1. Introduction

1.1 Intracranial vascular malformations (IVMs) are responsible for over one third of spontaneous (non-traumatic) intracerebral haemorrhage (ICH) in young adults, making them the leading cause in this age group.[1] IVMs also carry a risk of recurrent intracranial haemorrhage, epilepsy and chronic disability in young adults.

1.2 Despite their importance, there is uncertainty about the natural history of IVMs, and the prognosis they carry for specific individuals because the vast majority of studies have been hospital-based, retrospective survival cohorts with short, inconsistent follow-up and no actuarial analysis. However, a few generalisations can be made. The crude annual risk for the *first occurrence* of a haemorrhage from an unruptured brain arteriovenous malformation (AVM) is approximately 1%, whilst the risk of haemorrhage *recurrence* may be as high as 34% in the first year, with uncertainty about the risk thereafter.[2] The crude annual risk for the occurrence of haemorrhage from cavernous malformations (CMs) is 0.7%, although the risk of haemorrhage recurrence may be as high as 4.5%.[3]

1.3 Furthermore, the evidence supporting existing interventions for IVMs is composed of case series usually without a control group, let alone a randomised controlled design,[4] which makes treatment decisions extremely difficult.

1.4 Therefore, the **priorities for the evaluation of health services** in everyday clinical practice are: to ensure equity of access to treatment, to monitor patterns of intervention, to monitor the clinical effectiveness of these interventions, to assess the health economics of treatment use, and to strive for quality improvement in clinical services in Scotland.

1.5 Furthermore, the **priorities for research** are: to better understand IVM prognosis and how best to measure outcome, to perform the groundwork to inform the feasibility and design of randomised controlled trials of treatments, to investigate various questions about brain imaging (what constitutes haemorrhage from CMs, how can the observer variation in the assessment of AVMs be improved), and to investigate the genetic influences on the occurrence and behaviour of both familial and sporadic AVMs and CMs.

1.6 In order to address the priorities in 1.4 and 1.5, a multidisciplinary collaborative steering committee, representative of the four neuroscience centres in Scotland, established a nationwide, prospective, population-based disease register of IVMs in 1999: the Scottish Intracranial Vascular Malformation Study (SIVMS).[5] The recruitment of adults from 1999 to 2003 inclusive, and their ongoing follow-up, has enabled us to describe IVM incidence,[6] and our assessments of early prognosis, and audit of patterns of intervention at the four neuroscience centres, will be published imminently. In order to have enough power to assess the principal predictors of medium-term outcome, SIVMS must resume recruitment from 2006-2010 inclusive, and continue follow-up until at least 2020.

2. Objectives

2.1 Continue recruitment & follow-up in the Scottish Intracranial Vascular Malformation Study disease register.

2.2 Continue existing objectives:

- **Audit:** monitor the 'patient pathway' of every adult newly-diagnosed with an IVM in Scotland, observe the patterns and outcome of treatment using annual GP follow-up assessments and case note review, quantify economic burden.
- **Research:** study the utilities of various health-related outcome measures and develop IVM prognostic models

2.3 Start new research objectives for 2006-2010: explore the genetic influences on the occurrence and outcome of IVMs, using DNA from consenting participants in the 1999-2003 SIVMS cohort, and new participants identified 2006-.

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[1] Ruíz-Sandoval JL, Cantú C, Barinagarrementeria F. Intracerebral hemorrhage in young people: analysis of risk factors, location, causes, and prognosis. *Stroke* 1999;**30**:537-41

[2] Al-Shahi R, Warlow C. A systematic review of the frequency & prognosis of arteriovenous malformations of the brain in adults. *Brain* 2001;**124**:1900-26

[3] Moran NF *et al.* Supratentorial cavernous haemangiomas and epilepsy: a review of the literature and case series. *JNNP* 1999;**66**:561-68

[4] Al-Shahi R, Warlow CP. Interventions for treating brain arteriovenous malformations in adults. *Cochrane Database of Systematic Reviews*, Issue 1, 2006.

[5] Al-Shahi R, Bhattacharya JJ, Currie DG, Papanastassiou V, Ritchie V, Roberts RC *et al.* Scottish Intracranial Vascular Malformation Study (SIVMS): Evaluation of Methods, ICD-10 Coding, and Potential Sources of Bias in a Prospective, Population-Based Cohort. *Stroke* 2003;**34**:1156-62

[6] Al-Shahi R, Bhattacharya JJ, Currie DG, Papanastassiou V, Ritchie V, Roberts RC *et al.* Prospective, Population-Based Detection of Intracranial Vascular Malformations in Adults: The Scottish Intracranial Vascular Malformation Study (SIVMS). *Stroke* 2003;**34**:1163-9

3. Inclusion criteria

Disease register core: audit project

3.1 Diagnosis of any of the principal sub-types of IVM:
- Brain arteriovenous malformation (AVM)
- Dural arteriovenous fistula (AVF), including carotid-cavernous fistulae
- Cavernous malformation (CM), with or without a venous malformation

3.2 Age 16 years or over at the time of diagnosis

3.3 Permanently resident in Scotland at the time of diagnosis

3.4 Date of diagnosis (by imaging or histology)
- 1st January 1999 – 31st December 2003
- 1st January 2006 – 31st December 2010

3.5 For the purposes of SIVMS, a participant is defined an 'incident case' at the time a diagnostic image (computed tomography (CT), magnetic resonance (MR), or catheter angiogram) or diagnostic pathological examination (biopsy or autopsy) is performed. If there was a clinical suspicion of an IVM prior to this time, or symptoms antedated diagnosis by many years, the time of the diagnostic image or histology is still the time at which someone is 'incident' for this disease register. Certainty of diagnosis is established by our register's consultant neuroradiologist(s) who review the diagnostic imaging, thereby creating 'definite' / 'probable' / 'possible' subsets of included participants.

3.6 Participant does not opt out of the *audit* data collection

Disease register add-on projects: research studies

3.7 Participant *opt-in* consent required

4. Exclusion criteria

4.1 Incorrect diagnosis of an IVM *

4.2 Certain other types of vascular malformation:
- Venous malformation (developmental venous anomaly)
- Vein of Galen malformation
- Capillary malformation/telangiectasis
- Spinal vascular malformation

4.3 The participant opts out of the audit data collection.

* If any participant is found to have received an incorrect diagnosis of an IVM after review of their CT/MR/angiogram by the register's neuroradiologists, they will be excluded. However, less than 'definite' certainty, as above, does not necessarily exclude a participant, because their management may proceed with this working diagnosis and further investigation may not be undertaken.

5. Design

Disease register core: audit project

5.1 A longitudinal, concurrent cohort of newly-diagnosed ('incident') participants has been recruited from 1st January 1999 – 31st December 2003, using multiple overlapping sources of case ascertainment, and the same methods are used for the 2006-2010 cohort (see flowchart).

5.2 **Primary sources of case ascertainment are:**
- neuroradiologists at the four Scottish Neuroscience centres

- radiologists working at other departments in Scotland with CT and/or MR scanners
- all neurologists, neurosurgeons, stroke physicians and neuropathologists in Scotland

5.3 Collaborators let us know important identifying and diagnostic data about each participant using a standardised 'notification form' which they may post or fax to us. From 2006 onwards they can submit these data via a secure online form on the SIVMS website which uses Secure Sockets Layer (SSL) 128-bit encryption. 128-bit SSL is the strongest encryption supported by the current popular browsers, giving the highest level of protection for confidential transactions over the internet. This form can only be accessed by collaborators, who receive a unique URL (incorporating their identity) in emails sent to them to remind them about recruitment to the register.

5.4 **Secondary sources of case ascertainment:**
With the approval that we obtained from the Privacy Advisory committee on 3rd August 2007, the Information and Statistics Division will run an electronic search of hospital discharge (SMR01) and death certificate data on a six-monthly basis, seeking adults meeting our inclusion criteria (we have evaluated the accuracy of the limited ICD-9 and ICD-10 codes available for IVMs, and found the only worthwhile codes to use are those for brain AVMs[7])

5.5 A mailshot to all ~3,700 general practitioners (GP) in Scotland in 1999 only yielded 1 case unknown to SIVMS, so this labour-intensive method of recruitment has been abandoned.

Disease register add-on projects: research studies

5.6 **Health-related quality of life:** Participants who give their consent to receive annual questionnaires are sent a postal version of the Oxford Handicap Scale, Barthel Index, Short Form 36, and Hospital Anxiety and Depression Scale on every anniversary of their diagnosis until they die or opt out. The aim is to explore the clinimetric properties of these scales (especially their reliability and validity) in order to either discover the best generic scale for measuring IVM outcome, or develop a disease-specific scale.

5.7 **Genetic influences:** By recruiting 200 cases with brain AVMs from SIVMS, and 200 controls from the Scottish population, we will investigate the possible association of polymorphisms in the endoglin and ALK-1 genes with the presence of a brain AVM, and investigate whether genotype influences brain AVM presentation and prognosis. By sequencing the endoglin and ALK1 gene in 50 patients we will investigate whether a proportion of brain AVM patients have rare deleterious mutations in these genes.

6. Recruitment

Disease register core: audit project

6.1 Four weeks after an adult's notification to SIVMS, we approach their GP *and* hospital consultant by post to check the adult's demographic details and diagnosis. If these data are correct, confirming the adult's inclusion as a participant in the audit component of SIVMS, we copy their diagnostic CT scans, MR imaging, and catheter angiograms. At this stage, we also ask the GP and hospital consultant if the participant is still alive and aware of their diagnosis. We ask hospital consultants to inform patients of their diagnosis, if they have not been informed already, and to inform the patient of the passage of their details to this nationwide audit project.

6.2 We do not approach participants for opt-in consent to the audit, because it is not required for clinical audit by the Confidentiality and Security Advisory Group for Scotland (CSAGS).[8] The CSAGS report considered categories where implied (opt out) consent would be acceptable, and these include some of the core objectives of SIVMS, "planning, managing, funding and auditing, where identifiable data cannot be anonymised" and, "Multiple uses (if cannot be anonymised) e.g. disease registries, epidemiology, national data banks." Our collaborators take responsibility for informing their patients about passing their data on to the disease register. Health Rights Information Scotland (HRIS) is responsible for informing patients in NHS Scotland about the uses of their data for audit.

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[7] Al-Shahi R, Bhattacharya JJ, Currie DG, Papanastassiou V, Ritchie V, Roberts RC *et al.* Scottish Intracranial Vascular Malformation Study (SIVMS): Evaluation of Methods, ICD-10 Coding, and Potential Sources of Bias in a Prospective, Population-Based Cohort. *Stroke* 2003;**34**:1156-62

[8] Confidentiality and Security Advisory Group for Scotland (CSAGS). Protecting patient confidentiality. Scottish Executive Health Department, 2002.

6.3 If a participant opts out of the clinical audit, SIVMS honours that request, and they are excluded from the disease register (see 4.3 above).

Disease register add-on projects: research studies

6.4 Four weeks after an adult's notification to SIVMS, we ask the GP and hospital consultant to make an assessment of whether a living participant is suitable to be contacted with a postal consent pack, so that participants are given the opportunity to opt-in to the add-on research studies. When the consultant and GP deem a participant suitable for postal contact, we send a postal consent pack to the participant via their GP. We ask for the nomination of a welfare guardian / legal representative / nearest relative in the case of adults with mental incapacity, and use different consent forms and information leaflets in cases of mental incapacity. If the GP and consultant express contradictory opinions about a participant's awareness or suitability to be contacted, the SIVMS team tries to resolve the differences of opinion by post/telephone.

6.5 During the annual follow-up process, the GP becomes our principal point of contact about the participant because participants are usually followed-up for short periods, if at all, by their hospital consultant. In an effort to offer as many participants as possible the opportunity to opt-in to the research elements of SIVMS, we ask the GP if a participant (who was initially inappropriate for postal contact) could now be approached with a consent pack during the annual follow-up procedure.

6.6 We send a consent form, participant information leaflet and explanatory letter (written as if from the GP to the participant) to the GP for signature and forwarding to the participant. These materials have been reviewed by research ethics committees (RECs), and by staff at Scottish Practices and Professionals Involved in Research (SPPIRe), who are funded by the CSO under the auspices of the Scottish School of Primary Care.

6.7 The consent form asks the participant to opt-in to either or both of the following:
- completion of an annual, postal questionnaire (see 7.3 below)
- provision of a blood sample for DNA extraction, using postal phlebotomy pack mailed to the participant

7. Evaluations

7.1 **Audit and research:** We extract data on presenting features, co-morbidity and early clinical course from the GP and hospital case notes. We ask for stickers to be put on these case notes, so that they are not destroyed and GPs/consultants are reminded to send SIVMS copies of relevant correspondence about the participant during follow-up.

7.2 **Audit:** We send each participant's GP a questionnaire a few weeks before the anniversary of the participant's diagnosis to check the participant's demographic details and check they are still alive, to obtain information about any hospital admissions/investigations/appointments, and to obtain important outcome data (brain haemorrhage, epilepsy and the GP's rating of the participant's level of dependence on the Oxford Handicap Scale). We also follow-up every participant via their GP and hospital case notes on an annual basis. These outcome data underpin SIVMS as a high-quality clinical audit: survival and morbidity are two of the most meaningful outcomes for neurological disorders and their treatment, and morbidity is impossible to extract from the Scottish Morbidity Record (SMR01) which only codes the diagnoses listed on a discharge summary and does not rate dependence/disability.

7.3 **Research:** Once a participant's GP has responded to the annual follow-up questionnaire, indicating the participant's current status, SIVMS does one of 3 things:
- if we have never approached the participant for their opt-in consent for the add-on research studies, and the GP now deems this to be appropriate, we send a postal consent pack (6.6 above).
- if we have never approached the participant for their opt-in consent for the add-on research studies, and the GP still deems this to be inappropriate, the participant remains in the clinical audit and we re-visit their suitability for inclusion in add-on research studies at the time of the next GP annual follow-up questionnaire.
- if the participant has already consented to receive an annual questionnaire, and the GP confirms that they are still appropriate to receive one, we send the participant a questionnaire amalgamating the Oxford Handicap Scale, Barthel Index, Short Form-36 Health Status Questionnaire and the Hospital Anxiety and Depression Scale, with additional disease-specific questions.

Outcome measures for both clinical audit and research

7.4 The primary outcomes in SIVMS are dependence/disability/death rated by the general practitioner on the Oxford Handicap Scale, IVM-related death (case fatality), occurrence and/or recurrence of intracranial haemorrhage, seizure(s) after presentation, and time to being 1 or 2 years seizure-free (for those patients with a history of seizure(s)).

7.5 The secondary outcomes in SIVMS are participant-rated dependence/disability (Oxford Handicap Scale, Barthel Index), health-related quality of life (Short Form-36 questionnaire), anxiety and depression (Hospital Anxiety and Depression scale).

8. Data management and analysis

8.1 The SIVMS imaging library 1999-2003 comprises hard copies of all included participants' diagnostic angiograms, CT scans and MR imaging. It is either kept in Dr Jo Bhattacharya's office at the Institute of Neurological Sciences, Glasgow, or in secure storage in the Department of Clinical Neurosciences, Edinburgh.

8.2 The SIVMS imaging library 2006-2010 will be in digital format only, password-protected, and kept in duplicate on secure servers both in the Institute of Neurological Sciences in Glasgow and in the Department of Clinical Neurosciences in Edinburgh.

8.3 All clinical and radiological data are compiled in a password-protected, customised Microsoft Access database, kept on a secure server in the Department of Clinical Neurosciences in Edinburgh. An anonymised extract of the radiological data is kept in a password-protected database in Dr Bhattacharya's office in the Institute of Neurological Sciences in Glasgow. Identifiable data are not shared with any external agency, but they are required for communication with medical records departments at hospitals where participants have been seen and with participants' GPs, in order to collect essential outcome data for the clinical audit. We use anonymised data extracts for all research data analyses.

9. Ethics

9.1 Ethical approval was obtained from the MREC for Scotland (MREC/98/0/48). We are seeking extension of this approval for the add-on research studies until the end of 2010.

9.2 SIVMS is covered by the University of Edinburgh registration (C0627022) with the Data Protection Registrar under the Data Protection Act 1998.

9.3 From 2002-2004 a genetics sub-study was conducted, involving selected SIVMS participants who provided their written consent. The study involved the collection of family history data by postal questionnaire and a blood sample for DNA extraction by post. This study was approved by MREC (MREC/02/10/20). SIVMS' future DNA blood sample collection 2006-2010 is simply a continuation of part of the previous proposal, but postal family history questionnaires will no longer be sent. Extension of MREC/02/10/20 approval until 2010 is being sought.

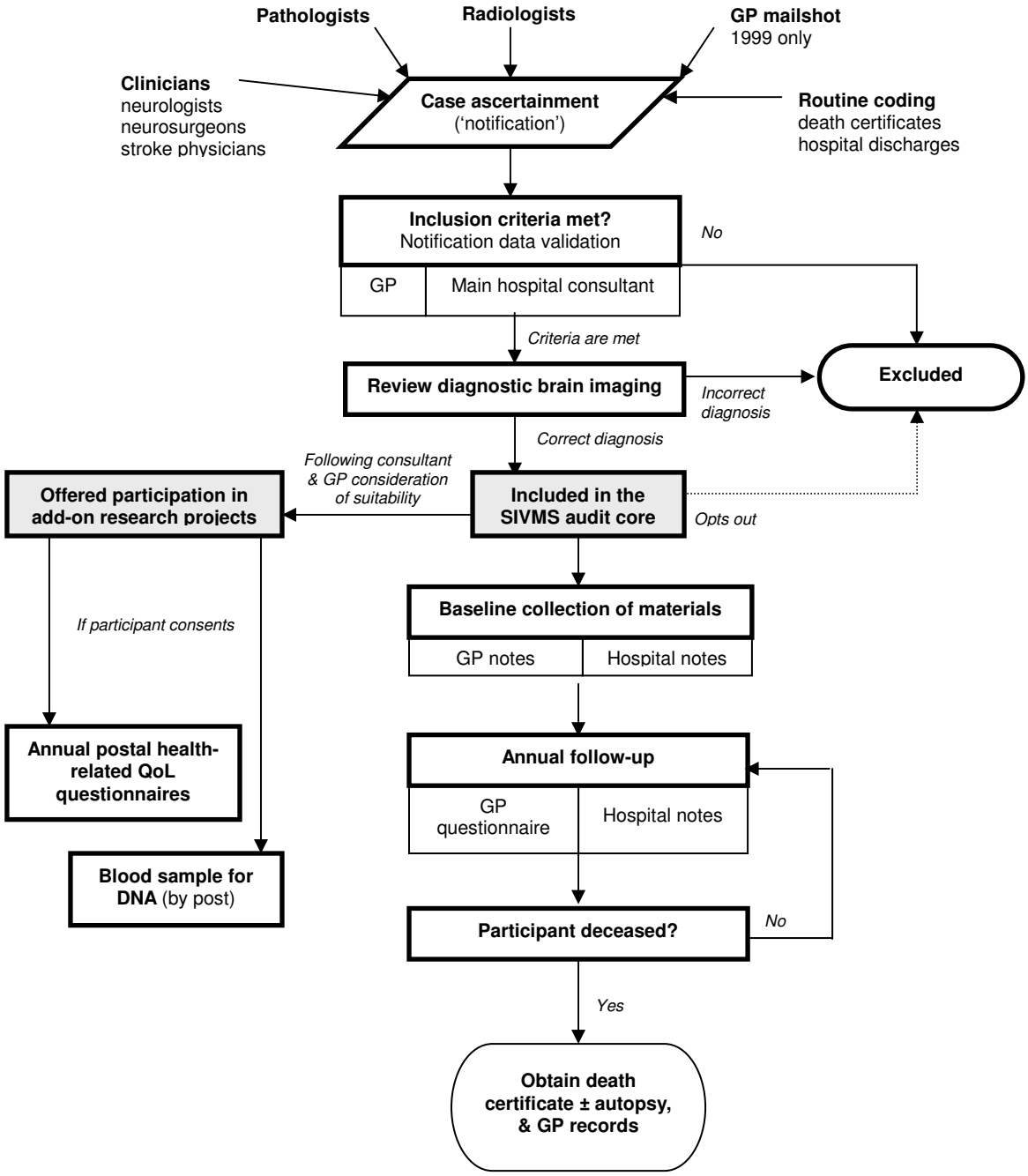
10. Withdrawal from the disease register

10.1 Participants may withdraw at any stage from the opt-out clinical audit or opt-in add-on research studies by contacting the SIVMS team at the Edinburgh Department of Clinical Neurosciences, as specified on the participant information sheet.

11. Funding

11.1 SIVMS is funded by a Clinician Scientist Fellowship (G108/613) from the Medical Research Council (MRC) from 2006 to 2010.

11.2 In the past, SIVMS was funded by a Clinical Training Fellowship from the MRC (G84/5176), Project Grants from the Chief Scientist Office of the Scottish Executive Health Department (K/MRS/50/C2704 and CZB/4/35), and a Project Grant from the UK Stroke Association (TSA04/01).


Pathologists
Radiologists
GP mailshot
1999 only
Clinicians
neurologists
neurosurgeons
stroke physicians
Case ascertainment
('notification')
Routine coding
death certificates
hospital discharges
Inclusion criteria met?
Notification data validation
No
GP
Main hospital consultant
Criteria are met
Review diagnostic brain imaging
Incorrect diagnosis
Excluded
Correct diagnosis
Following consultant & GP consideration of suitability
Offered participation in add-on research projects
Included in the SIVMS audit core
Opts out
If participant consents
Baseline collection of materials
GP notes
Hospital notes
Annual postal health-related QoL questionnaires
Annual follow-up
GP questionnaire
Hospital notes
Blood sample for DNA (by post)
Participant deceased?
No
Yes
Obtain death certificate ± autopsy, & GP records