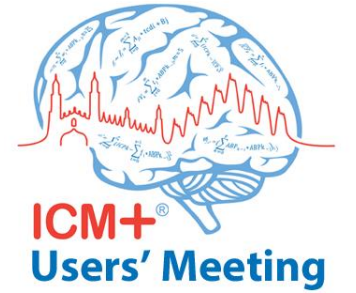




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# Use of ICM+ for running clinical trials

## Experiences from the CPPopt trial COGiTATE

Dr. Erta Beqiri  
erta.beqiri@gmail.com  
08/09/2019

Division of Neurosurgery, Department of Clinical Neurosciences

Brain Physics Lab



# COGiTATE



## CPPOpt Guided Therapy: Assessment of Target Effectiveness

Jeanette Tas on behalf of team



Tuesday 09:10-09:20

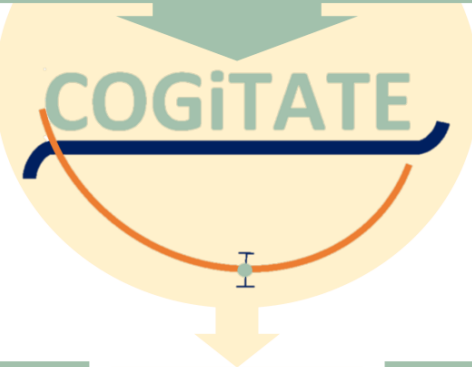
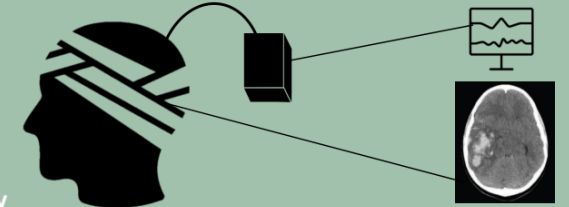
Room CAG



## CPPOpt Guided Therapy: Assessment of Target Effectiveness

Adult severe TBI  
ICP monitoring

Pregnant  
Moribund  
Decompressive craniectomy



### Control

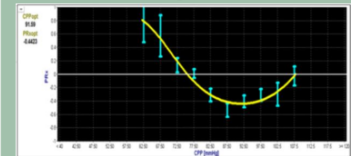
CPP between 60 and 70 mmHg

60 ——— 70  
Trauma Guidelines

### RANDOMIZE

### Intervention

Autoregulation guided CPP management



Brain Physics Lab



# Use of ICM+ for running clinical trials

- **interventional multicenter randomized controlled trial**
- **based on a parameter that requires real time data collection and processing**
- **that requires a feedback from the clinical team.**

All of the things I will show taking COGiTATE as an example, can be adapted to other trials with different protocols

# Daily life of a COGiTATE researcher



# Daily life of a COGiTATE researcher



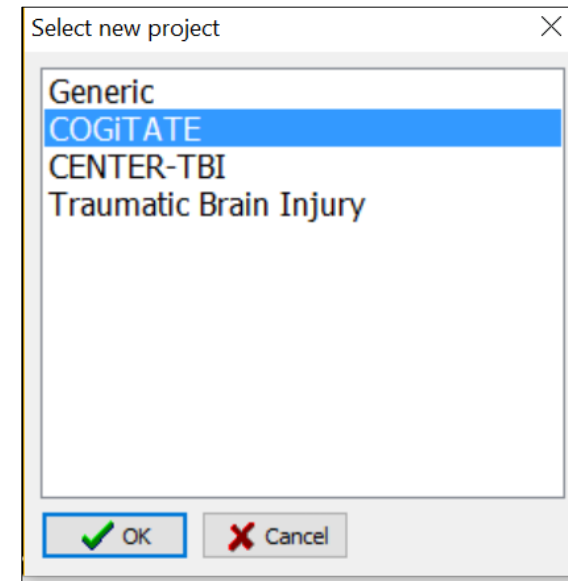
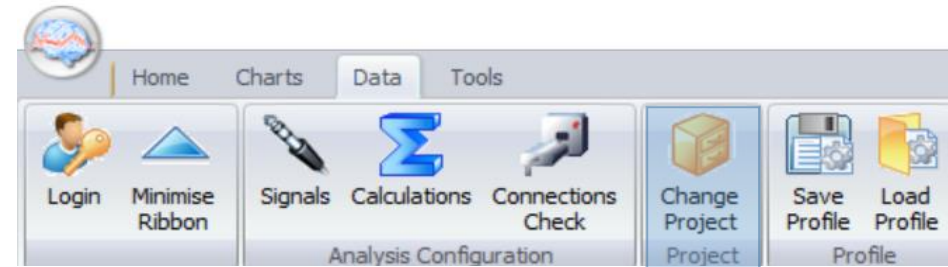
# Local data collection



# Local data collection



# Start COGiTATE in ICM+ - change project





# COGiTATE module in ICM+

Project Configuration

General Data Fields Events Data Archiving

Project Definition

Name: COGITATE Abbreviation: COGITATE

Description: Optimal CPP feasibility and effectiveness study .

Custom Module: COGITATE.dll

Data Folder: C:\Users\Jeanette\Documents\ICM+\Data\

Config Folder: C:\Users\Jeanette\Documents\ICM+\Configs\

Data File Name Format: <PROJECT>\_<DATE><TIME>\_<ANONYMID>\_<COMPUTER>

Default config profiles: COGITATE\_CPP.icmc  
COGITATE\_CPPopt.icmc

Enforce default configuration profiles

OK Cancel Keyboard


COGITATE

## Welcome to the COGiTATE study!

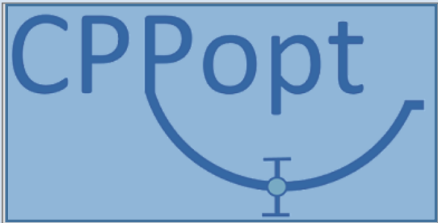
The COGiTATE study is a prospective intervention study that will assess the feasibility and effectiveness of autoregulation guided therapy (CPPopt) in severe traumatic brain injury patients.

The patient needs to be randomised into the CPPopt group or the standard of care group (CPP) by the local researchers using an external web based tool.

Please select the correct randomisation group below to continue.



CPP



CPPopt

# CPPopt arm

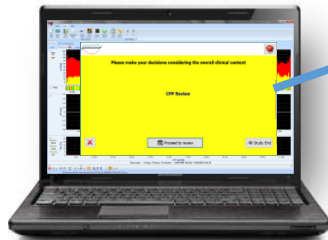


# CPP review

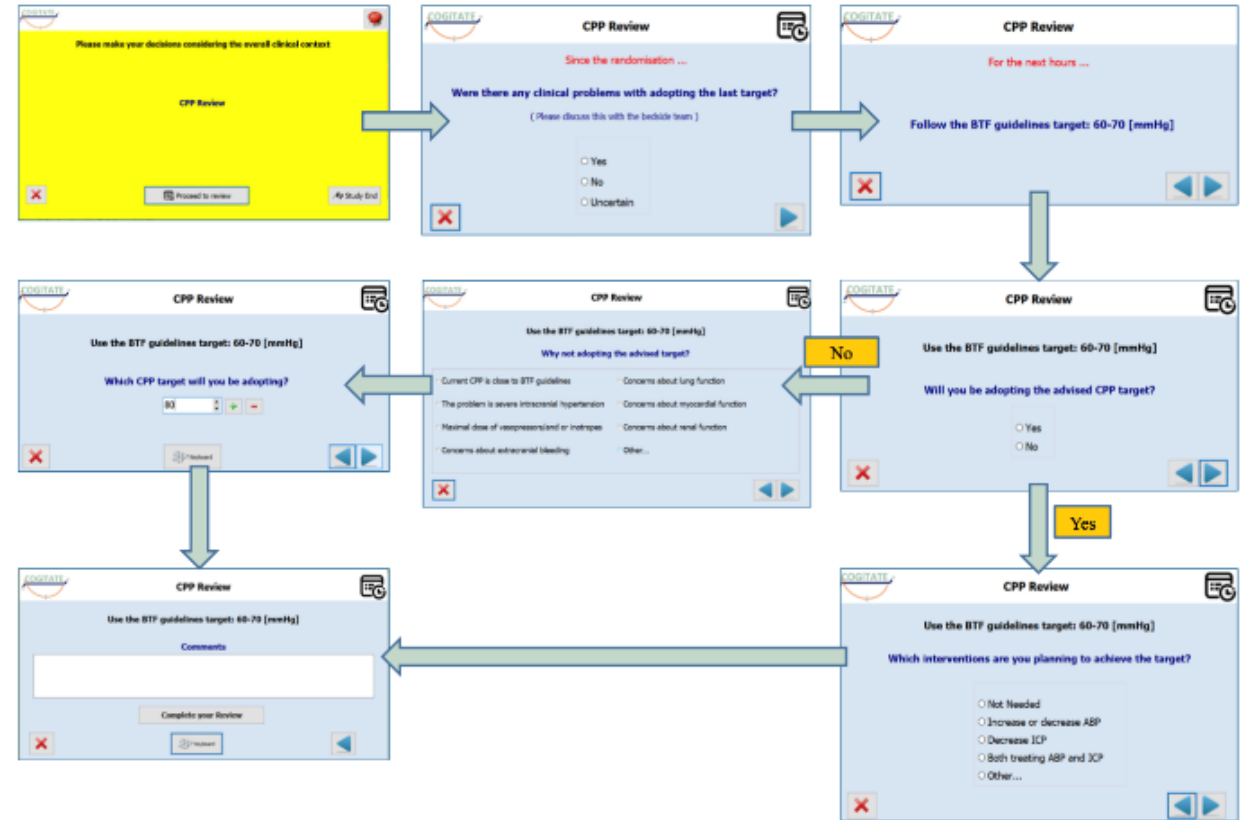
Bedside monitor



Laptop with ICM+



Clinical trial wizard plugins support



# What information at the review?

Function options

Function: **OptimalValueFlex**

Missing Data Limit [%]: 50

Number of bins: 16

Minimum bin value: 40

Maximum bin value: 120

Minimum bin data count [%]: 3

Minimum included data [%]: 50.00

Minimum Y span: 0.2

Minimum fit R2 value: 0.00

Min all data fit R2 value: 0.2

Concave:

Need not include 'best':

Use error weighting:

Enforce Y range:

Enforce Y region - Min: -0.3

Enforce Y region - Max: 0.6

Optimal range threshold: 0.25

Min value of lower breakpoint: 0.00

Max value of upper breakpoint: 0.00

Output value type: Optimal X

**Min Calc Period**: 7200

**Step**: 600

Multindow Treatment: Weighted Average

Window Weight Exp: 0

Fit Error Weight Exp: 1

Use R2 for fit quality:

Use full fit error:

Non-parabolic window weight: 0

OK Cancel Keyboard

On Line Analysis Configuration Dialog

Virtual Signals Primary Analysis Secondary Analysis 1 Secondary Analysis 2 Secondary Analysis 3 Secondary Analysis 4 Final Analysis

Data Acquisition Period [s]: 10.0 Adjust Calc. Period

Name	Formula	Units	Calc. Windo...	Updated [s]	Min	Max	En.
sABP	Mean(sABP)		60	60	0	0	Y
dABP	Mean(dABP)		60	60	0	0	Y
ICPmax	Mean(ICPmax)	mmHg	60	60	0	0	Y
ICPmin	Mean(ICPmin)	mmHg	60	60	0	0	Y
ppABP	Mean(ppABP)		60	60	0	0	Y
CPPmed	Mean(CPPmed)	mmHg	60	60	0	0	Y
CPPopt	MeanEW( CPPopt,'ALPHA=0.1' )	mmHg	7200	60	0	0	Y
PRxopt	MeanEW( PRxopt,'ALPHA=0.1' )	mmHg	7200	60	0	0	Y
LLA	MeanEW( LLA,'ALPHA=0.1' )	mmHg	7200	60	0	0	Y
ULA	MeanEW( ULA,'ALPHA=0.1' )	mmHg	7200	60	0	0	Y
CPP5min	Mean(CPP5min)	mmHg	60	60	0	0	Y
PAX	Mean(PAX)		60	60	0	0	Y
DeltaCPP	Mean( CPPmed )-Mean( CPPopt )	mmHg	60	60	0	0	Y

Modify Add Delete Clear Auto Fill Default Period [s]: 10.0

OK Cancel Save Load Advanced Keyboard

# What information at the review?

Function options

Function: **OptimalValueFlex**

Missing Data Limit [%]: 50

Number of bins: 16

Minimum bin value: 40

Maximum bin value: 120

Minimum bin data count [%]: 3

Minimum included data [%]: 50.00

Minimum Y span: 0.2

Minimum fit R2 value: 0.00

Min all data fit R2 value: 0.2

Concave:

Need not include 'best':

Use error weighting:

Enforce Y range:

Enforce Y region - Min: -0.3

Enforce Y region - Max: 0.6

Optimal range threshold: 0.25

Min value of lower breakpoint: 0.00

Max value of upper breakpoint: 0.00

Output value type: Optimal X

Min Calc Period: 7200

Step: 600

Multindow Treatment: Weighted Average

Window Weight Exp: 0

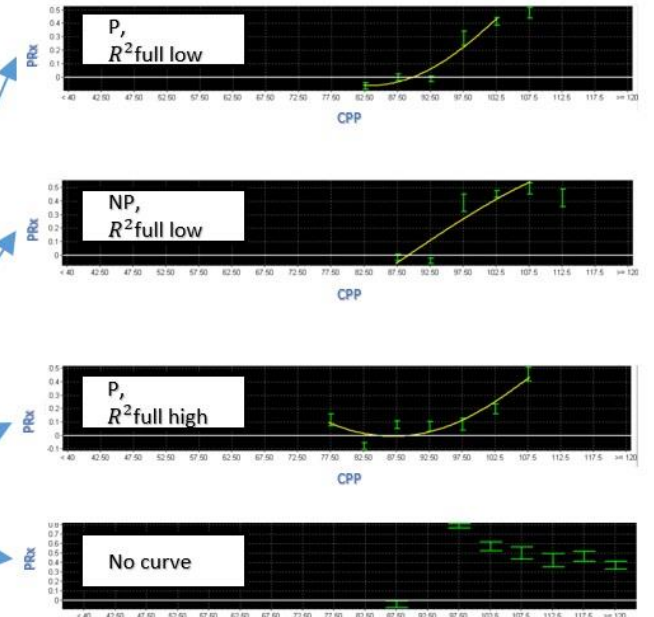
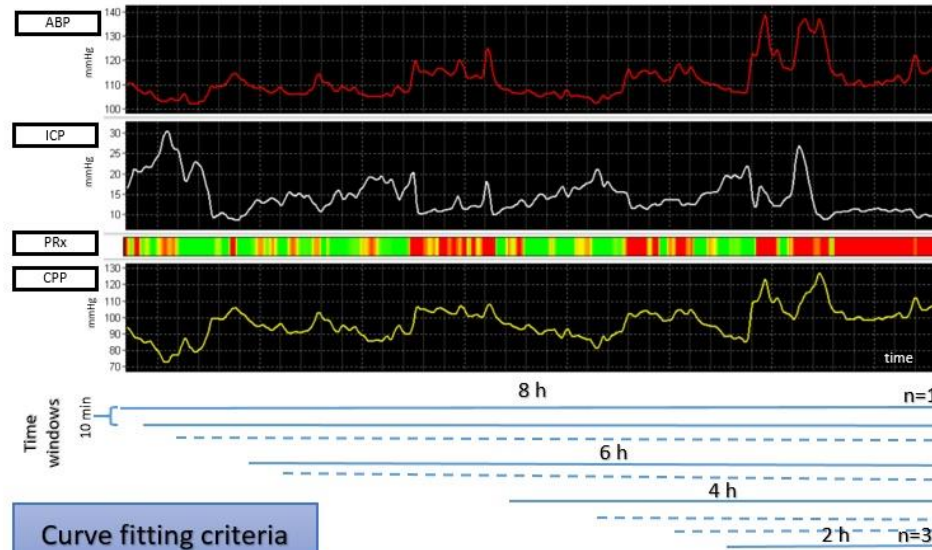
Fit Error Weight Exp: 1

Use R2 for fit quality:

Use full fit error:

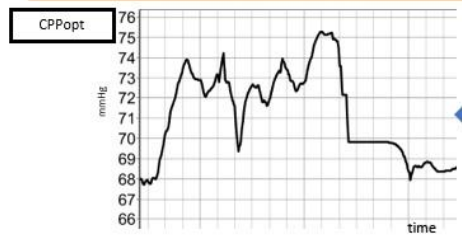
Non-parabolic window weight: 0

OK Cancel Keyboard



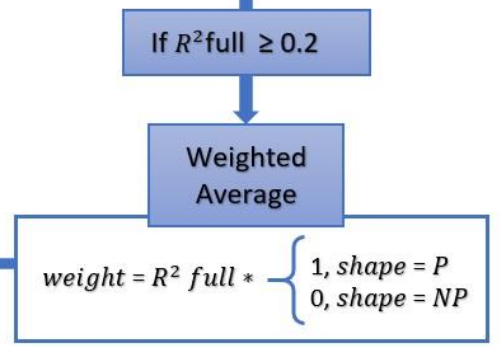
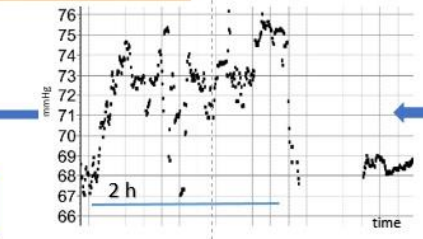
## Curve fitting criteria

- 1) Each CPP bin must represent at least 3% of the total data count. In this way, CPP values that are very scarcely represented, likely due to short spikes or drops, but not to the physiological trend, will be disregarded.
- 2) At least 50% of the data in the time window must be included in the curve fit.
- 3) A PRx variation of at least 0.2 is mandated (thus rejecting flatter PRx-CPP curves).
- 4) The PRx range of interest is enforced to be between -0.3 and 0.6: the algorithm will not return any CPPopt value when PRx is always very high (indicating a complete loss of pressure reactivity) or always very low (pressure reactivity preserved at each CPP value).



Exponentially Weighted Average

$weight = (1 - \alpha)^k$



# What information at the review?



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DEGLI STUDI  
DI MILANO

## Optimal cerebral perfusion pressure assessed with a multi-window weighted approach adapted for prospective use: a validation study

E.Begiri<sup>1-2</sup>, A.Ercole<sup>3</sup>, M.Aries<sup>4</sup>, M.Cabeleira<sup>1</sup>, A.Czigler<sup>1,5</sup>, A.Liberti<sup>4,2</sup>, J.Tas<sup>4</sup>, J.Donnelly<sup>1</sup>, L. Xiuyun<sup>1,6</sup>, M.Fedriga<sup>1,7</sup>, K.H.Chu<sup>1</sup>, FA.Zeiler<sup>3,8</sup>, M.Czosnyka<sup>1</sup>, P. Smielewski<sup>1</sup>

<sup>1</sup>Brain Physics Laboratory, Division of Neurosurgery, Department of Clinical Neurosciences, University of Cambridge, UK; <sup>2</sup>Department of Physiology and Transplantation, Milan University, Italy; <sup>3</sup>Division of Anaesthesia, University of Cambridge, UK; <sup>4</sup>Department of Intensive Care, Maastricht UMC, The Netherlands; <sup>5</sup>Department of Neurosurgery and Szentagothai Research Center, University of Pecs, Medical School, Pecs, Hungary; <sup>6</sup>Department of physiological nursing, university of California, San Francisco, CA,94122, USA; <sup>7</sup>Department of Anesthesia, Critical care and Emergency. Spedali Civili University Hospital, Piazzale Spedali civili 1, Brescia 25123, Italy; <sup>8</sup>Department of Surgery, Rady Faculty of Health Sciences, University of Manitoba, Canada

Poster n 305

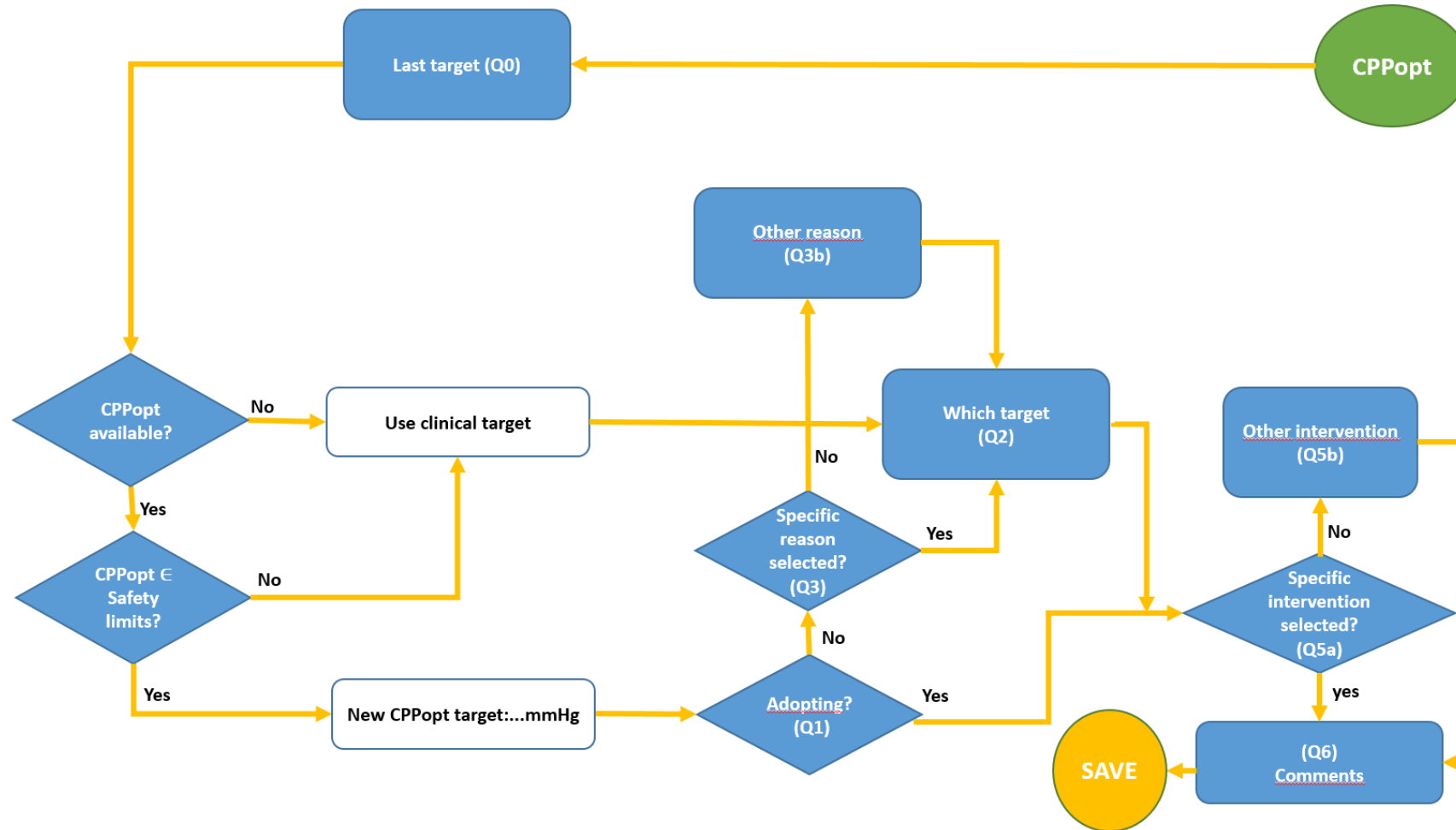


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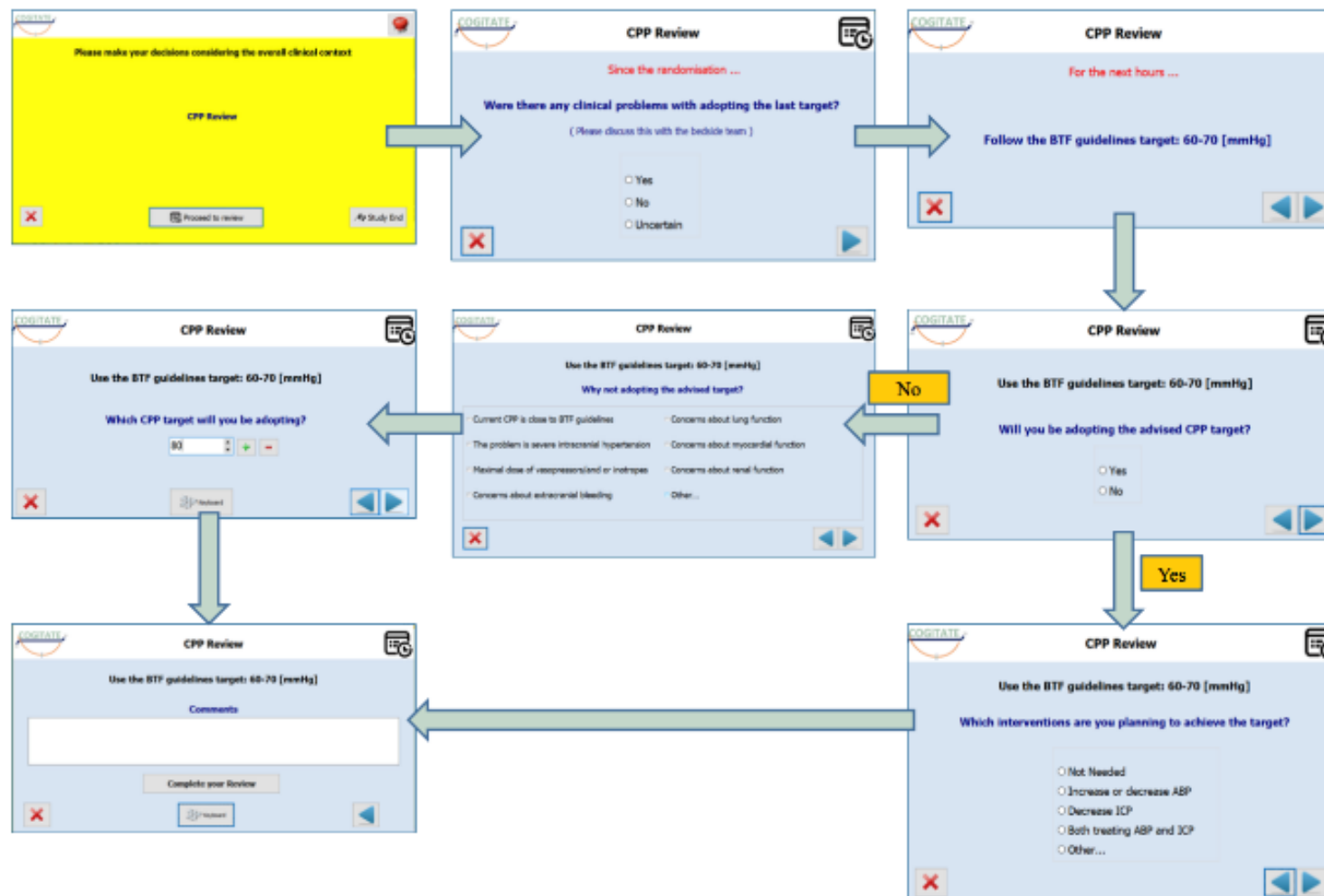
Brain Physics Lab



# Logic for trial assistance



# Forms for trial assistance

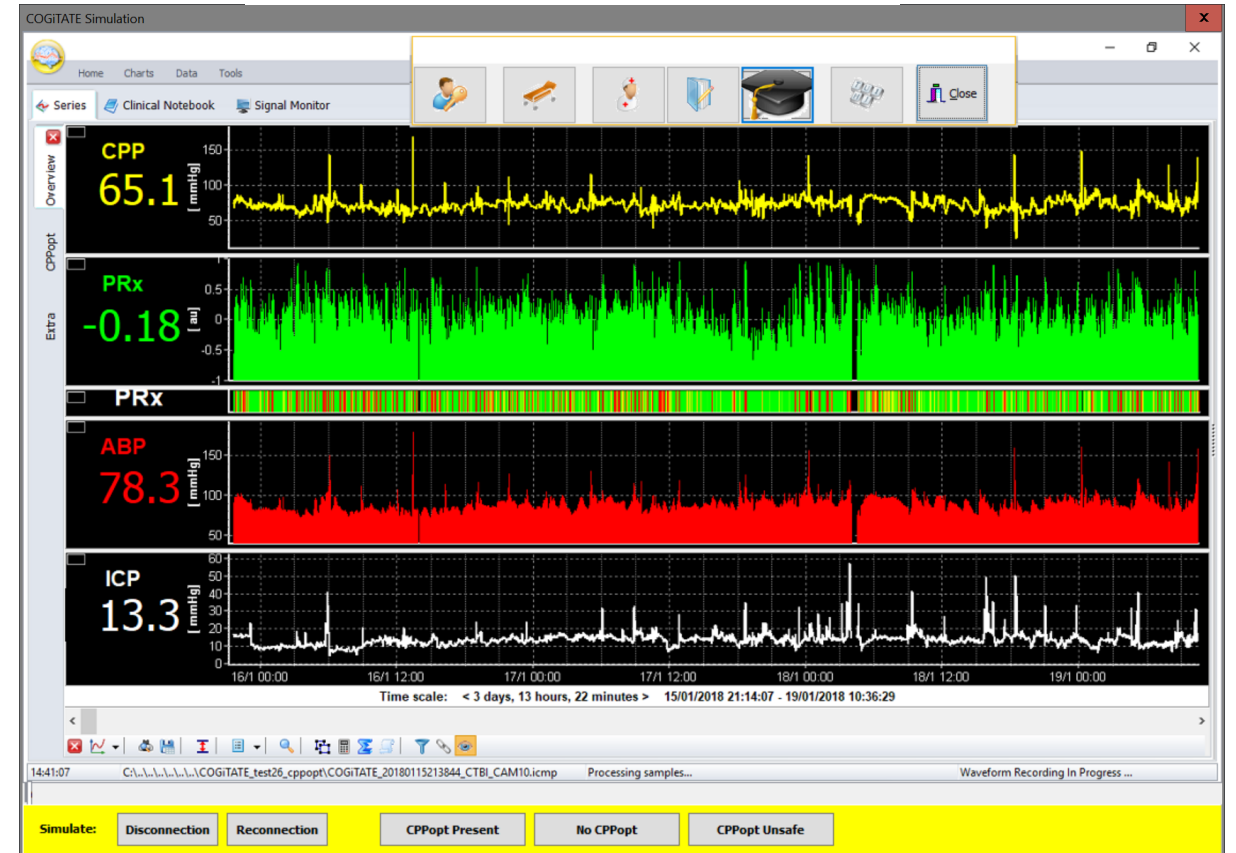




# Simulator



## COGiTATE\_Simul

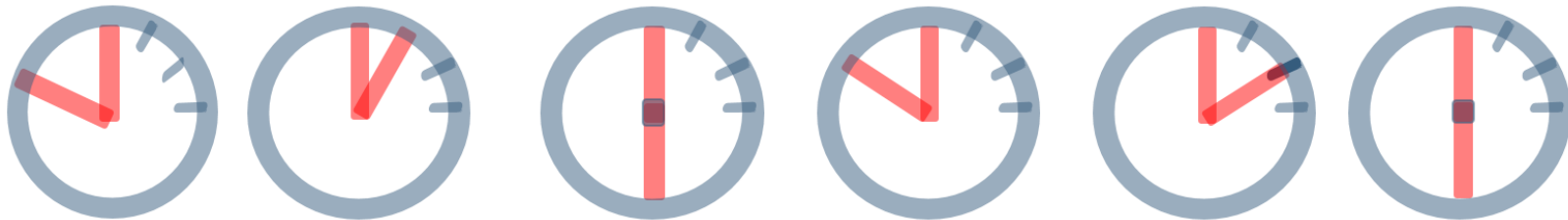


# Time settings

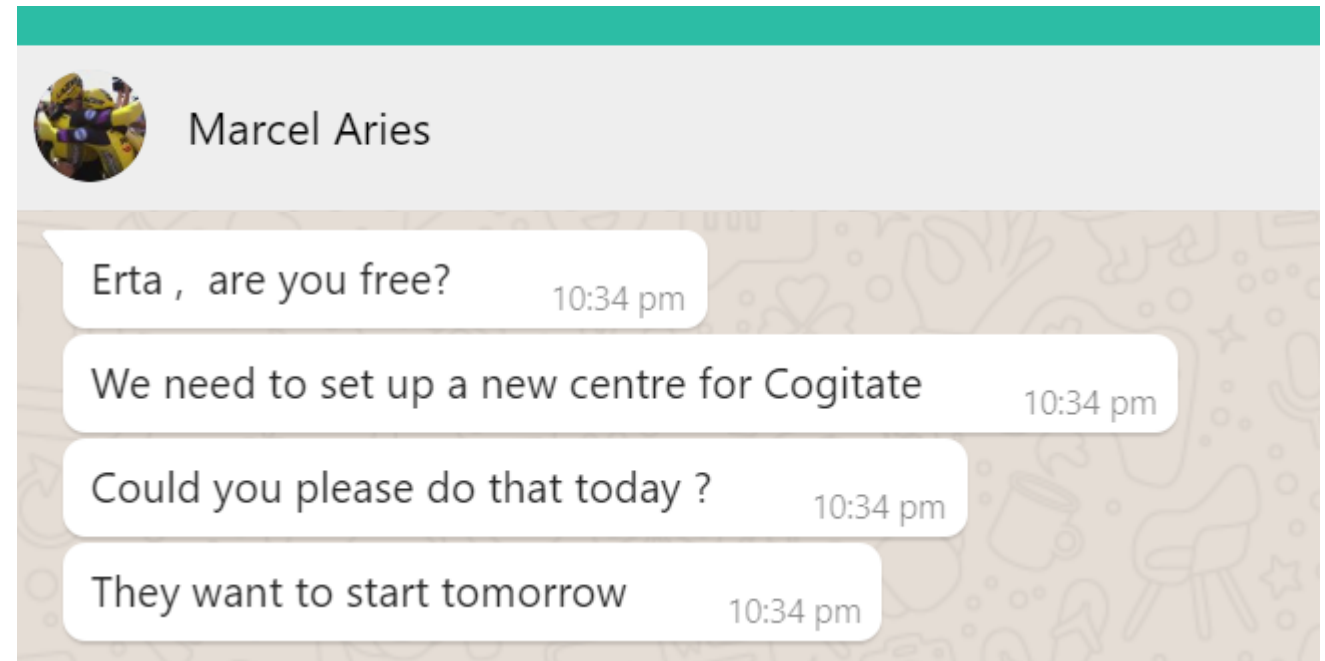
Bedside monitor



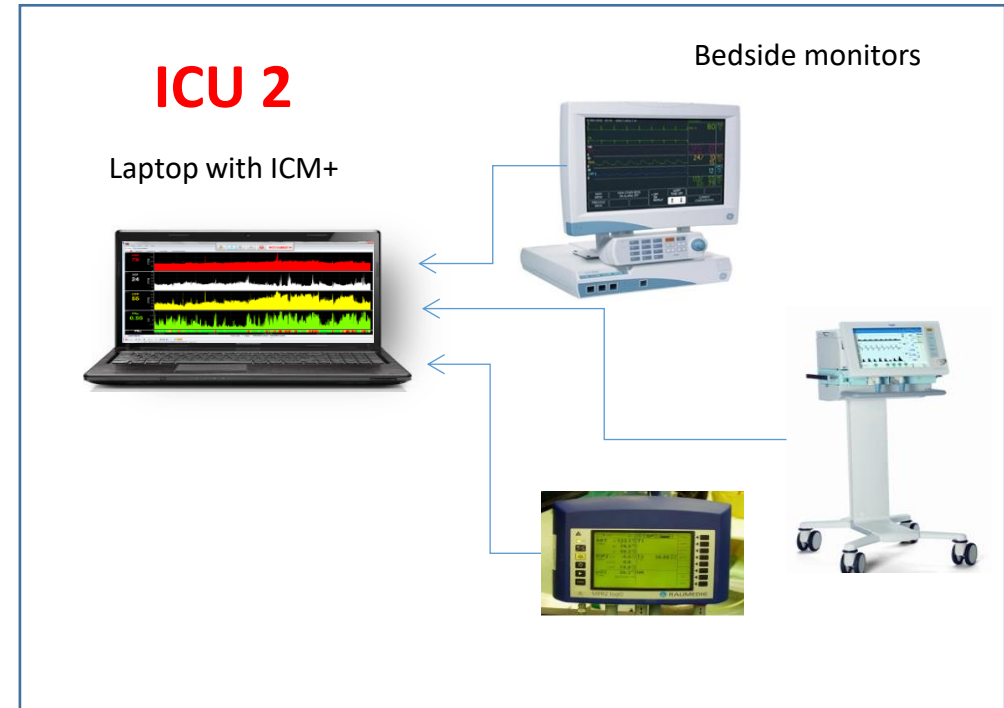
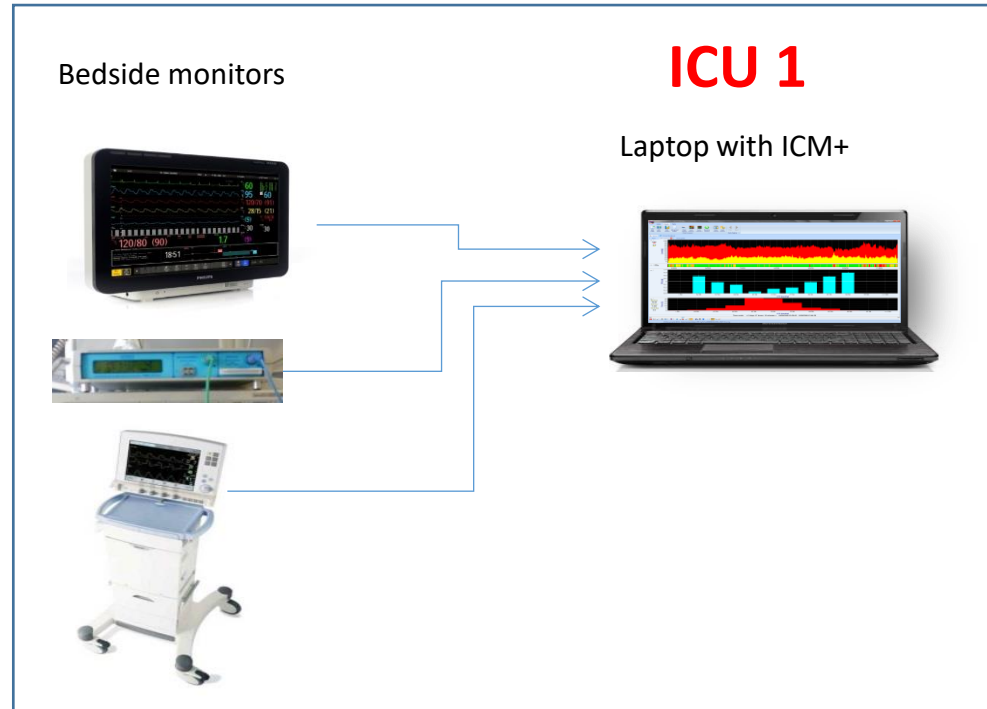
Laptop with ICM+




# New center setting up



# New center setting up



# New center setting up

 gesolar\_module\_v84101

 icmp.8.4.4.4

# New center setting up

File Explorer path: This PC > Windows (C:) > Users > Public > Public Documents > ICM+ > sysconfig >

Name	Date modified	Type	Size
copies	23/05/2019 00:12	File folder	
CustomForms	29/07/2016 09:05	File folder	
originals cog	31/05/2018 15:19	File folder	
SFTP	29/07/2016 09:05	File folder	
updates	13/12/2018 01:41	File folder	
<input checked="" type="checkbox"/> COGiTATE.dll	03/06/2018 11:15	Application extension	990 KB
cogitate	07/04/2019 21:52	Configuration settings	4 KB
COGITATE	05/03/2018 11:28	WAV File	4 KB
COGiTATE_FAQ	05/02/2018 00:54	Documento PDF	570 KB
cogitate_helpinfo	20/01/2018 19:36	Text Document	1 KB
COGITATE_ICMSOP	22/11/2017 23:12	Documento PDF	2,865 KB
COGITATE_PROTOCOL v5.4	22/11/2017 23:11	Documento PDF	1,165 KB
COGITATE_software module	03/06/2018 15:20	Documento PDF	3,923 KB
COGiTATE_software module	21/03/2018 12:53	Microsoft PowerPoint Macro-...	18,356 KB
COGITATE_TBI background module	22/11/2017 23:11	Documento PDF	3,570 KB
COGiTATE_test.dll	23/05/2019 00:37	Application extension	998 KB
cogitate_test	23/05/2019 00:48	Configuration settings	4 KB
events	23/07/2019 19:08	XML Document	97 KB
macros	17/04/2019 00:49	XML Document	7 KB
<input checked="" type="checkbox"/> projects.cogitate	07/09/2019 19:23	XML Document	3 KB

Project Configuration

General | Data Fields | Events | Data Archiving

Project Definition

Name: COGITATE      Abbreviation: COGITATE

Description: Optimal CPP feasibility and effectiveness study .

Custom Module: COGITATE.dll

Data Folder: C:\Users\Jeanette\Documents\ICM+\Data\

Config Folder: C:\Users\Jeanette\Documents\ICM+\Configs\

Data File Name Format: <PROJECT>\_<DATE><TIME>\_<ANONYMID>\_<COMPUTER>

Default config profiles: COGITATE\_CPP.icmc  
COGITATE\_CPPopt.icmc

Enforce default configuration profiles

OK Cancel Keyboard

# New center setting up

This PC > Windows (C:) > Users > Public > Public Desktop Objects

Name	Date modified
copies	23/05/2012
CustomForms	29/07/2012
originals cog	31/05/2012
SFTP	29/07/2012
updates	13/12/2011
<input checked="" type="checkbox"/> COGiTATE.dll	03/06/2012
cogitate	07/04/2012
COGITATE	05/03/2012
COGiTATE_FAQ	05/02/2012
cogitate_helpinfo	20/01/2012
COGITATE_ICMSOP	22/11/2011
COGITATE_PROTOCOL v5.4	22/11/2011
COGITATE_software module	03/06/2012
COGiTATE_software module	21/03/2012
COGITATE_TBI background module	22/11/2011
COGiTATE_test.dll	23/05/2012
cogitate_test	23/05/2012
events	23/07/2012
macros	17/04/2012
<input checked="" type="checkbox"/> projects.cogitate	07/05/2012

**Welcome to the COGiTATE study!**

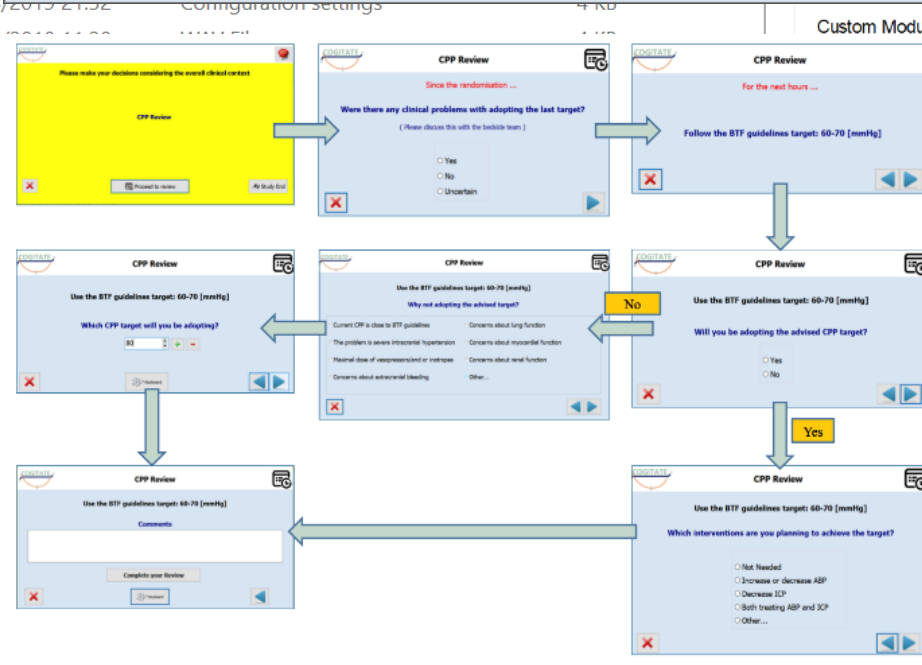
The COGiTATE study is a prospective intervention study that will assess the feasibility and effectiveness of autoregulation guided therapy (CPPopt) in severe traumatic brain injury patients.

The patient needs to be randomised into the CPPopt group or the standard of care group (CPP) by the local researchers using an external web based tool.

Please select the correct randomisation group below to continue.

CPP

CPPopt



Events Data Archiving

COGiTATE Abbreviation: COGiTATE

Optimal CPP feasibility and effectiveness study .

COGiTATE.dll

C:\Users\Jeanette\Documents\ICM+\Data\

C:\Users\Jeanette\Documents\ICM+\Configs\

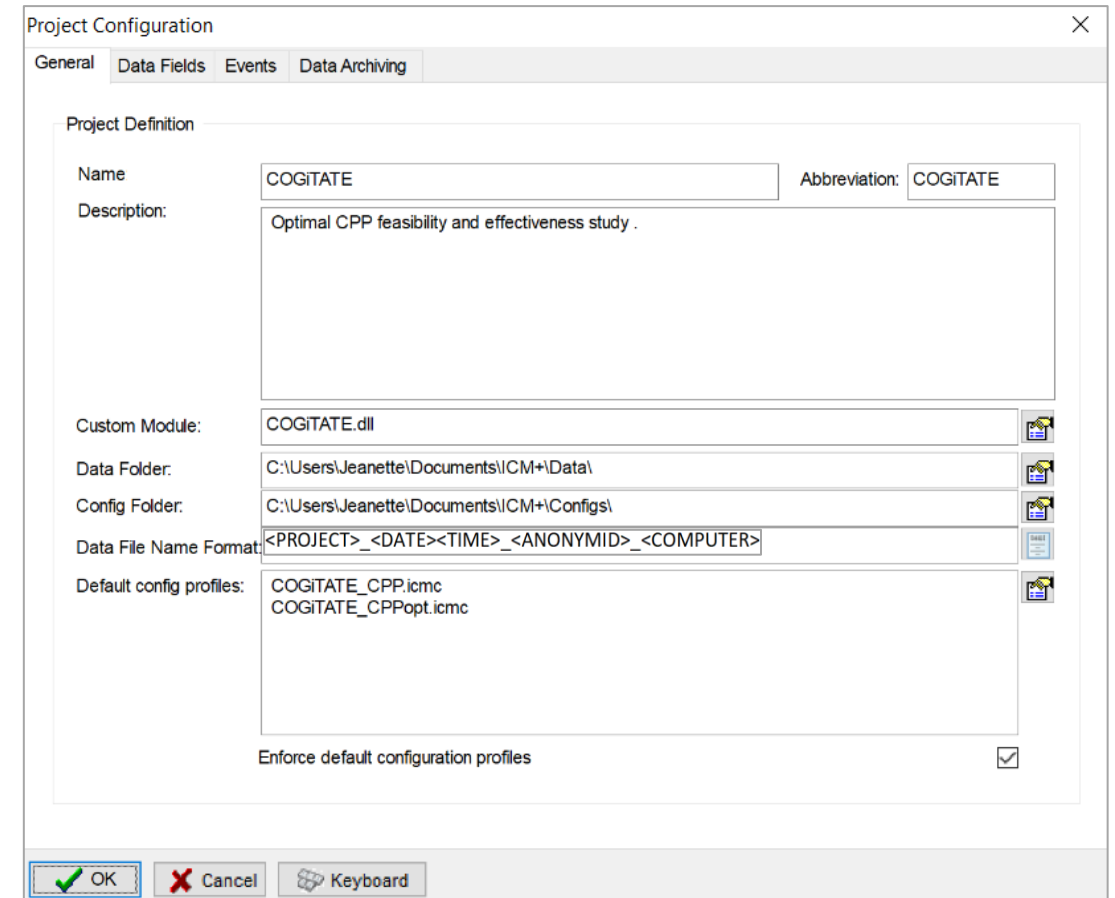
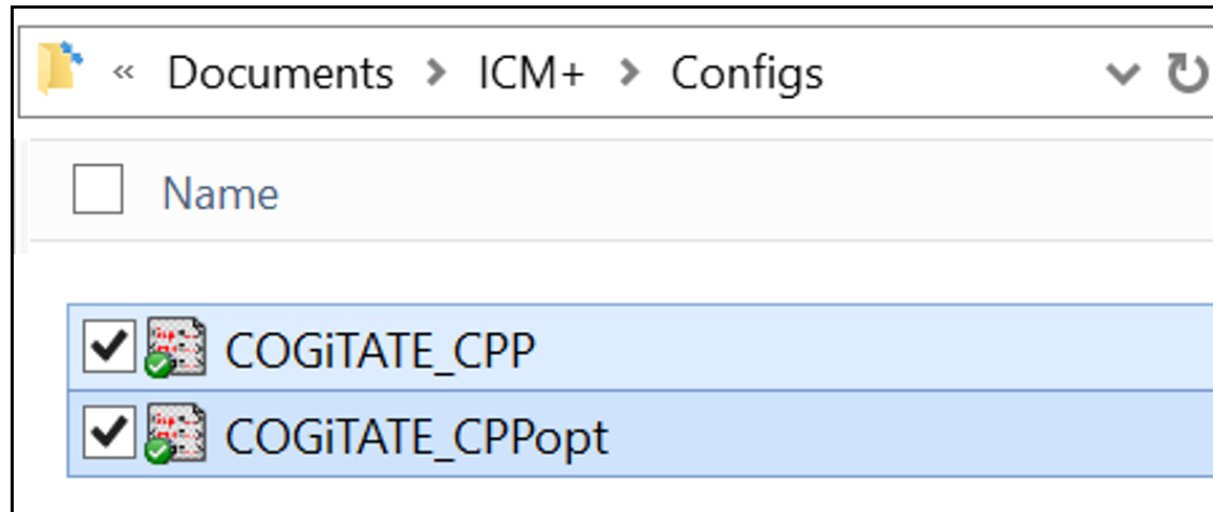
Format: <PROJECT>\_<DATE><TIME>\_<ANONYMID>\_<COMPUTER>

Files: COGiTATE\_CPP.icmc  
COGiTATE\_CPPopt.icmc

Enforce default configuration profiles

Cancel Keyboard

# New center setting up





# New center setting up



The image shows a Windows file explorer window on the left, displaying a folder named 'ICM+' with two sub-items: 'COGiTATE\_CPP' and 'COGiTATE\_CPPopt', both marked with checkmarks and green checkmarks. In the center is the 'On Line Analysis Configuration Dialog' window, which is currently on the 'Primary Analysis' tab. It features a 'Data Acquisition Period [s]' set to 10.0 and a table of analysis parameters. The table includes columns for Name, Formula, Units, Calc. Windo..., Updated [s], Min, Max, and En. The 'CPPopt' row is highlighted. Below the table are buttons for 'Modify', 'Add', 'Delete', 'Clear', and 'Auto Fill', along with a 'Default Period [s]' set to 10.0. At the bottom are 'OK', 'Cancel', 'Save', 'Load', 'Advanced', and 'Keyboard' buttons. To the right is the 'Project Configuration' window, showing an 'Abbreviation' field set to 'COGATE' and a text area containing 'effectiveness study .'. Below this is a file path field showing '>\_<ANONYMID>\_<COMPUTER>' and a 'files' checkbox.

Name	Formula	Units	Calc. Windo...	Updated [s]	Min	Max	En.
sABP	Mean(sABP)		60	60	0	0	Y
dABP	Mean(dABP)		60	60	0	0	Y
ICPmax	Mean(ICPmax)	mmHg	60	60	0	0	Y
ICPmin	Mean(ICPmin)	mmHg	60	60	0	0	Y
ppABP	Mean(ppABP)		60	60	0	0	Y
CPPmed	Mean(CPPmed)	mmHg	60	60	0	0	Y
CPPopt	MeanEW( CPPopt,'ALPHA=0.1' )	mmHg	7200	60	0	0	Y
PRxopt	MeanEW( PRxopt,'ALPHA=0.1' )	mmHg	7200	60	0	0	Y
LLA	MeanEW( LLA,'ALPHA=0.1' )	mmHg	7200	60	0	0	Y
ULA	MeanEW( ULA,'ALPHA=0.1' )	mmHg	7200	60	0	0	Y
CPP5min	Mean(CPP5min)	mmHg	60	60	0	0	Y
Pax	Mean(Pax)		60	60	0	0	Y
DeltaCPP	Mean( CPPmed )-Mean( CPPopt )	mmHg	60	60	0	0	Y

# New center setting up

« Documents » ICM+

Name

-  COGiTATE\_CPP
-  COGiTATE\_CPPopt



Abbreviation: COGiTATE

effectiveness study .

\\ICM+\Data\

\\ICM+\Configs\

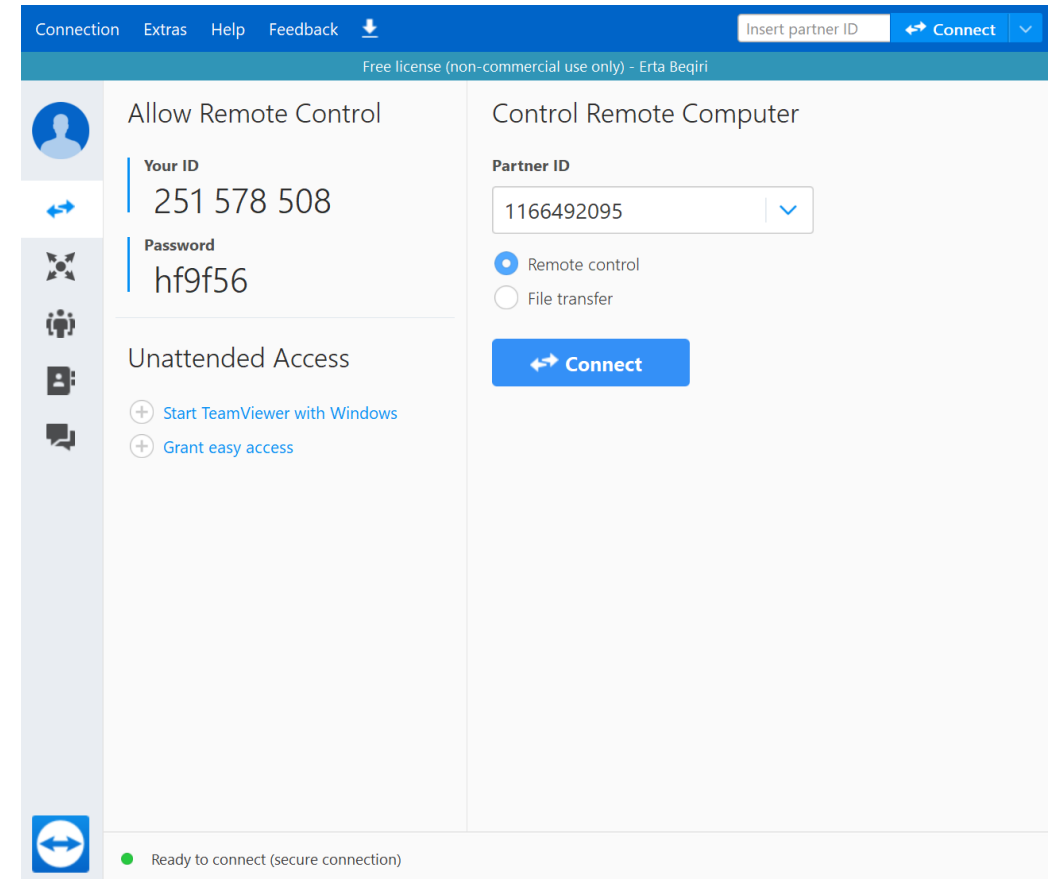
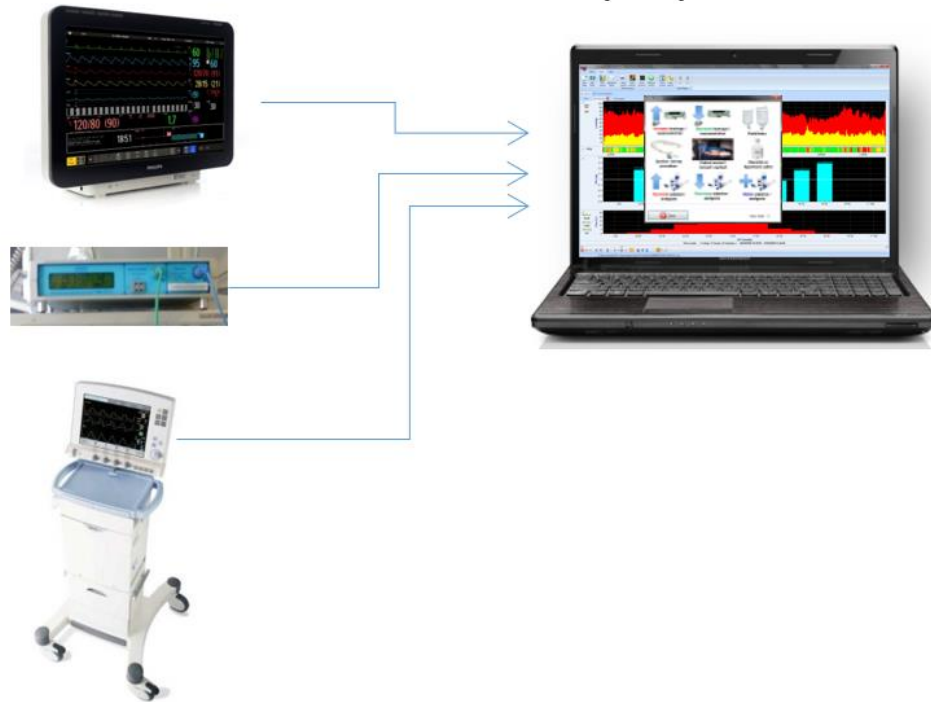
> <ANONYMID> <COMPUTER>

files

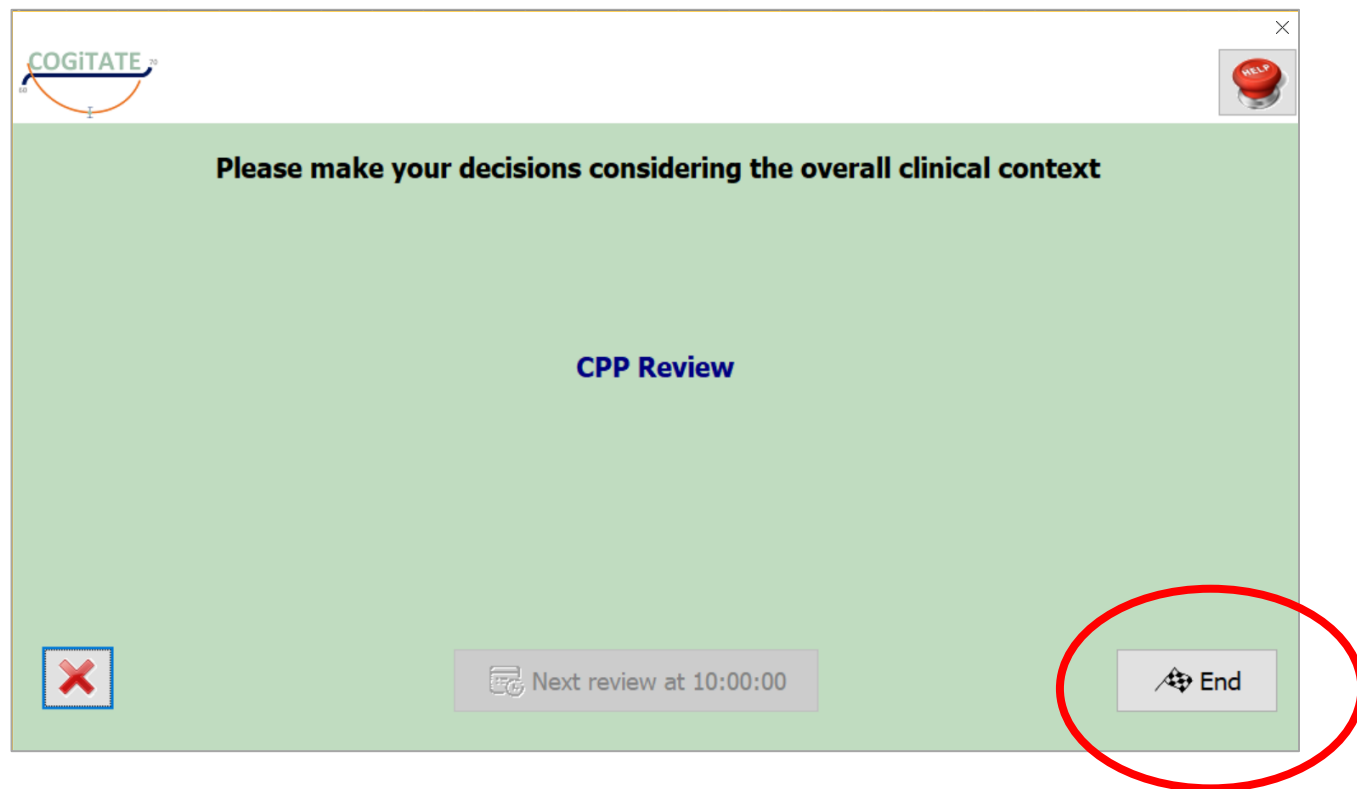
# Remote setting up and troubleshooting

Bedside monitors

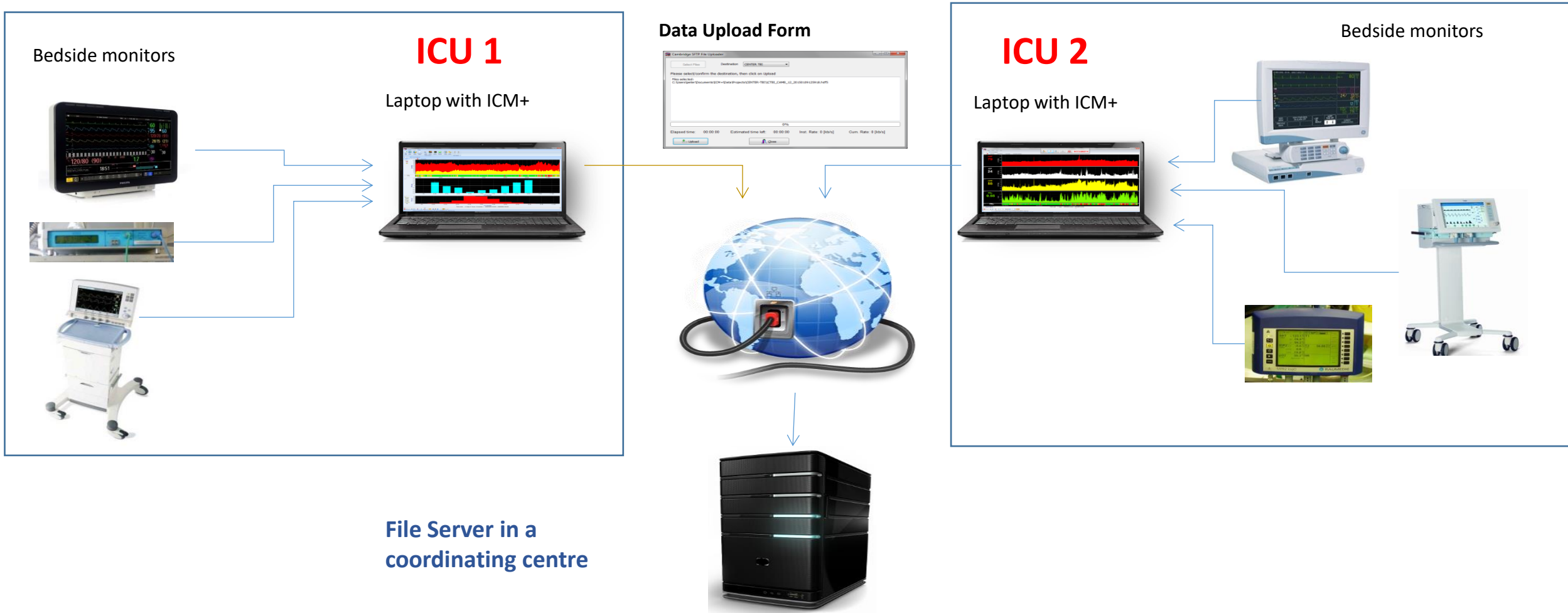
Laptop with ICM+



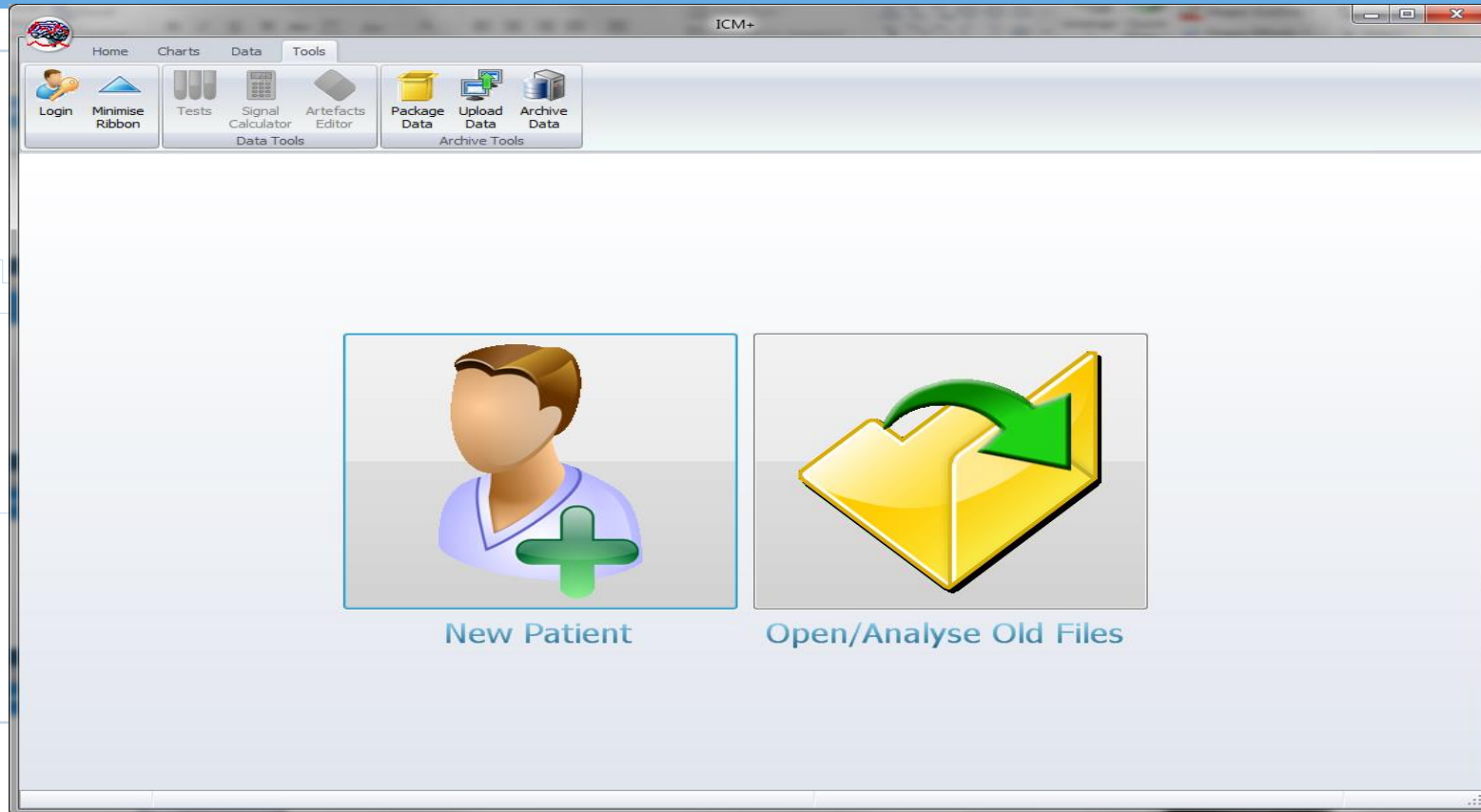
# End the study



# Data collection: multicentre collaborative tools



# Data collection: multicentre collaborative tools



File Server in a coordinating centre

Bedside monitors



Bedside monitors

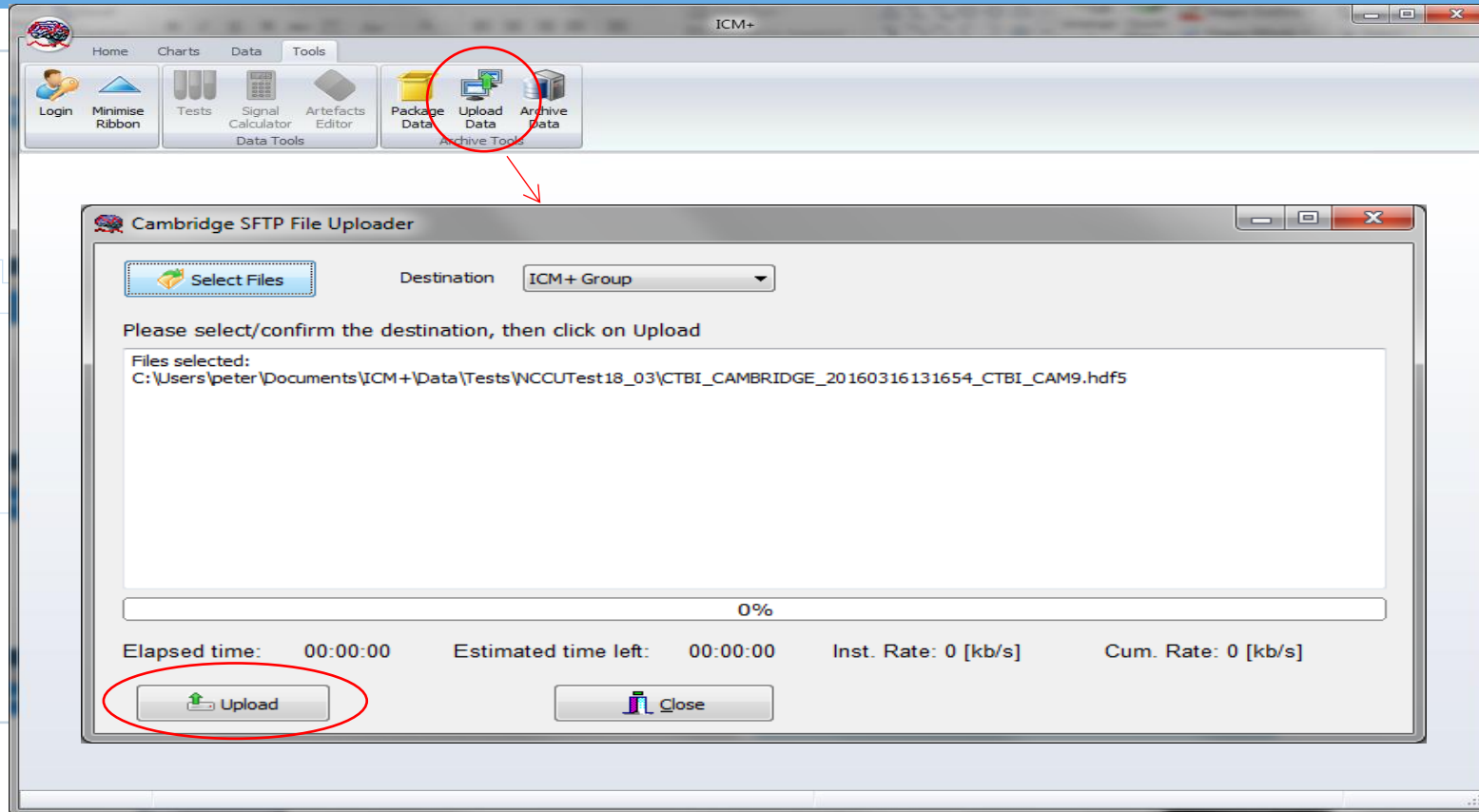


# Data collection: multicentre collaborative tools

Bedside monitors



Bedside monitors



File Server in a  
coordinating centre

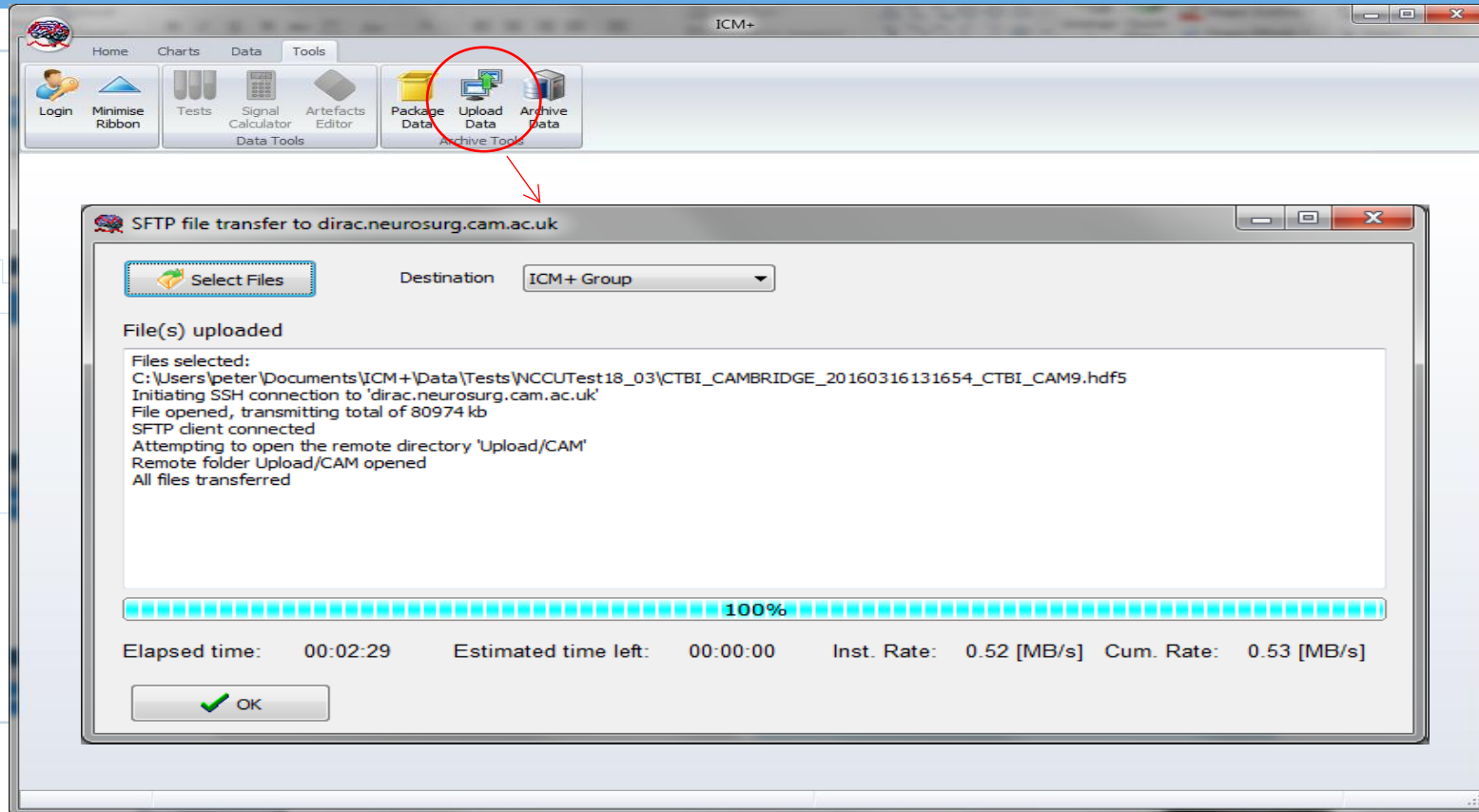


# Data collection: multicentre collaborative tools

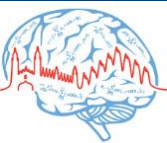
Bedside monitors



Bedside monitors



File Server in a  
coordinating centre





# Conclusions

- I showed you how we ran a prospective interventional **RCT with ICM+**: you can do the same for any other trial.
- **ICM+ is not a black box**: it does what you ask it to do! You need to know exactly how it works for your specific project, details are important! In particular if you make interventions based on its functioning
- **Please test everything!**
- The software in this case works as **integrated in a clinical setting**: don't forget it, make things work together.
- Keep the main actors involved and trained (**clinical team**) and they will love the study as much as you do 😊

