# Targeting Autoregulation-Guided Cerebral Perfusion Pressure after Traumatic Brain Injury (COGiTATE): A Feasibility Randomized Controlled Clinical Trial

Running title: Precision medicine in traumatic brain injury

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**Overview of Supplementary Digital Content**

| **Digital Content** | **Description** |
|---|---|
| Supplementary Appendix S1 | Supplementary extended information of the intervention protocol |
| Supplementary Fig. S1 | Example of the different review screens |
| Supplementary Fig. S2 | Study flow diagram: Traumatic Brain Injury patients admitted to the intensive care unit |
| Supplementary Fig. S3 | Study timeline |
| Supplementary Fig. S4 | Extended information regarding patient numbers and percentage of 'clinical' CPP targets |
| Supplementary Fig. S5 | Therapy Intensity Level (TIL) over time |
| Supplementary Fig. S6 | CPPopt values over time |
| Supplementary Fig. S7 | Glasgow Outcome Scale at six-months follow-up |
| Supplementary Table S1 | CPP targets compared to the Brain Trauma Foundation CPP target guideline |
| Supplementary Table S2 | Percentage of monitoring time concordant, above or below CPP targets of interest |
| Supplementary Table S3 | Individual 12 items of Therapy Intensity Level (TIL) score |
| Supplementary Table S4 | Longitudinal analysis of safety parameters |
| Supplementary Table S5 | Adverse- and Serious Adverse Events during intervention period |

**Abstract**

Managing traumatic Brain Injury (TBI) patients with a cerebral perfusion pressure (CPP) near to the cerebral autoregulation (CA) guided 'optimal' CPP (CPPopt) value is associated with improved outcome and might be useful to individualize care, but has never been prospectively evaluated. This study evaluated the feasibility and safety of CA-guided CPP management in TBI patients requiring ICP monitoring and therapy (TBIicp patients). The 'CPPopt Guided Therapy: Assessment of Target Effectiveness' (COGiTATE) parallel two-arm feasibility trial took place in 4 tertiary centers. TBIicp patients were randomized to either individualized CA-guided CPP targets (intervention group) or to the Brain Trauma Foundation guideline (BTF) CPP target range (control group). CPP targets were guided by six-times a day software-based alerts for up to five days. The primary feasibility endpoint was the percentage of time with CPP concordant (± 5 mmHg) with the set CPP targets. The main secondary safety endpoint was an increase in therapeutic intensity level (TIL) between CPPopt and BTF targets groups. 28 patients were randomized to the CPP control and 32 patients to the intervention group. CPP in the CA-guided group was in the target range for 46.5% (IQR 41.2–58.0) of the monitored time, significantly higher than the feasibility target specified in the published protocol (36%; $p<0.001$). There were no significant differences between groups for TIL or for other safety endpoints. Conclusively, targeting an individual and dynamic CA-guided CPP is feasible and safe in TBIicp patients. This encourages a prospective trial powered for clinical outcomes.

**Keywords:** traumatic brain injury, intensive care, precision medicine, cerebral autoregulation, optimal cerebral perfusion pressure, cerebral perfusion.

**Introduction**

It is increasingly recognised that patients with traumatic brain injury (TBI) may benefit from individualized clinical management.[1,2] Cerebral autoregulation (CA) may be able to maintain cerebral blood flow for adequate energetic requirements in response to changes in mean arterial pressure (MAP), by means of vasoconstriction and vasodilation.[3,4] In TBI patients, CA is frequently affected, and impaired CA is associated with poor clinical outcome.[5] Since dynamic slow variations in cerebral blood volume produced by CA are transmitted into changes in intracranial pressure (ICP), the relationship between slow changes in MAP and ICP (named the pressure reactivity index, PRx) can be considered a surrogate method for the assessment of CA.[6]

The brain trauma foundation (BTF) guideline recommend a target cerebral perfusion pressure (CPP) value between 60 and 70 mmHg. The 'optimal' CPP target within this range is, however, uncertain and may depend upon the patient's autoregulatory status.[7] In 2019 a consensus ICP management algorithm was published that incorporated the assessment of CA using a discrete MAP challenge to define individual CPP goals in TBI patients.[8] However, given the well-recognised temporal evolution of physiology following TBI, a continuous assessment of CA status and range might allow improved dynamic and precise MAP/CPP titration over the disease narrative. In this regard, a continuously updated PRx and its derived 'optimal' CPP (CPPopt) value could be advantageous. CPPopt is the CPP value where the patients' CA is best preserved and is derived automatically from the U-shaped (parabolic) CPP-PRx relationship typically seen.[9,10] Retrospective data demonstrated an association between improved outcome in patients who had a CPP value concordant with the CPPopt value.[9,10] Accordingly, we performed the first randomized controlled intervention trial: the 'CPPopt Guided Therapy: Assessment of Target Effectiveness' (COGiTATE) to assess feasibility as the percentage of monitoring time with CPP concordant with CPPopt in the intervention group and whether this leads to a potentially harmful need for higher Therapeutic Intensity levels (TIL) in TBI patients with ICP monitoring (TBIicp).

## Materials and Methods

### Trial design

The protocol has been published previously.[11] An extended summary of the methodology and (statistical) analysis can be found in Supplementary Appendix S1. COGiTATE was a multicenter, international, non-blinded, randomized controlled parallel phase II trial (RCT). Four tertiary hospitals that provide acute neurocritical care for TBI patients were involved. Ethical approval was obtained at all participating institutions.

### Participants

Eligible participants were patients with TBIicp meeting the following inclusion criteria: (1) adults (age ≥18 years) indicated for ICP-directed therapy for at least 24 hours; (2) randomization within 24 hours after intensive care unit (ICU) admission and (3) signed proxy informed consent. Exclusion criteria were: (1) primary decompressive craniectomy; (2) injury deemed to be unsurvivable at presentation; (3) known pregnancy. Each study center obtained approval by the center specific Institutional Review Board. Block randomization, with stratification according to trial site, was used to ensure a uniform patient distribution. Randomization was performed electronically using a centralised electronic case report form (eCRF) by a researcher. The study was powered to achieve a 20% increase in percentage of monitored time with CPP concordant ± 5 mmHg of the CPPopt values. From 30% (historical cohort) to 36% in the intervention group resulting in a sample size of 60 patients.[11]

### Data collections

Baseline and daily patient characteristics were collected. The daily characteristics included the TIL score [12,13], laboratory and diagnostic organ function parameters, measures of hemodynamic and ventilatory support intensity and predefined adverse events (AE) and serious adverse events (SAE). The aim of the summary (daily) TIL score is to provide a quantitative estimate of the ICP lowering interventions used in a given period (recommended 24 hours) by assigning numerical scores to each therapy intensity level of each intervention and summating these (0-38) [12,13]. The six-month neurological outcome was assessed using the Glasgow Outcome Scale (GOS).[11] In addition, the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) score was calculated.[15] High frequency monitoring data were collected using the research software ICM+® (http://icmplus.neurosurg.cam.ac.uk, Cambridge Enterprise, UK) at the bedside. MAP was monitored

by invasive arterial cannulation in the radial or femoral artery and zeroed at the tragus. ICP was recorded by a parenchymal microsensor.

**Interventions**

Patients were randomized to either targeting a 'dynamic' CPP (defined as the CPPopt) or targeting the BTF CPP range (60 - 70 mmHg).[7] According to the randomization group, the software displayed the appropriate physiological targets and CPP review information (Supplementary Figure S1) at the bedside.[11] CA information, including PRx, CPP-PRx curve, and the updated one-minute trend of CPPopt (further referred to as 'CPPopt trendline') was displayed for the intervention group only (Figure 1).[11,16] In the intervention group, patients were managed according to the calculated CPPopt, i.e. the CPP value extracted from the CPPopt trendline at the regular review timepoints (further referred to as 'CPP target'). How to achieve the CPP target was left to the discretion of the attending clinical team. The protocol ended after a maximum of five study days or after reaching predefined endpoints (Supplementary Appendix S1).[11]

*CPP Reviews*

The clinical team reviewed the CPP targets according to alerts generated by the software six-times a day. Until the first review alert, the protocol recommended to keep CPP between 60 - 70 mmHg in both groups (the period up to the first review alert was not used for data analysis). For the intervention group, a CPP was recommended at each review which was either (1) the calculated CPPopt trendline value or (2) a 'clinical' CPP value. The latter was suggested when the CPPopt calculation was not available, and the clinical team were to choose an appropriate target themselves.[11] In both groups, the clinical team was allowed to deviate from the software recommendation but requested to record their rationale and the chosen CPP target value in real-time.

**Outcome measures**

To assess the feasibility of the study protocol, we aimed to increase the percentage of the monitored time with measured CPP within a range of 5 mmHg above or below the CPP target to values above the predefined 36% in the intervention group (primary endpoint).[11] To examine safety, we identified a clinically relevant difference in daily TIL score as an averaged daily TIL score difference ≥3 between

the groups (main secondary endpoint). Between-group differences of physiological, diagnostic, treatment, AE/SAEs were assessed for additional evidence for safety. Finally, clinical outcome parameters were assessed.

**Data analysis**

*Data preparation* High frequency monitoring data including the one-minute average physiological data (including ICP, MAP, CPP, PRx, CPPopt) and the six-times a day review results were anonymised and packaged into HDF5 files[17] using ICM+ and imported into MATLAB (Release 2019b, The MathWorks, Inc., Natick, Massachusetts, United States) for further calculations. The patients' total mean (covering the study protocol period) and one-hour mean physiological values were calculated after automated removal of non-physiological values in MATLAB. The eCRF data were imported in R (R-Core Team, version 4.0.3).[18]

*Statistical analysis* Data are presented as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables. We used frequencies (%) for categorical variables. The primary feasibility endpoint was evaluated using a one-sample *t*-test. All other between-group comparisons were based on two-sample *t*-test/Mann-Whitney *U* test for continuous variables, and analyses of categorical variables were based on chi-squared/fisher-exact test. The Levene's test was used to test equality of variances between groups. A *p*-value <0.05 was considered statistically significant. All statistical analyses were performed in R.

**Results**

The enrollment flowchart and study timeline are summarized in Supplementary Figure S2 and Figure S3. From February 2018 until January 2020, 28 patients were randomized to the control group and 32 patients to the intervention group. The admission patient characteristics were slightly imbalanced between the groups (Table 1). Figure 1 shows a patient example with trends of patients' CPP, CPP targets and CPPopt over time. The CPPopt trendline was available for 76.6% (SD 16.5) of the monitored time in the intervention group. MAP was significantly higher for the intervention group (intervention 85 (SD 7.9) versus control 81 (SD 6.0) mmHg, $p<0.05$). Also, mean CPP was significantly higher (intervention 73 (SD 6.6) versus control 68 (SD 4.4) mmHg, $p<0.05$), with

significantly increased variability for the intervention group ($p$<0.05). In the intervention group PRx was on average lower compared to the control group (Table 2).

*Feasibility endpoint*

In the intervention group, CPPopt-based software recommendations were provided in 74% of the 552 reviews (i.e. no CPP targets were given 26% of the reviews, where the clinician were to choose an appropriate 'clinical' target until the next review, Table 1). Figure 2 shows the distribution of the CPP recommendations and final CPP targets in the intervention group (with the individual CPP targets and distributions over time in Figure 3 and Supplementary Figure S4).The number of deviations from the CPP recommendations in both groups was low (intervention 8.3% versus control 6.8%, respectively, Table 1).

The median CPP target was 70 mmHg (IQR 66 – 75) in the intervention group. In 37.9% (IQR 18 – 58) of the time the target was within the BTF CPP range (Table 2 and Supplementary Table S1). The median CPPopt trendline was slightly higher in the intervention group (intervention 72 (IQR 66 – 77) versus control 69 (IQR 67– 73) mmHg, $p$=0.448). In the intervention group, patients spent 46.5% (IQR 41.2 – 58.0) of the monitoring time with CPP concordant with the set CPP targets. This is significantly higher than the powered 36% ($p$<0.001, Table 2 and Supplementary Table S2).Table 2 and Supplementary Table S2 show the between-group comparisons of the retrospectively available CPPopt trendline values. Patients in the intervention group spent more time with their CPP concordant and above the CPPopt trendline ($p$=0.150 and $p$=0.573, respectively) but significantly less time below the CPPopt trendline (intervention 19.1% (IQR 13.8 – 29.3) versus control 34.6% (IQR 22.4 – 43.5), $p$<0.001). Patients in the intervention group spent less time with CPP values below 60 mmHg (intervention 6.71% (IQR 1.5 – 10.4) versus control 11.7% (IQR 5.46 – 21.5), $p$<0.05) but more time with a CPP above 70 mmHg (intervention 64.9% (IQR 44 – 82.5) versus control 30.7% (IQR 23 – 46.6), $p$<0.001).

*Safety endpoints*

The median TIL score showed no significant difference between the groups (intervention 7 (IQR 5 – 9) versus control 7 (IQR 6 –10), $p$=0.882). Data on individual TIL items are available in Supplementary Table S3. In addition, no significant between-group differences in parameters suggestive for lung, cardiac and kidney damage were observed (Table 3). Both groups received similar amounts of fluids,

and the median daily dose noradrenaline was comparable between the groups (intervention 10.4 (IQR 4.51 – 20.7) versus control 12.2 mg (IQR 7.42 – 18.8), *p*=0.514). No significant between-group differences over time were found for any of the secondary endpoints including TIL (*p*=0.245) and CPPopt (*p*=0.107) (Supplementary Table S4; Supplementary Figure S5 and S6). Similar numbers of AEs (intervention 9 versus control 7) and SAEs (intervention 1 versus control 1) were observed (Table 3 and Supplementary Table S5).

*Outcome*

The distribution of 6 months GOS of both groups is shown in Supplementary Figure S7. Fewer patients died in the intervention group (23%) compared to the control group (44%). None of the outcome results reached statistical significance (Table 1 and Table 2).

**Discussion**

The current study represents the first RCT evaluating CA-guided CPP management in TBIicp patients. Compared to retrospective pilot data,[11] we showed that patients in the intervention group spent a significant higher percentage of time with CPP concordant the set CPP target given by CPPopt. Since most CPP review recommendations were adopted (>90%), these results demonstrate the feasibility of using CPPopt as a novel digital biomarker for precision medicine in TBI management. Safety was demonstrated by a similar between-group TIL-scores, number of AE/SAE and biomarkers of organ-damage. Whilst the study was not designed to assess clinical outcomes, we found these to be comparable. The hemodynamic support, represented by the amount of administered fluids and vasopressors use, was (non-significantly) lower in the intervention group, although these patients ended up with significant higher mean absolute MAP/CPP values. Dynamic CPP targets probably explain the increased CPP variability in individuals in the intervention group.

The BTF guideline mentions that TBI patients with intact autoregulation are best served by higher CPP values while pressure-passive patients with dysfunctional pressure autoregulation do better with lower CPP values.[7] The recent SIBICC consensus ICP treatment suggests the use of intermittent MAP challenges for CA assessment.[8] This represents an effort to integrate CA into ICP management. However, MAP challenges are infrequent, occupy nursing and medical time, and may provoke ICP elevation when CA is compromised. Further, MAP challenges are only likely to be undertaken when ICP control is a problem, which neglects the optimisation of CPP as a continuous parameter. PRx offers a more, dynamic, safe, automated, and repeated evaluation of CA. Perhaps most critically, the protocol we suggest moves CA-related management beyond just a means of ICP control, to ensuring optimal physiology and wider beneficial impact on outcome. Moreover, PRx requires only invasive ICP and MAP for its calculation. However, this also implies that PRx values may be unreliable following periods with limited MAP fluctuations. This presumed effect might have contributed to CPPopt trendline values not being available in ~25% of the monitoring time (Table 2).

The mean CPP in the intervention group was 73 (SD 6.6) mmHg. However, mean values might mask intra- and interpatient variability over time as shown by the individual target distribution (Figure 3), increased CPP variability (Table 2) and large proportion of time with CPP targets outside the BTF guideline range in the intervention group (Supplementary Table S1). We postulate that these individual dynamic targets allow continuous finetuning of perfusion pressure potentially leading to outcome

benefit. Both groups spent <1% of the monitoring time with a CPP outside our predefined safety ranges (50 - 100 mmHg) which is reassuring. These periods were attributed to drops in ABP as ICP was on average well controlled in both groups (Table 3). Patients in the intervention group spent significant less time with their CPP below the CPPopt trendline and below the CPP threshold of 60 mmHg (group difference of 15.5% and 5%, respectively). In the intervention group the chosen CPP target was in only 37.9% (IQR 18.2 - 58.3) of the monitored time between 60 - 70 mmHg (Table 2 and Supplementary Table S2). This supports the potential benefits of our intervention protocol. Other retrospective TBI analyses demonstrated that impaired CA reduces the tolerability for low CPP and high ICP.[19–22] On average, CPP targets below 60 mmHg were less common (10%, Figure 2) compared to targets above 70 mmHg (55%, Figure 2). This might indicate that TBIicp patients indeed need (on average) higher CPP targets. An alternative explanation is that our understanding of CA and its monitoring are both imperfect. Tzeng et al. hypothesised that the CA may be better adapted to compensate for increasing than for decreasing MAP.[23] Moreover, animal studies have described less clear or more variable (individualized) upper CA limits.[24,25]

Multimodality neuromonitoring allows for a better understanding of the pathophysiology and therefore, for the application of individualized, targeted treatments in TBIicp patients.[1,26] Large RCTs are underway to prove the clinical benefit of using combinations of monitoring signals and/or physiological concept protocols. The Brain Oxygen Optimization in Severe TBI phase-II (BOOST-II) multicenter RCT reported that $PbtO_2$ augmentation could be safely implemented in patients where such monitoring was available. Interventions to optimise CPP were restricted to the ICP & $PbtO_2$ group only, showing parallels to our intervention study. [27] The main difference is that in COGiTATE, the CPP management target was generated using an automated, dynamically adaptive, algorithm as opposed to fixed, predefined thresholds.

Whilst the difference in CPP between the intervention and control groups was small across the study population this does not exclude the possibility that, at an individual level, CA-guided CPP management results in a more and individualized treatment since we know that the CA varies substantially between patients and over time.[28] Since the study centers have a history of using CPPopt in clinical research settings, it is also possible that these institutions already tend to target higher CPP values (i.e. closer to 70 mmHg) in the control patients. Our study set out to examine feasibility and

safety endpoints. A detailed examination of the effect of CA-guided management on neurological recovery or suitable surrogate outcome will require further prospective, randomized studies.

Our study has limitations. Firstly, our sample size limits conclusions about physiological interactions t, organ complications and outcome results. Secondly, both groups still spent a considerable amount of time away from the CPP target (± 5 mmHg) or outside the BTF target range. This is likely related to the lack of a continuous feedback about significant deviations from the target to the nursing team. Adding a continuous feedback may improve the percentage of time CPP concordant with CPPopt and probably the clinical relevance of the therapy. Third, our study was necessarily not blinded and the outcome assessors were aware of the group assignment. Fourth, in the intervention group, in 26% of the reviews CPPopt was not available. This is a limitation of the current methodology.[29,30] Fifth, we did not treat the patients according to a standardized hemodynamic management protocol. Sixth, we noticed a considerable delay before starting the intervention protocol after trauma ictus in both groups (Supplementary Figure S3). For a phase-II study, this is less important, but in a phase-III study the delay between ICU admission and start intervention can be minimized with application of a deferred consent procedure in all eligible patients.[31,32] Seventh, the study was performed in centers with experience in ICM+ research software. This limitation has to be taken into account with future study setup in less experienced centers. Finally, the software used in the intervention protocol is labelled as research software and therefore not commercially available for clinical purposes. Our study also has several unique strengths. The study protocol was prespecified[11], with a pragmatic design to test for the first time the interaction between a software algorithm and clinical team at the bedside six-times a day. This innovative approach was studied in four centers with different clinical teams involved over the 24-hour patient care. No additional invasive monitoring was required. We limited our protocol to a maximum of five days to overcome the overrepresentation of certain patients in the analysis.

**Conclusion**

Individualizing care by targeting a dynamic optimal CPP using CA guidance six-times a day is feasible and safe in TBIicp patients. These findings encourage a larger phase-III outcome study of this novel digital biomarker for precision medicine in these patients.

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**Author contribution**

All authors contributed to the study conception and design. Material preparation and data collection were performed by Jeanette Tas, Peter Smielewski, Erta Beqiri, Ruud CR van Kaam, Astrid CWE Hoedemaekers, Geert Meyfroidt, Bart Depreitere, Analisa L Liberti and Marcel JH Aries. Data analysis was performed by Jeanette Tas, Sander M.J. van Kuijk, Peter S Smielewski, Marek Czosnyka, Erta Beqiri, David K Menon, Ari Ercole and Marcel JH Aries. The first draft of the manuscript was written by Jeanette Tas and Marcel JH Aries and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Conflicts of Interest and Source of Funding**

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**Data availability**

Not applicable.

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**Table 1** Baseline patient and intervention characteristics

| Mean (SD) or Median (IQR) | CPP control (*n*=28) | CPP intervention (*n*=32) | Total (*n*=60) |
|---|---|---|---|
| Sex, men, *n* (%) | 21 (75) | 22 (69) | 43 (72) |
| Age, years (SD) | 48 (19) | 42 (17) | 45 (18) |
| Initial assessed median GCS Motor score (IQR) | 4 (2 - 5) | 4 (1 – 6) | 4 (1- 5) |
| Initial assessed GCS 3 - 8 category (%) | 21 (75) | 20 (63) | 41 (68) |
| Initial assessed GCS 9 -13 category (%) | 6 (21) | 7 (22) | 13 (22) |
| Initial assessed GCS 14 - 15 category (%) | 1 (4) | 5 (16) | 6 (10) |
| Pupil fixed and dilated, *n* (%)<br>Unilateral<br>Bilateral | <br>4 (14)<br>2 (7) | <br>3 (9)<br>1 (3) | <br>7 (12)<br>4 (7) |
| CT-Marshall classification, *n* (%) | | | |
| Diffuse injury (I) | 0 (0) | 1(3) | 1 (2) |
| Diffuse injury (II) | 17 (61) | 21(66) | 37 (63) |
| Diffuse injury (III) | 6 (21) | 2 (6) | 8 (14) |
| Diffuse injury (IV) | 3 (11) | 0 (0) | 3 (5) |
| Evacuated mass lesion (V) | 0 (0) | 4 (13) | 4 (7) |
| Non-evacuated mass lesion (VI) | 2 (7) | 4 (13) | 6 (10) |
| Isolated-head injury , *n* (%) | 9 (32) | 17 (53) (47) | 26 (43) |
| Median IMPACT outcome (mortality) prediction (IQR)[*] | 32 (25 – 46) | 29.5 (15.0 - 34.5) | 31.5 (23.5 – 39) |
| *Intervention characteristics*<br>*Number of reviews,(%)* | Control<br>*n*=459 | Intervention<br>*n*=552 | |
| Clinical target recommended, n (%)[†] | NA | 144 (26.1) | NA |
| Adopting provided CPPopt/CPP range? n,(%)[‡] | | | |
| Yes | 428 (93.2) | 374 (92) | 802 (93) |
| No | 31 (6.8) | 34 (8.3) | 65 (7.5) |
| *Problems with reaching previous CPP target? n* (%)[§] | | | |
| Yes | 99 (22) | 121 (22)[§] | 220 (22) |
| No | 353 (76.9) | 424 (76.8)[§] | 777 (77) |
| Uncertain | 7 (1.5) | 7 (1.3) | 14 (1.4) |

| | | | |
|---|---|---|---|
| *Which intervention(s) needed?, n (%)* [‖] | | | |
| Only ABP intervention | 117 (26) | 237 (43) | 354 (35) |
| Both ABP + ICP intervention | 89 (19) | 84 (15) | 173 (17) |
| Only ICP intervention | 18 (3.9) | 10 (1.8) | 28 (2.7) |
| No intervention | 231 (50) | 220 (40) | 451 (45) |
| Other interventions | 4 (0.87) | 1 (0.18) | 5 (0.5) |
| Reason to stop the intervention protocol, *n* (%) | | | |
| (1) Deceased | 1 (4) | 0 (0) | 1(2) |
| (2) ICP monitoring discontinued[¶] | 11 (39) | 13 (41) | 24 (40) |
| (3) Active treatment withdrawal | 1 (4) | 3 (9) | 4 (7) |
| (4) Study protocol stopped at day 5 | 10 (36) | 10 (31) | 20 (33) |
| (5) Other reason to stop | 5 (18) | 6 (19) | 11 (18) |

Presented percentages may not be equal to 100% as a result of rounding.

[*] The International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) score for moderate to severe traumatic brain injury [1]. Included patient characteristics in the prognostic model for mortality prediction at 6 months using the Core model: age, GCS-motor, and pupillary reactivity. IMPACT is validated for traumatic brain injury patients having an initial GCS ≤12 (control *n*=27, Intervention *n*=26). In addition, three patients with missing Glasgow Outcome Scale at 6 months (*n*=1 in control group and *n*=2 in Intervention group) were not included for the average IMPACT outcome prediction scores.

[†] When the software recommendation was use a 'clinical target' the questions 'adopting CPPopt target' was not presented.

[‡] Exact question: 'will you be adopting the advised CPPopt target/CPP range (yes/no)?' The percentages were computed in the intervention group without the 'clinical target' reviews (*n*=144).

[§] Exact question: 'where there any clinical problems with reaching the previous CPP target?'

[‖] Exact question: 'which interventions are you planning to achieve the new CPP target?'

[¶] ICP monitoring discontinuation was a clinical decision and not influenced by the intervention protocol.

*n* = number; SD = standard deviation; IQR = Interquartile range; ICU = intensive care unit

| **Table 2 Primary and secondary outcomes after intervention** | | | | |
|---|---|---|---|---|
| Mean (SD) or Median (IQR) | CPP control (*n*=28) | CPP intervention (*n*=32) | *p*-value* | *p*-value† (for variance) |
| *Primary endpoint* | | | | |
| %time CPP concordant with the CPP target value ± 5 mmHg | NA | 46.5 (41.2 – 58) | NA | NA |
| | | | | |
| *Secondary endpoints* | | | | |
| Safety, Daily Therapy Intensity Level (TIL) | 7 (6 - 10) | 7 (5 - 9) | 0.882 | *NA* |
| MAP (mmHg) | 81 (6) | 85 (8) | <0.05 | 0.123 |
| HR ($min^{-1}$) | 69 (12) | 96 (12) | 0.211 | 0.838 |
| ICP (mmHg) | 13 (4.7) | 12 (8.1 ) | 0.753 | 0.228 |
| CPP (mmHg) | 68 (4.4) | 73 (6.6) | <0.05 | <0.05 |
| PRx | 0.0331 (0.199) | -0.0417 (0.231) | 0.200 | 0.454 |
| | | | | |
| Total ICP/CPP monitoring time, hours | 71.8 (37.7– 104) | 61.7 (41.2 – 105) | 0.761 | 0.498 |
| Neuromonitoring (CPP) interruptions, minutes | 49 (2 – 141) | 55 (8 – 109) | 0.404 | 0.281 |
| CPP target value (mmHg)‡ | NA | 70 (66 – 75) | NA | NA |
| CPPopt trendline value (mmHg)§ | 69 (67 – 73) | 72 (66 – 77) | 0.448 | <0.05 |
| CPPopt trendline yield (%)‖ | 73.9 (18.5) | 76.6 (16.5) | 0.564 | 0.378 |
| | | | | |
| %time CPP concordant with the CPPopt trendline value§ ± 5 mmHg | 36 (31.4 – 46.7) | 42.6 (35.4 – 51.8) | 0.150 | 0.976 |
| | | | | |
| %time CPP above 70 mmHg | 30.7 (23 – 46.6) | 64.9 (44 – 82.5) | <0.001 | 0.077 |
| %time CPP below 60 mmHg | 11.7 (5.46 – 21.5) | 6.71 (1.5 – 10.4) | <0.05 | 0.745 |
| %time CPP target concordant with 60-70 mmHg range | NA | 37.9 (18.2 - 58.3) | NA | NA |
| | | | | |

| | | | | |
|---|---|---|---|---|
| GCS at ICU discharge, *n* (%) | | | | |
| Dead | 11 (39) | 7(22) | 0.160 | NA |
| 3-5 | 1(4) | 0 (0) | | |
| 6-8 | 2 (7) | 3 (9) | | |
| 9-12 | 9 (32) | 8 (25) | | |
| 13-15 | 5 (18) | 14 (44) | | |
| | | | | |
| GOS – 6 months outcome[¶] | | | | |
| Dead (%) | 44 | 23 | | |
| Favourable outcome, GOS 4-5 (%) | 34 | 50 | | |

[*]Unpaired sample *t*-test, Mann Whitney *U* test or Chi-squared or Fisher exact test was used.

[†] Levene's test was used to test equality of variances between groups.

[‡] CPP target. At a review alert a CPP target was set by the clinical team either by adopting the recommended CPPopt or by taking a 'clinical' CPP target.

[§] CPPopt trendline is the updated CPPopt value over time.

[‖] Calculated as the percentage of time CPPopt being available given CPP value being present.

[¶] The number of outcome values missing were 1 in the control group and 2 in the intervention group.

CPP = cerebral perfusion pressure; CPPopt = optimal cerebral perfusion pressure; HR = heart rate; ICP = intracranial pressure; MAP = mean arterial blood pressure; PRx = pressure reactivity index; GCS = Glasgow Coma Score; GOS = Glasgow Outcome Scale; ICU = intensive care unit

| **Table 3** Safety measures during study period | | | |
|---|---|---|---|
| Median (IQR) | CPP control (*n*=28) | CPP intervention (*n*=32) | *p*-value[*] |
| Daily Creatinine level (μMol/L)[†] | 62.2 (52.8 – 76.5) | 64.2 (49.2 – 59.9) | 1.00 |
| Troponin below critical threshold, *n* (%)[‡] | 18 (64.3) | 23 (71.9) | 0.725 |
| Troponin above critical threshold, *n* (%)[‡] | 10 (35.7) | 9 (28.1) | |
| Daily NT-pro BNP (ng/L)[§] | 138 (67.1 – 301) | 109 (53.0 – 268) | 0.641 |
| Highest daily $PaO_2/FiO_2$ ratio (mmHg/%) | 346 (284 – 448) | 380 (303 – 461) | 0.667 |
| Lowest daily $PaO_2/FiO_2$ ratio (mmHg/%) | 235 (202 – 314) | 267 (29 – 387) | 0.227 |
| | | | |
| Noradrenaline (mg) | 12.2 (7.42 – 18.8) | 10.4 (4.51 – 20.7) | 0.514<br>0.719[‖] |
| Daily total fluids given (ml) | +1470 (878 – 2210) | +1330 (1020 - 2170) | 0.784<br>0.569[‖] |
| Daily net fluid balance (ml) | +860 (397 – 1370) | +901 (391 – 1460) | 0.784<br>0.882[‖] |
| | | | |
| Monitoring time with ICP > 22 mmHg (%) | 2.25 (1.09- 9.71) | 1.27 (0.565 – 4.56) | 0.216 |
| Monitoring time with ICP > 25 mmHg (%) | 1.19 (0.36 – 2.42) | 0.710 (0.356 – 2.06) | 0.254 |
| Monitoring Time with CPP > 100 mmHg (%) | 0.0691 (0– 0.235) | 0.401 (0 – 1.16) | 0.055 |
| Monitoring time with CPP < 50 mmHg (%) | 0.95 (0.239 – 2.07) | 0.261 (0.346 – 0.778) | 0.034 |
| | | | |
| Adverse Events, *n*[¶] | 7 | 9 | |
| Serious Adverse Events, *n*[¶] | 1 | 1 | |

The laboratory and fluid administration values in Table 3 concerns median values. The values were first calculated per patient over the intervention period (values collected per day). Then, the study group median values are reported.

[*]Unpaired sample *t*-test, Mann Whitney *U* test or Chi-squared or Fisher exact test was used.

[†] Missing days: Control group: 1 day (0.9%), Intervention group: 3 days (2.5%). Missing patients *n*=0.

‡ High-sensitive-troponin including High-sensitive-troponin T and High-sensitive-troponin I were divided in values above/below a critical threshold (High-sensitive-troponin T, 14 ng/L, High-sensitive-troponin I, 58.1 ng/L (male), 39.6 ng/L (female). Missing patients: 0, Missing days: Control group *n*=8/107 (7.5%); Intervention group *n*=9/122 (7.4%).

§ Missing days: Control group: 12 (11%) days; Intervention group: 11 (9%) days. Missing patients *n*=0.

‖ Levene's Test was used to test equality of variances between groups.

¶ The specific adverse events and serious adverse events can be found in Supplemental Digital Content 13, Supplemental Table 5.

ICP = intracranial pressure; CPP = cerebral perfusion pressure; $PaO_2/FiO_2$ = partial pressure of oxygen/ fraction of inspired oxygen ratio; IQR = interquartile range; *n* = number.

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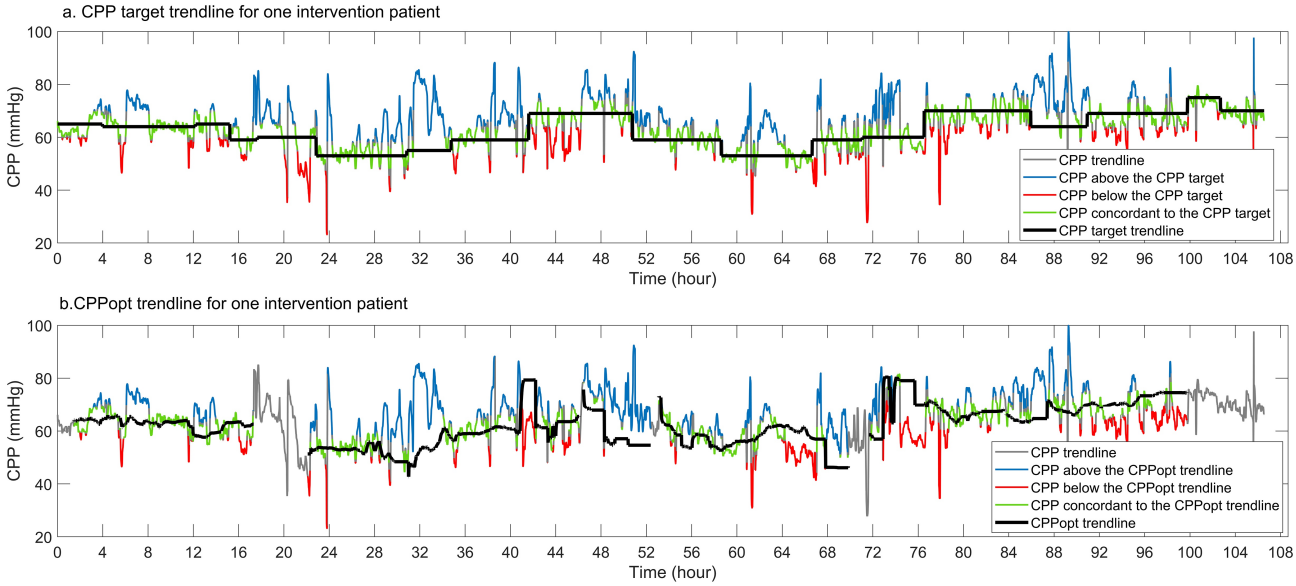
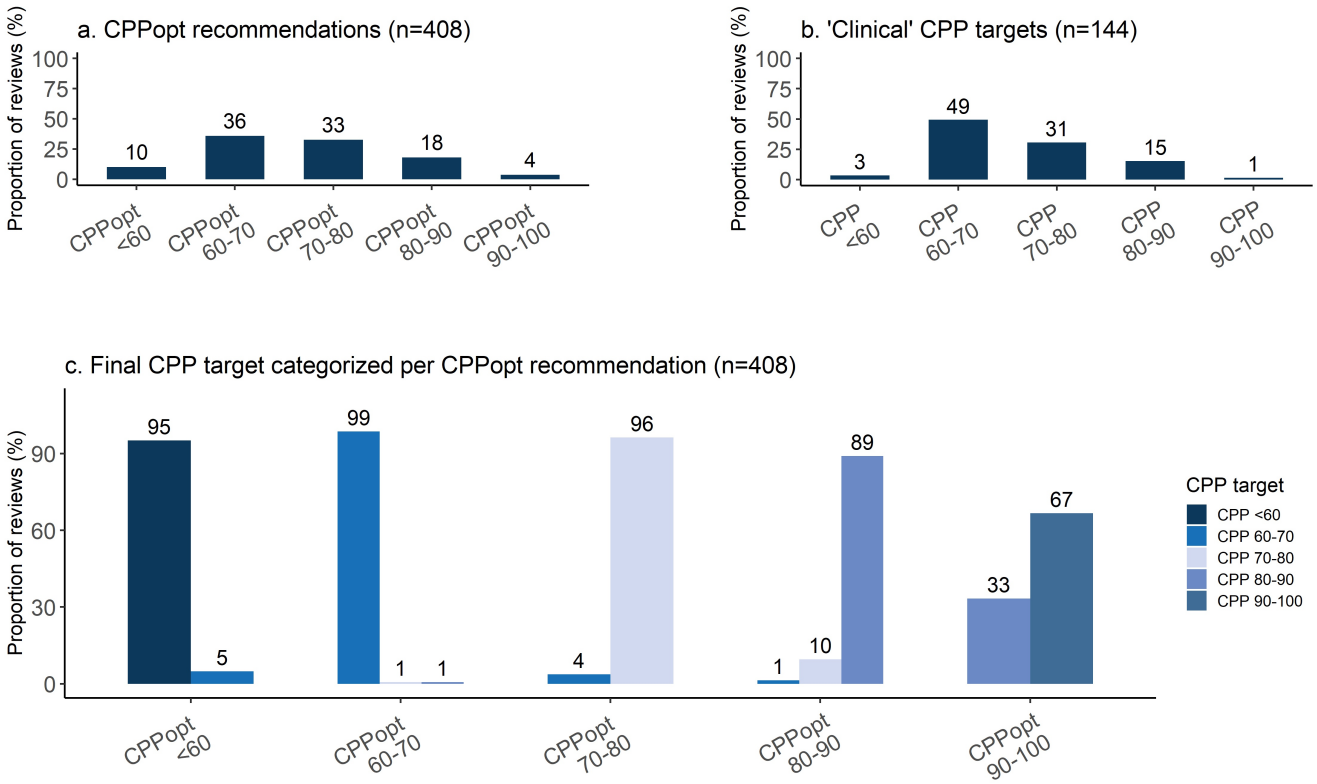
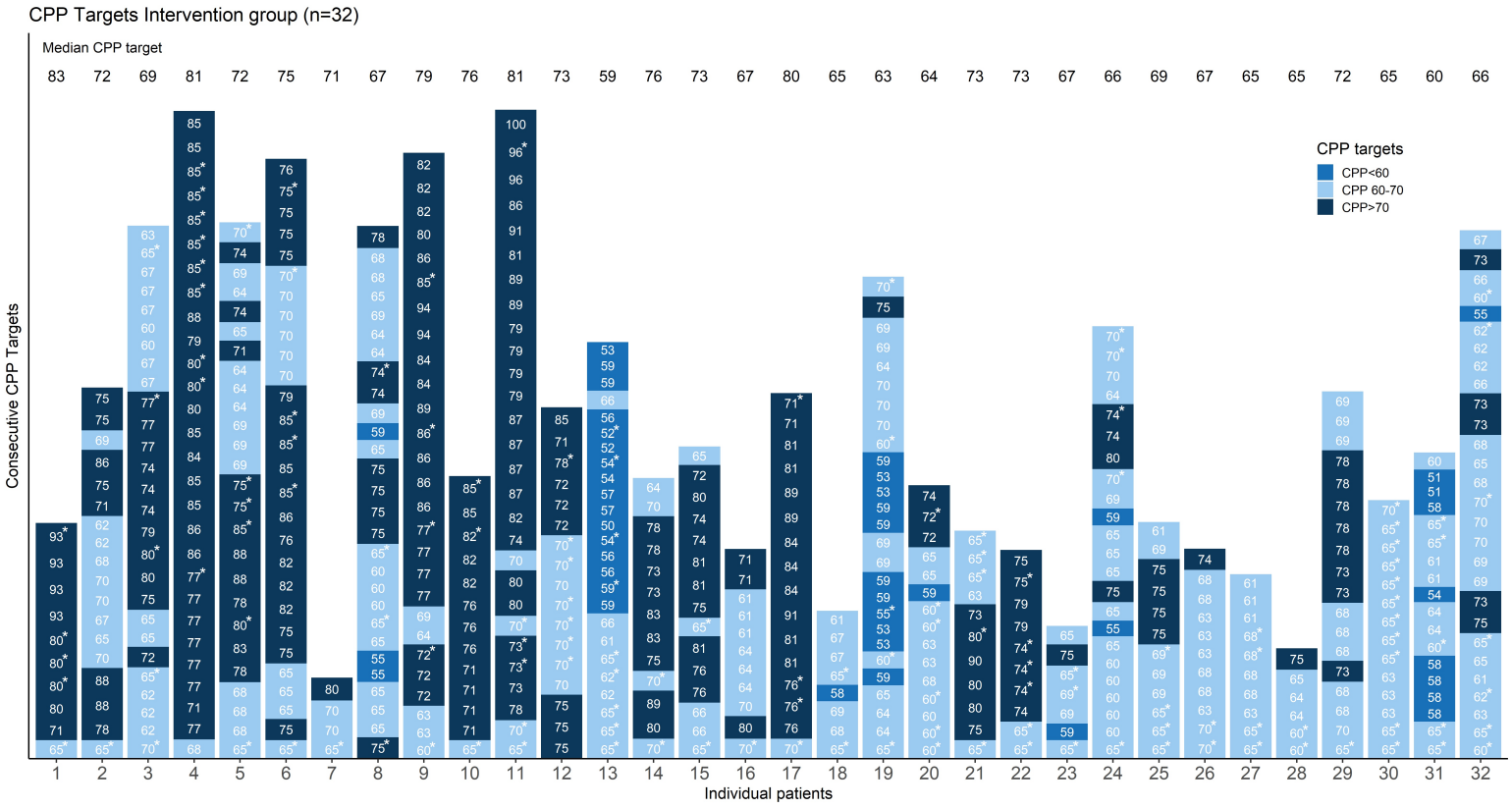

a. CPP target trendline for one intervention patient
CPP (mmHg)
Time (hour)
CPP trendline
CPP above the CPP target
CPP below the CPP target
CPP concordant to the CPP target
CPP target trendline
b.CPPopt trendline for one intervention patient
CPP (mmHg)
Time (hour)
CPP trendline
CPP above the CPPopt trendline
CPP below the CPPopt trendline
CPP concordant to the CPPopt trendline
CPPopt trendline


a. CPPopt recommendations (n=408)
Proportion of reviews (%)
100
75
50
25
0
10
36
33
18
4
CPPopt <60
CPPopt 60-70
CPPopt 70-80
CPPopt 80-90
CPPopt 90-100
b. 'Clinical' CPP targets (n=144)
Proportion of reviews (%)
3
49
31
15
1
CPP <60
CPP 60-70
CPP 70-80
CPP 80-90
CPP 90-100
c. Final CPP target categorized per CPPopt recommendation (n=408)
Proportion of reviews (%)
90
60
30
0
95
5
99
1
1
4
96
1
10
89
33
67
CPP target
CPP <60
CPP 60-70
CPP 70-80
CPP 80-90
CPP 90-100


CPP Targets Intervention group (n=32)
Median CPP target
83 72 69 81 72 75 71 67 79 76 81 73 59 76 73 67 80 65 63 64 73 73 67 66 69 67 65 65 72 65 60 66
CPP targets
CPP<60
CPP 60-70
CPP>70
Consecutive CPP Targets
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32
Individual patients

# Targeting Autoregulation-Guided Cerebral Perfusion Pressure after Traumatic Brain Injury (COGiTATE): A Feasibility Randomized Controlled Clinical Trial

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*Supplementary Appendix S1* ***Supplementary explanation of the intervention protocol***

In this supplemental document a background of CPPopt, a summary of items from the published study protocol and in depth description of certain analysis are provided that supports the methodological section in the main article. The full study protocol can be found here with a link to the publication.[1] The describes items are:

- Panel summarizing background and calculation of PRx, CPPopt and the CPPopt trendline
- Ethics approval
- Sample size calculation
- Patient randomization tool
- Clinical outcome follow-up
- Hemodynamic protocol
- Additional cerebral monitoring
- Termination of the intervention protocol
- CPP target recommendation
- Primary feasibility endpoint
- Secondary endpoints
- Longitudinal analysis (LME)
- Outcome model (proportional odds logistic regression model)

*Panel summarizing background and calculation of PRx, CPPopt and the CPPopt trendline*

Cerebrovascular pressure reactivity was studied by observing the effects of changes in arterial blood pressure slow waves (ABP) on intracranial pressure slow waves(ICP).[2] Trends in the cerebrovascular pressure reactivity are closely related to global changes in cerebral autoregulation.[3] Knowing the physiological model is important to understand the clinical concept of cerebral autoregulation guided CPP treatment in traumatic brain injury (TBI) patients. In three figures the clinical concept is visualized.

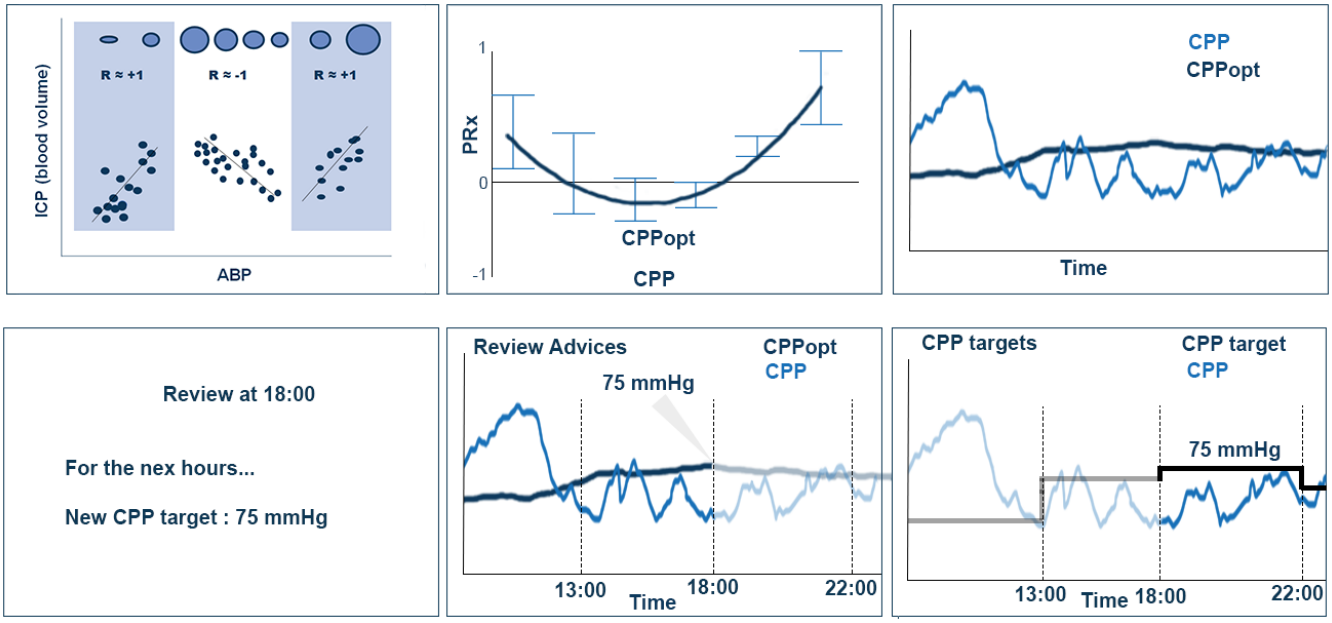


Figure appendix a-f

(Figure a) *PRx*: The Pressure Reactivity index is the statistical Pearson correlation between 10 sec averaged values of ABP and ICP over a 5-minute calculation window. The Pearson correlation index is updated every minute to provide a (moving) trend value. A negative PRx value indicates an intact cerebral autoregulation as slow increases in ABP are counteracting ICP by active vasoconstriction (Figure a, middle panel). A positive value indicates impaired cerebrovascular pressure reactivity as slow changes in ABP are passively followed by changes in ICP.[2] Both vasoconstriction (Figure a, left panel) and vasodilatation (Figure a, right panel) cannot control cerebral blood volume/flow and therefore ICP. A positive PRx is found.

(Figure b) *CPPopt*: The 'optimal' cerebral perfusion pressure concept was introduced in 2002. In a retrospective TBI cohort Steiner et al. showed that over a monitoring period of days plotting the PRx values against CPP showed a U-shaped curve. The nadir of the U-shape curve represents the CPP value for which PRx is minimal, and therefore cerebral autoregulation is best preserved.[4] Aries et al. extended this concept with a curve fitting algorithm that calculates automated CPPopt values over a 4-hourly moving time window (Figure b). They showed that individual CPP deviations from CPPopt were related to poor outcome in TBI patients.[5]

(Figure c) *CPPopt trendline:* Liu et al. added multiwindow and weighted features to the CPPopt algorithm that improved the availability and stability of individual CPPopt values at the bedside (Figure c).[1,6]

(Figure d-f) *CPPopt –Module:* The ICM+ software was further extended with the implementation of a customized research module that presents a CPPopt value on a review screen at set time-points. The CPPopt value presented in the review screen (Figure d) is the CPPopt value extracted from the CPPopt trendline (Figure e) at that specific timepoint (referred to as 'CPP target'). This CPP value is the target value to follow-up to the next review (Figure f). No CPP recommendation is provided when (1) no CPPopt value can be calculated or (2) the CPPopt value is outside the pre-defined safety ranges (50 > CPPopt >100). Then the clinician decides which CPP target to follow (referred to as 'clinical target').

Screenshots of the research module are shown in Supplementary Figure S1.

*Ethical approval*

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Coordinating center in Maastricht by Ethics Committee of Maastricht University Medical Center (29 December 2017/METC171023). Local approval and feasibility was granted by the Health Research Authority National Health System United Kingdom (30 October 2017, Research Ethics Reference 17/LO/119), the Ethics Committee of Academic Hospital Leuven (9 January 2018 B322201834820) and Ethics Committee of Radboud University Medical Center (20 February 2019 RvB19.51633).

*Sample size calculation details*

The study was powered using retrospective data from TBI patients. Retrospectively, we observed a target adherence of 30%, meaning that on a group level the CPP was on average concordant with CPPopt (± 5 mmHg) in 30% of the monitoring time. We expected a pragmatic relative increase of 20% resulting in a percentage of time concordant ± 5 mmHg CPP target from 30% to 36% (SD 8%). With an alpha of 5% and beta of 20% (power estimate of 80%), the estimated number of patients needed for the primary endpoint was 56. This number was increased to 60 to allow for drop-out, technical problems or need for a non-parametric analysis. The PWR library in R was used for the power calculation.[1,7]

*Patient randomization tool*

In our study we used a centralised electronic randomisation system that was incorporated in our electronic case report form (eCRF). An automatic email was sent to the central coordinator of the study in Maastricht with every new randomisation. Block randomisation, with stratification according to trial site, was used to ensure a uniform patient distribution.

*Clinical outcome follow-up*

Neurological outcome on the intensive care unit was assessed by the clinician prior to discharge to the ward in surviving patients using the Glasgow Coma Scale (GCS). Six-month neurological outcome was assessed using the Glasgow Outcome Scale (GOS) according to local TBIicp clinical follow-up strategies by either a physical or a telephone structured interview. Outcome assessors were not blinded of the group assignment.

*Hemodynamic protocol*

How to get to the CPP targets was left to the discretion of the clinical team. The protocol did not mandate a hemodynamic management policy which prioritised either fluids of vasoactive agents for CPP maintenance, since this had a high likelihood of changing local practice in other ways than either targeting dynamic CPP or BTF targets. This would have meant that we would be unable to robustly attribute any trial findings to the CPPopt intervention per se (rather than the means used to achieve it).

*Additional cerebral monitoring*

Additional cerebral monitoring was available according to local protocols but was not part of the study protocol.

*Termination of the intervention protocol*

The maximum duration of the intervention protocol was 5 days for both groups. Reasons for discontinuing the protocol earlier were: (1) the patient died; (2) ICP monitoring discontinued for clinical reasons; (3) Active treatment withdrawal.

*CPP target recommendation*

Six-times a day the software algorithm provided a CPP target recommendation. This was either a CPPopt based value or a 'clinical' target for the intervention group. A 'clinical' CPP target was recommended if: (1) the output of the automated CPPopt algorithm was null (no CPPopt target) and (2) the current CPPopt value was out of the set safety range defined as CPP between 50 and 100 mmHg. One important point is that the recommended CPPopt was not allowed to increase or decrease of more than 10 mmHg from the previous target. In the control group the software algorithm recommended the use of the Brain Trauma Foundation CPP guideline target range of 60-70 mmHg.[8]

*Primary feasibility endpoint*

The primary endpoint of this study is the percentage of CPP monitored time with patients' CPP concordant (± 5 mmHg) with the CPP target. The primary endpoint was calculated for the intervention group patients only. For this analysis, we calculated the percentage of monitoring time (%) each patient had one minute CPP values concordant (± 5 mmHg) with the CPP target. Monitoring time was defined as the period with CPP values being available from the first review till the termination of the intervention protocol (see above). The period till the first review was not used as during this period the protocol advised to target 60-70 mmHg in both groups.

*Secondary safety endpoint calculation*

The main secondary safety endpoint was powered to detect an average daily TIL score difference of > 3 between the groups as evidence for escalation of intracranial hypertension therapy. While designing the study we took into account that patients in the intervention group might require more CPP interventions to finetune CPP targets. This might lead to more fluid loading and vasopressor administration for maintenance of cerebral perfusion (each 1 point in TIL score). Therefore, a difference of 2 was expected and hence a difference of daily TIL ≥ 3 was thought as excess use of therapies for TBI management. As additional secondary analysis, we calculated, for both the intervention and control group, the percentage of time (%) each patient had CPP values concordant with (± 5 mmHg) the CPPopt trendline. The CPPopt trendline was for both groups retrospectively available (see Figure 1 in main manuscript).[9]

*Longitudinal analysis (LME)*

We performed different longitudinal analysis to evaluate temporal profiles for variables of interest.

*CPPopt* One possible clinical concern is that CPPopt guided therapy may drive ever-increasing CPPopt values over time.[10] Therefore, we explored the between-group difference in time course of CPPopt by fitting the one-hour average CPPopt trendline values using a linear mixed effect model (LME, R-package *nlme*)[11] with 'patient' and 'time (hours)' as random intercept and random slope, respectively and 'CPPopt trendline', 'time (hours)' and 'randomisation group' as fixed effects. We included the interaction term 'time*group' to assess differences in trajectory over time between the groups.

*Safety measures* We explored the time course of daily creatinine level, troponin I, troponin T, NT-proBNP, highest daily $PaO_2/FiO_2$ ratio, lowest daily $PaO_2/FiO_2$ ratio, noradrenalin, PRx, daily fluids given and daily net fluid balance in both groups. Therefore, in addition to between-group average differences (Table 3), we explored the between-group differences over time using a LME model with 'patient' and 'days' as random intercept and random slope, respectively and 'safety measure', 'day' and 'randomisation group' as fixed effects. We included the interaction term 'time*group' to assess differences in trajectory over time between the groups.

*Outcome model (proportional odds logistic regression model)*

A proportional odds logistic regression model[12] was constructed to explore the between-group difference in distribution of 6-months GOS clinical outcome (R-package, *MASS*).[13] The Brant function tested the proportional odds assumption (R-package, *brant*).[14,12]

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**Table 1** Baseline patient and intervention characteristics

| Mean (SD) or Median (IQR) | CPP control (*n*=28) | CPP intervention (*n*=32) | Total (*n*=60) |
|---|---|---|---|
| Sex, men, *n* (%) | 21 (75) | 22 (69) | 43 (72) |
| Age, years (SD) | 48 (19) | 42 (17) | 45 (18) |
| Initial assessed median GCS Motor score (IQR) | 4 (2 - 5) | 4 (1 – 6) | 4 (1- 5) |
| Initial assessed GCS 3 - 8 category (%) | 21 (75) | 20 (63) | 41 (68) |
| Initial assessed GCS 9 -13 category (%) | 6 (21) | 7 (22) | 13 (22) |
| Initial assessed GCS 14 - 15 category (%) | 1 (4) | 5 (16) | 6 (10) |
| Pupil fixed and dilated, *n* (%)<br>Unilateral<br>Bilateral | <br>4 (14)<br>2 (7) | <br>3 (9)<br>1 (3) | <br>7 (12)<br>4 (7) |
| CT-Marshall classification, *n* (%) | | | |
| Diffuse injury (I) | 0 (0) | 1(3) | 1 (2) |
| Diffuse injury (II) | 17 (61) | 21(66) | 37 (63) |
| Diffuse injury (III) | 6 (21) | 2 (6) | 8 (14) |
| Diffuse injury (IV) | 3 (11) | 0 (0) | 3 (5) |
| Evacuated mass lesion (V) | 0 (0) | 4 (13) | 4 (7) |
| Non-evacuated mass lesion (VI) | 2 (7) | 4 (13) | 6 (10) |
| Isolated-head injury , *n* (%) | 9 (32) | 17 (53) (47) | 26 (43) |
| Median IMPACT outcome (mortality) prediction (IQR)[*] | 32 (25 – 46) | 29.5 (15.0 - 34.5) | 31.5 (23.5 – 39) |
| *Intervention characteristics*<br>*Number of reviews,(%)* | Control<br>*n*=459 | Intervention<br>*n*=552 | |
| Clinical target recommended, n (%)[†] | NA | 144 (26.1) | NA |
| Adopting provided CPPopt/CPP range? n,(%)[‡] | | | |
| Yes | 428 (93.2) | 374 (92) | 802 (93) |
| No | 31 (6.8) | 34 (8.3) | 65 (7.5) |
| *Problems with reaching previous CPP target? n* (%)[§] | | | |
| Yes | 99 (22) | 121 (22)[§] | 220 (22) |
| No | 353 (76.9) | 424 (76.8)[§] | 777 (77) |
| Uncertain | 7 (1.5) | 7 (1.3) | 14 (1.4) |

| | | | |
|---|---|---|---|
| *Which intervention(s) needed?, n (%)* [‖] | | | |
| Only ABP intervention | 117 (26) | 237 (43) | 354 (35) |
| Both ABP + ICP intervention | 89 (19) | 84 (15) | 173 (17) |
| Only ICP intervention | 18 (3.9) | 10 (1.8) | 28 (2.7) |
| No intervention | 231 (50) | 220 (40) | 451 (45) |
| Other interventions | 4 (0.87) | 1 (0.18) | 5 (0.5) |
| Reason to stop the intervention protocol, *n* (%) | | | |
| (1) Deceased | 1 (4) | 0 (0) | 1(2) |
| (2) ICP monitoring discontinued[¶] | 11 (39) | 13 (41) | 24 (40) |
| (3) Active treatment withdrawal | 1 (4) | 3 (9) | 4 (7) |
| (4) Study protocol stopped at day 5 | 10 (36) | 10 (31) | 20 (33) |
| (5) Other reason to stop | 5 (18) | 6 (19) | 11 (18) |

Presented percentages may not be equal to 100% as a result of rounding.

[*] The International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) score for moderate to severe traumatic brain injury [1]. Included patient characteristics in the prognostic model for mortality prediction at 6 months using the Core model: age, GCS-motor, and pupillary reactivity. IMPACT is validated for traumatic brain injury patients having an initial GCS ≤12 (control *n*=27, Intervention *n*=26). In addition, three patients with missing Glasgow Outcome Scale at 6 months (*n*=1 in control group and *n*=2 in Intervention group) were not included for the average IMPACT outcome prediction scores.

[†] When the software recommendation was use a 'clinical target' the questions 'adopting CPPopt target' was not presented.

[‡] Exact question: 'will you be adopting the advised CPPopt target/CPP range (yes/no)?' The percentages were computed in the intervention group without the 'clinical target' reviews (*n*=144).

[§] Exact question: 'where there any clinical problems with reaching the previous CPP target?'

[‖] Exact question: 'which interventions are you planning to achieve the new CPP target?'

[¶] ICP monitoring discontinuation was a clinical decision and not influenced by the intervention protocol.

*n* = number; SD = standard deviation; IQR = Interquartile range; ICU = intensive care unit

| **Table 2 Primary and secondary outcomes after intervention** | | | | |
|---|---|---|---|---|
| Mean (SD) or Median (IQR) | CPP control (*n*=28) | CPP intervention (*n*=32) | *p*-value* | *p*-value† (for variance) |
| *Primary endpoint* | | | | |
| %time CPP concordant with the CPP target value ± 5 mmHg | NA | 46.5 (41.2 – 58) | NA | NA |
| | | | | |
| *Secondary endpoints* | | | | |
| Safety, Daily Therapy Intensity Level (TIL) | 7 (6 - 10) | 7 (5 - 9) | 0.882 | *NA* |
| MAP (mmHg) | 81 (6) | 85 (8) | <0.05 | 0.123 |
| HR ($min^{-1}$) | 69 (12) | 96 (12) | 0.211 | 0.838 |
| ICP (mmHg) | 13 (4.7) | 12 (8.1 ) | 0.753 | 0.228 |
| CPP (mmHg) | 68 (4.4) | 73 (6.6) | <0.05 | <0.05 |
| PRx | 0.0331 (0.199) | -0.0417 (0.231) | 0.200 | 0.454 |
| | | | | |
| Total ICP/CPP monitoring time, hours | 71.8 (37.7– 104) | 61.7 (41.2 – 105) | 0.761 | 0.498 |
| Neuromonitoring (CPP) interruptions, minutes | 49 (2 – 141) | 55 (8 – 109) | 0.404 | 0.281 |
| CPP target value (mmHg)‡ | NA | 70 (66 – 75) | NA | NA |
| CPPopt trendline value (mmHg)§ | 69 (67 – 73) | 72 (66 – 77) | 0.448 | <0.05 |
| CPPopt trendline yield (%)‖ | 73.9 (18.5) | 76.6 (16.5) | 0.564 | 0.378 |
| | | | | |
| %time CPP concordant with the CPPopt trendline value§ ± 5 mmHg | 36 (31.4 – 46.7) | 42.6 (35.4 – 51.8) | 0.150 | 0.976 |
| | | | | |
| %time CPP above 70 mmHg | 30.7 (23 – 46.6) | 64.9 (44 – 82.5) | <0.001 | 0.077 |
| %time CPP below 60 mmHg | 11.7 (5.46 – 21.5) | 6.71 (1.5 – 10.4) | <0.05 | 0.745 |
| %time CPP target concordant with 60-70 mmHg range | NA | 37.9 (18.2 - 58.3) | NA | NA |
| | | | | |

| | | | | |
|---|---|---|---|---|
| GCS at ICU discharge, *n* (%) | | | | |
| Dead | 11 (39) | 7(22) | 0.160 | NA |
| 3-5 | 1(4) | 0 (0) | | |
| 6-8 | 2 (7) | 3 (9) | | |
| 9-12 | 9 (32) | 8 (25) | | |
| 13-15 | 5 (18) | 14 (44) | | |
| | | | | |
| GOS – 6 months outcome[¶] | | | | |
| Dead (%) | 44 | 23 | | |
| Favourable outcome, GOS 4-5 (%) | 34 | 50 | | |

[*]Unpaired sample *t*-test, Mann Whitney *U* test or Chi-squared or Fisher exact test was used.

[†] Levene's test was used to test equality of variances between groups.

[‡] CPP target. At a review alert a CPP target was set by the clinical team either by adopting the recommended CPPopt or by taking a 'clinical' CPP target.

[§] CPPopt trendline is the updated CPPopt value over time.

[‖] Calculated as the percentage of time CPPopt being available given CPP value being present.

[¶] The number of outcome values missing were 1 in the control group and 2 in the intervention group.

CPP = cerebral perfusion pressure; CPPopt = optimal cerebral perfusion pressure; HR = heart rate; ICP = intracranial pressure; MAP = mean arterial blood pressure; PRx = pressure reactivity index; GCS = Glasgow Coma Score; GOS = Glasgow Outcome Scale; ICU = intensive care unit

| **Table 3** Safety measures during study period | | | |
|---|---|---|---|
| Median (IQR) | CPP control (*n*=28) | CPP intervention (*n*=32) | *p*-value[*] |
| Daily Creatinine level (μMol/L)[†] | 62.2 (52.8 – 76.5) | 64.2 (49.2 – 59.9) | 1.00 |
| Troponin below critical threshold, *n* (%)[‡] | 18 (64.3) | 23 (71.9) | 0.725 |
| Troponin above critical threshold, *n* (%)[‡] | 10 (35.7) | 9 (28.1) | |
| Daily NT-pro BNP (ng/L)[§] | 138 (67.1 – 301) | 109 (53.0 – 268) | 0.641 |
| Highest daily $PaO_2/FiO_2$ ratio (mmHg/%) | 346 (284 – 448) | 380 (303 – 461) | 0.667 |
| Lowest daily $PaO_2/FiO_2$ ratio (mmHg/%) | 235 (202 – 314) | 267 (29 – 387) | 0.227 |
| | | | |
| Noradrenaline (mg) | 12.2 (7.42 – 18.8) | 10.4 (4.51 – 20.7) | 0.514<br>0.719[‖] |
| Daily total fluids given (ml) | +1470 (878 – 2210) | +1330 (1020 - 2170) | 0.784<br>0.569[‖] |
| Daily net fluid balance (ml) | +860 (397 – 1370) | +901 (391 – 1460) | 0.784<br>0.882[‖] |
| | | | |
| Monitoring time with ICP > 22 mmHg (%) | 2.25 (1.09- 9.71) | 1.27 (0.565 – 4.56) | 0.216 |
| Monitoring time with ICP > 25 mmHg (%) | 1.19 (0.36 – 2.42) | 0.710 (0.356 – 2.06) | 0.254 |
| Monitoring Time with CPP > 100 mmHg (%) | 0.0691 (0– 0.235) | 0.401 (0 – 1.16) | 0.055 |
| Monitoring time with CPP < 50 mmHg (%) | 0.95 (0.239 – 2.07) | 0.261 (0.346 – 0.778) | 0.034 |
| | | | |
| Adverse Events, *n*[¶] | 7 | 9 | |
| Serious Adverse Events, *n*[¶] | 1 | 1 | |

The laboratory and fluid administration values in Table 3 concerns median values. The values were first calculated per patient over the intervention period (values collected per day). Then, the study group median values are reported.

[*]Unpaired sample *t*-test, Mann Whitney *U* test or Chi-squared or Fisher exact test was used.

[†] Missing days: Control group: 1 day (0.9%), Intervention group: 3 days (2.5%). Missing patients *n*=0.

‡ High-sensitive-troponin including High-sensitive-troponin T and High-sensitive-troponin I were divided in values above/below a critical threshold (High-sensitive-troponin T, 14 ng/L, High-sensitive-troponin I, 58.1 ng/L (male), 39.6 ng/L (female). Missing patients: 0, Missing days: Control group *n*=8/107 (7.5%); Intervention group *n*=9/122 (7.4%).

§ Missing days: Control group: 12 (11%) days; Intervention group: 11 (9%) days. Missing patients *n*=0.

‖ Levene's Test was used to test equality of variances between groups.

¶ The specific adverse events and serious adverse events can be found in Supplemental Digital Content 13, Supplemental Table 5.

ICP = intracranial pressure; CPP = cerebral perfusion pressure; $PaO_2/FiO_2$ = partial pressure of oxygen/ fraction of inspired oxygen ratio; IQR = interquartile range; *n* = number.

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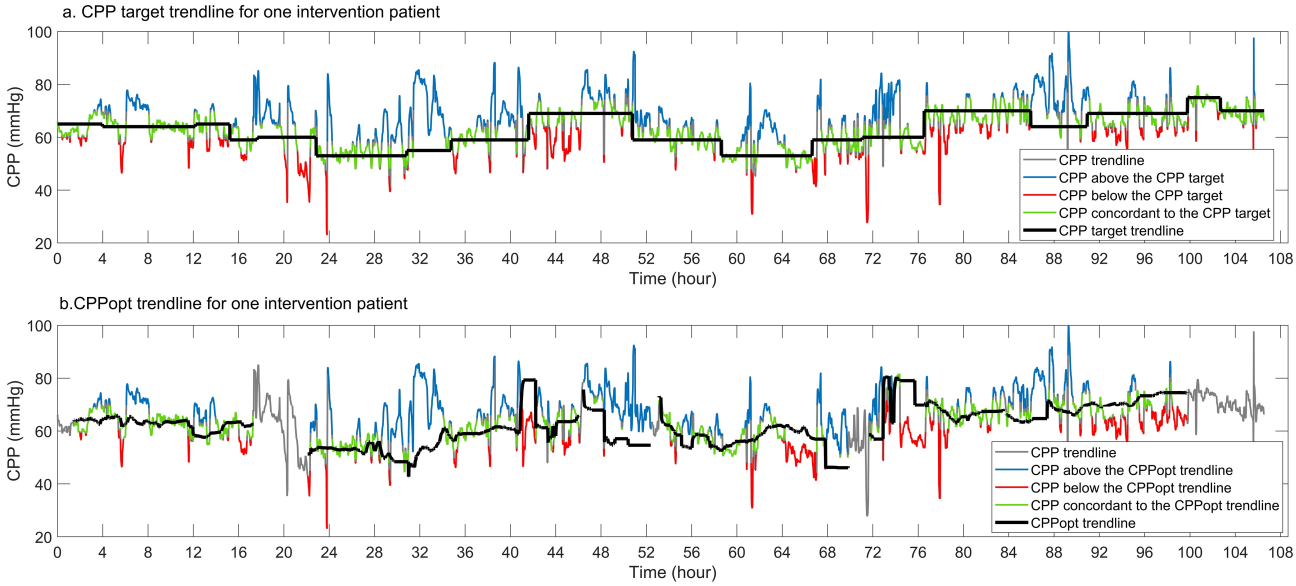
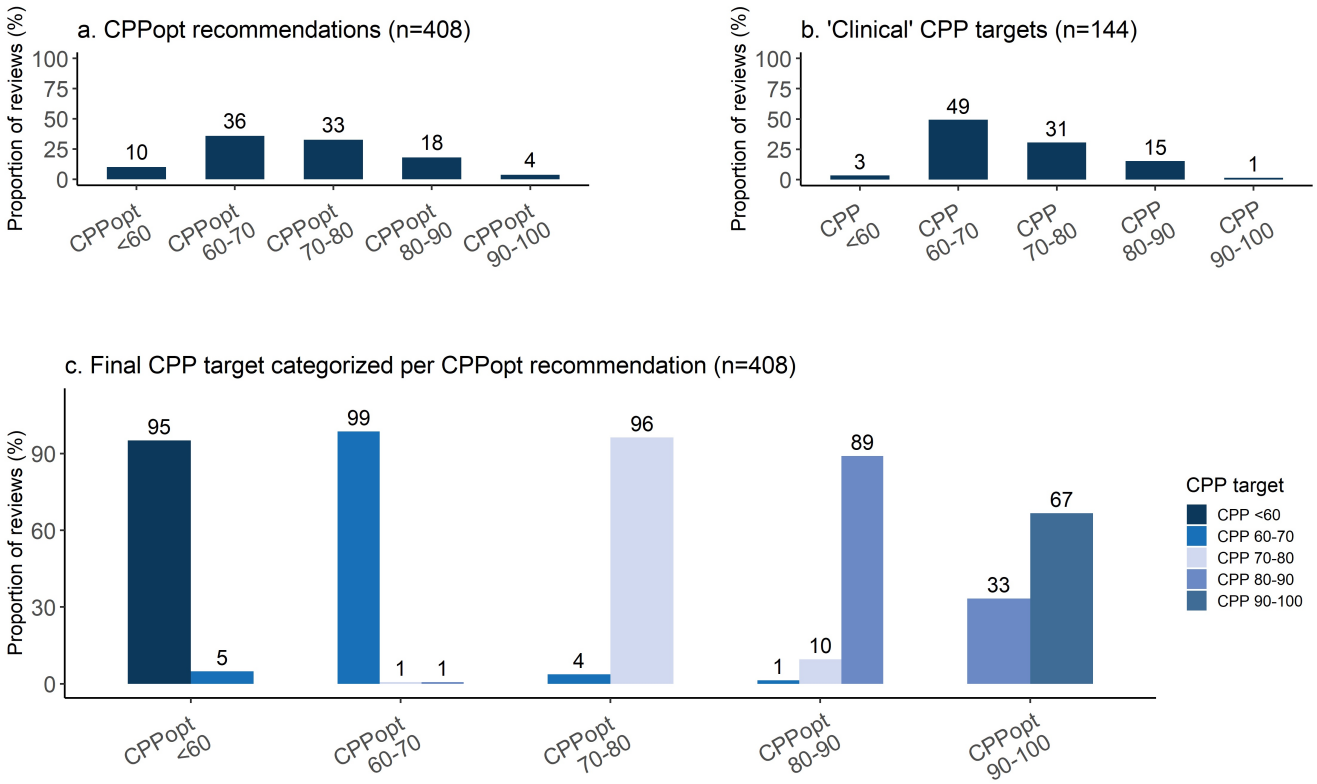
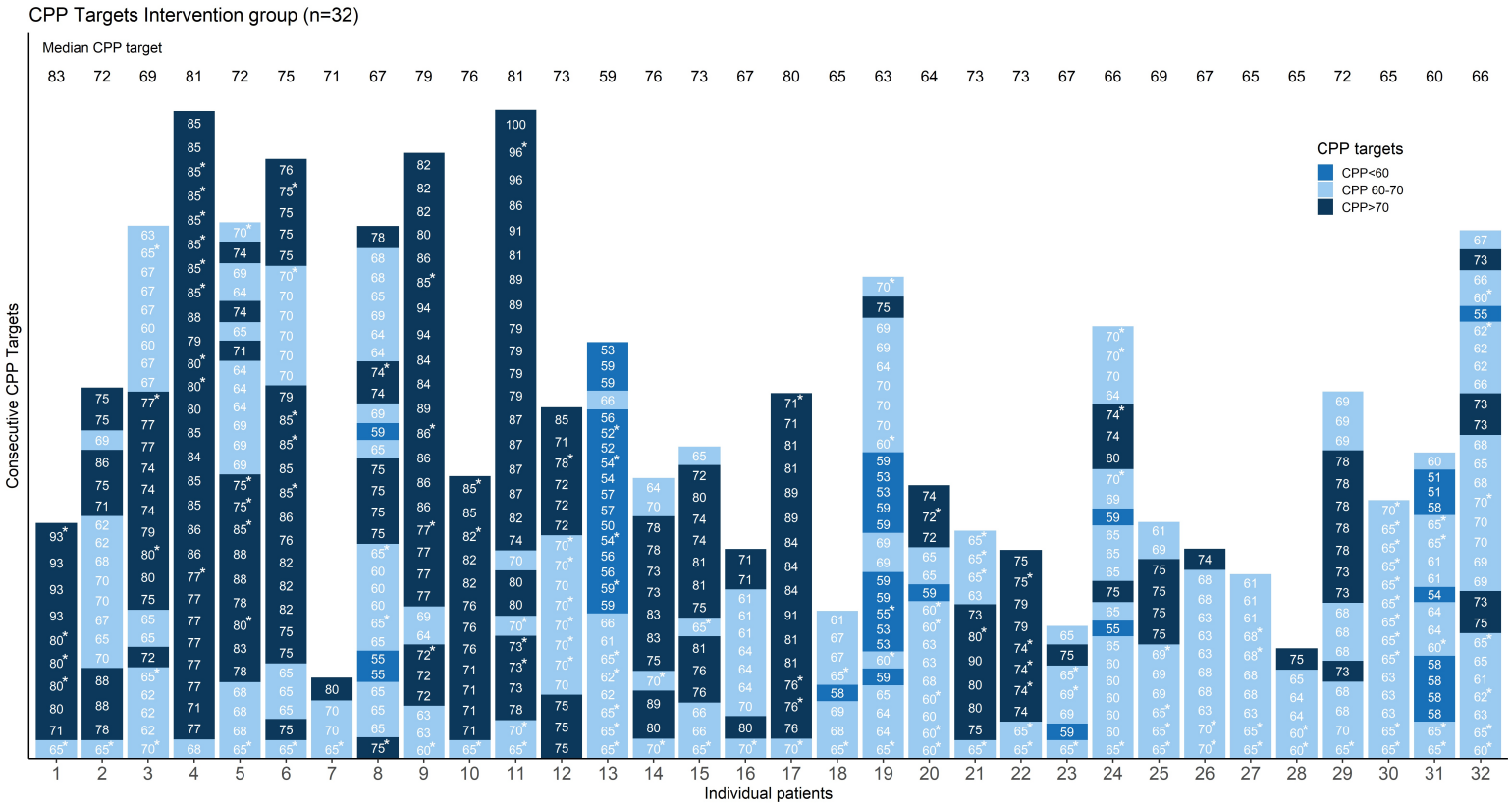

a. CPP target trendline for one intervention patient
CPP (mmHg)
Time (hour)
CPP trendline
CPP above the CPP target
CPP below the CPP target
CPP concordant to the CPP target
CPP target trendline
b.CPPopt trendline for one intervention patient
CPP (mmHg)
Time (hour)
CPP trendline
CPP above the CPPopt trendline
CPP below the CPPopt trendline
CPP concordant to the CPPopt trendline
CPPopt trendline


a. CPPopt recommendations (n=408)
Proportion of reviews (%)
100
75
50
25
0
10
36
33
18
4
CPPopt <60
CPPopt 60-70
CPPopt 70-80
CPPopt 80-90
CPPopt 90-100
b. 'Clinical' CPP targets (n=144)
Proportion of reviews (%)
3
49
31
15
1
CPP <60
CPP 60-70
CPP 70-80
CPP 80-90
CPP 90-100
c. Final CPP target categorized per CPPopt recommendation (n=408)
Proportion of reviews (%)
90
60
30
0
95
5
99
1
1
4
96
1
10
89
33
67
CPP target
CPP <60
CPP 60-70
CPP 70-80
CPP 80-90
CPP 90-100


CPP Targets Intervention group (n=32)
Median CPP target
83 72 69 81 72 75 71 67 79 76 81 73 59 76 73 67 80 65 63 64 73 73 67 66 69 67 65 65 72 65 60 66
CPP targets
CPP<60
CPP 60-70
CPP>70
Consecutive CPP Targets
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32
Individual patients

# Targeting Autoregulation-Guided Cerebral Perfusion Pressure after Traumatic Brain Injury (COGiTATE): A Feasibility Randomized Controlled Clinical Trial

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*Supplementary Appendix S1* ***Supplementary explanation of the intervention protocol***

In this supplemental document a background of CPPopt, a summary of items from the published study protocol and in depth description of certain analysis are provided that supports the methodological section in the main article. The full study protocol can be found here with a link to the publication.[1] The describes items are:

- Panel summarizing background and calculation of PRx, CPPopt and the CPPopt trendline
- Ethics approval
- Sample size calculation
- Patient randomization tool
- Clinical outcome follow-up
- Hemodynamic protocol
- Additional cerebral monitoring
- Termination of the intervention protocol
- CPP target recommendation
- Primary feasibility endpoint
- Secondary endpoints
- Longitudinal analysis (LME)
- Outcome model (proportional odds logistic regression model)

*Panel summarizing background and calculation of PRx, CPPopt and the CPPopt trendline*

Cerebrovascular pressure reactivity was studied by observing the effects of changes in arterial blood pressure slow waves (ABP) on intracranial pressure slow waves(ICP).[2] Trends in the cerebrovascular pressure reactivity are closely related to global changes in cerebral autoregulation.[3] Knowing the physiological model is important to understand the clinical concept of cerebral autoregulation guided CPP treatment in traumatic brain injury (TBI) patients. In three figures the clinical concept is visualized.

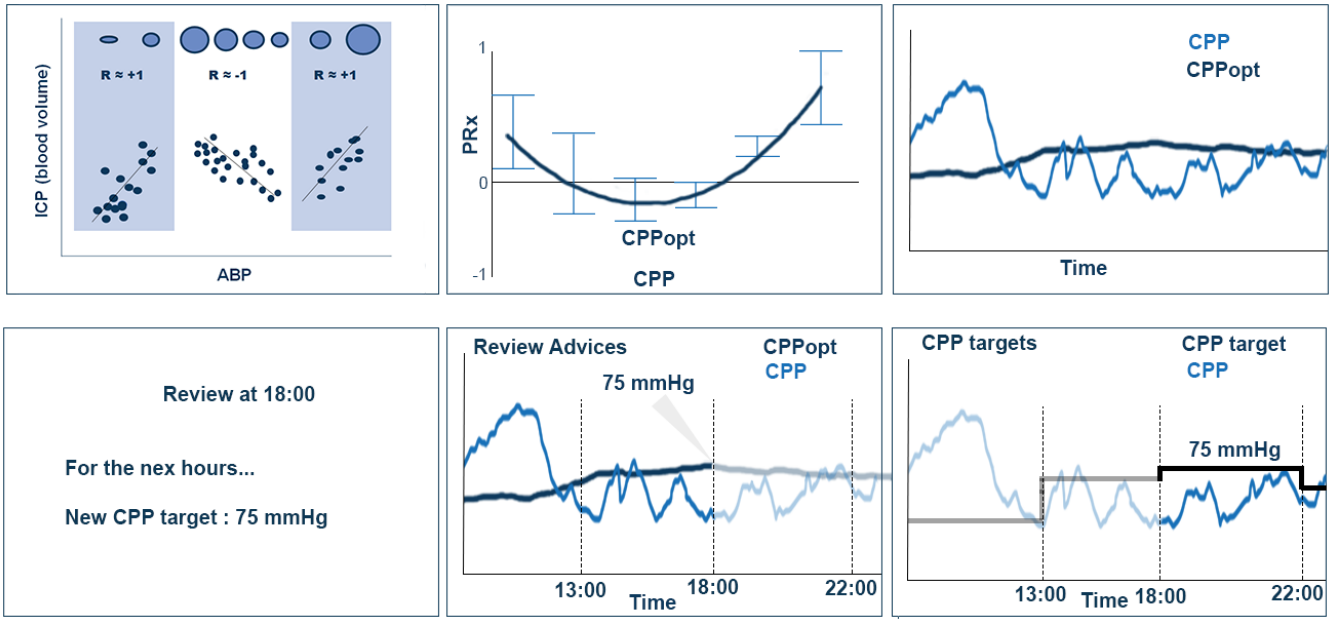


Figure appendix a-f

(Figure a) *PRx*: The Pressure Reactivity index is the statistical Pearson correlation between 10 sec averaged values of ABP and ICP over a 5-minute calculation window. The Pearson correlation index is updated every minute to provide a (moving) trend value. A negative PRx value indicates an intact cerebral autoregulation as slow increases in ABP are counteracting ICP by active vasoconstriction (Figure a, middle panel). A positive value indicates impaired cerebrovascular pressure reactivity as slow changes in ABP are passively followed by changes in ICP.[2] Both vasoconstriction (Figure a, left panel) and vasodilatation (Figure a, right panel) cannot control cerebral blood volume/flow and therefore ICP. A positive PRx is found.

(Figure b) *CPPopt*: The 'optimal' cerebral perfusion pressure concept was introduced in 2002. In a retrospective TBI cohort Steiner et al. showed that over a monitoring period of days plotting the PRx values against CPP showed a U-shaped curve. The nadir of the U-shape curve represents the CPP value for which PRx is minimal, and therefore cerebral autoregulation is best preserved.[4] Aries et al. extended this concept with a curve fitting algorithm that calculates automated CPPopt values over a 4-hourly moving time window (Figure b). They showed that individual CPP deviations from CPPopt were related to poor outcome in TBI patients.[5]

(Figure c) *CPPopt trendline:* Liu et al. added multiwindow and weighted features to the CPPopt algorithm that improved the availability and stability of individual CPPopt values at the bedside (Figure c).[1,6]

(Figure d-f) *CPPopt –Module:* The ICM+ software was further extended with the implementation of a customized research module that presents a CPPopt value on a review screen at set time-points. The CPPopt value presented in the review screen (Figure d) is the CPPopt value extracted from the CPPopt trendline (Figure e) at that specific timepoint (referred to as 'CPP target'). This CPP value is the target value to follow-up to the next review (Figure f). No CPP recommendation is provided when (1) no CPPopt value can be calculated or (2) the CPPopt value is outside the pre-defined safety ranges (50 > CPPopt >100). Then the clinician decides which CPP target to follow (referred to as 'clinical target').

Screenshots of the research module are shown in Supplementary Figure S1.

*Ethical approval*

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Coordinating center in Maastricht by Ethics Committee of Maastricht University Medical Center (29 December 2017/METC171023). Local approval and feasibility was granted by the Health Research Authority National Health System United Kingdom (30 October 2017, Research Ethics Reference 17/LO/119), the Ethics Committee of Academic Hospital Leuven (9 January 2018 B322201834820) and Ethics Committee of Radboud University Medical Center (20 February 2019 RvB19.51633).

*Sample size calculation details*

The study was powered using retrospective data from TBI patients. Retrospectively, we observed a target adherence of 30%, meaning that on a group level the CPP was on average concordant with CPPopt (± 5 mmHg) in 30% of the monitoring time. We expected a pragmatic relative increase of 20% resulting in a percentage of time concordant ± 5 mmHg CPP target from 30% to 36% (SD 8%). With an alpha of 5% and beta of 20% (power estimate of 80%), the estimated number of patients needed for the primary endpoint was 56. This number was increased to 60 to allow for drop-out, technical problems or need for a non-parametric analysis. The PWR library in R was used for the power calculation.[1,7]

*Patient randomization tool*

In our study we used a centralised electronic randomisation system that was incorporated in our electronic case report form (eCRF). An automatic email was sent to the central coordinator of the study in Maastricht with every new randomisation. Block randomisation, with stratification according to trial site, was used to ensure a uniform patient distribution.

*Clinical outcome follow-up*

Neurological outcome on the intensive care unit was assessed by the clinician prior to discharge to the ward in surviving patients using the Glasgow Coma Scale (GCS). Six-month neurological outcome was assessed using the Glasgow Outcome Scale (GOS) according to local TBIicp clinical follow-up strategies by either a physical or a telephone structured interview. Outcome assessors were not blinded of the group assignment.

*Hemodynamic protocol*

How to get to the CPP targets was left to the discretion of the clinical team. The protocol did not mandate a hemodynamic management policy which prioritised either fluids of vasoactive agents for CPP maintenance, since this had a high likelihood of changing local practice in other ways than either targeting dynamic CPP or BTF targets. This would have meant that we would be unable to robustly attribute any trial findings to the CPPopt intervention per se (rather than the means used to achieve it).

*Additional cerebral monitoring*

Additional cerebral monitoring was available according to local protocols but was not part of the study protocol.

*Termination of the intervention protocol*

The maximum duration of the intervention protocol was 5 days for both groups. Reasons for discontinuing the protocol earlier were: (1) the patient died; (2) ICP monitoring discontinued for clinical reasons; (3) Active treatment withdrawal.

*CPP target recommendation*

Six-times a day the software algorithm provided a CPP target recommendation. This was either a CPPopt based value or a 'clinical' target for the intervention group. A 'clinical' CPP target was recommended if: (1) the output of the automated CPPopt algorithm was null (no CPPopt target) and (2) the current CPPopt value was out of the set safety range defined as CPP between 50 and 100 mmHg. One important point is that the recommended CPPopt was not allowed to increase or decrease of more than 10 mmHg from the previous target. In the control group the software algorithm recommended the use of the Brain Trauma Foundation CPP guideline target range of 60-70 mmHg.[8]

*Primary feasibility endpoint*

The primary endpoint of this study is the percentage of CPP monitored time with patients' CPP concordant (± 5 mmHg) with the CPP target. The primary endpoint was calculated for the intervention group patients only. For this analysis, we calculated the percentage of monitoring time (%) each patient had one minute CPP values concordant (± 5 mmHg) with the CPP target. Monitoring time was defined as the period with CPP values being available from the first review till the termination of the intervention protocol (see above). The period till the first review was not used as during this period the protocol advised to target 60-70 mmHg in both groups.

*Secondary safety endpoint calculation*

The main secondary safety endpoint was powered to detect an average daily TIL score difference of > 3 between the groups as evidence for escalation of intracranial hypertension therapy. While designing the study we took into account that patients in the intervention group might require more CPP interventions to finetune CPP targets. This might lead to more fluid loading and vasopressor administration for maintenance of cerebral perfusion (each 1 point in TIL score). Therefore, a difference of 2 was expected and hence a difference of daily TIL ≥ 3 was thought as excess use of therapies for TBI management. As additional secondary analysis, we calculated, for both the intervention and control group, the percentage of time (%) each patient had CPP values concordant with (± 5 mmHg) the CPPopt trendline. The CPPopt trendline was for both groups retrospectively available (see Figure 1 in main manuscript).[9]

*Longitudinal analysis (LME)*

We performed different longitudinal analysis to evaluate temporal profiles for variables of interest.

*CPPopt* One possible clinical concern is that CPPopt guided therapy may drive ever-increasing CPPopt values over time.[10] Therefore, we explored the between-group difference in time course of CPPopt by fitting the one-hour average CPPopt trendline values using a linear mixed effect model (LME, R-package *nlme*)[11] with 'patient' and 'time (hours)' as random intercept and random slope, respectively and 'CPPopt trendline', 'time (hours)' and 'randomisation group' as fixed effects. We included the interaction term 'time*group' to assess differences in trajectory over time between the groups.

*Safety measures* We explored the time course of daily creatinine level, troponin I, troponin T, NT-proBNP, highest daily $PaO_2/FiO_2$ ratio, lowest daily $PaO_2/FiO_2$ ratio, noradrenalin, PRx, daily fluids given and daily net fluid balance in both groups. Therefore, in addition to between-group average differences (Table 3), we explored the between-group differences over time using a LME model with 'patient' and 'days' as random intercept and random slope, respectively and 'safety measure', 'day' and 'randomisation group' as fixed effects. We included the interaction term 'time*group' to assess differences in trajectory over time between the groups.

*Outcome model (proportional odds logistic regression model)*

A proportional odds logistic regression model[12] was constructed to explore the between-group difference in distribution of 6-months GOS clinical outcome (R-package, *MASS*).[13] The Brant function tested the proportional odds assumption (R-package, *brant*).[14,12]

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| *Supplementary Table S1* CPP targets compared to the Brain Trauma Foundation CPP guideline | |
|---|---|
| Median (IQR) | CPP intervention group (*n*=32) |
| %time with CPP target within 60-70 mmHg CPP range (%) | 37.9 (18.2 - 58.3) |
| %time with CPP target above 70 mmHg (%) | 49.7 (21.9 - 81.8) |
| %time with CPP target below 60 mmHg (%) | 0 (0 – 0)* |
| *Four patients had values different from 0%. The %time with CPP target below 60 mmHg for these patients were 4%,11%, 42%, 68%, respectively.<br>CPP = cerebral perfusion pressure | |

*Supplementary Table S2* **Percentage of monitoring time concordant, above or below CPP targets of interest**

| Median (IQR) | CPP control group (*n*=28) | CPP intervention group (*n*=32) | *p*-value (for effect)* | *p*-value (for variance)† |
|---|---|---|---|---|
| %time CPP concordant with the CPPopt trendline value‡ ± 5 mmHg (%) | 36 (31.4 – 46.7) | 42.6 (35.4 – 51.8) | 0.150 | 0.976 |
| %time CPP concordant with the CPP target value§ ± 5 mmHg (%) | NA | 46.5 (41.2 – 58) | NA | NA |
| %time CPP within the 60 - 70 mmHg range (%) | 49.6 (42.4 – 58) | 30.2 (16 – 43.8) | <0.001 | 0.271 |
| %time CPP above the CPPopt trendline value + 5 mmHg (%) | 22.2 (13.2 – 33.1) | 32.3 (23.8 - 43) | 0.573 | 0.507 |
| %time CPP above the CPP target value + 5 mmHg (%) | NA | 36.5 (25.4 – 43.4) | NA | NA |
| %time CPP above 70 mmHg (%) | 30.7 (23 – 46.6) | 64.9 (44 – 82.5) | <0.001 | 0.077 |
| %time CPP below the CPPopt trendline - 5 mmHg (%) | 34.6 (22.4 – 43.5) | 19.1 (13.8 – 29.3) | <0.001 | 0.191 |
| %time CPP below CPP target - 5 mmHg (%) | NA | 15.2 (10.4 - 17) | NA | NA |
| %time with CPP below 60 mmHg(%) | 11.7 (5.46 – 21.5) | 6.71 (1.50 – 10.4) | <0.05 | 0.745 |

*Mann Whitney *U* test was used.

†Levene's Test was used to test equality of variances between groups.

‡ CPPopt trendline is the updated CPPopt values over time.

§ Calculated as the percentage of time CPPopt being available given CPP value being present.

‖ CPP target. At a review time point a CPP target was set by the clinical team either by adopting the provided CPPopt or by taking a 'clinical' CPP target.

CPP = cerebral perfusion pressure; CPPopt = optimal cerebral perfusion pressure; IQR = interquartile range; NA = not applicable

*Supplementary Table S3* ***Individual 12 items of Therapy Intensity Level (TIL) score***

| Number of patients, *n (%)* | Control group (*n*=28) | Intervention group (*n=32)* | *p*-value* |
|---|---|---|---|
| *(1) Positioning* | | | |
| Head elevation for ICP control | 28 (100) | 31 (97.5) | 1.0 |
| Nursed flat (180°) for CPP management | 0 | 1 (2.5) | |
| *(2) Sedation*† | | | |
| No sedation | 1 (3.6) | 1(3.12) | 1.0 |
| Low dose sedation | 3 (10.7) | 4 (12.5) | |
| Higher dose sedation for ICP control | 18 (64.3) | 21 (65.6) | |
| High dose propofol or barbiturates for ICP control | 6 (21.4) | 6 (18.8) | |
| *(3) Neuromuscular blockade* | | | 0.482 |
| No | 25 (89.3) | 26 (81.2) | |
| Yes | 3 (10.7) | 6 (18.8) | |
| *(4) CSF drainage* | | | |
| No | 25 (89.3) | 30 (93.8) | 0.331 |
| CSF drainage-low volume, < 120 mL/day (< 5 mL/h) | 0 | 1 (3.1) | |
| CSF drainage-high volume, > 120 mL/day (> 5 mL/h) | 3 (10.7) | 1 (3.1) | |
| *(5) Fluid loading* | | | |
| No | 21(75) | 24 (75) | 1.0 |
| *Yes* | 7 (25) | 8 (25) | |
| *(6)Vasopressor therapy* | | | |
| No | 1 (3.6) | 2 (6.3) | |
| Yes | 27 (96.4) | 30 (93.8) | |
| *(7)Ventilatory management* | | | |
| Normocapnia (>5.3 kPa) | 6 (21) | 6 (18.8) | 1.0 |
| Mild hypocapnia (4.6-5.3 kPa) | 15 (54) | 16 (50) | |
| Moderate hypocapnia (4.0-4.5 kPa) | 7 (25) | 9 (28) | |
| Intensive hypocapnia (< 4 kPa) | 0 | 1 (3.1) | |
| *(8) Mannitol bolus infusion* | | | |
| No | 25 (89.3) | 30 (93.8) | 0.794 |
| ≤ 2g/kg/24h | 1 (3.6) | 0 (0) | |
| > 2g/kg/24h | 2 (7.1) | 2 (6.3) | |
| *(9) Hypertonic bolus saline infusion* | | | |

| | | | |
|---|---|---|---|
| Not received | 24 (85.7) | 27 (84.4) | 0.578 |
| ≤ 0.3g/kg/24h | 3 (10.7) | 5 (15.6) | |
| > 0.3g/kg/24h | 1 (3.6) | 0 (0) | |
| *(10)Temperature control* | | | |
| No | 18 (64.3) | 23 (71.9) | 0.872 |
| Treatment of fever (T>38°C) or spontaneous T<34.5°C | 5 (17.9) | 4 (12.5) | |
| Cooling for ICP control (≥35°C) | 3 (10.7) | 4 (12.5) | |
| Hypothermia (<35°C) | 2 (7.1) | 1 (3.1) | |
| *(11) Intracranial operation during intervention period* | | | |
| No | 27 (96.4) | 31(96.9) | 1.0 |
| Yes | 1(3.6) | 1(3.1) | |
| *(12) Decompressive craniectomy during intervention period* | | | |
| No | 26 (92.9) | 29 (90.6) | 1.0 |
| Yes | 2 (7.1) | 3 (9.4) | |

* Chi-squared or Fisher exact test was used.

The numbers presented are calculated as follows: First, the presented numbers are calculated as the median value per patient over the intervention period; Second, the frequencies (%) of these median values are represented per TIL item. Exceptions are item 11 and 12 as these frequencies (%) include the total number of operations performed during the intervention period.

† Low sedation means ‘as required for mechanical ventilation’; ‘Higher dose sedation for ICP control’ means not aiming for burst suppression; ‘High dose propofol or barbiturates used for ICP control’ includes therapy to achieve metabolic suppression.

TIL = therapy intensity level score; ICP = intracranial pressure; CSF = cerebral spinal fluid; CPP = cerebral perfusion pressure; T = temperature

*Supplementary Table S4* ***Longitudinal analysis for safety parameters***

| Variables | Regression coefficient (95%-confidence interval) *Group difference (reference = control)* | *p*-value | Regression coefficient (95%-confidence interval) *Interaction 'group' * 'time' (reference = control)* | *p*-value |
|---|---|---|---|---|
| TIL score | 0.94 (-0.67; 2.56) | 0.245 | -0.35 (-1; 0.302) | 0.291 |
| PRx | -0.06 (-0.17; 0.06) | 0.318 | -0.00094 (-0.0; 0.0) | 0.457 |
| | | | | |
| Creatinine level (µMol/L)* | -6.6 (-18.2; 5.07) | 0.264 | -1.56 (-9.13; 6.02) | 0.685 |
| Troponin T (ng/L)† | -8.9 (-40.2; 22.4) | 0.572§ | 9.23 (-13.0 ; 31.5) | 0.419 |
| Troponin I (ng/L)‡ | -11.4 (-35.4; 12.6) | 0.332§ | 14.3 (-0.83; 29.5) | 0.063 |
| NT-pro BNP (ng/L) | 13.7 (-324; 352) | 0.936 | 45.2 (-44.1;134) | 0.319 |
| Highest daily $PaO_2/FiO_2$ ratio (mmHg/ %) | 21.6 (-38.1; 82.2) | 0.473 | -2.7 (-29.1; 23.7) | 0.840 |
| Lowest daily $PaO_2/FiO_2$ ratio (mmHg/ %) | 20.4 (-31.6; 72.4) | 0.436 | 1.57 (-18.8; 21.9) | 0.879 |
| Noradrenalin (mg) | -0.049 (-5.51; 5.41) | 0.986 | -0.30 (-3.5; 2.9) | 0.853 |
| Daily fluids given (ml) | 78.8 (-399; 556)§ | 0.743§ | -16.3 (-226; 194) | 0.879 |
| Daily net fluid balance (ml) | 136 (-211; 483) | 0.437 | -35.8 (-317; 245) | 0.802 |

The results of the linear mixed effect (LME) models showed that the interaction terms (group*time) - indicating a different trajectory over time between the groups – was not significant for any of the tested variables and therefore not including in the final model. The variables have time in days except from PRx which has time in hours. In the final model, none of the variables showed a difference in regression coefficients indicating similar trajectories of safety parameters in both groups.

* Missing days: Control: 1 day (0.9%), Intervention: 3 days (2.5%). Missing patients *n*=0.

† High Sensitive Troponin T was used in three centres (Control *n*=19; Intervention *n*=21). Missing patients*: n*=0; Missing days: Control *n*=7 (9.6%); Intervention *n*=7 (9.3%).

‡ High Sensitive Troponin I was used in one centre (Control *n*=9; Intervention *n*=11). Missing patients: *n*=0. Missing days: Control *n*=1 (2.9%); Intervention *n*=2 (4.3%). Note: Control *n*=27 (79%); Intervention *n*=41 (87%) values were '0' indicating a High Sensitive Troponin I value < 17.

NA = not applicable; TIL = therapy intensity level; $PaO_2/FiO_2$ ratio = partial pressure of oxygen/ fraction of inspired oxygen ratio.

*Supplementary Table S5a* ***Adverse- and serious adverse events during intervention period***

| *Categories* | CPP control group (*n*=28) | CPP intervention group (*n*=32) |
|---|---|---|
| *AE* | | |
| Neurological | 1 | 4 |
| Pulmonary | 2 | 3 |
| Cardiovascular | 2 | 2 |
| Gastro-intestinal | 2 | 0 |
| Nephrological | 0 | 0 |
| *SAE* | | |
| Cardiovascular | 1 | 1 |
| Total number | 8 | 10 |

The total number of adverse events (AE) and serious adverse events (SAE) per organ system were scored during the intervention period (maximal 5 days) on the intensive care unit.

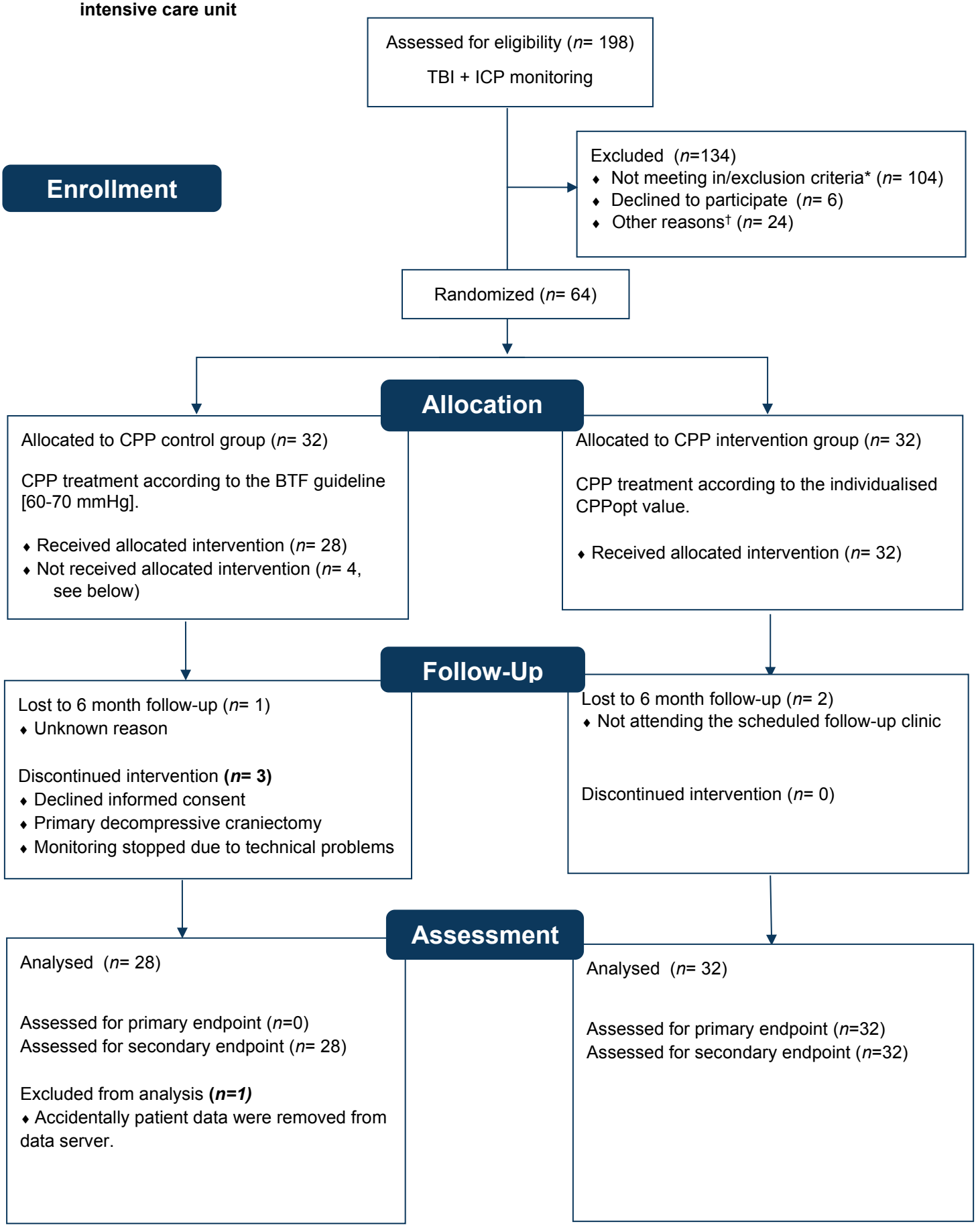
| *Supplementary Table S5b* **Predefined adverse events (AE) during the intervention period** | |
|---|---|
| Neurological | Central nervous system infection (proven by culture and treated with antibiotics) |
| | Hyponatraemia (SIADH/CSWS/iatrogenic) |
| | Hypernatremia (central diabetes insipidus/iatrogenic) |
| | (any) Seizures |
| | New diagnosed motor weakness (focal/general) |
| Pulmonary | Haematothorax |
| | Pneumothorax |
| | Pneumonia (proven by culture and treated with antibiotics) |
| | Adult Respiratory Distress Syndrome |
| Cardiovascular | Myocardial ischaemia (diagnosed by cardiologist) |
| | Aortic dissection |
| | Major intrathoracic hemorrhage, needing > 1unit packet cell transfusion |
| | Limb ischemia |
| | Infectious endocarditis |
| | Cardiac tamponade |
| | Heart failure (diagnosed by cardiologist) |
| | New arrhythmias (requiring treatment) |
| Gastro-intestinal | Intestinal perforations |
| | Ileus (mechanical or paralytic) |
| | Pancreatitis |
| | Hepatitis |
| | Peritonitis |
| | Abdominal hemorrhage, needing >1 unit packed cell transfusion |
| | Acute or acute on chronic liver failure |
| | Cholecystitis/cholangitis (proven by culture and treated with antibiotics) |
| Nefrological | Acute Kidney Injury defined as stage 2 or 3 according to KDIGO criteria |
| | Any renal replacement therapy |
| | Urinary tract infections (proven by culture and treated with antibiotics) |
| Other | Vascular catheter-related bloodstream infections (proven by culture) |
| | Pressure sores (decubitus) |
| | Skin infections |
| | Bacteriaemia (proven by culture) without focus |
| The predefined adverse events (AE) that were listed and reported during the study period (maximum five days).<br>SIADH = syndrome of inappropriate antidiuretic hormone; KDIGO = kidney disease improving lobal outcome guideline; CSWS = cerebral salt wasting syndrome | |

*Supplementary Fig. S1* ***Example of the different review screens***


*Supplementary Fig. S1 legend* Example of the different review screens from a patient in the intervention group. In the background the neuromonitoring trends are shown. The seven sections in the figure are explained in detail. Six-times a day (section 1) the review alert appeared as a yellow pop-up screen; the CPP target recommendation was presented to the clinical team (section 2) followed by additional questions (section 3-5); after saving the review report, the reviewing clinician was requested to instruct the bedside nursing staff about the new target and record the new target in the electronic patient dossier (section 6); in addition, the report summary was automatically saved in the ICM+ monitoring software. The summary of the review report could be viewed at any time (section 7).

CPP = cerebral perfusion pressure; CPPopt = optimal cerebral perfusion pressure; ICM+ = Intensive Care Monitoring software; PRx = Pressure Reactivity Index.

*Supplementary Fig. S2* **Study flow diagram: Traumatic Brain Injury patients admitted to the intensive care unit**



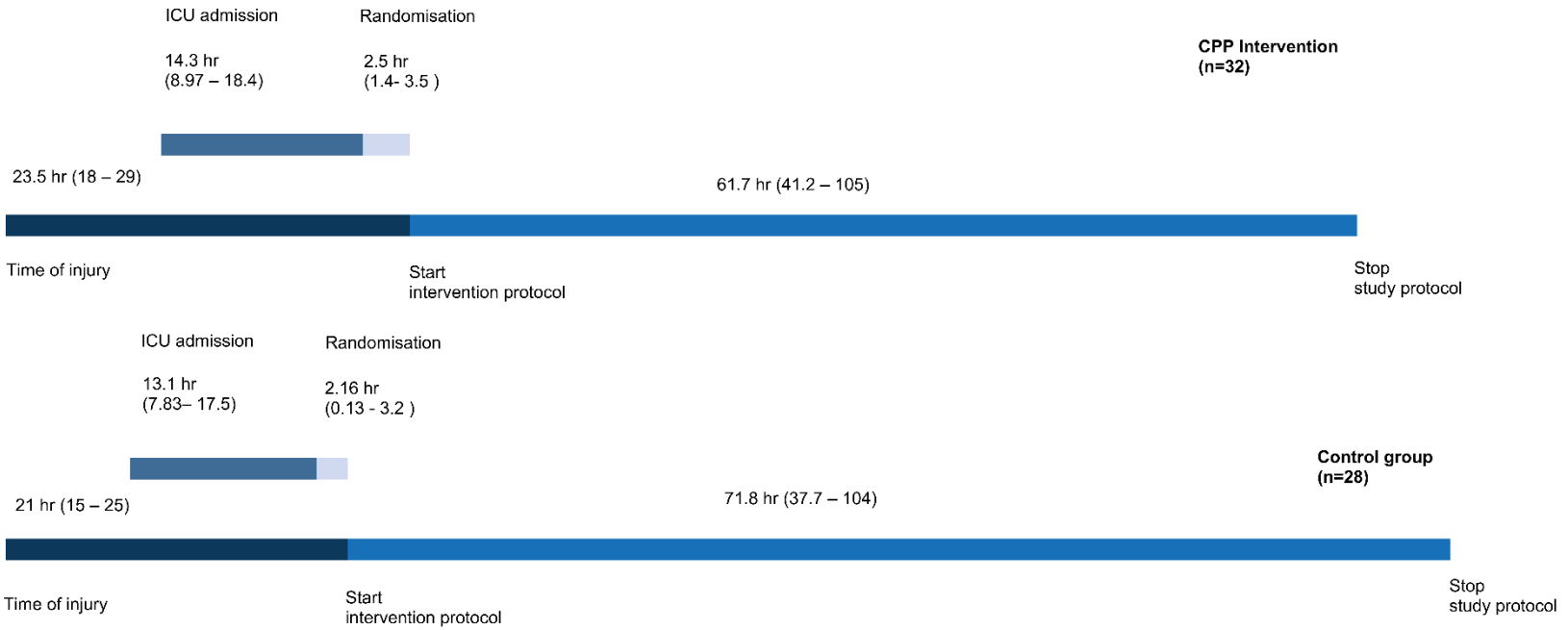
*Supplementary Fig.S2 legend* **Study flow diagram**.

*Reasons for not meeting the inclusion and exclusion criteria (53%) are: age <18 (*n*=5), deemed unsurvivable at presentation (*n*=10), primary or early decompressive craniectomy (*n*=26), no family present for informed consent < 24 hours after ICU admission (*n*=14), estimated duration of ICP monitoring < 24 hour (*n*=21), ICP monitoring started > 24 hour after ICU admission (*n*=9) and patient included in another intervention study (*n*=19).

†Other reasons for not including were (12%): no researcher available to set up brain monitoring software (*n*=15), uncertainty of contribution of acute stroke or intoxication to TBI injury (*n*=2), sedation and neuromonitoring mainly for severe agitation (*n*=2), severe hemodynamic instability with active abdominal hemorrhage (*n*=1), planned decompressive craniectomy not performed within 24 hour from ICU admission (*n*=1), technical maintenance of monitoring capacities (*n*=3).

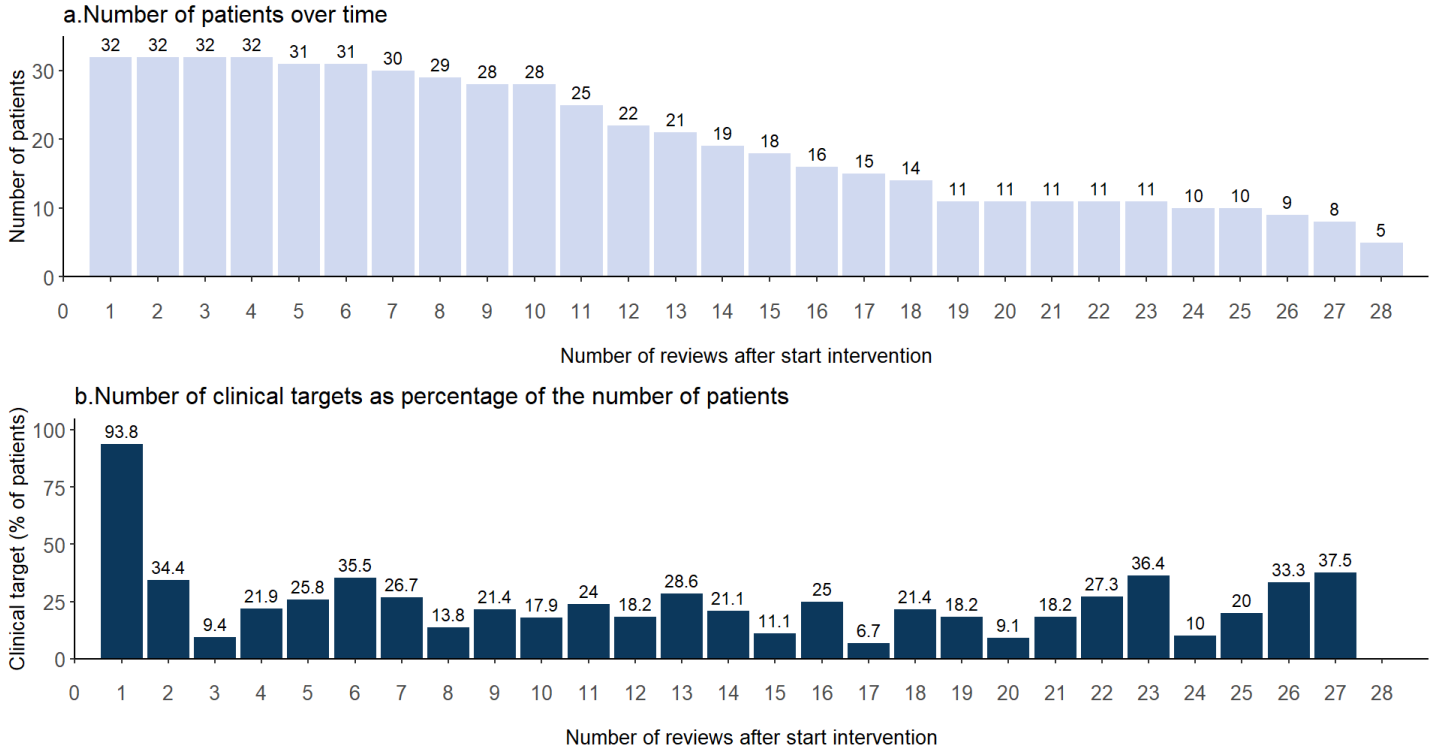
ICU = intensive care unit; TBI = traumatic brain injury; ICP = intracranial pressure; BTF = Brain Trauma Foundation

*Supplementary Fig. S3* **Study timeline**




*Supplementary Fig. S3 legend* Timeline from trauma ictus until study completion. The timeline starts with the estimated time of trauma (from admission notes) followed by time of ICU admission and study randomisation. Randomisation time is the time that the patient was randomised in the eCRF. During the first period after randomisation, the protocol recommended for both groups to target a CPP value between 60-70 mmHg. 'Start intervention' is the moment that the first CPP target recommendation was provided by the software algorithm. Figure constructed in MATLAB (Release 2019b, The MathWorks, Inc., Natick, Massachusetts, United State. CPP = cerebral perfusion pressure; ICU = intensive care unit; eCRF = electronic case record form.

*Supplementary Fig. S4* ***Extended information regarding patient numbers and percentage of 'clinical' CPP targets per review period in the intervention group***

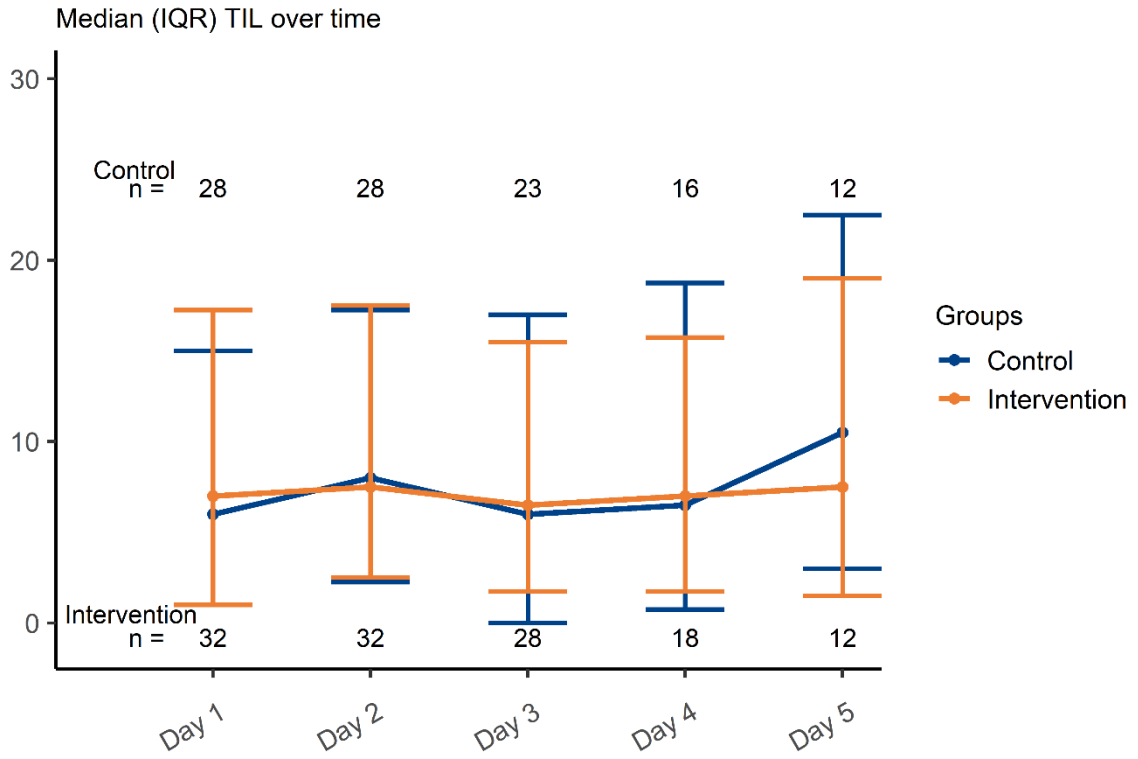



*Supplementary Fig. S4* legend a. The total number of patients per consecutive review period in the intervention group are depicted. The duration between the reviews is approximately 4 hour. b. The percentage of CPP recommendations with a 'clinical target', expressed as the percentage of the CPP recommendations per review period. The algorithm required at least 4 hours of continuous data before the first CPPopt recommendation becomes available. The first period after randomisation was in most cases shorter than 4 hours explaining the high percentage of 'clinical targets' (93.8%) during the first review.[1]

**REFERENCE:**

1. Beqiri, E., Smielewski, P., Robba, C., Czosnyka, M., Cabeleira, M.T., Tas, J., Donnelly, J., Outtrim, J.G., Hutchinson, P., Menon, D., Meyfroidt, G., Depreitere, B., Aries, M.J., and Ercole, A. (2019). Feasibility of individualised severe traumatic brain injury management using an automated assessment of optimal cerebral perfusion pressure : the COGiTATE phase II study protocol. BMJ Open.

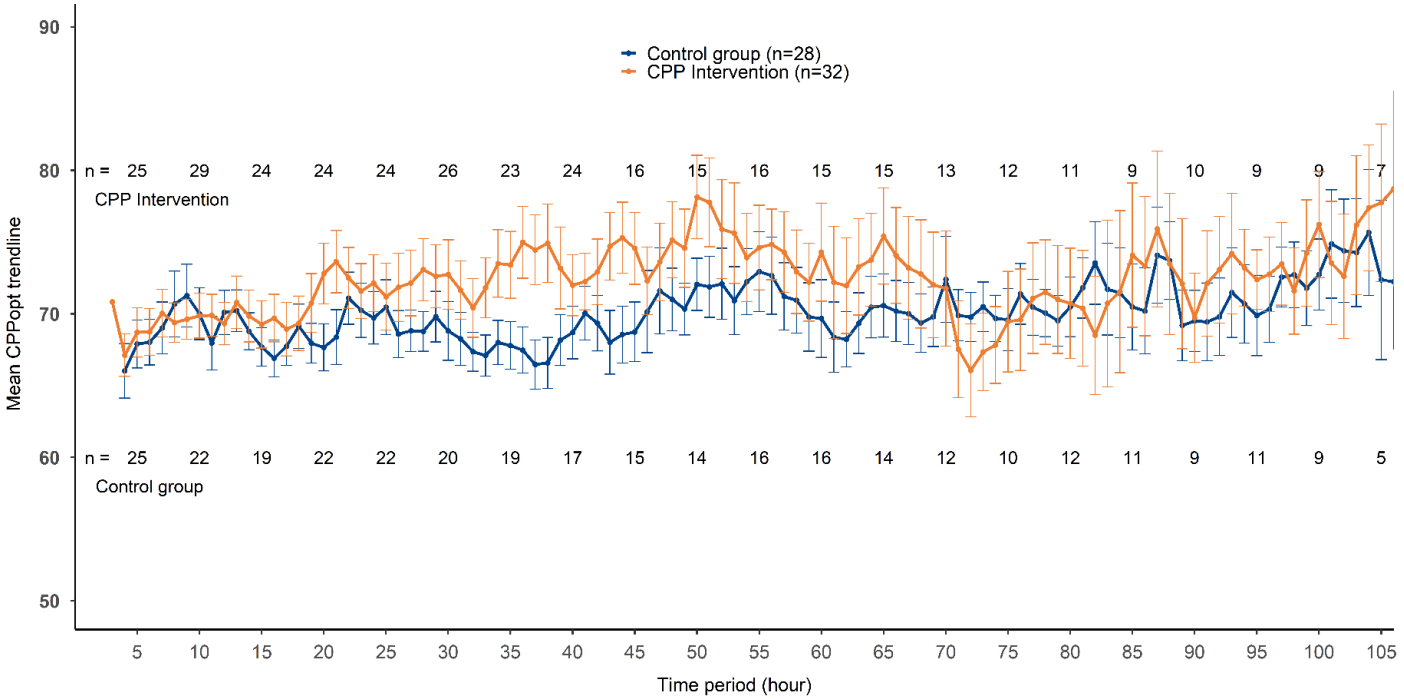
*Supplementary Fig. S5* ***Therapy Intensity Level (TIL) over time***




*Supplementary Fig. S5 figure legend* Therapy Intensity Level (TIL) score was depicted over time. During the intervention period the daily TIL score was collected. The trajectories of the TIL for both randomization groups are presented. The number of patients (*n*) that contribute to the median values for each day are put above and below the error bars (with median and interquartile ranges). The result of the linear mixed effect model (LME) showed that the interaction term 'group * time' did not show a significant influence and was not included in the final LME model (RC -0.35 (95%-CI -1; 0.302), *p*=0.291). Overall, the slope was not different for the groups (RC 0.94 (-0.67; 2.56), *p*=0.245), with the control group as the reference. Figure constructed in R (R-Core Team, version 4.0.3).

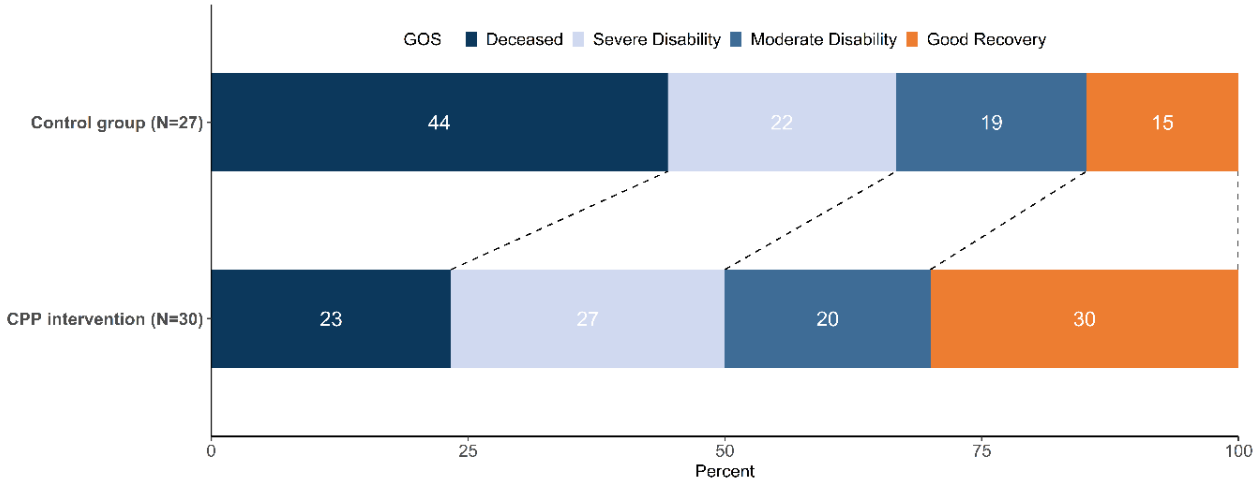
RC = regression coefficient; 95%-CI: 95%-confidence interval

*Supplementary Fig. S6* ***CPPopt values over time***




*Supplementary Fig. S6 legend* CPPopt trajectory is visualized with one hour average (± standard error) CPPopt values over time. The CPPopt trendline was prospectively available for the intervention group (*n*=32) and retrospectively for the control group (*n*=28). Above and below the trendlines the number of patients that contribute to a certain CPPopt value are noted. The result of the linear mixed effect (LME) model shows that the interaction term 'group * time' did not show a significant influence and was not included in the final model (RC 0.004 (95%-CI -0.09; 0.090), *p*=0.928). Overall, the slope was not different for the groups (RC 2.17 (95%-CI -0.48; 4.8), *p*=0.106), with the control group as the reference. Figure constructed in R (R-Core Team, version 4.0.3). RC= regression coefficient, 95%-CI = 95%-confidence interval.

*Supplementary Fig. S7* ***Glasgow Outcome Scale at six-months follow-up***




*Supplementary Fig. S7 figure legend* At six months after randomisation, the distribution of GOS is presented as a bar chart with following categories: deceased (GOS=1), severe disability (GOS=3), moderate disability (GOS=4) and good recovery (GOS=5). No patients were assigned as with a vegetative state (GOS=2). The number of outcome values missing were 1 in the control group and 2 in the intervention group. The proportional odds logistic regression model showed a non-significant difference in distribution between groups with an odds ratio of 2.35 (95%-CI 0.9 – 6.12) for improved outcome ($\chi^2$ *test, p*=0.08). The proportional odds ratio assumption was confirmed to be valid. Figure constructed in R.

GOS = Glasgow Outcome Scale; 95%-CI = 95%-confidence interval.