Reviewer’s report

Title: The effects of continuous prostacyclin infusion on regional blood flow and cerebral vasospasm following subarachnoid haemorrhage. Design and rationale for a randomized, blinded, placebo-controlled, clinical pilot trial

Version: 1 Date: 6 March 2012

Reviewer: Peter Sandercock

Reviewer’s report:

1. The paper and background focus on vasospasm, but the SAH trials community regard delayed ischaemic neurological deficit (DIND) as the key concept now. It is the DIND that results in neurological impairment, death and disability. Vasospasm is only the presumed cause of arterial narrowing as imaged by angiography, or altered cerebral blood flow velocity on Doppler ultrasound. Not all patients with vasospasm develop impaired perfusion or DIND. Not all with DIND have vasospasm. The antiplatelet effects of prostacyclin may also be relevant to preventing ischaemic deficits. This should all be mentioned in the introduction which should discuss the complex relationship between vasospasm and DIND in much more detail. The Dutch group in Utrecht have published a great deal on the topic1, and I am surprised their work has not been mentioned at all.2-4

2. DIND is a secondary outcome, and will be important in any phase III trial. The authors should cite the key paper by Vergouwen1 here as well and give the definition of DIND to be used in the study, and the process by which it will be determined for patients in the trial.

3. More details of the process of randomisation are needed. Exactly how will nurses access the list and how will security of the allocation list be maintained?

4. There is no stratification / minimisation to reduce imbalance, so will the analyses be adjusted for baseline covariates or not? If yes, how?

5. What adverse events will be recorded? What will the process for reporting SARs and SUSARs be?

6. Is there a data monitoring committee? If not, will there be any independent review of the accumulating safety data?

7. The rationale for the dose selected is extremely brief and should be expanded.

8. Which institution is acting as the sponsor for the trial?

9. How is the trial funded, and what role does the funding source have in the trial?

10. How will GOS be analysed (dichotomous, sliding dichotomy, ordinal or
other)? There is a good case to use an ordinal analysis to maximise statistical efficiency (add ref here).

11. The statistical analysis plan should be set out in much greater detail before the code is broken (though it does not need to be included at this stage, the journal may be sympathetic to publishing the SAP as a follow-on to the protocol).

Reference List


