Statistical analysis plan for the second INTEnsive blood pressure Reduction in Acute Cerebral hemorrhage Trial (INTERACT2): a large-scale investigation to solve longstanding controversy over the most appropriate management of elevated blood pressure in the hyperacute phase of intracerebral hemorrhage

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The Statistical analysis plan (SAP) for the second INTEnsive blood pressure Reduction in Acute Cerebral hemorrhage Trial (INTERACT2).

Key words: clinical trial, hypertension, intracerebral hemorrhage, methodology, stroke

There is no proven effective medical therapy for acute stroke due to spontaneous intracerebral hemorrhage (ICH), a condition that affects over one million people in the world each year, most of whom either die or are left seriously disabled (1). Among the various prognostic factors for ICH, hematoma growth is an attractive therapeutic target as it is both modifiable and present in nearly all patients. To date, however, a potent haemostatic approach to attenuating hematoma growth administered very early after the onset of ICH has failed to demonstrate any clear beneficial effects (2). The first (pilot phase) INTERACT1 clinical trial demonstrated that early lowering of elevated BP to a 140 mmHg systolic target can reduce hematoma growth (3), and that the size of the treatment effect is dependent on both the timing and the degree of BP lowering (4,5). Any potential clinical benefit of early BP lowering is, therefore, likely to be most evident in patients in whom the management strategy is commenced early and where this BP lowering target is reached rapidly in ICH.

The INTERACT2 study (6) (NCT00716079, ISRCTN73916115 and ACTRN12608000362392) was designed to not only provide a definitive answer to longstanding controversy over the most appropriate management of the common occurrence of elevated BP in the hyperacute phase of ICH, but also for it to have pragmatic features and include patients from a broad range of health care settings so that the results can be widely generalizable in their influence on clinical practice. More specifically, the sample size was set at 2800 to provide at least 90% power to detect a 14% relative (7% absolute) reduction in a poor outcome, defined as either death or dependency at 90 days, associated with at least 13 mmHg difference in systolic BP at one hour between patients allocated to intensive BP lowering (target systolic BP, 140 mmHg) compared to those allocated to guideline-recommended BP control (target systolic BP, 180 mmHg). Secondary analyses of the INTERACT1 cohort (7), and a meta-analysis of studies of the early recombinant activated clotting factor VIIa (rFVIIa) (8), suggest that the effect of early intensive BP lowering resulting in a 2–4 ml reduction in hematoma growth could translate into a 10–20% better outcome in ICH. The expected magnitude of benefit, in terms of cases of death or dependency prevented, equates to a number needed-to-treat of 15. This is considered to be a minimum clinically worthwhile benefit of the treatment, which could be applied widely as a standard of care.

The INTERACT2 Investigators wish to outline in detail and make public the pre-determined SAP for the main analyses associated with the primary report of the results. The SAP was finalized before completion of the data collection and is what investigators will adhere to in analyzing data on the two management regimes, targeting either a lower ('intensive') or higher ('standard') systolic BP level, in patients within six hours of ICH. The SAP indicates that all data collected by participating researchers will be reviewed and formally assessed, and outlines the key descriptive elements pertaining to the baseline characteristics of

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patients. In addition, information relevant to the BP lowering treatment and the process of care and delivery of other treatments has been classified and, for each item, the descriptive statistical analyses planned for comparisons between randomized groups are outlined. Finally, for the trial outcomes that are classified as primary, secondary or tertiary, the statistical comparisons that will be made between randomized groups are described.

In summary, a SAP has been developed for the results of the INTERACT2 study before completion of data collection. We provide a comprehensive description of how we plan to present baseline characteristics, features of the process of care, and trial treatments, along with pre-determined statistical assessments of relevant outcome measures, in a way that is transparent, available to the public, verifiable and evidently pre-determined. As randomized trials can yield biased results if they lack methodological rigor, our approach is to avoid analytical bias arising from prior knowledge of the study findings.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1 Statistical analysis plan (INTERACT2).