27° Meeting GiViTI

7-8-9 Novembre 2018
Alexander Hotel, Abano Terme

Sandra Magnoni
Anestesia e Rianimazione 1
Ospedale Santa Chiara, APSS-Trento

UCL

Imperial College London

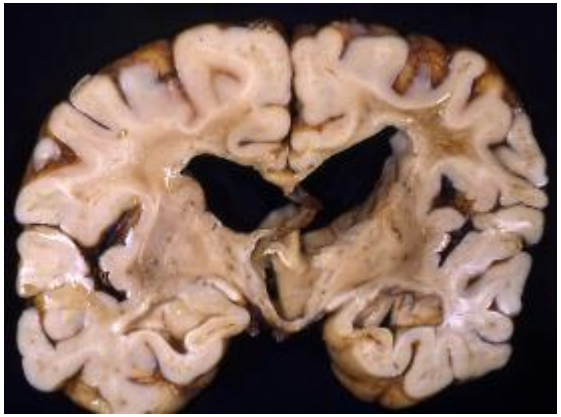
creactive GiViTI

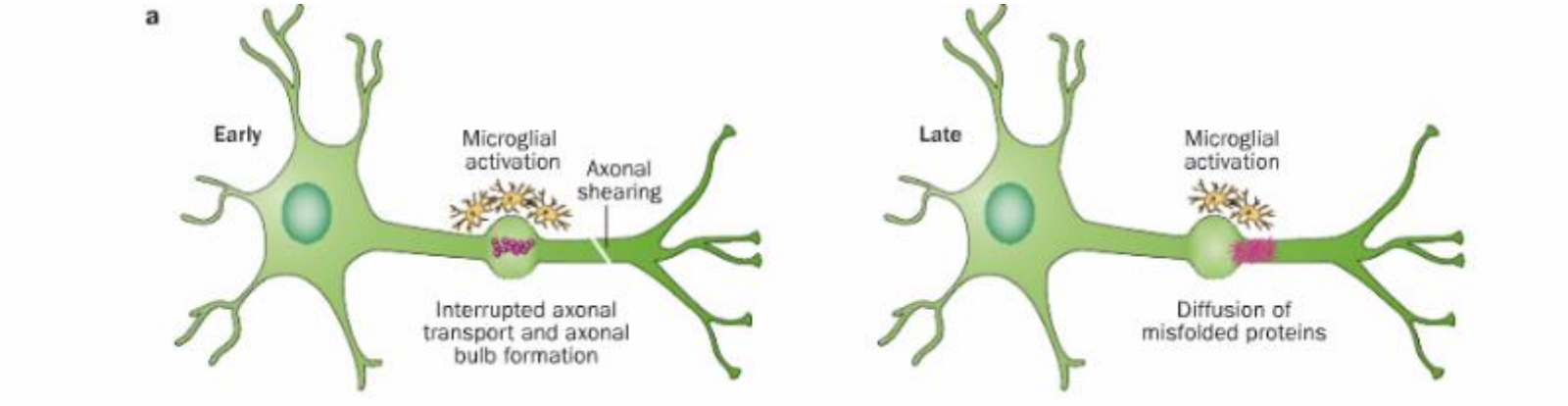
UNIL | Université de Lausanne

FONDAZIONE IRCCS CA' GRANDA
OSPEDALE MAGGIORE POLICLINICO

Developing and validating blood and imaging BIOmarkers of AXonal injury following Traumatic Brain Injury (**BIO-AX-TBI)**

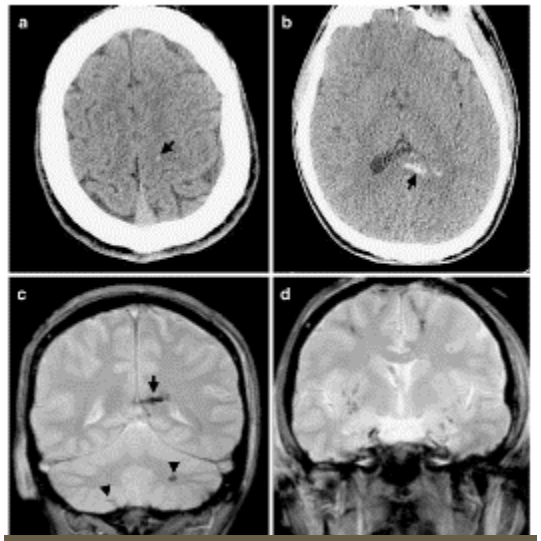
Histo & pathophysiology of traumatic axonal injury (TAI)



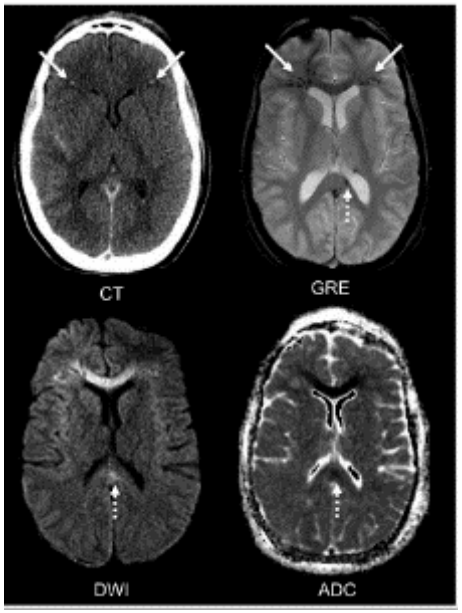


Sharp et al. Nat Rev Neurol 2014

TAI Neuroimaging markers

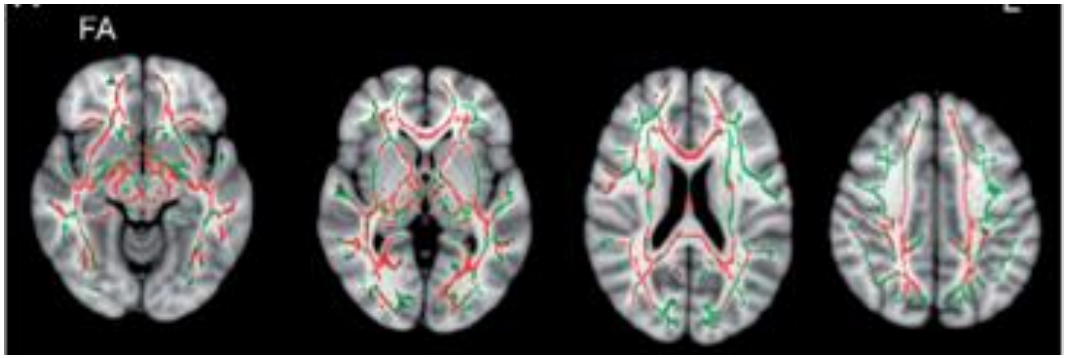


Hemorrhagic TAI

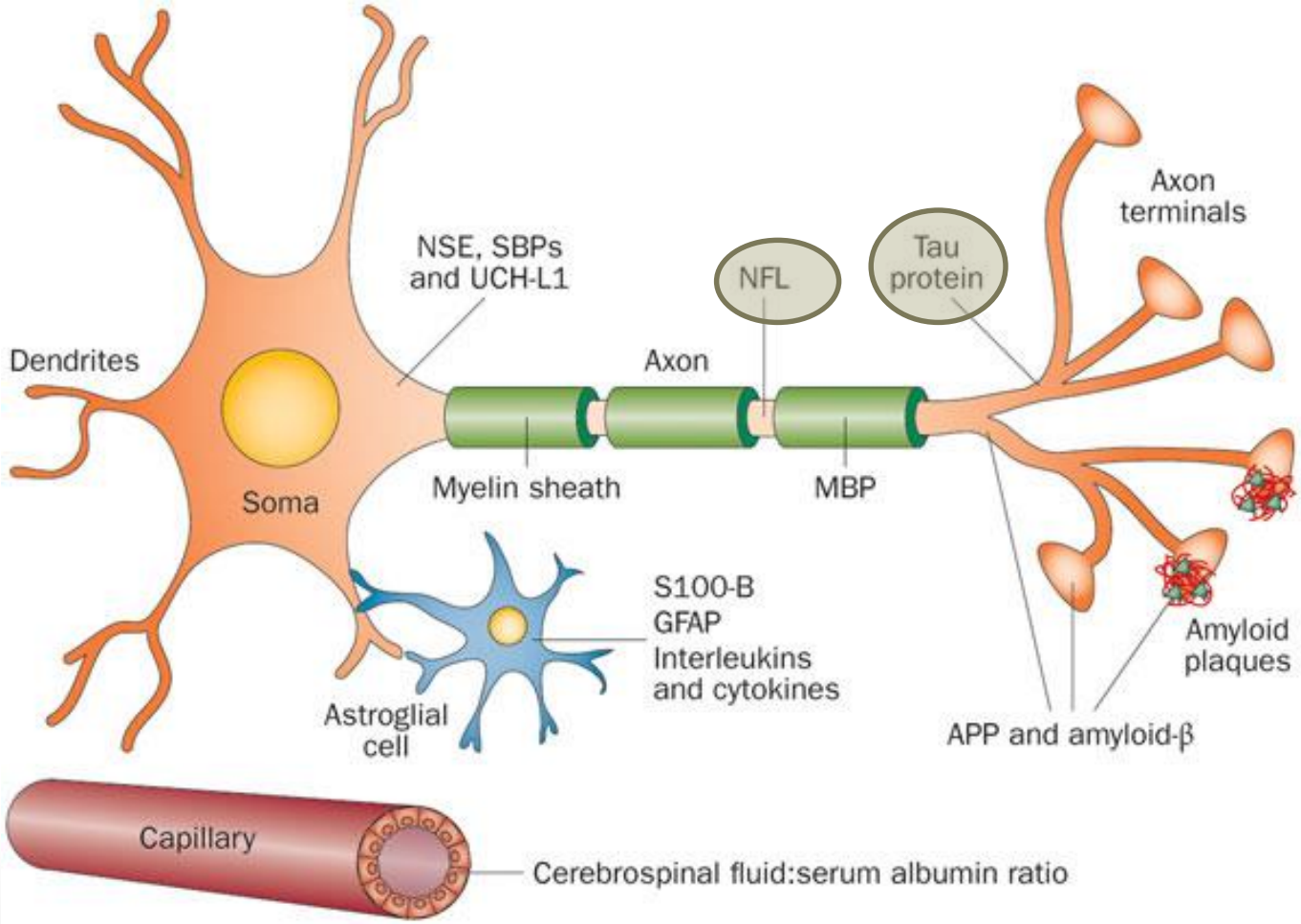


Non-Hemorrhagic TAI

Diffusion Tensor Imaging (DTI) of TAI

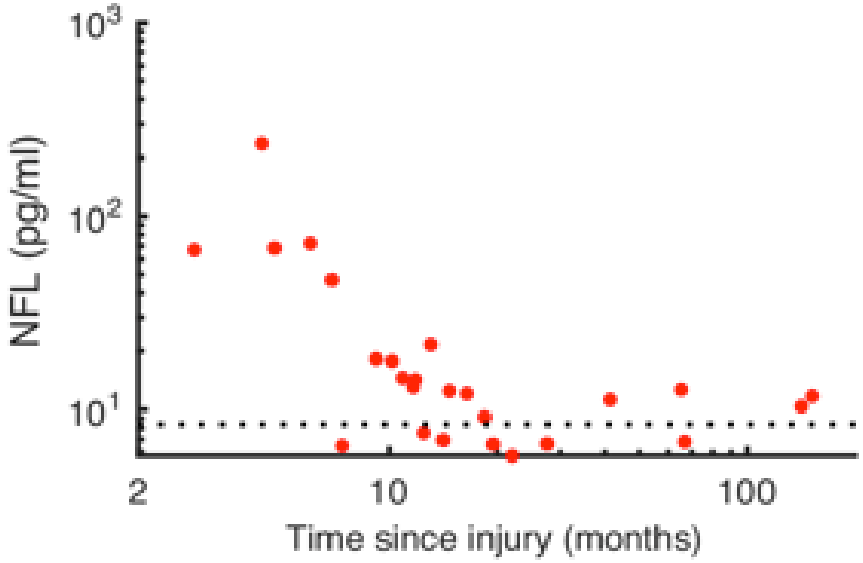


Candidate biomarkers of TAI



Zetterberg, H. et al. Nat. Rev. Neurol.2013

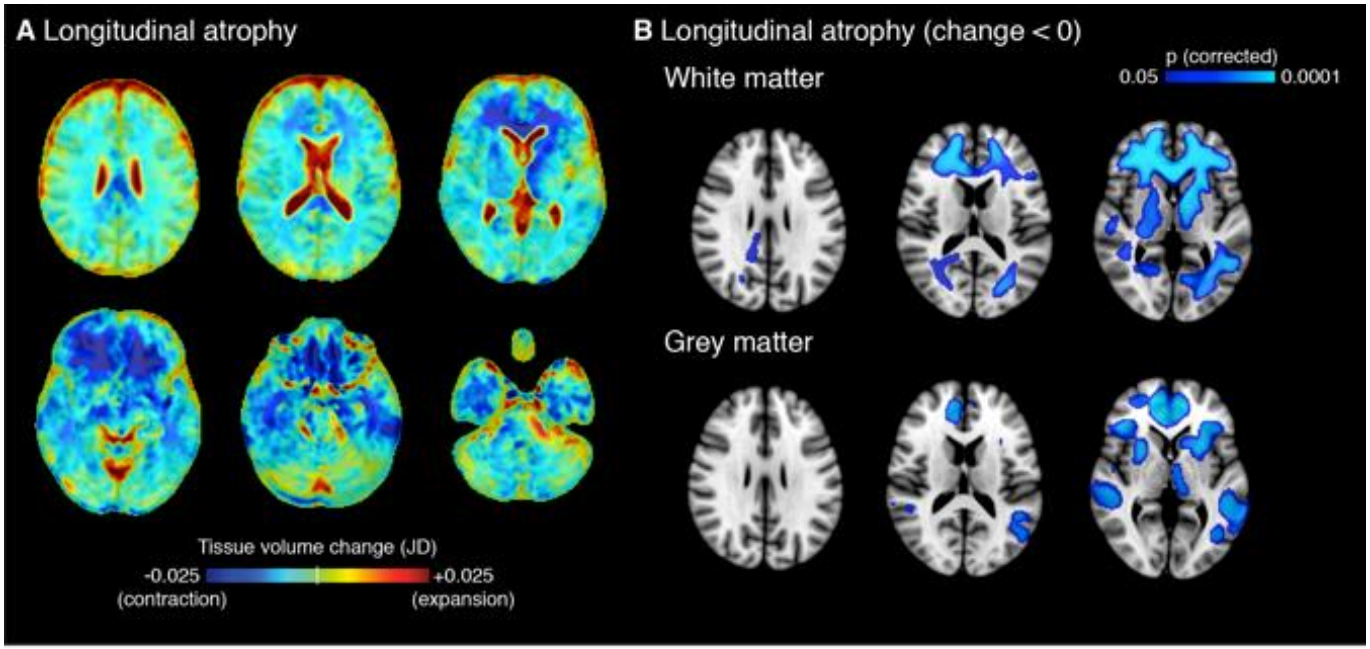
Preliminary data on NFL as blood biomarker

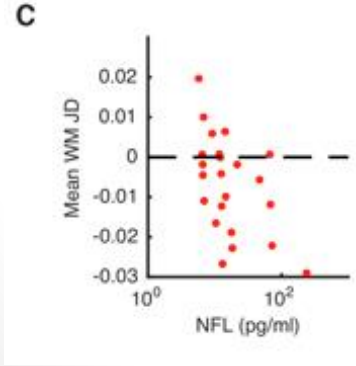


NFL decline with time, but remains elevated in some patients >1 year

Courtesy of David Sharp, Imperial College London, UK

NFL correlates with post TBI atrophy





Courtesy of David Sharp, Imperial College London, UK

ERA-NET NEURON

Funded Projects

19 transnational research consortia are funded under the umbrella of the NEURON JTC 2016 "External Insults to the Nervous System" that is co-funded by the European Commission. In total, 92 research groups from 14 European countries, Canada and Israel collaborate in these projects. The total funding volume of the call amounts to about 17.9 M€.

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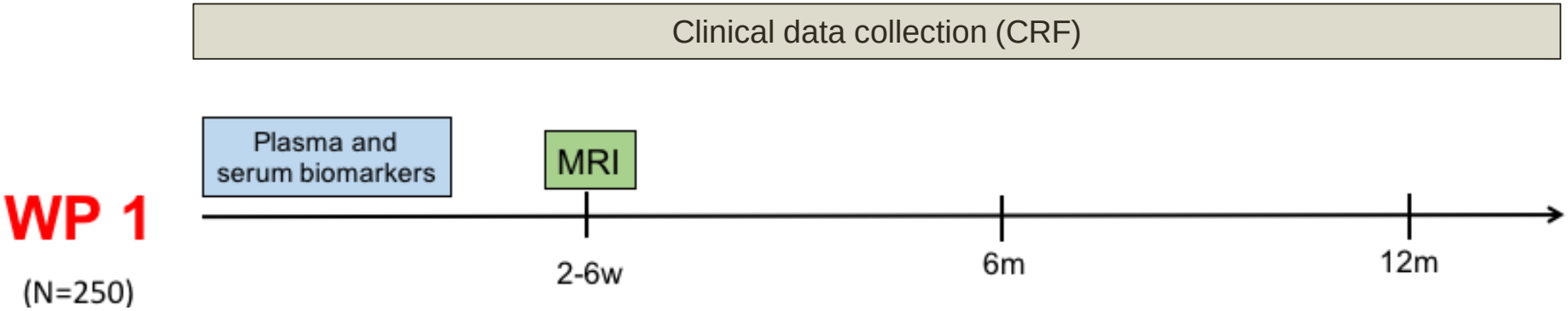
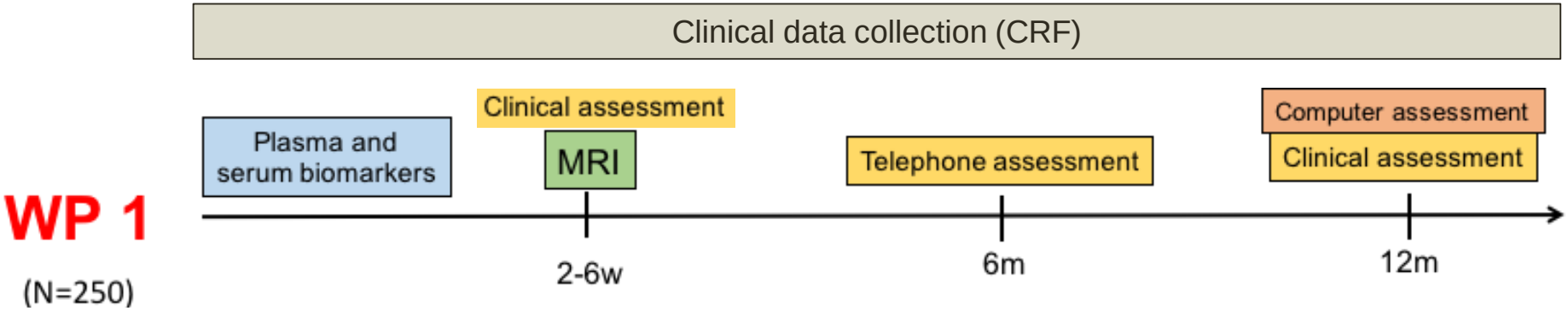
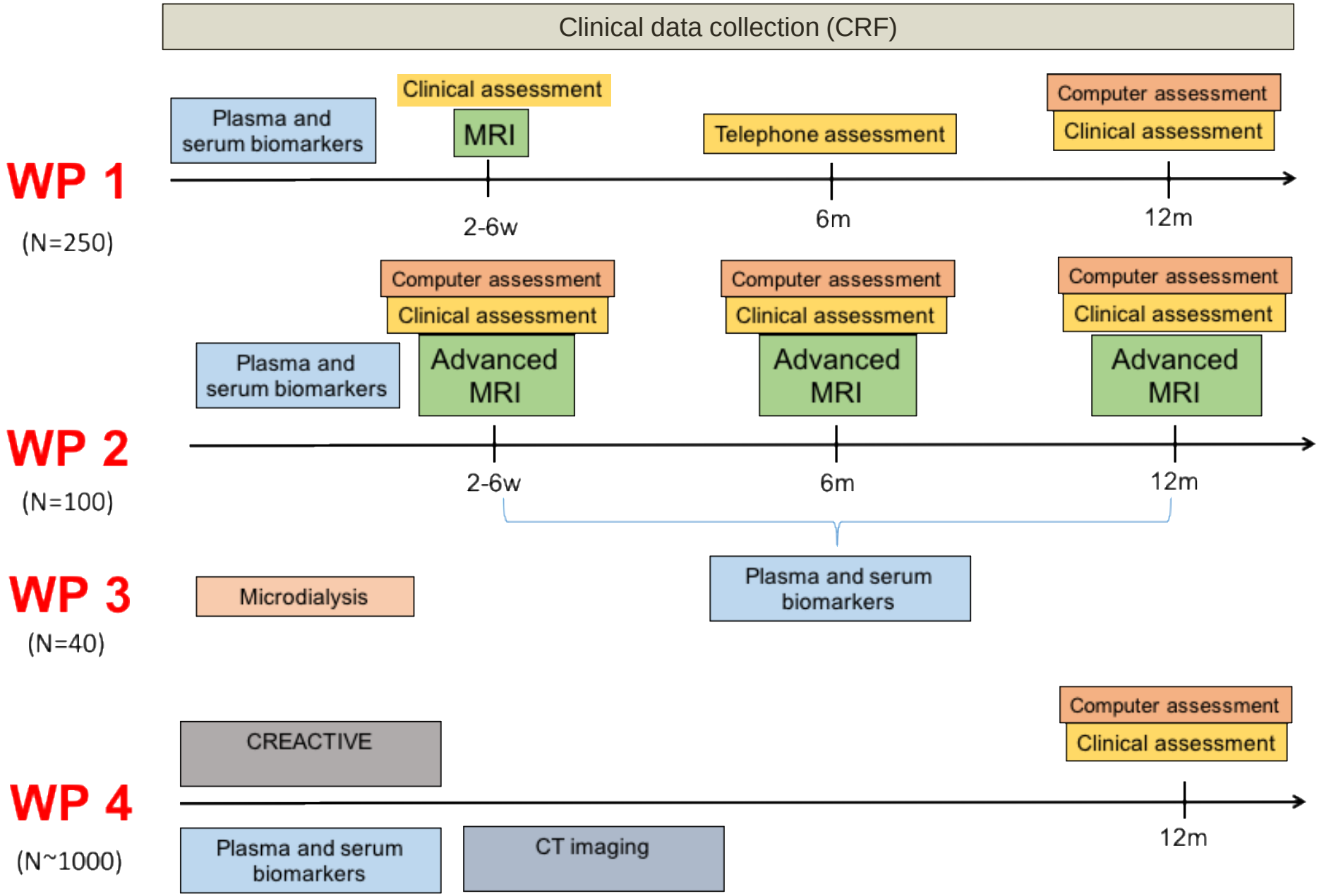
Developing and validating blood and imaging BIOmarkers of AXonal injury following Traumatic Brain Injury

AIM: We will investigate the relationship between blood, microdialysis and neuroimaging markers of axonal injury after traumatic brain injury (TBI). New methods provide 100-1000 fold increases in sensitivity. We exploit this advance to investigate neurofilament light (NFL) and tau proteins, as well as other plasma markers, with advanced magnetic resonance imaging (MRI) measures of axonal injury. WORK PLAN: We will perform a multicenter study of adult TBI closely aligned with the InTBIR collaborative effort and linked to the large CREACTIVE TBI study. Work Package (WP) 1 will study these factors in a large cohort of moderate/severe TBI patients. WP 2 will investigate the longitudinal relationship between neuroimaging and plasma biomarkers. WP 3 will combine microdialysis, neuroimaging and plasma sampling of axonal proteins to provide a mechanistic understanding of axonal injury progression and validate the axonal origin of the plasma biomarkers. WP 4 will validate findings from the study in an additional 1000 patients from CREACTIVE. EXPLOITATION OF RESULTS: The results will guide the incorporation of plasma biomarkers and advanced MRI measures of axonal injury into medical practice. Our aim is provide robust evidence about the best measures for the early assessment of axonal injury. By validating neuroimaging and plasma biomarkers for axonal injury we will facilitate prognostication after TBI, as well provide tools to inform the selection and evaluation of treatment.

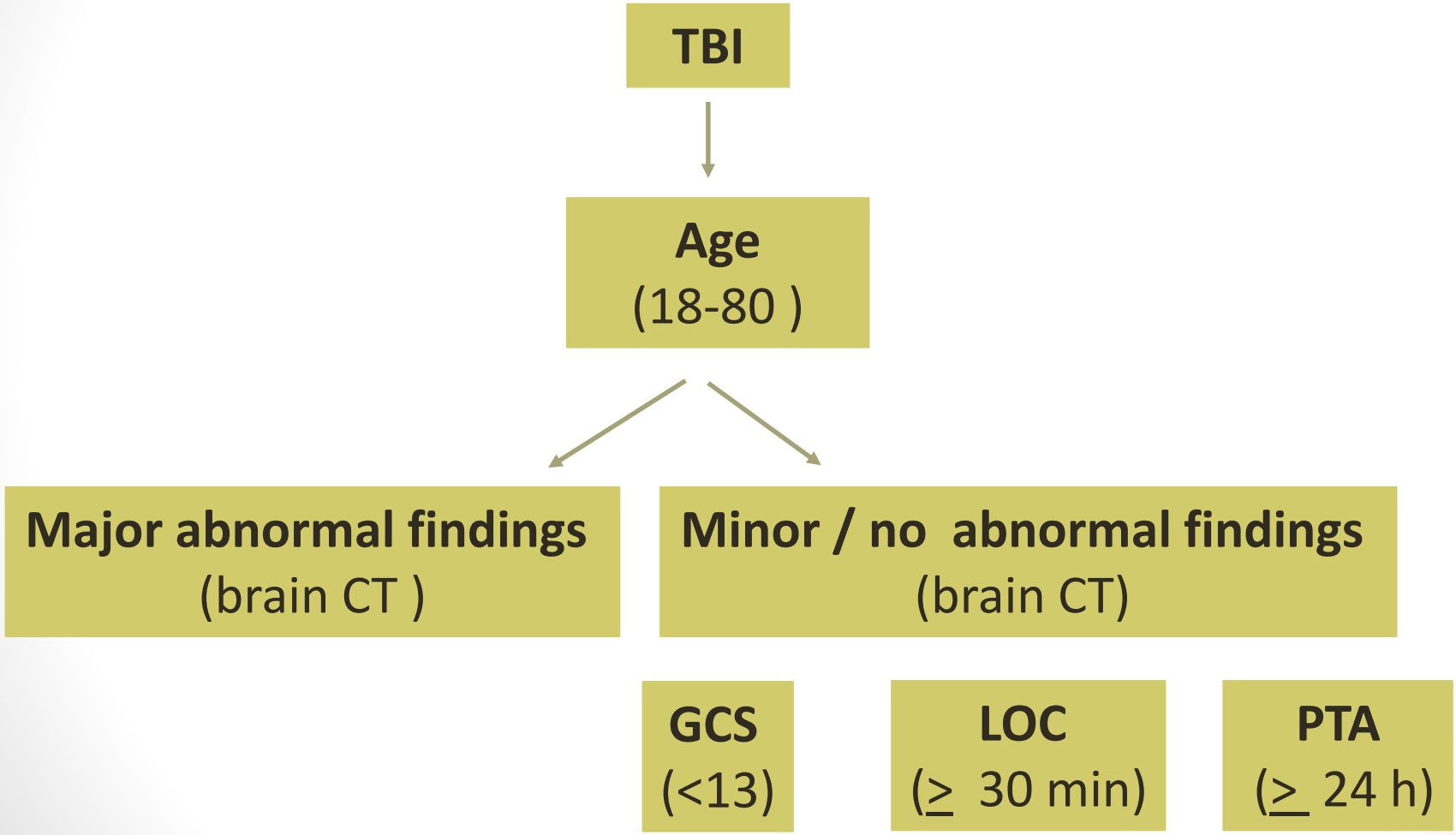
Acronym BIO-AX-TBI


Clinical data collection (CRF)
Plasma and serum biomarkers
MRI
WP 1
(N=250)
2-6w
6m
12m


Clinical data collection (CRF)
WP 1
(N=250)
Plasma and serum biomarkers
Clinical assessment
MRI
Telephone assessment
Computer assessment
Clinical assessment
2-6w
6m
12m


Clinical data collection (CRF)
WP 1
(N=250)
Plasma and serum biomarkers
Clinical assessment
MRI
Telephone assessment
Computer assessment
Clinical assessment
2-6w
6m
12m
WP 2
(N=100)
Computer assessment
Clinical assessment
Plasma and serum biomarkers
Advanced MRI
Computer assessment
Clinical assessment
Advanced MRI
Computer assessment
Clinical assessment
Advanced MRI
2-6w
6m
12m
Plasma and serum biomarkers
WP 3
(N=40)
Microdialysis
WP 4
(N~1000)
CREACTIVE
Computer assessment
Clinical assessment
12m
Plasma and serum biomarkers
CT imaging

BIO-AX-TBI:Inclusion criteria

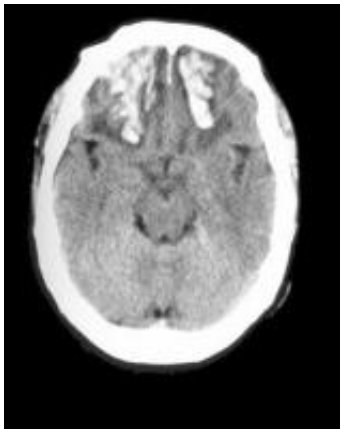


Mayo Clinic classification of Traumatic Brain Injury (TBI)

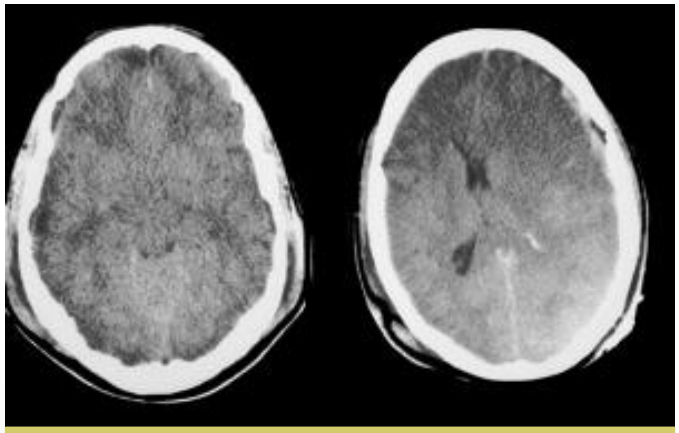
Inclusion criteria:
major brain CT abnormal findings

Subdural H

Epidural H



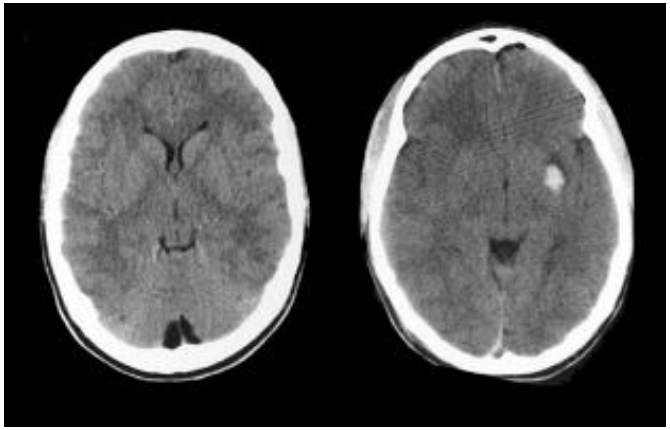
Contusion



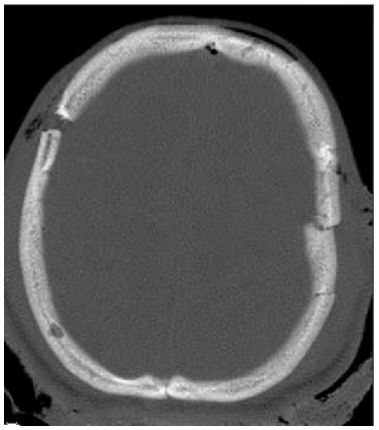
Brain edema
(Marshall Diffuse III-IV)

T-SAH

Inclusion criteria:
minor brain CT abnormal findings



NO brain edema (Marshall Diffuse I-II)



skull fracture (isolated)

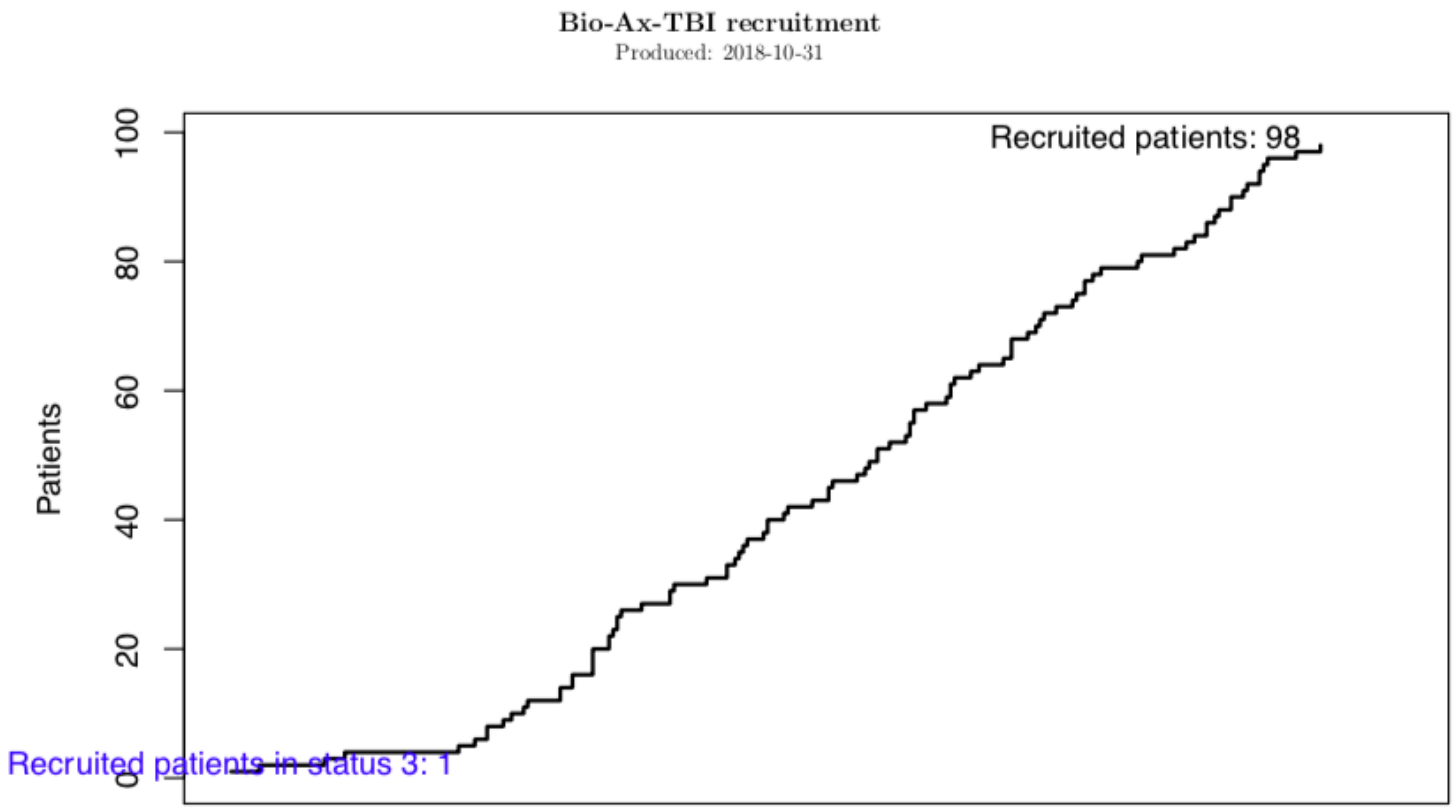
Exclusion criteria

- Absolute contra-indications to MRI (e.g. pace maker)
- GCS = 3 AND Pupils at admission = Bilaterally dilated and non-reactive
- GCS not evaluable AND Pupils at admission = Bilaterally dilated and non-reactive

BIO-AX-TBI Recruiting centers

- **Imperial College, London**
- **Niguarda, Milano**
- **Lausanne, CH**
- **Ljubljana, Slovenia**
- **Policlinico, Milano**
- **Careggi, Firenze**
- **Santa Chiara, Trento**

BIO-AX-TBI
Recruitment progression

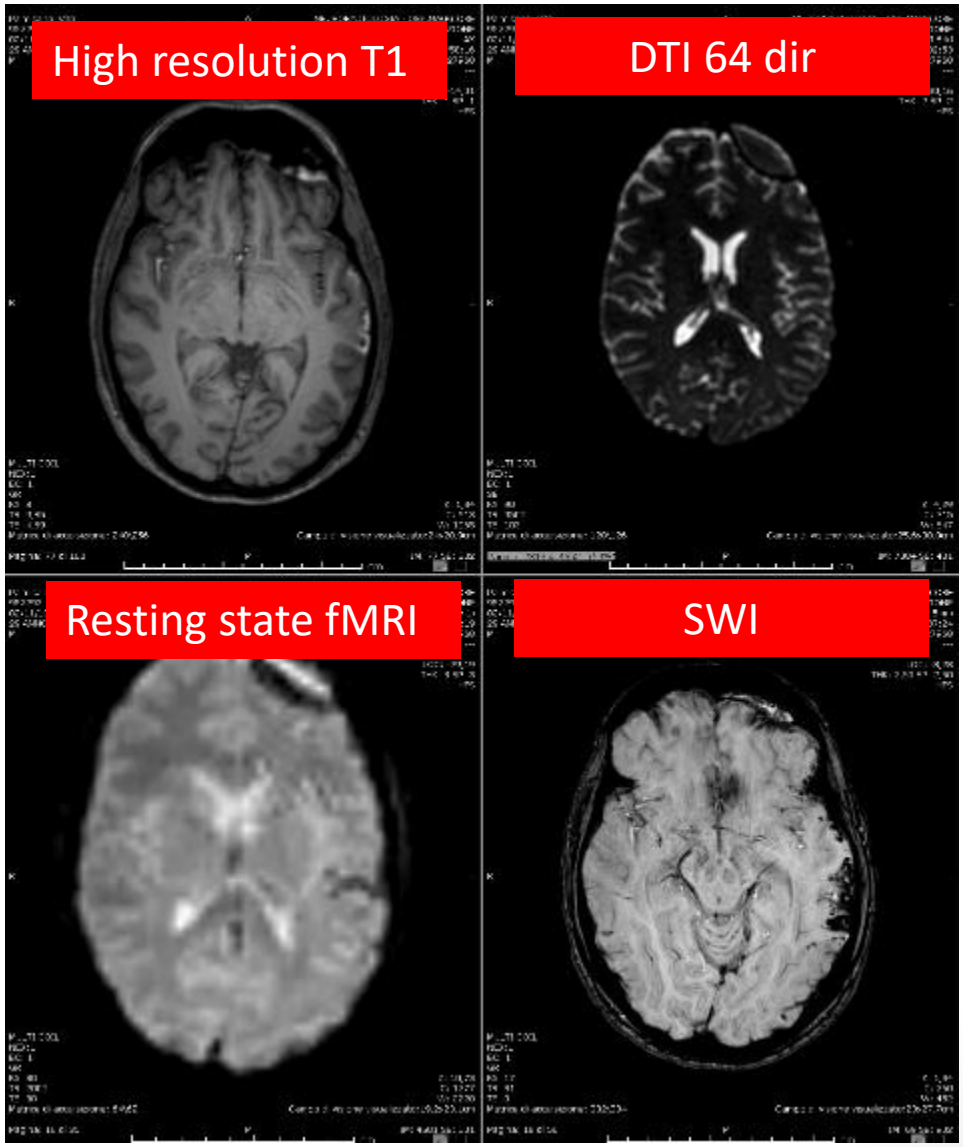


January 2018

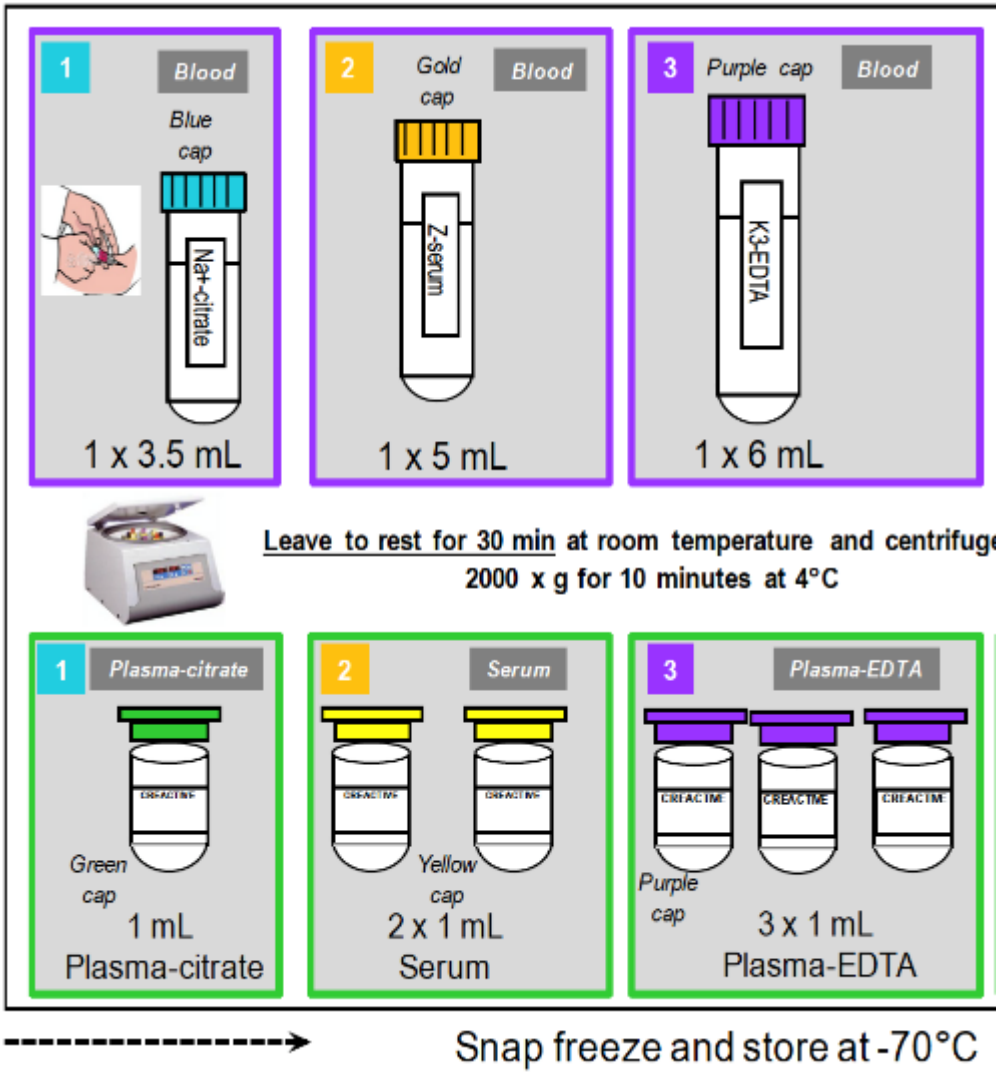
MRI protocol

WP1

- 3D-T1
- FLAIR
- SWI
- DTI
- FMRI resting state

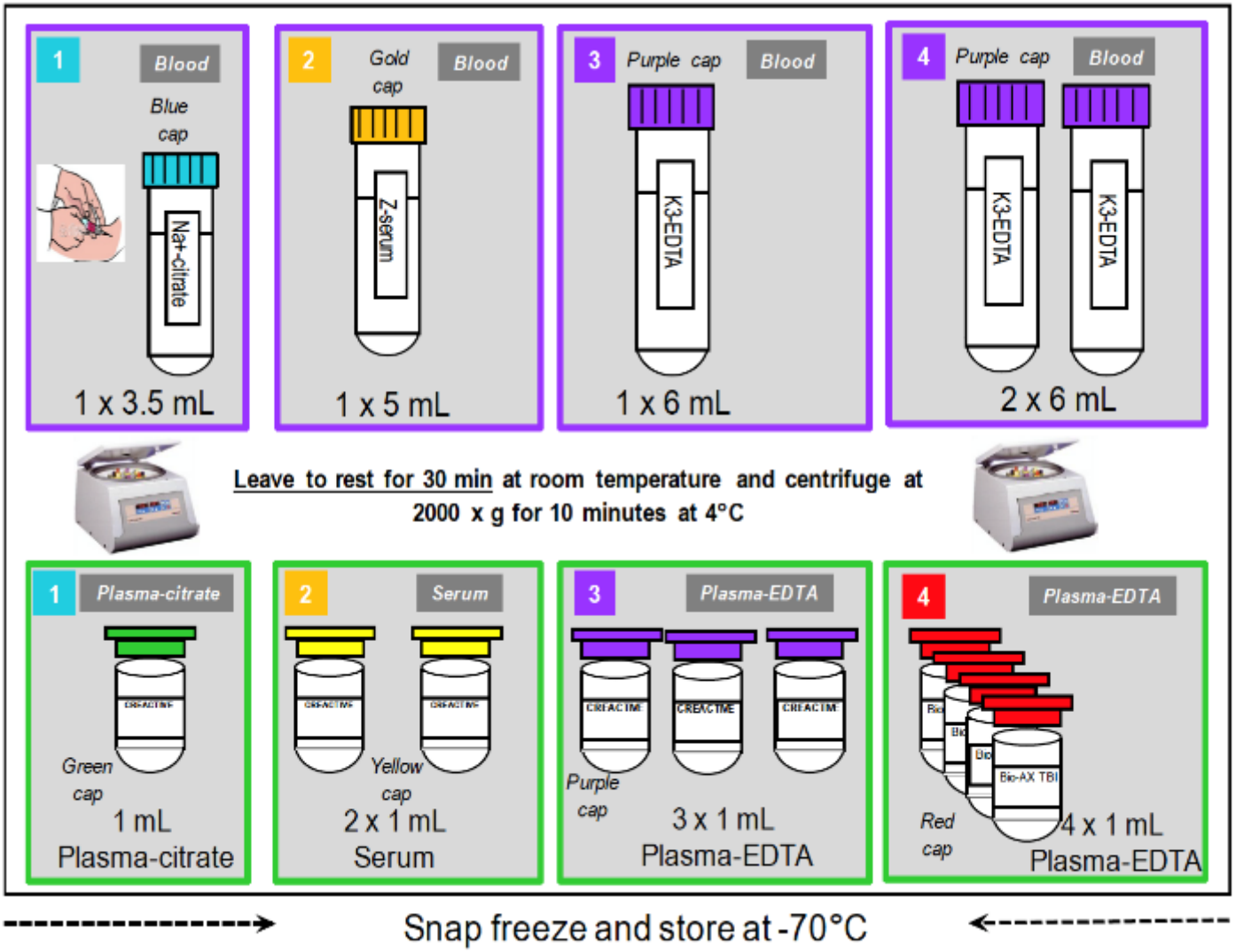


Blood sampling



CREACTIVE

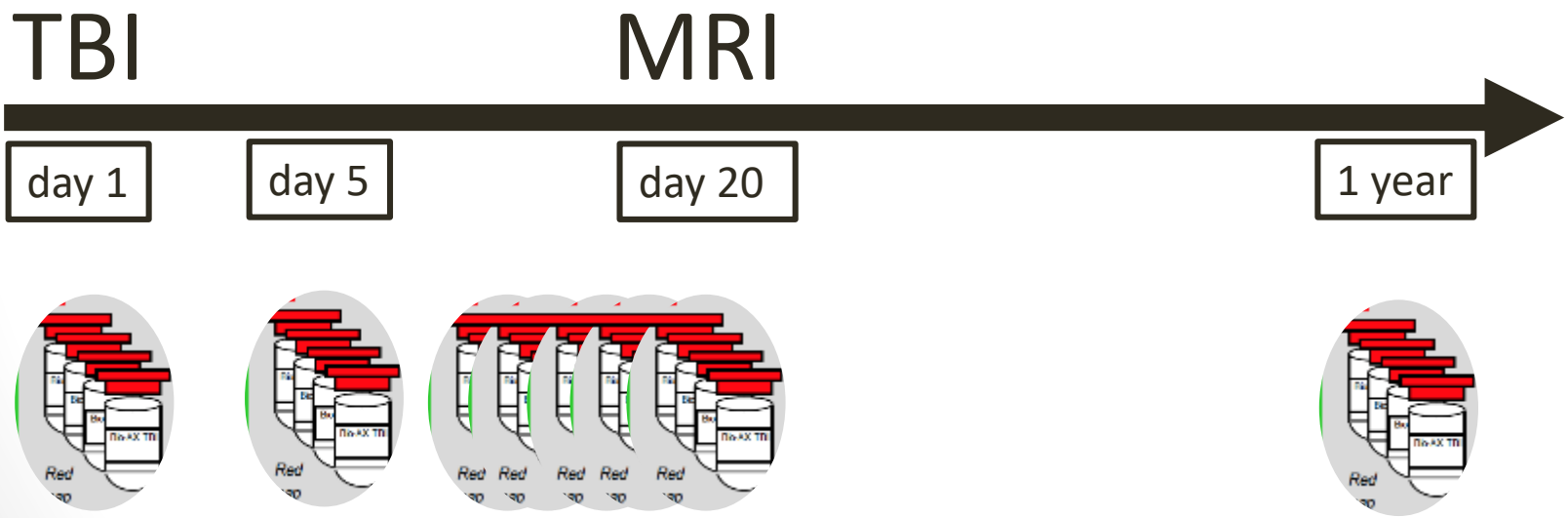
Blood sampling



CREACTIVE

BIO AX TBI

Blood sampling



Clinical assessment at follow up

Telephone Interview

Ambulatory visit

TBI → ICU discharge → 6 months → 12 months

- **Glasgow Outcome Scale (GOSE)**
- **Quality of life scale (QOLIBRI-OS)**
- **Rehabilitation Pathway Questionnaire**

12 months – ambulatory visit

- **Administered at 12 months, aligned with CREACTIVE protocol**
- Motor impairment assessment

- Computerised assessment
  - Working memory (N back)
  - Inhibition (Go-No-Go)
  - Spatial working memory (Corsi blocks)
  - **Imperial computerised assessment**

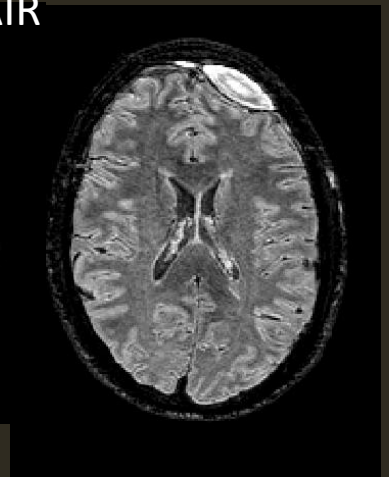
- Questionnaires
  - Hospital acquired anxiety and depression scal
  - Post-traumatic stress disorder (PTSD) PCL 5
  - Insomnia Severity Index scale
  - **Mayo-Portland Adaptability Inventory**

- Montreal Cognitive Assessment (MOCA)

Case discussion: conventional MRI

IT078-CASE 1

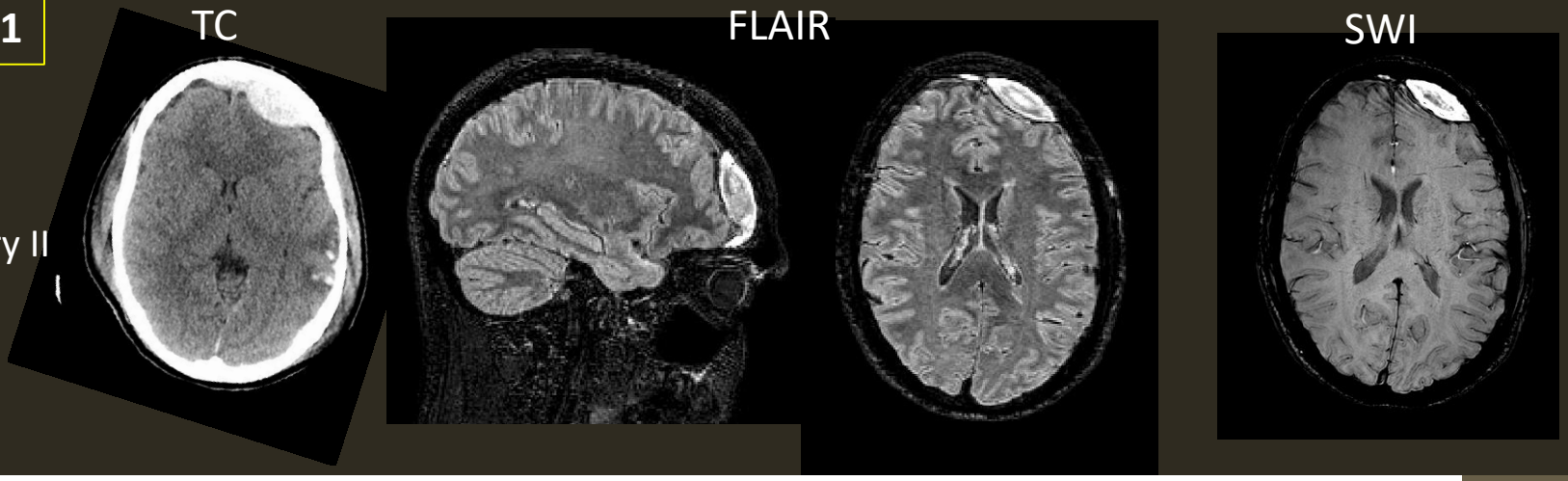
*Age 30
*GCS 12
*Diffuse injury II



Case discussion: conventional MRI

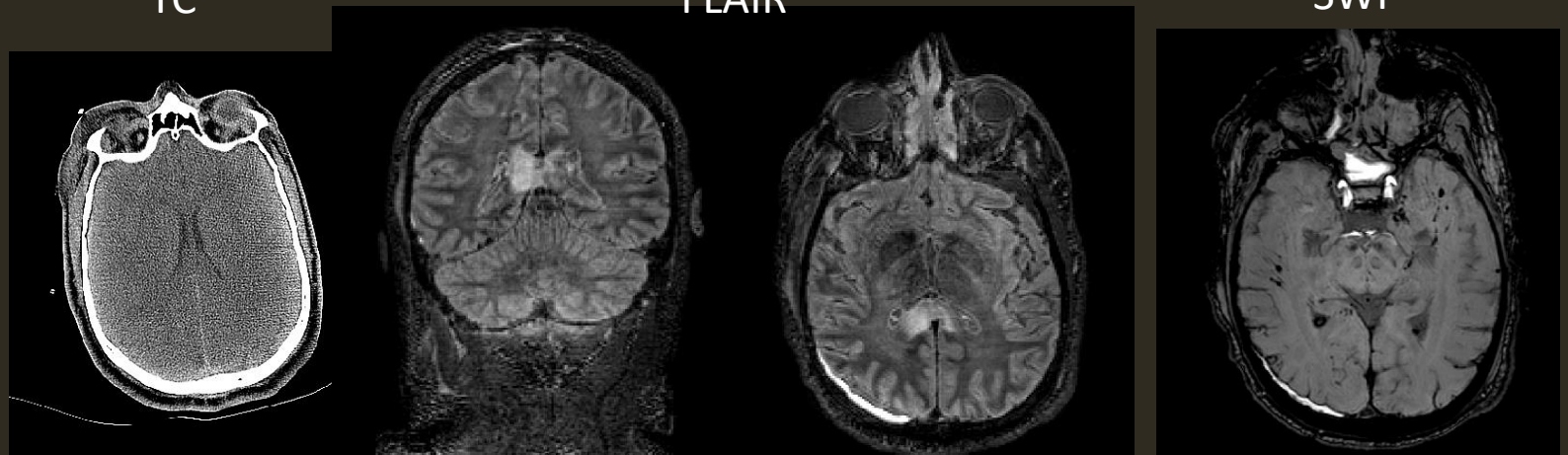
IT078-CASE 1

*Age 30
*GCS 12
*Diffuse injury II



IT078-CASE 2

*Age 54
*GCS 4
*Diffuse injury III



Case discussion – FA in the Corpus callosum

Red regions of the Corpus Callosum were patient-2 has 30% reduction in FA

Thank you