOSE self-report questionnaire scored centrally as already described. Questionnaires could be completed by patients alone, by patients with the help of carers, or by relatives / carers alone.

(4) Deaths assigned using date of death in the database. Central scoring added the outcome rating 'dead' to the composite GOSE variables when appropriate. 'Dead' is assigned if (a) the date of death occurs before the follow-up window for the timepoint has closed, (b) no other outcome has been assigned to the composite (from interview or self-report sources), (c) A follow-up is due at the timepoint per protocol.

Approaches to GOSE assessment used in CENTER-TBI were sufficiently well aligned to justify construction of composite and derived variables for use in subsequent analyses.

In Mica/Opal you will find the following available GOSE variables:

*Outcomes.GOSEScore:*

This GOSE Structured rating was assigned by the rater/interviewer at the time of the interview and entered in the e-CRF for a particular follow-up time-point, along with responses on the sections of the interview.

*Outcomes.DerivedCompositeGOSE:*

This GOSE rating is a derived composite score calculated from sources in the following order of precedence:.

(a) Central scoring based on GOSE interview questionnaires completed by investigators

(b) Central scoring based on GOSE self-report questionnaires completed by patients and/or carers

(c) Interviewer ratings for survivors, when neither the interview or self-report questionnaires have been completed

(d) From date of death or investigator recorded death

*Subject.GOSE6monthEndpointDerived:*

A six month GOSE endpoint that uses both observed ratings (i.e. *Outcomes.DerivedCompositeGOSE)* and imputed values (when the observed value was missing or outside the pre-specified time window (5-8 months))

*Subject.DerivedImputed180DaysGOSE:*

This variable contains a GOSE that has been imputed at exactly 180 days after injury. In this variable the observed values also were replaced by imputed values.

We recommend using **Subject.GOSE6monthEndpointDerived** for analyses. This variable conforms to conventional expectations that imputation is only used when observed values are not available.

For predictive modelling, the imputed variable **Subject.DerivedImputed180DaysGOSE** might be preferred. This variable takes advantage of smoothing accomplished by the imputation process, and avoids using a hybrid of observed and imputed values.

These variables have very similar values and the choice of which to use will have little in the way of practical implications.

A MSM model has been used for imputation in both variables
(see also https://www.liebertpub.com/doi/10.1089/neu.2019.6858).

*Outcomes.GOSEScore* and *Outcomes.DerivedCompositeGOSE* contain a higher number of missing values and are not being recommended for general-purpose use in subsequent analyses.

The GOSE was collected at 3 months and 6 months across all strata, and at 12 months in the admission and ICU strata. Depending on the strata and on the MRI sub-study the GOSE may have been collected in other subgroups at particular timepoints. The same rules and models have been applied for 3 month and 12 month outcome, leading to the following variables available in Mica/Opal:

Subject.GOSE3monthEndpointDerived

Subject.DerivedImputed90DaysGOSE

Subject.GOSE12monthEndpointDerived

Subject.DerivedImputed360DaysGOSE

**GOSE scoring OzENTER (Australia) dataset:**

GOSE was measured by either a postal questionnaire or a structured telephone interview by a trained assessor.

*Subject.GOSE6monthEndpointDerived*: does not include imputed values in the OzENTER data set. It equals the composite GOSE at 6 months.

**GOSE scoring CINTER India dataset:**

*Outcomes.GOSEScore*

For the 3 and 6 month GOSE scoring, the Indian investigators did not perform a structured interview (as was done in CENTER-TBI), since this was too time consuming for many patients. The investigator asked some general questions about quality of life and how the patient felt and then completed the GOSE questionnaire in the e-CRF based on their clinical judgement. Hence, the "Outcomes.GOSEScore" variable is a guided interview, in line with the original GOS approach, in which the clinician has a description of different GOS categories and, based on the information available, makes a judgement about the overall rating.

*Outcomes.DerivedCompositeGOSE / Subject.GOSE6monthEndpointDerived:*

Data entered in the Postal GOSE, is a copy of the interview GOSE – no postal questionnaires were performed.

As questionnaires were only interview based, no composite or derived variable is available for the Indian dataset, the variable "Outcomes.GOSEScore" should be used.

# Annex 4: Outcome data: Cantab

Researchers who wish to understand the way that the CANTAB tests are administered and the outcomes are derived, should refer to the CANTAB Eclipse Test Administration Guide that is available through this link: https://www.center-tbi.eu/manual/CANTAB-RS6-v20140728

The guide to modes and outcome measures that gives the key to the specific CENTER-TBI outcomes as recommended by Cambridge Cognition can be found below.

There is some redundancy among these outcomes and researchers may want to be selective in their final choice of variables.

The main (confounding) covariates for these tests are age and education level, and particularly the former. These need considered in analyses.

The CANTAB outcomes can be skewed and/or have outliers, and depending on your analysis you may want to transform (e.g. Log10) and/or truncate variables or otherwise deal with these problems.

***CANTAB: Guide to Modes and Outcome Measures for CENTER-TBI study***

Cambridge Cognition. February 2016
Research - Cantab Research Suite


## Attention Switching Task (AST)

Designed to assess: executive function that provides a measure of cued attentional set-shifting (cognitive flexibility)

Mode: *8d1-8d2-40d2a-8s-40sa-8s8d-40s40da*

| Block | Number of Trials | Rule? | Practice or Assessed? | Feedback |
|---|---|---|---|---|
| **1** | 8 | Direction | Practice | Yes |
| **2** | 8 | Direction | Practice | Yes |
| **3** | 40 | Direction | Assessed | No |
| **4** | 8 | Side | Practice | Yes |
| **5** | 40 | Side | Assessed | No |
| **6** | 16 | Direction and Side | Practice | Yes |
| **7** | 80 | Direction and Side | Assessed | No |

Duration: ~8 minutes

| Key Outcome Measures | Definition |
|---|---|
| **Median Switching cost** | The difference between the median latency of response (from stimulus appearance to button press) during assessed blocks in which the rule is switching versus assessed blocks in which the rule remains constant. Calculated by subtracting the median latency of response during non-switching block(s) from the median latency of response during switching block(s). This measure is complex in sense. Close to zero indicates less variation in latencies across non-switch and switch trials. A positive score indicates that the subject responds more quickly in non-switching block(s). |

| | |
|---|---|
| **Median Congruency cost** | **The difference between the median latency of response (from stimulus appearance to button press) on the trials that were congruent versus the trials that were incongruent. Calculated by subtracting the median congruent latency (in ms) from the median incongruent latency. This measure is complex in sense. Close to zero indicates less variation in latencies across congruent and incongruent trials. A positive score indicates that the subject is faster on congruent trials and a negative score indicates that the subject is faster on incongruent trials.** |
| **Median Reaction Latency** | The median latency of response (from stimulus appearance to button press), calculated across all correct, assessed trials |

## Paired Associates Learning (PAL)

Designed to assess: episodic memory and visuospatial learning

Mode: *Clinical*

| Stage | Number of Patterns | Number of Boxes | Practice or Assessed | Max Number of Attempts |
|---|---|---|---|---|
| **1, 2** | 1 | 6 | Assessed | 10 |
| **3, 4** | 2 | 6 | Assessed | 10 |
| **5, 6** | 3 | 6 | Assessed | 10 |
| **7** | 6 | 6 | Assessed | 10 |
| **8** | 8 | 8 | Assessed | 10 |

Duration: ~10 minutes

| Key Outcome Measures | Definition |
|---|---|
| **Total errors (adjusted)** | The number of times the subject chose the incorrect box for a stimulus on assessment problems but with an adjustment for the estimated number of errors they would have made on any problems, attempts & recalls they did not reach due to failing or aborting the test |
| **First trial memory score** | The number of correct box choices that were made on the first attempt during assessment problems. |
| **Stages completed** | The number of stages that the subject passed. |

## Reaction Time (RTI)

Designed to assess: reaction time, movement time and vigilance

Mode: *RTI TBI*

| Stage | 1 or 5 choice? | Practice or Assessed | Number of Trials | Max Trials Allowed |
|---|---|---|---|---|
| **1** *(identical to stage 2 in Clinical mode)* | 5-choice<br><br>Touchscreen | Practice | 12 trials (stage repeated if less than 5 out of 12 correct) | 40 |
| ***2*** *(identical to stage 5 in Clinical mode)* | 5-choice<br><br>Press-pad | Assessed | 8 trials (stage repeated if less than 5 out of 8 correct) | 40 |

Duration: ~X minutes

Mode: *Clinical*

| Stage | 1 or 5 choice? | Practice or Assessed | Number of Trials | Max Trials Allowed |
|---|---|---|---|---|
| **1** | Simple<br><br>Touchscreen | Practice | 9 (stage repeated if less than 5 out of 9 correct) | 18 |
| ***2*** | 5-choice<br><br>Touchscreen | Practice | 12 (stage repeated if less than 5 out of 12 correct) | 40 |
| **3** | Simple<br><br>Press-pad | Practice | 9 (stage repeated if less than 5 out of 9 correct) | 18 |
| **4** | Simple<br><br>Press-pad | Assessed | 9 (stage repeated if less than 5 out of 9 correct) | 18 |
| ***5*** | 5-choice<br><br>Press-pad | Assessed | 8 (stage repeated if less than 5 out of 8 correct) | 40 |

Duration: ~6 minutes

| Key Outcome Measures | Definition |
|---|---|
| **Median 5-choice reaction time** | The median duration between the onset of the stimulus and the time at which the subject released the button. Calculated for correct, assessed trials in which the stimulus could appear in any one of five locations |
| **Median 5-choice movement time** | The median time taken to touch the stimulus after the button has been released. Calculated for correct, assessed trials where stimuli could appear in any one of five locations |

## Rapid Visual Information Processing (RVP)

Designed to assess: sustained attention and concentration

Mode: *Clinical*

| Stage | Target Sequence | Practice or Assessed |
|---|---|---|
| **1** | 357 | Practice |
| **2** | 357 | Practice |
| **3** | 357 | Practice |
| **4** | 357; 246; 468 | Practice |
| **5** | 357; 246; 468 | Assessed |
| **6** | 357; 246; 468 | Assessed |
| **7** | 357; 246; 468 | Assessed |

Duration: ~7 minutes (1 minute per stage, 9 target sequences per minute)

| Key Outcome Measures | Definition |
|---|---|
| **A' prime** | A' (A prime) is the signal detection measure of sensitivity to the target, regardless of response tendency (the expected range is 0.00 to 1.00; bad to good). In essence, this metric is a measure of how good the subject is at detecting target sequences |
| **Median latency** | The median response latency during assessment sequence blocks where the subject responded correctly |

## Stockings of Cambridge (SOC)

Designed to assess: spatial planning and spatial working memory

Mode: *Clinical*

| Problem Number | Practice or Assessed? | Number of Trials | Min. number of Moves Required | 'Too Many Moves' |
|---|---|---|---|---|
| **1,2,3,4** | Practice | 4 | 1 | 3 |
| **5,6** | Practice | 2 | 2 | 5 |
| **7,8** | Assessed | 2 | 2 | 5 |
| **9,10** | Assessed | 2 | 3 | 7 |
| **11,12** | Assessed | 2 | 4 | 9 |
| | Follow-phase | *The computer replicates the moves the subject made to complete the previous 8 problems, and the subject must simply follow the moves on screen* | | |
| **13,14** | Practice | 2 | 2 | 5 |
| **15,16** | Assessed | 2 | 4 | 9 |
| **17,18,19,20** | Assessed | 4 | 5 | 12 |
| | Follow-phase | *The computer replicates the moves the subject made to complete the previous 8 problems, and the subject must simply follow the moves on screen* | | |

Duration: ~10 minutes

Mode: *Clinical-no follow*

| Overall Stage | Practice or Assessed | Number of Trials | Number of Moves Required | 'Too Many Moves' |
|---|---|---|---|---|
| **1** | Practice | 4 | 1 | n/a |
| - | Practice | 2 | 2 | n/a |
| **2** | Assessed | 2 | 2 | 5 |
| - | Assessed | 2 | 3 | 7 |
| - | Assessed | 2 | 4 | 9 |
| **3** | Practice | 2 | 2 | n/a |
| - | Assessed | 2 | 4 | 9 |
| - | Assessed | 4 | 5 | 12 |

Duration: ~8 minutes

NB: use the Clinical mode if you want to look at thinking time as well as accuracy scores, whereas the Clinical-no follow mode should be used if you only want to look at accuracy scores and not latency scores

| Key Outcome Measures | Definition |
|---|---|
| **Problems solved in minimum moves** | The number of times the subject has successfully completed a problem in the minimum possible number of moves |
| **Initial thinking time**<br><br>***(NB: Applicable to the Clinical mode only)*** | The mean difference of the time taken to select the first ball in the solve problem phase and the time taken to select the first ball in the follow problem phase. For *n* move problems |
| **Subsequent thinking time** | The subject's mean speed of movement after the initial move has been made for *n* move problems |

## Spatial Working Memory (SWM)

Designed to assess: executive function and spatial working memory

Mode: *Clinical*

| Stage | Number of Tokens | Number of Boxes | Practice or Assessed | Max Number of Inspections (per problem) |
|---|---|---|---|---|
| **1** | | | | |
| **2** | | | | |
| **3** | | | | |
| **4** | | | | |
| **5** | | | | |
| **6** | | | | |
| **7** | | | | |
| **8** | | | | |
| **9** | | | | |

Duration: ~5 minutes

| Key Outcome Measures | Definition |
|---|---|
| **Between errors** | The total number of times the subject revisits a box in which a token has previously been found in the same problem (calculated for assessed problems only) |
| **Strategy** | For assessed problems with six boxes or more, the number of distinct boxes used by the subject to begin a new search for a token, within the same problem |

## Annex 5: Biomarkers and blood sampling data

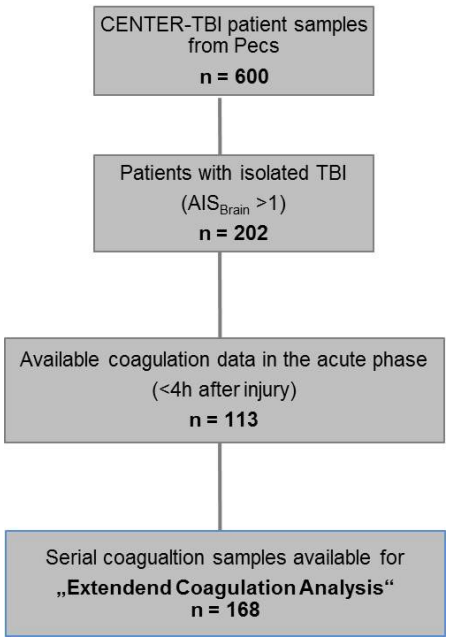
For all blood samples the curated Sample ID, collection date and time and freezer date and time, etc. has been uploaded to Mica/Opal.

We recommend using the "Biomarkers." domain, "CentralHaemostasis." domain and "Genetics." domain primarily (instead of the "labsampling."), as these contain the curated sample ID and curated collection/freezer dates and times.

In addition, for the biomarkers samples, the results of the following analyses were uploaded into Opal:

- ✓ Biomarkers.S100B
- ✓ Biomarkers.NSE
- ✓ Biomarkers.GFAP
- ✓ Biomarkers.UCH-L1
- ✓ Biomarkers.NFL
- ✓ Biomarkers.Tau

Concerning the extended coagulation analyses (CentralHaemostasis.), 600 patient samples from 9 sites were received. TBI patients with extracranial injuries and AIS Brain ≤1 were excluded, which gave a cohort of 202 patients, who had an isolated TBI. We focused on iTBI patients who received a coagulation test within the first 4 hours after TBI injury. In total, 113 iTBI had the information about early coagulation tests, together with serial blood collection samples, hence we achieved a sample number of 168 iTBI patients. Based on this iTBI cohort, an extended coagulation analysis was performed for which you will also find the results in Mica/Opal.




In addition to the data found in Mica/Opal, access can be requested to the following additional files through the Center-TBI office:

| Data files | file format(s) | number of files |
|---|---|---|
| **Biomarker results ABCDx Cytokines** | csv | 2 |
| **Biomarker results ABCDx GFAP & IL10** | csv | 1 |

# Annex 6: Frequency tables

We have been developing Frequency Tables for the CENTER-TBI data. These Frequency Tables do not lend themselves to analyses of the CENTER-TBI data, but serve to provide some orientating insight into the availability and distribution of data in the CENTER-TBI dataset.

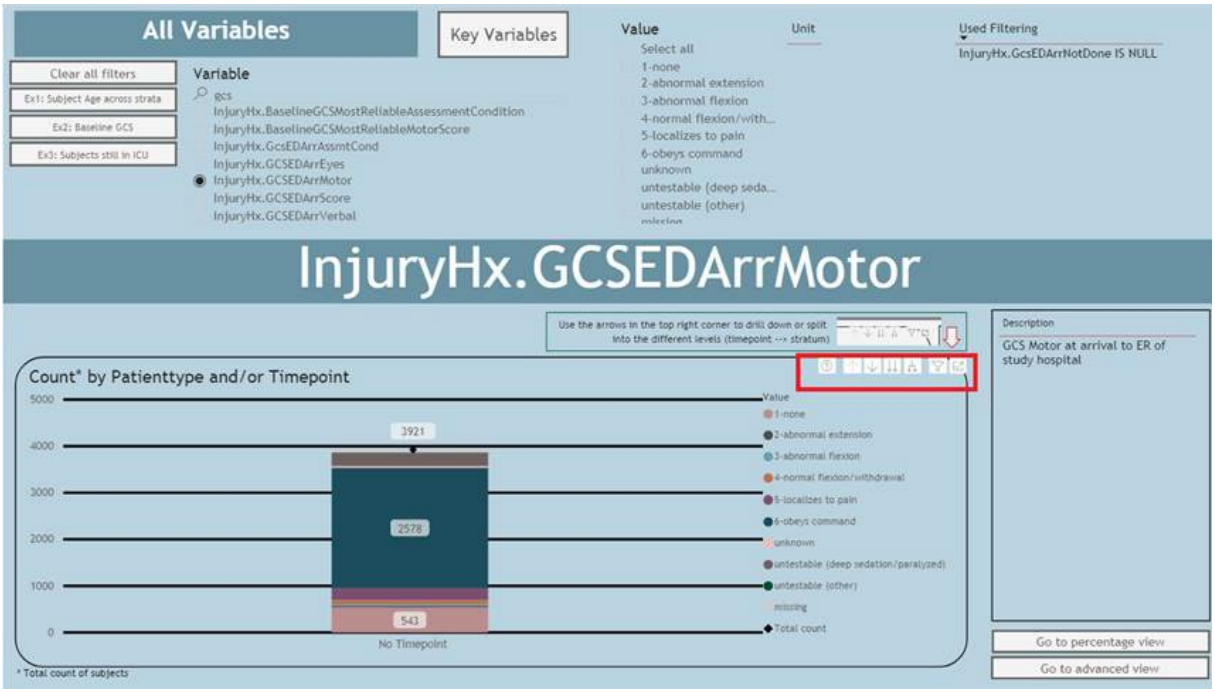
The Frequency Tables are available through the CENTER-TBI Data Dictionary:

When you select a variable in the list of the Frequency Tables, the corresponding values, unit (if applicable) and frequency table will appear per patient type (ER, Admission, ICU).

In the upper right corner of the "all variables" view you will also see the rules used to establish missingness (as not all variables are applicable for all patients) under "Used Filtering" (when rules apply).

If you move your mouse to the top right corner of the table (underneath the green frame), arrows will appear (see screen shot) on which you can click to see the data per timepoint (for longitudinal data) or the total amount of data.

In the downright corner of the screen, you will see a button to go to the percentage view or advanced view. In the advanced view, you will find more parameters about this variable. You can click on them & select the ones that interest you.



# Annex 7: Upload of statistical scripts for analyses to CENTER-TBI Gitlab

According to the data access and publication policies of CENTER-TBI, researchers are requested to save their final variable search and to upload the final statistical scripts used in preparation of CENTER-TBI manuscripts (please also see the SOP manual for data access and publication requests on the CENTER-TBI website (https://www.center-tbi.eu/data)).

**Save statistical scripts:**

Login to the script application on the website: https://www.center-tbi.eu/scripts/**.** (Use the same login credentials that are used to login to Mica/Opal)

You will see on the left an "explorer" part where you can navigate through the folders to see the available shared-scripts and download scripts you would like to use.

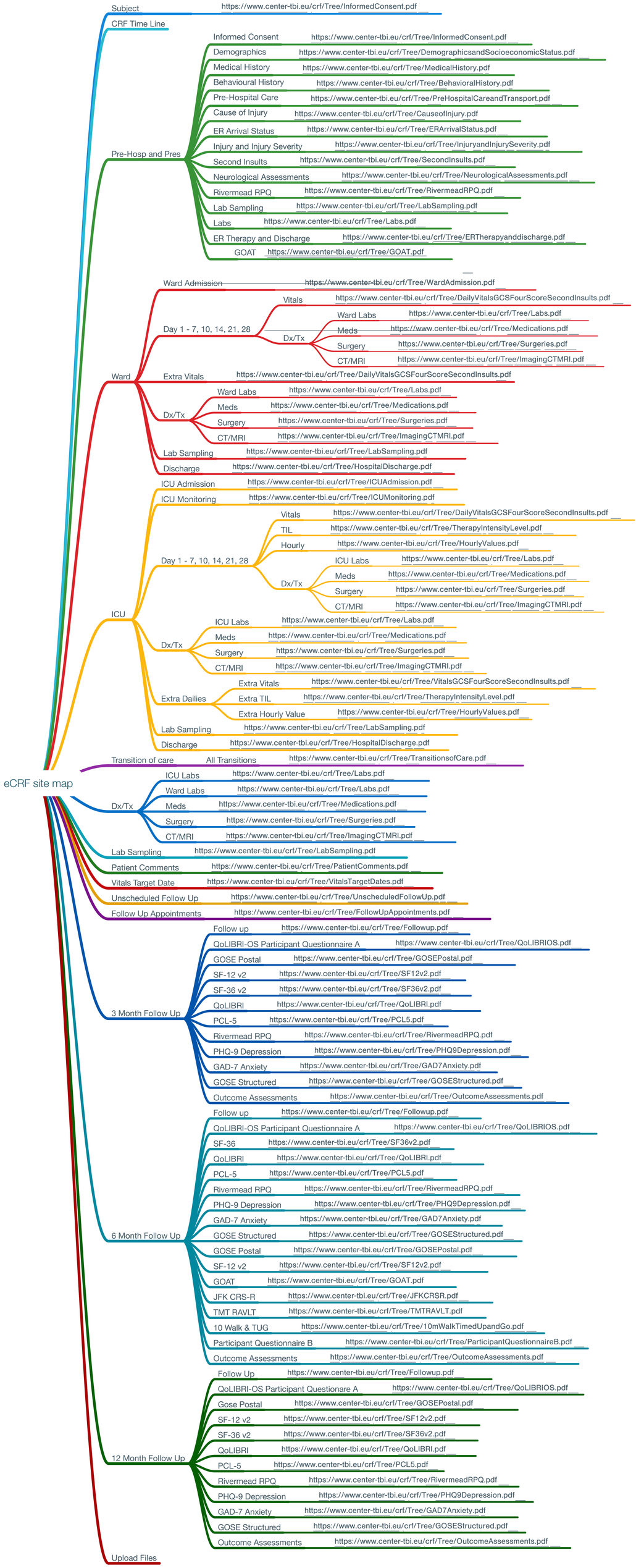
Below the explorer part, you see an "upload form" where you can upload a new script (or several scripts) you would like to share. Make sure to mention the Study Plan number or Manuscript reference in the Notes section, together with a brief description. Once uploaded, your script will be reviewed and then released.

On the right part, you see the "info box" with text from the README file pertaining to the folder you open in the explorer part.

And below that you see the list of "latest uploads" with the status (approved or awaiting approval). When you have uploaded a script, you can see here if your script has been approved yet or is still awaiting approval.

# Annex 8: eCRF overview tree structure and linked forms

See next page.


eCRF site map
Subject
https://www.center-tbi.eu/crf/Tree/InformedConsent.pdf
CRF Time Line
Pre-Hosp and Pres
Informed Consent
https://www.center-tbi.eu/crf/Tree/InformedConsent.pdf
Demographics
https://www.center-tbi.eu/crf/Tree/DemographicsandSocioeconomicStatus.pdf
Medical History
https://www.center-tbi.eu/crf/Tree/MedicalHistory.pdf
Behavioural History
https://www.center-tbi.eu/crf/Tree/BehavioralHistory.pdf
Pre-Hospital Care
https://www.center-tbi.eu/crf/Tree/PreHospitalCareandTransport.pdf
Cause of Injury
https://www.center-tbi.eu/crf/Tree/CauseofInjury.pdf
ER Arrival Status
https://www.center-tbi.eu/crf/Tree/ERArrivalStatus.pdf
Injury and Injury Severity
https://www.center-tbi.eu/crf/Tree/InjuryandInjurySeverity.pdf
Second Insults
https://www.center-tbi.eu/crf/Tree/SecondInsults.pdf
Neurological Assessments
https://www.center-tbi.eu/crf/Tree/NeurologicalAssessments.pdf
Rivermead RPQ
https://www.center-tbi.eu/crf/Tree/RivermeadRPQ.pdf
Lab Sampling
https://www.center-tbi.eu/crf/Tree/LabSampling.pdf
Labs
https://www.center-tbi.eu/crf/Tree/Labs.pdf
ER Therapy and Discharge
https://www.center-tbi.eu/crf/Tree/ERTherapyanddischarge.pdf
GOAT
https://www.center-tbi.eu/crf/Tree/GOAT.pdf
Ward
Ward Admission
https://www.center-tbi.eu/crf/Tree/WardAdmission.pdf
Day 1 - 7, 10, 14, 21, 28
Vitals
https://www.center-tbi.eu/crf/Tree/DailyVitalsGCSFourScoreSecondInsults.pdf
Dx/Tx
Ward Labs
https://www.center-tbi.eu/crf/Tree/Labs.pdf
Meds
https://www.center-tbi.eu/crf/Tree/Medications.pdf
Surgery
https://www.center-tbi.eu/crf/Tree/Surgeries.pdf
CT/MRI
https://www.center-tbi.eu/crf/Tree/ImagingCTMRI.pdf
Extra Vitals
https://www.center-tbi.eu/crf/Tree/DailyVitalsGCSFourScoreSecondInsults.pdf
Dx/Tx
Ward Labs
https://www.center-tbi.eu/crf/Tree/Labs.pdf
Meds
https://www.center-tbi.eu/crf/Tree/Medications.pdf
Surgery
https://www.center-tbi.eu/crf/Tree/Surgeries.pdf
CT/MRI
https://www.center-tbi.eu/crf/Tree/ImagingCTMRI.pdf
Lab Sampling
https://www.center-tbi.eu/crf/Tree/LabSampling.pdf
Discharge
https://www.center-tbi.eu/crf/Tree/HospitalDischarge.pdf
ICU
ICU Admission
https://www.center-tbi.eu/crf/Tree/ICUAdmission.pdf
ICU Monitoring
https://www.center-tbi.eu/crf/Tree/ICUMonitoring.pdf
Day 1 - 7, 10, 14, 21, 28
Vitals
https://www.center-tbi.eu/crf/Tree/DailyVitalsGCSFourScoreSecondInsults.pdf
TIL
https://www.center-tbi.eu/crf/Tree/TherapyIntensityLevel.pdf
Hourly
https://www.center-tbi.eu/crf/Tree/HourlyValues.pdf
Dx/Tx
ICU Labs
https://www.center-tbi.eu/crf/Tree/Labs.pdf
Meds
https://www.center-tbi.eu/crf/Tree/Medications.pdf
Surgery
https://www.center-tbi.eu/crf/Tree/Surgeries.pdf
CT/MRI
https://www.center-tbi.eu/crf/Tree/ImagingCTMRI.pdf
Dx/Tx
ICU Labs
https://www.center-tbi.eu/crf/Tree/Labs.pdf
Meds
https://www.center-tbi.eu/crf/Tree/Medications.pdf
Surgery
https://www.center-tbi.eu/crf/Tree/Surgeries.pdf
CT/MRI
https://www.center-tbi.eu/crf/Tree/ImagingCTMRI.pdf
Extra Dailies
Extra Vitals
https://www.center-tbi.eu/crf/Tree/VitalsGCSFourScoreSecondInsults.pdf
Extra TIL
https://www.center-tbi.eu/crf/Tree/TherapyIntensityLevel.pdf
Extra Hourly Value
https://www.center-tbi.eu/crf/Tree/HourlyValues.pdf
Lab Sampling
https://www.center-tbi.eu/crf/Tree/LabSampling.pdf
Discharge
https://www.center-tbi.eu/crf/Tree/HospitalDischarge.pdf
Transition of care
All Transitions
https://www.center-tbi.eu/crf/Tree/TransitionsofCare.pdf
Dx/Tx
ICU Labs
https://www.center-tbi.eu/crf/Tree/Labs.pdf
Ward Labs
https://www.center-tbi.eu/crf/Tree/Labs.pdf
Meds
https://www.center-tbi.eu/crf/Tree/Medications.pdf
Surgery
https://www.center-tbi.eu/crf/Tree/Surgeries.pdf
CT/MRI
https://www.center-tbi.eu/crf/Tree/ImagingCTMRI.pdf
Lab Sampling
https://www.center-tbi.eu/crf/Tree/LabSampling.pdf
Patient Comments
https://www.center-tbi.eu/crf/Tree/PatientComments.pdf
Vitals Target Date
https://www.center-tbi.eu/crf/Tree/VitalsTargetDates.pdf
Unscheduled Follow Up
https://www.center-tbi.eu/crf/Tree/UnscheduledFollowUp.pdf
Follow Up Appointments
https://www.center-tbi.eu/crf/Tree/FollowUpAppointments.pdf
3 Month Follow Up
Follow up
https://www.center-tbi.eu/crf/Tree/Followup.pdf
QoLIBRI-OS Participant Questionnaire A
https://www.center-tbi.eu/crf/Tree/QoLIBRIOS.pdf
GOSE Postal
https://www.center-tbi.eu/crf/Tree/GOSEPostal.pdf
SF-12 v2
https://www.center-tbi.eu/crf/Tree/SF12v2.pdf
SF-36 v2
https://www.center-tbi.eu/crf/Tree/SF36v2.pdf
QoLIBRI
https://www.center-tbi.eu/crf/Tree/QoLIBRI.pdf
PCL-5
https://www.center-tbi.eu/crf/Tree/PCL5.pdf
Rivermead RPQ
https://www.center-tbi.eu/crf/Tree/RivermeadRPQ.pdf
PHQ-9 Depression
https://www.center-tbi.eu/crf/Tree/PHQ9Depression.pdf
GAD-7 Anxiety
https://www.center-tbi.eu/crf/Tree/GAD7Anxiety.pdf
GOSE Structured
https://www.center-tbi.eu/crf/Tree/GOSEStructured.pdf
Outcome Assessments
https://www.center-tbi.eu/crf/Tree/OutcomeAssessments.pdf
6 Month Follow Up
Follow up
https://www.center-tbi.eu/crf/Tree/Followup.pdf
QoLIBRI-OS Participant Questionnaire A
https://www.center-tbi.eu/crf/Tree/QoLIBRIOS.pdf
SF-36
https://www.center-tbi.eu/crf/Tree/SF36v2.pdf
QoLIBRI
https://www.center-tbi.eu/crf/Tree/QoLIBRI.pdf
PCL-5
https://www.center-tbi.eu/crf/Tree/PCL5.pdf
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https://www.center-tbi.eu/crf/Tree/RivermeadRPQ.pdf
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GAD-7 Anxiety
https://www.center-tbi.eu/crf/Tree/GAD7Anxiety.pdf
GOSE Structured
https://www.center-tbi.eu/crf/Tree/GOSEStructured.pdf
GOSE Postal
https://www.center-tbi.eu/crf/Tree/GOSEPostal.pdf
SF-12 v2
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GOAT
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JFK CRS-R
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TMT RAVLT
https://www.center-tbi.eu/crf/Tree/TMTRAVLT.pdf
10 Walk & TUG
https://www.center-tbi.eu/crf/Tree/10mWalkTimedUpandGo.pdf
Participant Questionnaire B
https://www.center-tbi.eu/crf/Tree/ParticipantQuestionnaireB.pdf
Outcome Assessments
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12 Month Follow Up
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Outcome Assessments
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# CENTER-TBI Core Data Collection : Guide to timing of assessments and investigations differentiated by stratum + Early MR imaging + Ultra early MR + External completion studies

CORE DATA

MR

Ultra Early MR

HR ICU

Extended Coagulation

| TIME POINT | | Day 1 (Adm)* | Post-op | Day 2 | Day 3 | Day 4 | Day 5 | 2-3 Week | 3 Month | 6 Month | 12 Month | 24 Month |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ER STRATUM: 1800** | | | | | | | | | | | | |
| **Clinical data : on presentation/discharge ER and at time of follow-up** | | | | | | | | | | | | |
| **Blood Sampling** | **Routine hospital** | All | | | | | | | | | | |
| | **Biomarkers** | All | | | | | | MR Sites | MR Sites[2] | | | |
| | **Genetics** | All | | | | | | | | | | |
| | ROTEM/TEG[3] | ROTEM/TEG[3] | | | | | | | | | | |
| MRI (only MR sites) | | Ultra early MR | | | | | | MR Sites | MR Sites[2] | | | |
| **Outcome Measures** | **Neuropsych** | | | | | | | MR Sites | MR Sites[2] | All | | |
| | **Questionnaires** | | | | | | | All | All(F2F) | All | | |
| **ADMISSION STRATUM: 1800** | | | | | | | | | | | | |
| **Clinical data : on presentation, day 1-7, day 10, day 14, day 21 and day 28 unless discharge earlier** | | | | | | | | | | | | |
| **Blood Sampling** | **Routine hospital** | All | | | | | | | | | | |
| | **Biomarkers** | All | | | | | | MR Sites | | All | MR Sites | MR Sites |
| | **Genetics** | All | | | | | | | | | | |
| | Ext. Coag[3] | Ext. Coag[3] | | | | | | | | | | |
| MRI (only MR sites) | | Ultra early MR | | | | | | MR Sites | | MR Sites | MR Sites | MR Sites |
| **Outcome Measures** | **Neuropsych** | | | | | | | | | All | MR Sites | MR Sites |
| | **Questionnaires** | | | | | | | MR Sites | All | All | All | MR Sites |
| **ICU STRATUM: 1800** | | | | | | | | | | | | |
| **Clinical data : on presentation, day 1-7, day 10, day 14, day 21 and day 28 unless discharge earlier** | | | | | | | | | | | | |
| **Blood Sampling** | **Routine hospital** | All | | All | All | All | All | | | | | |
| | **Biomarkers** | All | | All | HR ICU | HR ICU | HR ICU | MR Sites | | All | MR Sites | MR Sites |
| | **Genetics** | All | | | | | | | | | | |
| | Ext. Coag[3] | Ext. Coag[3] | Ext. Coag[3] | Ext. Coag[3] | | | | | | | | |
| MRI (only MR sites) | | Ultra early MR | | | | | | MR Sites | | MR Sites | MR Sites | MR Sites |
| **Outcome Measures** | **Neuropsych** | | | | | | | | | All | MR Sites | MR Sites |
| | **Questionnaires** | | | | | | | | All | All | All | MR Sites |

Day 1 = Defined as day of Admission; in most cases this will be the same as day of injury, but in some (those patients presenting in the evening) it may be the next day.
Day 2 = Day after Admission
HR ICU: only sites participating in the HR ICU sub-study
[2] Initially target all patients scanned at 2-3 weeks, may later be restricted to only those with an abnormal MR at 2-3 weeks
[3] only sites participating in the extended coagulation sub-study