Online supplemental appendix 1: Protocol for a systematic review and meta-analysis on the treatment of cerebral cavernous malformations

Background
Cerebral cavernous malformations (CCM) are lesions of the capillaries that include the central nervous system. Macroscopically identifiable by their well-circumscribed, purple colored appearance. Typical are the abnormally enlarged capillary cavities without intervening brain parenchyma. These cavities are filled with blood, but, as a rule, are angiographically-occult vascular malformations (AOVMs). Although pathological examination is the reference standard for diagnosis, MRI is the non-invasive diagnostic modality of choice. Not every CCM is symptomatic, but the most severe and potential fatally symptom is hemorrhage. At this moment treatment standards for specific CCM interventions are lacking. CCM treatment with neurosurgical excision or stereotactic radiosurgery (SRS) aims to decrease the risks of death, intracranial hemorrhage (ICH), and non-hemorrhagic focal neurological deficit (FND), but treatment also confers a risk of these outcomes.

Purpose
To determine the influences on outcome (especially the risk of hemorrhage) for CCM after intervention (microsurgical excision or stereotactic radiosurgery), using a Poisson meta-regression analysis.

Methods/design
We will follow the recommendations made by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Data sources
We aim to identify intervention studies on CCM by means of searches of Ovid Medline, EMBASE and The Cochrane Library from 1984 to July 31th 2012. Reference lists of identified will be crosschecked to identify additional studies until this method of crosschecking does not identify further studies.

Search strategy
We developed a systematic search strategy with structured terms. (see online supplemental appendix 2). There is no restriction on the study language.

Eligibility criteria
Studies will be included if they fulfilled the following criteria:
- CCM diagnosis confirmed by MRI or pathological confirmation in all cases
- 20 or more patients treated in the total cohort, not per treatment modality.
- No age restrictions
- Original treatment data
- Outcome data quantified per patient (any or all of: death, ICH, FND).
- Only articles in peer reviewed journals
- Proportion of patients in the study population with extra-cerebral or extra-cranial cavernous malformations must not exceeded 10%.
- Lost to follow-up <20% (However, if follow-up is not described, we will included cohorts if we could extract outcomes that occurred within 30 days of treatment.)

**Study selection**
One author (MHFP) will screen the titles and abstracts of studies identified from initial searches. A standard screening checklist based on the eligibility criteria above will be employed for each study. Studies that do not meet the criteria according to the titles or abstracts will be excluded. Full-text versions of the remaining studies, including those that are potentially eligible studies and uncertain, will be retrieved for a second review by at least two reviewers (MHFP, RA-SS) independently to determine the eligibility. If more than one publication reports the results from the same study cohort, we will choose the publication with the largest sample size.

**Data extraction**
We will develop a data extraction form. The data items mainly abstracted are as follows:

*Qualitative aspects of the study*
Year of publication, institution and country, study group (population, multicentre, one hospital), years in which treatment took place, cohort mid-year (defined as the middle of the time frame of the years in which treatment took place), study design (retrospective study, prospective study, prospective patient collection + retrospective follow-up), consecutive patient series, authors’ own patients, selection criteria of the study.

*Risk of bias*
Inception cohort, follow-up (fixed period in years for all patients with length), completeness of follow-up, median/mean duration of follow-up and range, total patient-years.

*Patient characteristics*
Age (mean/median and range), number of children (up to and incl. 17), number of female patients, number of patients with a family history, number of patients with a genetic mutation.

*CCM characteristics*
Number of patients with multiple CCMs, mean/median size in mm and range, number of CCMs associated with a developmental venous anomaly (radiologically confirmed diagnosis), location (lobar supratentorial, basal ganglia and thalamus, brainstem, cerebellar hemisphere, extra-cerebral & intracranial, extra-cerebral & extra-cranial)

*Presenting symptoms*
Symptomatic hemorrhage, asymptomatic (incidental finding).

*Type of intervention*
Neurosurgery, radiosurgery with dose (margin and maximum dose with range), number of patients who are treated surgically before receiving radiosurgery.

*Cohort outcomes*
Whether outcome assessment was done by an independent observer and blinded to treatment. We will quantify the occurrence of our composite outcome (death, non-fatal ICH, and non-fatal new or worse non-hemorrhagic persistent FND after CCM treatment, if they were attributed to the CCM or its treatment) in specific time intervals after treatment (<30 days, 30 days – 1 year, >1 year, or during the entire period of follow-up specified).

**Data analysis:**
We will separate our analyses of cohorts according to whether they reported the effects of neurosurgical excision or SRS. We will quantify the occurrence of outcomes during total person-years of follow-up. If total person-years was not described, we will calculate the person-years by multiplying the median or mean follow-up period by the total number of treated patients. We will calculate outcome event incidence rates and 95% confidence intervals (CIs) per 100 person-years. We will pre-specify the following characteristics of the included cohorts as the baseline covariates of interest: study mid-year, average age of the patients at the time of treatment, proportion of female patients, proportion of patients with a brainstem CCM, proportion of patients with a prior symptomatic ICH from their CCM, and the proportion of children. We will restrict our analyses to covariates that were reported in at least five cohorts (arbitrary cutoff). Differences in proportions of these characteristics between studies describing neurosurgical excision and those describing SRS will be assessed with Mann Whitney U tests with a p-value <0.05 indicating significant differences. We will perform Poisson meta-regression analyses of cohort characteristics on the incidence of the composite outcome. For the assessment of the overall incidence rate, we will use the intercept of a Poisson model without covariates. We will assess the relationship of cohort characteristics to each outcome by calculating adjusted rate ratios (RRs) with corresponding 95% CIs, adjusting for four pre-specified cohort characteristics because of their known, or likely, influence on our chosen outcome events: age, sex, proportion of brainstem CCM, and proportion of patients who had presented with hemorrhage. We will express adjusted RRs per 1% increase in the proportion of patients with a cohort characteristic or per 1-year increase in age or midyear.

Assessment of heterogeneity and sensitivity analysis
Heterogeneity across all the cohorts will be assessed by $i^2$ statistic. The latter could reflect the magnitude of between-study variation attributed to heterogeneity, which is preferred with an increased number of included studies.
We will also perform sensitivity analysis to assess the robustness of results restricted to high-quality studies (defined as being an inception cohort, having a prospective design, or using independent outcome assessment blind to treatment).