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Primary care

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 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

Hitherto, the United Kingdom has nurtured extremely high quality disease registers, epidemiological studies, and health services research. These studies have been robust because they have avoided bias by being representative of the entire population or patient group. Often, identifiable data have been required for essential purposes such as record linkage using secondary data sources, identification of individuals during follow-up, and the avoidance of double counting. However, to use such 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,[1] a blanket requirement for consent has become the "default position" for most regulatory bodies and doctors in primary and secondary care.

Similar epidemiological research at the Mayo Clinic Foundation, Rochester MN, United States, was threatened by national privacy standards that were part of the 1996 Health Insurance Portability and Accountability Act.[2] In the US, however, a supplementary privacy rule sanctioned the disclosure of information without patients' consent for public health use and medical records research,[3] whereas in the UK statutory regulations and professional guidance continue to contradict each other.[1]

The UK Data Protection Act 1998 does not apply to the dead and makes exemptions for some forms of medical research, but the General Medical Council document *Confidentiality: Protecting and Providing Information* (2004, page 3) 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." Furthermore, 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 it 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. However, what remains untested in a court of law is the overall balance between the privacy interests of an individual and the public interest of unbiased research.

One would anticipate that consent might be impossible to obtain from those who are untraceable or deny their diagnosis, and particular groups of patients who are often of the greatest importance (such as those who have died, are cognitively impaired, or have a comorbid mood disorder). Excluding such 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,[4] but, since lack of consent is the root cause, we prefer to 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)

The Scottish intracranial vascular malformation study comprises a cohort of adults resident in Scotland whose intracranial vascular malformation was first diagnosed on or after 1 January 1999.[5] 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 with a postal consent pack. If they deem sending a consent pack to be inappropriate they are asked for a reason, and any differences of opinion are resolved by correspondence. The team prepares the consent pack, having checked the patient's address, but sends the pack to each patient via his or her general practitioner on behalf of the study team. 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 from a patient the team sends postal reminders via the general practitioner at three and six weeks after the initial approach.

Ethical approval for the study

The Multicentre Research Ethics Committee for Scotland approved these recruitment methods (MREC/98/0/48) on the basis of both the study team's initial application for ethical approval and subsequent clarification of the study's 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 (in which case no further data would be gathered). 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

The variables we examined at the patients' first presentation with a brain arteriovenous malformation were age, sex, side of brain affected, socioeconomic status (measured by deprivation category of their residential postcode sector according to the 2001 census, obtained from the MRC Social and Public Health Sciences Unit in Glasgow, www.msoc-mrc.gla.ac.uk), mode of presentation, and dependence (assessed with the modified Rankin scale). The variables examined during follow-up were receipt of interventional treatment for the brain arteriovenous malformation, survival (death from any cause), and morbidity (modified Rankin scale at one 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).
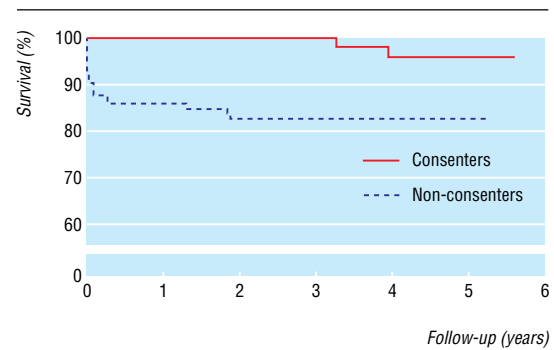
Fig 1 Kaplan-Meier survival curve for death from all causes among 187 adults with brain arteriovenous malformations by their consent to participate in an observational study (consenters 2 deaths, non-consenters 12 deaths; log rank=15.8, P=0.0001)

The statistical tests used were analysis of variance (for mean age), χ^2 test (for sex, modified Rankin scale ≥ 3 at presentation and ≥ 3 or 3-5 at one year, receipt of interventional treatment during follow-up), Fisher's exact test (for side of brain affected, mode of presentation), and χ^2 test for trend (for deprivation category).

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. The reasons given were anxiety about diagnosis (21 patients), dead at the time of trying to gain consent (15), and cognitive impairment (9); no reason was given for six patients and there was no reply to the questionnaire for five. 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 to non-consenters in their mean age, sex distribution, and socioeconomic status (table). However, the consenters differed significantly in the way they presented, being less likely to present with haemorrhage and more likely to present with seizure(s) than non-consenters. Furthermore, consenters were significantly less likely to be dead or dependent (modified Rankin scale ≥ 3) at presentation than non-consenters.

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 (fig 1). 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). However, consenters did have a significantly shorter time to first epileptic seizure after their initial presentation than non-consenters (fig 2). There was no significant difference between the 37 consenters and 12 non-consenters who had presented
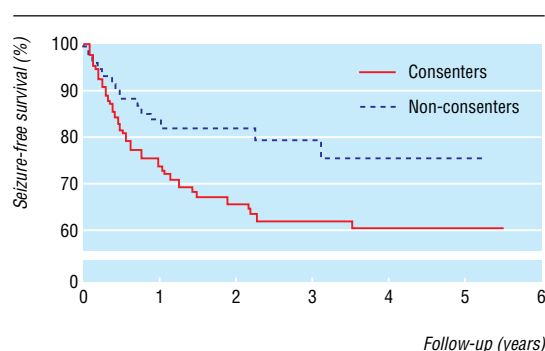
Fig 2 Kaplan-Meier analysis of time to first seizure among 187 adults with brain arteriovenous malformations by their consent to participate in an observational study (consenters 42 events, non-consenters 13 events; log rank=4.1, P=0.044)

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

These differences between consenters and non-consenters affected the overall results of the study. After excluding the non-consenters from our analyses, 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). Although consenters significantly differed from non-consenters in their mode of presentation and dependence at one year, the

whole cohort did not differ from the consenters alone in these analyses (table).

However, the important clinical finding of an association between mode of initial presentation and risk of intracranial haemorrhage during follow-up (before treatment) 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

Our main finding is that in an observational disease register that obtained explicit consent from almost two thirds of its cohort, 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.

We found that there were no significant differences in demographic variables between consenters and non-consenters, nor was there a greater proportion of non-consenters harbouring a brain arteriovenous malformation in the dominant (left) cerebral hemisphere. However, 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, con-

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)*
At presentation				
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 ≥3	78 (42, 36 to 48)	34 (31, 24 to 38)	44 (58, 48 to 67)	0.0002
During follow-up				
Received interventional treatment	126 (67, 62 to 73)	84 (76, 68 to 82)	42 (55, 46 to 64)	0.003
Modified Rankin scale ≥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).

senters 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 and found that it was vulnerable to consent bias. If the initial presenting feature of a brain arteriovenous malformation is intracranial haemorrhage, it is generally accepted that there is a higher subsequent risk of haemorrhage compared with other modes of presentation.[6] In clinical practice, this partly influences the decision to treat a brain arteriovenous malformation. In our study, we confirmed this association when the whole cohort was analysed, but the association disappeared when only consenters were analysed.

Our study has benefited from having a large, population based cohort with outcome data on both consenters and non-consenters. Because our disease register started when data privacy legislation and guidance were changing dramatically in the UK, a reappraisal of our methods by the Multicentre Research Ethics Committee for Scotland was necessary. Our clear demonstration of consent bias has been possible because the committee recognised the support for medical research given by section 33 of the Data Protection Act, the committee also endorsed our hypotheses about consent bias, and because Scotland is not subject to the Health and Social Care Act.

Our results show how the modern era of data privacy could seriously prejudice the findings of observational research. Although we studied a specific disease, brain arteriovenous malformation, it provides a good example of the difficulties of obtaining consent from a group of people with considerable physical and psychological morbidity. Such serious illness requires effective treatment or prevention, which must be improved by unbiased research, which in turn must encompass those patients with adverse outcomes (from whom it is more difficult to obtain consent).

Comparison with other studies

The 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 Rochester, Minnesota, to which 79% of adults had given consent, Jacobsen et al found that adults were less likely to permit researchers to study their medical records if they were female, younger than 60, living close to the Mayo Clinic, and had a sensitive diagnosis (such as mood disorder).[7] More recently, in observational research involving interview and medical record review, the organisers of the Registry of the Canadian Stroke Network 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.[4]

The proportion of patients giving consent in our study (59%) and our methods straddle these two studies; our findings concur with those of the stroke registry, yet our consenters did not show the demographic differences observed in the Mayo Clinic medical records study or in the health survey literature. 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 either in direction or size.

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

Conclusions and recommendations

Several unanswered questions remain. 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, as they were in our study. 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 (constituting 30% of our cohort) are necessarily regarded as proxy non-consenters, but is it not paternalistic to deny patients or their relatives the option of consenting to participate in research into their own disease?

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.

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