**Appendix A – Signal Acquisition and Processing Details**

Arterial blood pressure (ABP) was obtained through either radial or femoral arterial lines connected to pressure transducers (Baxter Healthcare Corp. CardioVascular Group, Irvine, CA). ICP was acquired via an intra-parenchymal strain gauge probe (Codman ICP MicroSensor; Codman & Shurtleff Inc., Raynham, MA), parenchymal fiber optic pressure sensor (Camino ICP Monitor, Integra Life Sciences, Plainsboro, NJ, United States; https://www.integralife.com/) or external ventricular drain. All signals were recorded using digital data transfer or digitized via an A/D converter (DT9801; Data Translation, Marlboro, MA), where appropriate, sampled at frequency of 100 Hertz (Hz) or higher, using the ICM+ software (Cambridge Enterprise Ltd, Cambridge, UK, http://icmplus.neurosurg.cam.ac.uk) or Moberg CNS Monitor (Moberg Research Inc, Ambler, PA, USA) or a combination of both. Signal artifacts were removed using both manual and automated methods prior to further processing or analysis.

The arterial line transducer zero level varied between institutions, with some using the tragus and some using the level of the right atrium. The CENTER-TBI database provides some information on arterial line zeroing, however it is incomplete in many cases or provided without details on elevation of the head of the bed. As such, it is difficult to accurately adjust MAP based on arterial line transducer level for this cohort with the current available data. Given PRx (and all continuous time-domain indices of cerebrovascular reactivity) are based on the moving Pearson correlation between slow-wave fluctuations in two signals, both the sign and magnitude of the index are independent of the magnitude of the individual raw signals. Thus, arterial line transducer level does not impact the calculation or value of PRx, or the results of the analysis of PRx and ICP in this study.

*Signal Processing:*

Post-acquisition processing of the above signals was conducted using ICM+. CPP was determined as CPP = MAP – ICP. Ten second moving averages (updated every 10 seconds to avoid data overlap) were calculated for all recorded signals: ICP, ABP (which produced mean arterial pressure (MAP)), AMP and CPP. PRx was derived via the moving correlation coefficient between 30 consecutive 10 second mean windows of the parent signals (ICP and MAP), updated every minute.[1,2] This methodology for PRx determination has been employed for over 20 years, with this metric having been preliminarily validated as a measure of the lower limit of autoregulation in experimental animal models.[3–5] Though it must be acknowledged that PRx is not a “pure” measure of cerebrovascular reactivity, in that it contains some information regarding autoregulation, but also other information regarding cerebral physiology and may be influenced by local, regional and global factors. Data was provided in minute-by-minute comma separated variable sheets for the entire duration of recording for each patient.

*References:*

1. Czosnyka M, Smielewski P, Kirkpatrick P, Laing RJ, Menon D, Pickard JD. Continuous assessment of the cerebral vasomotor reactivity in head injury. Neurosurgery. 1997;41:11–7; discussion 17-19.

2. Zeiler FA, Donnelly J, Calviello L, Smielewski P, Menon DK, Czosnyka M. Pressure Autoregulation Measurement Techniques in Adult Traumatic Brain Injury, Part II: A Scoping Review of Continuous Methods. J Neurotrauma. 2017;34:3224–37.

3. Brady KM, Lee JK, Kibler KK, Easley RB, Koehler RC, Shaffner DH. Continuous measurement of autoregulation by spontaneous fluctuations in cerebral perfusion pressure: comparison of 3 methods. Stroke. 2008;39:2531–7.

4. Zeiler FA, Donnelly J, Calviello L, Lee JK, Smielewski P, Brady K, et al. Validation of pressure reactivity and pulse amplitude indices against the lower limit of autoregulation, Part I: experimental intra-cranial hypertension. J Neurotrauma. 2018;In Press.

5. Zeiler FA, Lee JK, Smielewski P, Czosnyka M, Brady K. Validation of ICP derived cerebrovascular reactivity indices against the lower limit of autoregulation, Part II: experimental model of arterial hypotension. J Neurotrauma. 2018;Epub Ahead of Print.