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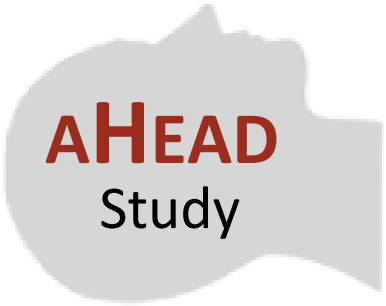

Monitoring anticoagulated patients who suffer head injury

Health Services Research
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"Protocol"

1. Background

Head injury is a common problem for patients attending UK emergency departments and internationally. There is poor evidence to support how anticoagulated patients should be managed when they suffer head injury. It is recognised that there is an increased risk from severe intracranial bleeding following head injury amongst this group of patients because of their coagulation status and there is currently very little research that supports the most appropriate way to manage this group in the immediate post-injury period. Current practice is variable, and based on anecdotal evidence not standardised across health communities. Therefore better evidence is required to determine the incidence of clinically significant complications and the clinical and cost effectiveness of current management strategies.

Prospective research is needed in order to understand the range and frequency of outcomes following head injury in this group of patients and to develop robust clinical guidance for how they should be optimally managed to reduce the risk of intracranial complications and death.

In addition, experiences and satisfaction with care received need to be evaluated in this patient group, along with robust research to identify predictors of adverse clinical outcomes and cost-effectiveness of different models of care.

This prospective multi-centre study will examine the clinical and cost outcomes following head injury in anticoagulated patients who attend up to 30 UK emergency departments. In addition, experiences and satisfaction in this patient group with care received will also be evaluated. Patients will be followed up at 6 weeks in order to establish their levels of satisfaction and preferences for care in these situations, their health outcomes and use of other health services following injury. Data analysis will identify the most useful and cost-effective investigations and management strategies required to optimise care.

1.1 Current system characteristics that may influence outcomes in emergency medical care

It is anticipated that this study will inform a change in practice throughout the UK in relation to improving and standardising the management of head injured patients taking anticoagulant medication. Although NICE guidelines exist for head injury[11], they do not currently address the specific management of patients in this group. There have previously been no adequately powered prospective studies that have demonstrated the risk of serious sequelae following injury, documented outcome following injury, or evaluated the clinical and cost effectiveness of different clinical management strategies. This study will provide evidence to allow inclusion of recommendations relating to anticoagulated patients in NICE guidance.

1.2 Rationale for our proposed approach to evaluation in service delivery

Determining the safest and most cost-effective way to manage anticoagulated patients following head injury is relevant for the UK population and also internationally. Head injury is common (conservative estimates 1.4 million patients attending UK EDs each year [1]); at least 1% may be on anticoagulant medication for associated medical conditions. The risk of serious intracranial bleeding, adverse neurological outcome and death is not known. Much work has been done in defining which head injured patients require CT imaging [3,4,5] however less robust work has addressed the higher risk and therefore clinically important subgroup of anticoagulated patients. It is widely accepted that anticoagulated patients are at higher risk for intracranial haemorrhage [6,7] with a reported mortality of 45-70% [6,8,9,10]. However, no adequately powered prospective studies have been undertaken to fully assess the risk of intracranial complication and the impact this has on management of this patient group compared to non-anticoagulated patients.

In order to improve patient care provided throughout the UK in emergency care settings, it is vital that robust evidence drives our practice. This patient group represents a classic example where practice has evolved but is not based on evidence, hence the lack of consistency in the clinical approach. This study will provide guidance that will inform optimum practice throughout the whole of the UK and have synergies for international practice.

1.3 Past and current research relevant to the proposal

Head injury accounts for a large number of consultations in the Emergency Department (ED), with at least 1.4 million patients attending each year in the UK with head injury [1]. Roughly 1% of the UK populous receives anticoagulation, most commonly warfarin, the chief indications being embolic prophylaxis in atrial fibrillation and management of venous thrombotic disease [2]. To date there have been no adequately powered prospective studies of patients who are anticoagulated and have suffered head injury. In addition, there is no consensus on the safest and most cost-effective way to manage these patients in UK Emergency Departments (EDs).

Use of anticoagulant medication such as warfarin is likely to increase in the UK with the recent introduction of NICE guidelines on the management of atrial fibrillation reiterating anti-coagulation as a central tenet for management of this condition[14].

A recent review of the literature undertaken by some of the AHEAD study team show that the risk of intracranial haematoma is increased 10-fold amongst patients taking warfarin, with the majority of bleeds being spontaneous. It is acknowledged that intracranial haemorrhage in anticoagulated patients is preceded by apparently innocuous trauma in a minority of patients, although large studies to calculate this risk are not yet available [7,15].

Previous studies of anticoagulated patients with head injury have identified the risk of subsequent intracranial bleeding to be between 6.2% to 7.8% [17,18], with other studies calculating an odds ratio of between 2.73 and 5.48 for the same outcome [19,20]. All these studies also demonstrated wide variation in the investigation, admission and subsequent management of anticoagulation for these patients.

Some of the AHEAD study team have undertaken a UK survey of Emergency Departments in order to identify current practice and variation in clinical management of this patient group. To date, the results indicate that the majority of EDs do not investigate these patients at initial presentation with Computerised Tomography (CT) head scans (74%), with just over half preferring to admit patients for neurological observation (59%). Whilst nearly all patients will have blood tests in the ED to confirm the level of anticoagulation (International Normalised Ratio (INR) test), only 31% advised patients to withhold anticoagulant medication following injury.

These results illustrate the variation in current practice that emphasise the need for robust evidence to firstly identify the level of risk, and secondly to outline an appropriate, safe, acceptable and cost effective clinical management plan. The AHEAD study aims to address this current gap in evidence and to inform future clinical practice using robust methods to evaluate risk, assess costs and patient satisfaction whilst also identifying important factors in the assessment and management of this patient group.

2. Aims and objectives

This study aims to:

1. Identify the outcomes of anticoagulated patients attending the ED following head injury
2. Collect prospective data to enable the risk of serious intracranial pathology to be calculated for this patient group (defined in this study as death or neurosurgery resulting from the initial injury, or Computerised Tomography (CT) scan finding mandating admission or readmission to hospital)
3. Use baseline and follow up data to identify useful predictors of adverse outcome in this patient group
4. Evaluate the cost-effectiveness of different clinical management strategies for this patient group

5. Identify important factors in the clinical consultation and assessment process following head injury that may be useful as a diagnostic tool.
6. Assess levels of satisfaction amongst anticoagulated patients following ED attendance with their minor head injury.

Plan:

1. To undertake a multi-centre prospective study of anticoagulated patients presenting to the emergency department following a head injury and to document:
   a) Clinical presentation including features such as demographic details, loss of consciousness, presence of amnesia and vomiting, mechanism of injury, time delay since injury, presence of neurological deficit and anatomical details of injury in relation to site, type and depth of wound
   b) Initial management including laboratory and radiological investigations such as measurement of international normalised ratio or INR (a blood level indicating the degree of anticoagulation), computerised tomography of the head (CT), and skull x-ray
   c) Hospital admission rate and length of stay
   d) Initial and medium term outcome following injury
   e) Hospital head injury after care instructions and prescribed medications on discharge home
2. To undertake a follow up study of this patient cohort at **six** weeks using routine hospital and ED data, along with patient survey to identify:
   a) Patient satisfaction with the initial management of their presentation
   b) **C**ognitive function using the Glasgow Outcome Scale (GOS) [12,29]
   c) Quality of life at using the EQ5D questionnaire[13]
   d) Subsequent health service use for a related condition in 6 weeks, and for up to 6 weeks
      a. post initial admission date
   e) Proportion dying within 6 weeks and documented cause of death
   f) Reattendance at the ED or for hospital admission with a related clinical problem and timing of any clinical deterioration
3. To undertake focus groups with study volunteers from one participating hospital Trust in order to document important factors in the clinical consultation, assessment, investigation and follow up process following experiences of head injury. In addition, these sessions will explore patient acceptability and views on the safety of different management strategies.
4. To use clinical and investigative data in a multivariate analysis to identify useful predictors of adverse clinical outcome in this patient group which may be further developed as a clinically useful diagnostic support tool in clinical settings.
5. To undertake an analysis of costs associated with the different management strategies of this patient group using routinely available clinical and resource use data and patient follow up data. Also to undertake a modelling study to evaluate the impact on costs of applying different actual and theoretical clinical models of care to this cohort of patients.

3. Plan of investigation

The AHEAD study is designed as a prospective, multi-centre, pragmatic observational cohort study of clinical outcome and cost-effectiveness. We will recruit anticoagulated patients presenting with a head injury to participating type I EDs (Emergency Departments providing a consultant led 24 hour service with full resuscitation facilities and designated accommodation for the reception of emergency patients).

3.1 Setting

Up to 30 acute hospital trusts that have Type I Emergency Departments (ED) will be approached to participate in this study.

3.2 Participants/ patient population

Inclusion criteria: The study will recruit consecutive anticoagulated adult patients (16 years or older), presenting to any of the participating EDs with a head injury (defined as a clinically apparent injury to the head - including facial trauma) within the preceding 48 hours.

Exclusion criteria: Patients with obvious penetrating or depressed cranial injury, or those with a spontaneous intracranial event causing their head injury will be excluded from primary data collection.

3.3 Data Collection

Standardised demographic and clinical data will be collected on a range of pre-determined variables [11,21] and will include demographics (age, sex, co-morbid medical conditions) time since injury, mechanism of injury, history of loss of consciousness, vomiting, amnesia, headache, and presence of seizure activity. Glasgow Coma Scale score (GCS. A scale used routinely to measure the conscious level of an individual [22]), neurological examination findings and grading of injury (type, size, depth, and anatomical site) will also be collected and recorded. All patient clinical data will be anonymised at each participating hospital site, and entered locally to the AHEAD study secure on-line web based database by local departmental research nurses, along with information relating to clinical assessments undertaken on admission which will be standardised across all sites based on available NICE recommendations on head injury assessment. The AHEAD study on-line database will be managed by the Clinical Trials Research Unit based at the University of Sheffield. A subset of patients will be assessed by a second independent healthcare professional to judge inter observer agreement. The need for laboratory tests (such as measurement of the International Normalised Ratio (INR)), head CT, hospital admission or discharge is to be left to the assessing physician's discretion. Outcome data will record the results of any investigation the patient has undergone, the disposition of the patient (including length of hospital stay) and any formal arrangements made for patient follow up. In addition, other advice provided to patients will be recorded such as the provision of written head injury instructions or medication.

Eligible patients will be identified locally when they attend the Emergency Department at each participating site. They will be contacted by the site research nurses using **a** postal questionnaire containing EQ5D and GOS scales (and associated consent forms) at 6 weeks following their hospital ED admission [12,13,29]. Opportunity to dissent from the anonymous data collection phase of the study will be presented to all patients both in the study information leaflet posted out with the questionnaire, and also in departmental publicity posters which will be displayed at each participating ED site on commencement of the study. An invitation to volunteer for study focus groups will be included with the questionnaire and posted to a subset of study patients from one participating site. The focus groups will be facilitated by staff based at the University of Sheffield.

Patient Follow up

Patients will be followed up using two methods:

- Health outcomes and satisfaction with services received will be assessed by one structured questionnaire administered to consenting patients. The questionnaire will be administered six weeks after contact for the head injury which documents patients' level of satisfaction with the service they received, their understanding of information provided and advice given in the event of a problem arising. Additionally ongoing symptoms relating to the initial injury will be recorded and the patients'subsequent health status measured using the EQ-5D [13] and Glasgow Outcome Scale [12,29]. Patients who do not respond to the questionnaire within 4 weeks will be sent a reminder to their home address.
- Data from each participating hospital will be checked to identify patients who may have reattended the ED or been admitted to hospital. Where this is found to have occurred, clinical records will be reviewed to identify whether the reattendance was related to the initial head

injury. In cases where this is found, details of the subsequent attendance including investigations, neurosurgical intervention, length of hospital stay and subsequent outcome will be recorded. Where patients are found to have died, information on the cause of death will be obtained from local Trust records and bereavement officers.

4. Outcome

Primary outcomes:

- Incidence of clinically significant brain injury as defined by death or neurosurgery resulting from the initial injury, or CT finding mandating admission or readmission to hospital.

Secondary outcomes will include:

- Prevalence of ongoing symptoms relating to the head injury such as headache, impaired cognitive function (assessed by the Glasgow Outcome Scale [12,29]), seizure or neurological deficit and failure to achieve pre-injury activities of daily living (assessed by the EQ5D [13]).
- Identification of early predictors of adverse clinical outcome including clinical features and initial investigations which may be useful as a diagnostic tool.
- Costs per patient of the head injury as managed in the participating centres and when applied to a derived 'ideal' model.
- Patient satisfaction with initial management.
- Patient acceptance and preference for different management strategies.

5. Sample Size

The primary outcome of interest is to accurately estimate the risk of complication in these patients within the follow up 6 week period. Up to 30 emergency departments will participate in this study. Based on attendance rates at one of the proposed participating centres, it is anticipated that up to 10 patients per week will be recruited from each centre. Our sample size requirements have been calculated using a confidence interval approach [23]. We expect our primary outcome to be rare, hence e feel a conservative and reasonable pre-study estimate of incidence is 5%. If this is the true risk of complications then a study size of 3000 will correspond to an expected 95% confidence interval with a lower limit of 0.042 and upper limit of 0.058.

For subsequent analysis to identify factors associated with adverse outcomes we will use a case-control design. Again assuming the 5% risk of complications is true 3000 patients should result in 150 patients with complications. The subsequent analysis will examine a number of clinical markers to assess their potential as early predictors of adverse clinical outcome. This number of cases (and the same number of controls) would correspond to 80% power (at the .5% alpha level) to detect a risk factor with a 20% frequency in controls and conferring a relative risk of 2. Using more controls (up to five per case as described in section 6.0) will give us increased power and enable us to detect statistical associations with clinical factors present at a lower control frequency than 20%. We set the low type 1 error rate of 0.5% as the Bonferroni correction to allow for the multiple hypothesis testing of up to 10 distinct clinical markers.

6. Planned data analysis

Data Analysis

The primary outcome analysis will consist of calculating the proportion of the recruited head injury patients who develop a clinically significant brain injury and reporting the 95% confidence interval for this proportion. With respect to the analysis of the secondary outcomes the study has a closed cohort design. The evaluation of screening practices or variables correlated with outcome will be assessed using general linear models. We will adopt a nested case-control design to control for confounders such as age, sex and treatment hospital, as hospitals are likely to implement different practices. We will match each case (patient with a significant complication) with up to five controls (patients with no complications). If the risk of complications is higher than our pre-study estimate then power will be

increased. All collected variables will be assessed for correlation with adverse outcome, by conditional logistic regression. Continuous data (INR) will also be analysed to determine risk associated with differing threshold levels.

Stepwise multiple conditional logistic regression analysis will be undertaken to determine which combination of the clinical and investigative measured variables best predicts the outcome measures. The predictive power of the selected models will be evaluated by computing the concordance index. Based on these results, we hope to formulate a decision tool. The stability of the best fitting model(s) will be assessed by cross-validation using standard procedures such as leave-one-out. The simple conditional regression analyses and the full predictive model will identify the subset of co-variates that will be taken forward in further study designs for more powerful evaluation, refinement and validation of the preliminary decision tool.

7. Cost effectiveness analysis

The cost-effectiveness study will be in two parts. Initially, an analysis of costs associated with current management strategies for these patients. Secondly, a modelling study to evaluate the impact on costs of applying different clinical models of care to this cohort of patients.

1. Resource use

Resource use costs will be taken directly from the AHEAD study. These will include the costs of diagnostic tests (laboratory tests, CT and skull X-ray), hospital admission and neurosurgical intervention.

Outcomes will be estimated as QALYs accrued following the decision to employ each management strategy. Utilities will be derived from the quality of life data collected as part of the AHEAD study. These will include the utility associated with early or delayed neurosurgery, uncomplicated head injury (no bleeding), intracranial bleeding with early surgery, intracranial bleeding with delayed surgery and the disutility of the surgical procedure.

The time frame for the model will be the lifetime of the patient. We will assume that only patients with intracranial bleeding will incur long term costs that are likely to be influenced by their initial diagnostic management, so long term costs will only be estimated for patients in the model who survive intracranial bleeding. We will estimate discounted long term costs by extrapolating follow-up costs from patients with significant head injury identified from another study underway within ScHARR at the University of Sheffield - the Health And Long term Outcomes (HALO) study over the anticipated lifetime of the patient. For this study, researchers have been collecting diagnosis and baseline GCS, along with costs and quality of life data up to 15 years after significant injury (including head injury). Sensitivity analysis will be used to explore uncertainty in estimates of long-term costs. The baseline analysis will not include productivity losses but secondary analysis will be undertaken including productivity losses to explore the effect of changing assumptions regarding the role of productivity losses. We will value productivity losses in the model by applying an average salary cost to estimated time off work as a result of intracranial bleeding.

The literature review previously undertaken to estimate the effects of radiation exposure associated with radiological investigations (CT brain scan and skull X-ray) will be updated and made relevant to anticoagulated patients. We will then model these data to estimate a QALY loss and/or cost associated with each radiological investigation. This QALY loss and/or cost will then be applied to every patient in the model who receives a radiological investigation.

Analysis will be conducted in accordance with the NICE reference case24. Net benefit analysis will be used to identify the most cost-effective option at varying thresholds of willingness to pay [26]. The optimal strategy at the threshold currently used by NICE for decision-making will be presented as the optimal strategy for the NHS. The methodology used in the decision analytic model will be dependent on the data that are available and the number of health states following the minor head injuries that are necessary to incorporate, with the most appropriate technique selected.

Probabilistic sensitivity analyses (PSA) will be conducted in order that any interactions and non-linearities within the modelling are properly considered. Jack-knife techniques [27] will be conducted to ensure that a sufficient number of PSA runs have been conducted to ensure that the average calculated from all runs for a management strategy is robust. Additionally the uncertainty associated in the actual mean net benefit will be provided using the percentile method in order that the full uncertainty in the results is reported. These analyses will facilitate the calculation of both full and partial expected value of perfect information, and if it is deemed appropriate an evaluation of the expected value of sample information will also be conducted [27,28].

2. Cost-effectiveness modelling

The decision-analysis model used will estimate the costs and QALYs accrued by each potential management strategy for head injury, including a theoretical "zero option" strategy of discharging all patients home without investigation. Each strategy will be applied to a theoretical cohort of patients attending the ED with head injury allowing a direct comparison of results. We will investigate the feasibility of obtaining sensitivity and specificity data from the AHEAD study to determine, for each strategy, the proportion of patients with clinically significant brain injury and the proportion with clinically significant brain injury who undergo diagnostic testing and/or admission to hospital. If it is not possible to obtain this data from the AHEAD study, then sensitivity and specificity estimates from a literature review (undertaken in the previous HTA work and updated by us) will be used.

This model will be adapted to include decision nodes based on the decision strategies that are adopted according to INR thresholds used in the participating EDs.

8. Ethical and Other Implications

The main ethical consideration for the AHEAD study is related to the need to obtain detailed prospective clinical data for a large cohort of patients in the emergency setting within a relatively short time frame. Approaching potentially anxious and distressed patients with head injuries (and possible associated complications) for consent to obtain routine admission data within a 24 hour 7 days a week period may, we feel, compromise patient care and the overall running of busy departments.

As such, we plan to extract anonymised data from those records of eligible patients attending participating NHS sites. This data will be obtained from standard ED admission and clinical records, along with results of associated hospital tests used routinely for managing individual cases. No additional information will be taken for use in the study other than patient re-admission, discharge and (where applicable) date and cause of death from hospital patient administration systems. All patient clinical records will remain within the premises of each participating hospital site and will be accessed (for the purposes of the study) only by Trust clinical staff and authorised members of the AHEAD study team. Patient data will be effectively anonymised for use in the study through the omission of details relating to name, place of residence, date of birth, and associated hospital identification numbers. The local CLRN (Comprehensive Local Research Networks) or departmental study research nurse undertaking data entry for the study will be appropriately trained in this role by the study team. Each set of patient data will be allocated with a unique study identifying number linking the record at the NHS site source. User use to the secure on-line AHEAD study database known as “PROSPECT” which is managed by the Clinical Trials Research Unit at the University of Sheffield will be controlled by issue of usernames and passwords and all data entry for the AHEAD study will take place on NHS Trust premises using hospital computer terminals.

We will use study publicity posters displayed in each participating ED to inform patients of the anonymised data collection procedure underway, and will give details of how patients (and/or their relatives or carers) can contact the appropriate member of ED staff locally should they wish to withhold clinical head injury admission details or opt-out of the study. Opportunity to dissent will again be provided with details given in study information leaflets accompanying postal questionnaires and associated consent forms.

9. Public involvement

The patient representative, Rosemary Harper, involved in the development of this study has extensive experience of being involved in research planning and implementation within the School of Health and Related Research at the University of Sheffield. She is a member of the Sheffield Emergency Care Forum (for patient and public involvement in clinical research) and will continue her involvement with the AHEAD study as a member of the Steering Committee. Rosemary will also be involved in the interpretation of the study findings ensuring this is disseminated in an interpretable way for patients in the future.

The study will also seek the views of a sub-group of the AHEAD study cohort with the development of focus group meetings. These focus groups or interviews will aim to gather users' views on the initial management of patients suffering minor head injury, expectations from initial care, subsequent problems that may be encountered and factors that might improve care in this patient group. In addition, these sessions will explore patient acceptability and views on the safety of different management strategies. Analysis of data collected from focus groups carried out in one of the participating EDs will be analysed using thematic analysis (TA). This method is flexible and has the potential to identify, analyse and report themes within the data [30]. A broadly theoretical TA approach will be taken in order that analysis is driven by the research aim of identifying key themes related to the management of anticoagulated patients who suffer head injury.

10. Timescale

It is anticipated that the study will be completed within 24 months as follows:

Months 1-6: seek agreement from participating sites, ethical approval, R&D approval, draft final versions of patient survey, agree and pilot data collection items, tools and strategies.

Months 7-18: Recruitment of patients from all participating sites, clinical data collection, participant follow up through survey , noting deaths and hospital re-attendances in six weeks.

Months 19-24: Finalise data collection, data entry, data analysis and write final report. Plans for dissemination.

11. Project Management

This project will involve collaboration between Health Service Researchers, Clinicians, and associated local hospital staff involved in delivering emergency medical care. A project management group will meet every three months to oversee the project. A steering Group will be assembled to meet every six to twelve months to provide independent advice to the project management group.

The Research Team will include:

Lead Applicant, Suzanne Mason, Professor of Emergency Medicine and Director of Health Services Research in the School of Health and Related Research (ScHARR) at the University of Sheffield, and Honorary Consultant in Emergency Medicine, Sheffield Teaching Hospitals.

Dr Matthew Stevenson, Senior Operational Research Analyst, Health Economics and Decision Science, (HEDS), ScHARR, University of Sheffield. (Health Economist and steering group member).

Dr Dawn Teare, Lecturer in Genetic Epidemiology, Academic Unit of Mathematical Modelling & Genetic Epidemiology, ScHARR, University of Sheffield. (Statistician and steering group member)

Michael Holmes, Operational Research Analyst, Health Economics and Decision Science (HEDS), ScHARR, University of Sheffield. (Health economist and member of steering group)

Dr Ramlakhan Shammi, Consultant in Emergency Medicine, Emergency Department, Sheffield Teaching Hospitals. (Expert advisor and member of steering group).

Rosemary Harper, Patient Representative, Sheffield Emergency Care Forum, c/o ScHARR, University of Sheffield. (Lay representative and member of steering group).

Professor Steve Goodacre, Professsor of Emergency Medicine, Health Services Research, ScHARR, University of Sheffield, Emergency Department, Northern General Hospital. (Expert advisor and member of steering group).

The study will fund a Project Manager (responsible for the day to day running of the study), a research nurse, and clerical officer, all of whom will based at the University of Sheffield.

12. Exploitation and Dissemination

This research is unlikely to generate commercially exploitable results.

The results of this study will be of interest and relevance to clinicians, managers, policy makers and service users in the field of Emergency Medicine throughout the UK and also internationally. The findings will be made available following consultation with the research team and the steering committee. The results will be disseminated as:

- The principal output of the final research will be a report to the NIHR and Department of Health detailing the findings of the study in relation to the aims and objectives set out.
- A report for distribution to policy makers, managers and specialist organisations such as the UK College of Emergency Medicine, the Society of British Neurological Surgeons and the British Society for Haematology.
- A series of research papers for publication in relevant peer reviewed journals.
- Presentation of the findings at relevant Emergency Medicine, neurosurgery and haematology meetings, for example the Annual Scientific Meeting of the College of Emergency Medicine.
- Utilising patient groups and charities (such as HEADWAY) in order to disseminate the research findings to users and volunteers and receive feedback on the study findings and proposed changes to patient care it identifies.

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