

**What is already known on this topic**

Ethics committees are seeking to tighten the rules governing recruitment of patients to research studies, with an opt-in method increasingly required

Opting in is associated with poor response rates and selection bias in medical record linkage studies

How an opt-in method for patient contact affects response rates and the characteristics of the recruited study population is not known

**What this study adds**

Patients contacted with an opt-in method had a greater than 10% lower response rate than patients contacted with an opt-out method

Patients recruited with the opt-in method were healthier and less relevant to the study than patients recruited with the opt-out method

The opt-out approach should be the default recruitment strategy for studies that pose a low risk to patients

infringement of personal autonomy if the patient is informed, every effort is made not to pressurise patients during the phone conversation, and refusal is accepted without question. Currently, the two recruitment approaches rest on opposing assumptions: that non-response is an indication of refusal (opt-in) or an indication of willingness (opt-out) to participate. The consequences for the validity and potential societal benefits of future research are potentially large: a 10% lower response, for example, might have serious scientific and financial implications. Given our findings, we believe that the opt-out approach to study recruitment should be the default strategy for studies that pose a low risk to patients.

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## Bias from requiring explicit consent from all participants in observational research: prospective, population based study

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### Abstract

**Objective** To evaluate the differences between adults who consent to participate in observational research, and those who do not.

**Design** Prospective, population based cohort study.

**Setting** Primary and secondary care throughout Scotland.

**Participants** 187 adults (aged ≥ 16 years) resident in Scotland at the time of their first diagnosis of a brain arteriovenous malformation in 1999-2002.

**Intervention** Postal consent form sent via participants' general practitioner.

**Main outcome measures** Differences between consenters and non-consenters in demographic and clinical features at first presentation, and outcome during follow-up.

**Results** 111 adults (59%) consented to participate in the study. These consenters were not significantly different from non-consenters in age, sex, or socioeconomic status at first presentation. However, consenters were significantly more likely than non-consenters to present alive and independent, and with a seizure. During follow-up, consenters were significantly more likely to receive interventional treatment. Although consenters' survival was significantly better, they were more likely to have a seizure during follow-up. Presentation with intracranial haemorrhage conferred a higher risk of

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subsequent haemorrhage when the whole cohort was analysed, but not when it was restricted to consenters.

**Conclusions** We have found differences between adults who consent to participate in observational records-based research and those who do not, or cannot, consent. Blanket requirements for explicit consent for the use of individuals' identifiable data can bias disease registers, epidemiological studies, and health services research.

## Introduction

To use identifiable data in observational research, UK researchers are now under pressure to obtain informed consent from each and every individual. Because of the inconsistencies in data protection law and confidentiality guidance in the UK,<sup>1</sup> a blanket requirement for consent has become the "default position" for most regulatory bodies and doctors in primary and secondary care.

Similar epidemiological research in Minnesota was threatened by national privacy standards that were part of the 1996 Health Insurance Portability and Accountability Act.<sup>2</sup> However, a supplementary privacy rule sanctioned the disclosure of information without patients' consent for public health use and medical records research.<sup>3</sup> In the UK statutory regulations and professional guidance continue to contradict each other.<sup>1</sup> The UK Data Protection Act 1998 does not apply to the dead and makes exemptions for some forms of medical research. The General Medical Council states that doctors should "seek patients' express consent to disclosure of information, where identifiable data [are] needed for any purpose other than the provision of care or for clinical audit." The Health and Social Care Act 2001 has established a bureaucratic framework for approving the use of identifiable data without patients' explicit consent, but it applies only to England and Wales—not Scotland—and is intended to be a temporary measure until such time as health data are anonymised. The legislation in the two acts is supplemented by doctors' duty of confidentiality to their patients under common law.

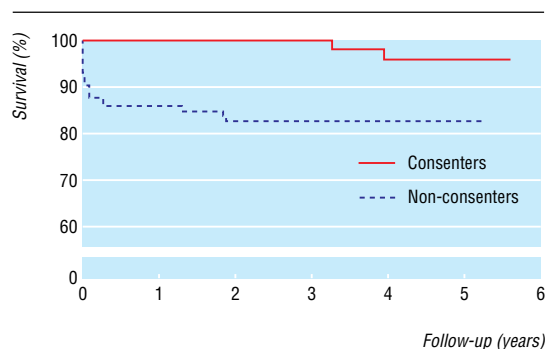
Excluding patients because of their lack of consent is likely to bias observational research. This phenomenon has been variously termed response, refusal, participation, or authorisation bias when applied to surveys and medical records research.<sup>4</sup> Since lack of consent is the root cause, we call it consent bias.

We have had a unique opportunity to examine the direction and size of consent bias in a prospective, population based study in which we could not obtain consent from every participant, yet we had research ethics committee approval to collect baseline and follow-up data on the whole cohort.

## Methods

### Scottish intracranial vascular malformation study (SIVMS)

This study comprises a cohort of adults resident in Scotland whose intracranial vascular malformation was first diagnosed on or after 1 January 1999.<sup>5</sup> After each patient is notified to the study team, the team asks the patient's general practitioner and hospital consultant whether it is appropriate to approach the patient



Kaplan-Meier survival curve for death from all causes among 187 adults with brain arteriovenous malformations by their consent to participate in an observational study (consenters 2 deaths, non-consenters 12 deaths; log rank=15.8,  $P=0.0001$ )

with a postal consent pack. If they deem this inappropriate they are asked for a reason. Differences of opinion are resolved by correspondence. The team prepares the consent pack and sends it to each patient via his or her general practitioner. The consent form requests permission to examine the patient's medical records and to send an annual postal questionnaire (incorporating the modified Rankin scale, short form 36, hospital anxiety and depression scale, and the Barthel index questionnaires); each patient can consent to either, both, or neither of these options. If there is no response to the first consent pack, a postal reminder is sent after three and six weeks.

### Ethical approval for the study

The Multicentre Research Ethics Committee for Scotland approved these recruitment methods. The committee also accepted that every patient in the cohort could be followed up prospectively each year until they died by means of just annual questionnaires to their general practitioners and medical record surveillance rather than direct contact with the patients, unless patients explicitly refused disclosure of such information. The committee approved these methods in view of the public interest of avoiding consent bias.

### Analysis of consent bias

This study includes all adults in Scotland in whom the commonest subtype of intracranial vascular malformation, a brain arteriovenous malformation, was first diagnosed in 1999-2002. We reviewed the consensus reached by each patient's general practitioner and hospital consultant about whether the patient could receive a consent pack, and the patient's decision if sent a consent pack within a year of the patient's notification to the study. We examined differences between patients who consented ("consenters") and those who did not ("non-consenters") in their demographic variables at recruitment and their outcome over a median follow-up of 3.3 years (range 0-5.8 years).

### Statistical methods

At the patients' first presentation we examined age, sex, side of brain affected, socioeconomic status, mode of presentation, and dependence (assessed with the modified Rankin scale). The variables examined during follow-up were receipt of interventional treatment, survival, and morbidity (modified Rankin scale at one

Characteristics of 187 adult patients with brain arteriovenous malformations by their consent to participate in an observational study (values are numbers (percentages, with 95% confidence intervals) of patients unless stated otherwise)

Characteristic	All patients (n=187)	Consenters (n=111)	Non-consenters (n=76)	P value (consenters v non-consenters)*
<b>At presentation</b>				
Mean (SD) age (years)	45 (16)	44 (14)	47 (18)	0.18
Women	85 (46, 40 to 52)	49 (44, 37 to 52)	36 (47, 38 to 57)	0.66
Location of brain AVM:				
Left	92 (49, 43 to 55)	57 (51, 44 to 59)	35 (46, 37 to 56)	0.58
Midline	7 (4, 2 to 7)	5 (5, 2 to 9)	2 (3, 1 to 8)	
Right	88 (47, 41 to 53)	49 (44, 37 to 52)	39 (51, 42 to 61)	
Deprivation category:				
1 (most affluent)	4 (2, 1 to 5)	2 (2, 1 to 5)	2 (3, 1 to 8)	0.94
2	25 (13, 10 to 18)	16 (14, 10 to 21)	9 (12, 7 to 19)	
3	44 (24, 19 to 29)	29 (26, 20 to 34)	15 (20, 13 to 28)	
4	54 (29, 24 to 35)	27 (24, 18 to 32)	27 (36, 27 to 45)	
5	29 (16, 12 to 20)	15 (14, 9 to 20)	14 (18, 12 to 27)	
6	24 (13, 9 to 17)	18 (16, 11 to 23)	6 (8, 4 to 15)	
7 (most deprived)	7 (3, 2 to 7)	4 (4, 2 to 8)	3 (3, 2 to 9)	
Mode of presentation:				
Haemorrhage	91 (49, 43 to 55)	46 (41, 34 to 49)	45 (59, 50 to 68)	0.009
Epilepsy	49 (26, 21 to 32)	37 (33, 26 to 41)	12 (16, 10 to 24)	
Focal neurological deficit	8 (4, 2 to 7)	7 (6, 3 to 11)	1 (1, 0 to 6)	
Incidental	39 (21, 16 to 26)	21 (20, 14 to 26)	18 (24, 17 to 33)	
Modified Rankin scale $\geq 3$	78 (42, 36 to 48)	34 (31, 24 to 38)	44 (58, 48 to 67)	0.0002
<b>During follow-up</b>				
Received interventional treatment	126 (67, 62 to 73)	84 (76, 68 to 82)	42 (55, 46 to 64)	0.003
Modified Rankin scale $\geq 3$ at one year	42 (23, 18 to 28)	13 (12, 8 to 18)	29 (38, 30 to 48)	0.00001
Modified Rankin scale 3-5 at one year†	26 (16, 12 to 21)	13 (12, 8 to 18)	13 (23, 15 to 34)	0.05

AVM=arteriovenous malformation. \*See methods section for details of statistical tests used. †Denominator is the number alive at one year (111 consenters and 56 non-consenters).

year, time to first intracranial haemorrhage, and time to first epileptic seizure for all patients; and, for patients with epilepsy, time to being free of seizures for one or two years). See [bmj.com](http://bmj.com) for statistical tests used.

## Results

In 1999-2002, 187 adults had a brain arteriovenous malformation diagnosed. Within the first year of their notification to the study, the study team was discouraged from approaching 56 (30%) of these patients for consent by their general practitioner or consultant (see [bmj.com](http://bmj.com)). Twenty adults (11% of the whole cohort, 15% of those approached) did not respond to the postal invitation to consent. None explicitly withheld consent to the team examining his or her medical records. The remaining 111 adults (59%) in the cohort gave their explicit informed consent.

### Comparison of consenters and non-consenters

At the time their brain arteriovenous malformations were diagnosed, consenters were similar sociodemographically to non-consenters (table). However, consenters were significantly less likely to present with haemorrhage and more likely to present with seizure(s). Furthermore, consenters were significantly less likely to be dead or dependent (modified Rankin scale  $\geq 3$ ) at presentation.

At one year follow-up, consenters were significantly less likely to be dead or dependent than non-consenters (table). This difference was largely attributable to our inability to obtain consent from adults who died soon after presentation (figure). The difference in disability (modified Rankin scale 3-5) between surviving consenters and non-consenters approached statistical significance (table).

During the entire follow-up period, consenters and non-consenters showed no significant difference in the probability of intracranial haemorrhage (log rank = 0.97,  $P = 0.33$ ). Consenters had a significantly shorter time to first epileptic seizure after their initial presentation than non-consenters (see [bmj.com](http://bmj.com)). There was no significant difference between the 37 consenters and 12 non-consenters who had presented with seizure(s) in their time to becoming seizure-free for one year (31/37 v 11/12,  $P = 0.43$ ) or two years (21/37 v 7/12,  $P = 0.56$ ). Consenters were more likely to receive interventional treatment for their brain arteriovenous malformation after presentation (table).

### Effects of consent on results

The differences between consenters and non-consenters affected the overall results. After excluding the non-consenters, we found the consenters differed significantly from the whole cohort in the proportion dead or dependent at presentation and at one year (even after limiting the analysis to just those who were alive at presentation) and in their receipt of interventional treatment during follow-up (table).

However, the important clinical finding of an association between mode of initial presentation and risk of intracranial haemorrhage during follow-up differed, depending on whether non-consenters were excluded from the analysis. Initial presentation with intracranial haemorrhage conferred a significantly higher risk of subsequent haemorrhage than other modes of presentation when the whole cohort was analysed (two bleeds among 95 adults who had not bled at presentation, eight bleeds among 92 adults who had bled at presentation; log rank = 8.4,  $P = 0.004$ ), but this association disappeared when the analysis was restricted to consenters (one bleed among 59 adults who had not

bled at presentation, two bleeds among 52 adults who had bled at presentation; log rank = 1.3, P = 0.26).

## Discussion

In an observational disease register that obtained explicit consent from almost two thirds of its cohort, we found that adults who consented were significantly different from those who did not in both anticipated and unpredictable ways. This kind of consent bias probably invalidates the findings of many observational studies, as it would have our own if non-consenters had been excluded.

Consenters were significantly less likely to have intracranial haemorrhage or to be dead or dependent at presentation, reflecting the difficulty in gaining consent from brain damaged patients (and, of course, from those who had died before the study team knew about them). During follow-up, consenters were significantly more likely to receive interventional treatment, less likely to die, and more likely to have an epileptic seizure. These differences affected the overall result of the study if non-consenters were excluded from the final analysis.

We tested one clinically important prognostic variable, presentation of a brain arteriovenous malformation with intracranial haemorrhage, and found that it was vulnerable to consent bias. Our results show how the modern era of data privacy could seriously prejudice the findings of observational research.

### Comparison with other studies

Existing literature on consent bias has primarily focused on large health surveys that involve data collection either by post or by interview in person. These studies have generally found consenters or responders to be more likely to be young, male, healthier, non-smokers, better educated, and of higher socioeconomic status.

In medical records research in Minnesota, adults were less likely to permit researchers to study their medical records if they were women, younger than 60, living close to the Mayo Clinic, and had a sensitive diagnosis (such as mood disorder).<sup>6</sup> In observational research involving interview and medical record review in Canada, the researchers managed to obtain consent from only 39% of patients, and 51% when trained nurses sought consent: they also found that inpatient mortality was much lower for the patients who gave written informed consent than for those who did not.<sup>4</sup>

Although consent bias is likely to be affected by the nature of the research and the disease group being studied, it does not seem to be wholly predictable, in either direction or size.

### Conclusions and recommendations

Individuals who do not respond to invitations for consent pose a dilemma. If explicit consent is desired, non-responders might be deemed implicit non-consenters. Sometimes consent is implied in environments where public information about data privacy is displayed, and explicit refusals are acted on, in which case non-responders are regarded as implicit consenters. Furthermore, individuals who are deemed unsuitable by their doctors to be approached for consent are necessarily regarded as proxy non-consenters. This may be paternalistic.

## What is already known on this subject

Informed consent is desirable for the use of medical data from which patients can be identified in observational research

Many regulations demand that patients who do not or cannot consent are excluded

Participants in health surveys tend to be more likely to be young, male, healthier, non-smokers, better educated, and of higher socioeconomic status

## What this study adds

In an observational disease register, adults who consented were both predictably and unpredictably different from those who did not consent

A blanket requirement for consent from every patient in observational research can bias studies' findings

Further research should be directed towards exploring consent bias in other disease groups and in other research designs to see if the bias is pervasive and remains unpredictable. If so, this would strengthen the argument for complete and representative data collection for observational and non-intrusive epidemiological research, as is currently the case for medical audit (which does not require consent).

Patients, the public, and professional organisations must consider the implications of blanket requirements for consent from each and every patient, before epidemiology and health services research are regarded as too biased to rely on.

At the time of this analysis, the Scottish Intracranial Vascular Malformation Study Steering Committee were Rustam Al-Shahi, Robin J Sellar, and Charles Warlow, Western General Hospital, Edinburgh; Jo J Bhattacharya and Vakis Papanastassiou, Southern General Hospital, Glasgow; Carl E Counsell, Aberdeen Royal Infirmary, Aberdeen; Julie M Hall, Newcastle General Hospital, Newcastle upon Tyne; Vaughn Ritchie, Fauldhouse Health Centre, Fauldhouse; Richard C Roberts, Ninewells Hospital and Medical School, Dundee.

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