Project title: Clinical and demographic characteristics associated with delay in help-seeking behaviour in patients with Acute Coronary Syndrome (ACS)

Background and Rationale: This small project, analysing routinely collected data (from the Myocardial Ischaemia National Audit Project (MINAP)database), will provide information vital to the development and evaluation of interventions aimed at reducing patient delay in calling for emergency services following symptoms of Acute Coronary Syndrome. Such delay is now one of the major factors in sub-optimal outcomes for patients with ACS.

Acute Coronary Syndrome: Acute Coronary Syndrome (ACS) is an umbrella term for a set of conditions that arise from ischaemic heart disease: the two main conditions are unstable angina (UA) and Myocardial Infarction (MI). MI is sub-categorised into two main types based on findings from the electrocardiogram (ECG) and release of biomarkers such as the troponins(1): these are ST-elevation Myocardial Infarction (STEMI) and non-ST-elevation Myocardial Infarction (nSTEMI). Between 2001 and 2006, these cardiovascular diseases were the largest contributors to avoidable deaths in the UK. From 2007 to date, neoplasms have taken their place, in part because treatment for ACS has improved. But, effective treatment is time dependent. In particular, treatments involving clot-busting drugs and, more recently, small balloons inserted into the affected coronary artery, have reduced mortality and morbidity following STEMI. To be effective, treatment must commence within 12 hours of symptom onset but earlier is better as irreversible death of cardiac muscle begins at around 2 hours (2). Further, all ACS patients benefit from early health-care intervention in terms of symptom control and of monitoring for dangerous sequelae (3, 4).
For this reason, much policy attention has focused on reducing the time taken to process patients with ACS once professionals are involved; measures such as 'call-to-balloon time' are used to audit this (5). These times have improved over the last decade (6, 7). However, the time between symptom onset and the patient (or bystander) seeking professional help has altered little; indeed, in the period 2000-2003, median delay in seeking help increased from 75 to 80 minutes for patients with STEMI (8). In contrast, in 2011 around 92% of eligible patients in England were treated within 90 minutes of arrival at a Heart Attack Centre. It follows that the delay in making a call for help (in particular, for an ambulance) is an important barrier to rapid treatment and thus to optimum outcomes.

Existing research: Existing research on this topic of patient delay divides broadly into that examining i) who delays and ii) which interventions reduce delay. Little of this research is from the UK; this

matters because help-seeking behaviour is likely to be affected by local cultural and political differences. For example, the delay in help-seeking behaviour noted in the United States (9) might well be a function of the lack of a universal health-insurance system there and might not be seen in the United Kingdom with its, current, free-to-all medical system. In the UK, then, what has research shown about patient delay?

i) *Who delays?*

On the questions of who delays, Ben-Shlomo et al (10) used the MINAP dataset 2002-3 to examine ethnic differences in healthcare-seeking behaviour relating to acute chest pain. (The MINAP dataset is a centrally collated collection of statistics on all patients admitted to hospitals who are given a diagnosis of Acute Coronary Syndrome.) Using the broad categories of 'South Asians' and 'Caucasians' the study found that the former were less likely to arrive by ambulance. The authors conjoin this finding to a suggestion that South Asians delay longer. While this seems credible, data to support this assertion are not given. There are two small-scale surveys (11, 12) but little else from the UK. In particular, there seem to be no other published studies using MINAP or any other UK data to study factors associated with delay. Drawing on studies beyond the UK (13), the following categories have been found or proposed as associated with delay:

- Socio-demographic: for example, the following were positively associated with delay in some studies: older age (14, 15), , being female (13, 14, 16), inadequate health insurance (17), ethnicity (15, 17, 18), (19), low socioeconomic status (17, 18) and country (20). Studies that included a broad age range also have found increased delay at younger ages (15, 18, 19), which is thought to occur because the condition is rarer in young age groups and unexpected. And, there is some contradiction in which gender is most likely to delay (e.g. (17)). This possibly arises from interactions between gender and age or ethnicity as differences in subgroups have been noted (e.g., (19, 21).
- Clinical a) Past medical history and family history: for example, a history of CHD was associated with reduced delay (13, 20) as was the presence of diabetes mellitus (13); b) Presenting condition: for example, nSTEMI and UA were associated with delay compared with STEMI - in turn this might have been because the symptoms of STEMI were more marked (20, 21).
- Mental Health: for example, depression was associated with delay (e.g., (22)).
- Cognitive: for example, the recognition that symptoms might be cardiac in origin was associated with reduced delay (23-25).
- Other: for example, being alone when symptoms start was associated with delay (14, 26, 27); this may explain why there is increased delay in those who are unmarried (e.g., (9)) although this

relationship is not seen in all countries (e.g., (14)) and consulting a spouse or others is reported to increase delay (e.g. (12, 28)).

Presenting symptoms may affect delay such that the more marked the symptoms, the less the delay (29, 30) although a recent study conflicts with this, showing the presence of chest pain to be associated with more delay (13). The explanation for this might lie with studies by Rawles et al suggesting (31, 32) that the initiation of a call was largely unexplained in terms of worsening symptoms. This suggests that patients may be responding to other stimuli such as those resulting from deteriorating left ventricular function (33). However, the Rawles material is decades old; practice has certainly changed in this time and patient behaviour may have as well.

ii) Interventions

Turning to interventions aimed at reducing delay, Mooney et al (34) reviewed interventions, published between 1986 and 2010, aimed at reducing pre-hospital delay, which categorises the research into decision delay and transportation delay. Eight interventions were found, reported in multiple papers. None were from the UK. Seven were mass media campaigns and one targeted individuals at high risk. Whilst some showed success in increasing knowledge and awareness, none showed convincing evidence of reducing delay in help-seeking behaviour. There have been UK campaigns run, for example, by the British Heart Foundation but these have not been evaluated in a publicly available document. Crucial here is that only a about half of people with chest pain who call 999 turn out to have ACS (35). Of the remainder, some would require emergency treatment anyway; the rest can be termed 'false positives'. The difficulty is, then, to find interventions that reduce the time people with genuine ACS take to call emergency services in the UK without disproportionately increasing the number of false positives. It might be thought that charity-funded campaigns aimed at reducing delay can at least do no harm to the patient; however, this is not so because an increase in false positives hampers the ability of ambulance services to respond to other patients.

Rationale for the current study

Aside from the Ben-Schlomo (10) study mentioned above, which only focused on a crude categorisation of ethnicity, the association between patient decision delay and the large range of clinical and socio-demographic factors collected in the MINAP database has not been examined. Thus interventions aimed at reducing delay are designed against an unnecessarily blank backdrop of information about correlates and presumed causes of delay. Without it, policy makers, commissioners and practitioners in the UK have, for example, been blind to whether gender or

deprivation needs to be taken into account in targeting interventions. This study is envisaged as the start of a programme leading to the development and testing of interventions.

Aims and Objectives

To use routinely collected data to find patterns of delay by clinical characteristics, such as medical history, and by the demographic characteristics of sex, social class, ethnicity and age. The demographic characteristics were chosen because of their central role in social determinants of health and because they have been noted in non-UK studies as important in delay.

Research Plan

Design

This is a cohort study (i.e. observational) using administrative data from MINAP, the Myocardial Ischaemia National Audit Project, which is a dataset for acute myocardial infarction and other acute coronary syndromes. The dataset contains all patients in England or Wales who triggered the PCI pathway however, a small number will not have a diagnosis of ACS(troponin positive)/nSTEMI and discharge diagnosis will be used to confirm ACS status. The dataset is "commissioned by the Healthcare Quality Improvement Partnership (HQIP) who hold commissioning and funding responsibility for MINAP and other national clinical audits. An academic group, which reports to the Steering Group, has been established to facilitate research use of the data. It is the long term aim of the project […] to provide, for all interested groups, including patients, commissioning bodies, cardiac networks of care, and academic researchers, first class data on the care for acute coronary syndromes within England and Wales." (MINAP website http://www.ucl.ac.uk/nicor/audits/minap)

This study will be based on national ACS data from MINAP, participation in which is mandated for all hospitals in England and Wales. Data are collected prospectively at each hospital by a secure electronic system, developed by the Central Cardiac Audit Database (CCAD), electronically encrypted and transferred on-line to a central database. MINAP is overseen by a multi-professional steering group representing the stakeholders and by the National Institute for Cardiovascular Outcomes Research (NICOR) Executive. As such, this study includes data collected on behalf of the British Cardiovascular Society under the auspices of NICOR in which patient identity is protected. Each MINAP entry provides details of the patient's management across 122 fields, and date of all-cause mortality from linkage to the Medical Research Information System, part of the NHS Information Centre using a unique NHS number. Data entry is subject to routine on-line error checking. There is a mandatory annual data validation exercise for each hospital. For more information please see (6).

Variables

Retrospective data from MINAP (3 years of data or 240,000 cases) will be requested with the following variables:

- For delay: Date/time of symptom onset; Date/time of call for help
- Socio-demographic characteristics: sex; postcode-level deprivation index (IMD); ethnicity; age. MINAP does not collect data on a patient's language; moreover, in our experience from other research with hospital data, it is not reliably recorded. We acknowledge that this is an important issue that will be investigated in future research.
- Main clinical characteristics: admission method; initial diagnosis; ECG determining treatment; discharge diagnosis; site of infarct; location at time of symptoms, procedure performed
- Initial observations on admission to hospital: Systolic BP, Heart Rate, Cardiac arrest
- Indicators of disease severity/risk of death such as the mini-GRACE score and infarct size estimated from biomarker data. (36)
- all cause mortality and date of death

Analysis

The analysis falls into two stages:

A) Analysis of the data 'as is':

1) Examine the association between delay of help seeking and factors: a) socio-demographic, and b) clinical.
2) A reaffirmation of the previously identified relationship between mortality and delay

B) Modelling the missing values in MINAP to make more efficient inferences and enhance the utility of these data.

In this this study, the outcome of the analysis is delay, categorised as: ≤ 60 minutes; 60-120 minutes; ≥120-360 minutes; ≥ 360 minutes: these categories are based on clinical effectiveness of treatment (37).

As we have a categorical outcome variable, a multinomial logistic model will be most appropriate for the analysis (38), p 720-3). Logistic regression can be extended to handle outcomes with more than two categories as either ordinal (ordered categories) or nominal (unordered categories). In this analysis we will use ordinal logistic regression as it has two advantages: a) a more parsimonious

model and b) increased power. Interactions will also be examined, for example, we would seek to find whether any delay based on age is associated also with ethnicity or deprivation.

As the multinomial model does not make any assumptions of normality, linearity, and homogeneity of variance for the independent variables, it is preferable to use discriminate analysis if the data do not satisfy these assumptions. To assess the associations between the individual independent variables and the outcome variable two types of tests will be used in this model:
a) Likelihood ratio test, which allows us to evaluate the overall relationship between an independent variable and the outcome variable (39, 40).
b) Wald test, which evaluates whether or not the associations between independent variable and outcome variable is statistically significant in differentiating between the groups in each of the embedded dichotomous logistic comparisons (41).

Further analysis will be considered if any nonlinear associations is found between the outcome and dependent variables. In this case, semi-parametric (e.g. generalized additive model) analysis will be considered for further investigation (42).

Multiple imputations Analyses (Missing data)

This dataset has a significant proportion of missing data (see Table 1) although these are concentrated in only a few variables. In this stage, we will assess the monotone patterns and the joint probability of missingness across variables. Then we will identify the potential predictors of each variable which needs to be modelled (43).

Table 1: Rates of missing data across variables in MINAP dataset

Variables:	**Data missingness rate**
Date/time of symptom onset	16.5%
Date/time of call for help	2.9% for direct admissions; 5.6% inter-hospital transfers included.
sex	Negligible *
postcode-level deprivation index (IMD)	~1%
Ethnicity	~3%
Age	Negligible
admission method	Negligible
initial diagnosis	None as this is compulsory field
ECG determining treatment	34.6% - covers missing and unknowns
discharge diagnosis	None as STEMI is the selection criteria
site of infarct	20% - includes missing, unknowns.
location at time of symptoms	approx. 15% since implementation of field on 1 June 11.
Systolic BP	20%

Heart Rate	20%
Cardiac arrest	5.3%
Creatinine	14%
Elevated enzymes/markers	4.5%

* less than 10 in every 10,000 patients

One analytic option is to use only that patient data which is complete; another is to replace the missing values (a process termed 'imputation'). The simplest imputation replaces the missing value with mean or median value for that variable. However, this is not a desirable process when one is examining the relationships between variables.

More sophisticated methods, termed 'multiple imputation', predict missing values for a variable using existing values from other variables. The predicted values, called "imputes", are substituted for the missing values, the results are combined, and this results in a full data set called an "imputed data set" (44). No matter which complete-data analysis is used, the process of combining results from different data sets is essentially the same. In other words, we use the data from units where both (Y, X) are observed to learn about the relationship between Y and X. Then, we use this relationship to complete the data set by drawing the missing observations from Y|X. This process is completed at least N=5 times, giving rise to N complete data sets. Each of these imputed data sets is then analysed and the results combined using specific rules. This process does not involve an attempt to estimate each missing value through simulated values but rather to represent a random sample of the missing values (43, 44). Multiple imputations inference involves three distinct phases:

1) Create imputed data sets which are plausible representations of the data.
2) Perform the chosen statistical analysis on each of these imputed data sets by using standard procedures.
3) The results from the complete data sets are combined to an "average" for the inference to produce one set of results.

Analyses based on multiply imputed data will avoid bias only if enough variables that predict the missing values are included in the imputation models. Therefore, including as many predictors as possible tends to make the missing-at-random assumption more plausible (43). However, including more than 25 predictors will increase the variance explained in the prediction equations (45).

Multiple imputation represents a good balance between quality of results and ease of use. It has been shown to preform favourably compared to other methods in a variety of missing data

situations (46, 47). It can also produce unbiased parameter estimates which reflect the uncertainty associated with estimating missing data. Furthermore, it has been shown to be robust to departures from normality assumptions and provides adequate results in the presence of low sample size or high rate of missing data.

There are multiple imputation methods, such as Expectation Maximization (EM-algorithm) (48, 49) or the Monte Carlo Markov chain (MCMC) (50) method. The results of some previous studies showed there was no significant difference between EM algorithm and MCMC method for item imputation, and number of items used for imputation has little impact, either (51).

In this study, we will use MCMC method that is based on pseudo-random draws; this will allow us to obtain several imputed data sets. It is known that MCMC can be used with both arbitrary and monotone patterns of missing data. It is known as a collection of techniques for simulating random draws from difficult probability distributions via Markov chains. MCMC also is especially useful in Bayesian statistical analyses and for solving difficult missing-data problems (48).

Assumptions about missing data

If MINAP data were completely at random, the observations would constitute a random sample of the complete dataset. Multiple imputation assumes that the observed variables are predictive of the missing values and that data are not missing at random.

Missing data are said to be missing at random (MAR) if the probability that data are missing does not depend on unobserved data but may depend on observed data. Missing completely at random (MCAR) can be viewed as a particular case of MAR. On the other hand, if the subjects are withdrawn from the study for ethical reasons, missing would not be MAR. This type of missing-data mechanism is called missing not at random (MNAR). For such missing data, the reasons for its missingness must be accounted for in the model to obtain valid results.

Missing data pattern. We will look at missing data patterns and also assess the extent of missing data in the variables that will be included in the analysis. We will also look for monotone missingness in longitudinal variables and see whether Y j is observed only if Y j-1 is observed to check if there is a monotone or arbitrary pattern. After identifying the potential predictors for each variable to be imputed, we will run ordinary regression to find out which predictors are the most important.

Nonlinear relationships will be treated using semi parametric models (e.g. generalised additive models (GAMs).

It is important to include the outcome variable (in this case, delay in seeking for help) as a predictor in the imputation model because failing to do so will dilute the associations between the outcome and the other variables (52, 53).

Normality assumption. The multiple imputation models assume normality of the variables being imputed, and it is important to check that this assumption will be approximately satisfied. As we have a large dataset (Approx. 240 000 observations), variables are assumed to be approximately normally distributed using the central limit theorem.

However, a transformation to approximate normality will be applied for those variables that are found to have a non-normal distribution.

Imputation Methods

A multiple-imputation method is said to be proper if it produces proper multiple imputations, which we are about to define. A full technical definition for proper multiple imputations was reported by Rubin (43).

Multiple imputations are said to be proper if:

1. Multiple Imputation estimates are asymptotically normal with the mean and a consistent variance-covariance estimate.
2. The within-imputation variance estimate is a consistent estimate of the variance–covariance estimate with variability of a lower order than the variance of all imputation estimates.

In practice it is difficult to determine whether an imputation method is proper. Several examples of proper and improper imputations were described and reported by Rubin (43) and Binder and Sun (54). Rubin recommended drawing imputations from a Bayesian posterior predictive distribution of missing values under the chosen model for the data and the missing-data mechanism. Our selected method (MCMC) is applied as a method for exploring posterior distributions in Bayesian approach. Through MCMC, we will be able simulate the entire joint distribution of the unknown quantities and obtain simulation-based estimates of posterior parameters that are of interest. The chosen imputation model is also more appropriate for the completed-data statistics likely to be used at the

analysis. Schafer (48) pointed out that from a practical standpoint, it is more important that the chosen imputation model performs well over the repeated samples than that it is technically proper; this can be checked via simulation.

The imputation model will include all predictors relevant to the missing-data mechanism; and it must preserve all data characteristics likely to be explored at the analysis. For instance, if there was a correlation between two variables, then omitting either of those variables from the imputation model will lead to estimates of the correlation biased toward zero. Further, when an outcome variable of the analysis model is not used in the imputation model that may lead to biased estimates as well.

The hospital of admission will be included as a fixed effect; therefore allowance will be made for the fact that MINAP is a multicentre observational study. Using fixed effects is unlikely to bias the results of analyses based on imputed data unless the clustering is explicitly the focus of the analysis (55). Hospital admission could also be included as a random effect in clustering cases when multilevel imputation models are applied.

Computations will be carried out using STATA 12 software in this study. A number of imputation methods, including flexible methods accommodating variables of different types and an iterative Markov chain Monte Carlo method based on multivariate normal, are available in STATA 12. We will also consider Monte Carlo error estimates to lessen the simulation (Monte Carlo) error based on White Royston and Wood (56) .

Sample size calculation

Several researchers have noted the importance of using reliable measures in order to provide sufficient rigour to the research design by reducing the measurement error and explaining higher variance, thus increasing power. Missing data and the impact on power has been extensively assessed in the literature. A common approach for sample size calculations for data with missing is to simulate the patient data thousands of times to obtain the empirical power. This is often a very time-consuming endeavour (57).

Diggle et al. (58) improved closed-form sample size formulas to compare the time-averaged responses and the rates of change in studies assuming no missing data, an equal number of subjects between two groups under study, and the compound correlation among observations from the

same subject. Liu and Wu (59) have extended this formula for time-averaged differences to unbalanced clinical trials. Further, Zhang and Ahn (60) investigated how repeated measurements affect the sample size requirement in repeated measurement studies, where statistical inference is obtained based on time-averaged differences. The sample size formula used here is general enough to accommodate various missing data patterns, such as random missing or monotone missing, and various correlation structures, represented by a damped exponential family that includes autoregressive correlation with order 1 (AR(1)) and compound symmetry (CS) correlation as special cases (60). Using this formula as reported in (60) P1 (1, 0.8, 0.7,..), P2 (1,0.9,08,..) and P3 (1,1, 0.9,..) describe the scenarios where an increasing number of subjects miss visits over time and use P4(1,1,1,..) to denote no missing data. While, φ denote various correlation structures, p is the probability that the observation is non-increasing over time, p 1 ≥ p 2 ≥ ••• ≥ p m. The study investigated the proposed sample size approach, for every combination of the aforementioned factors (σ 2, ρ, φ, observation probability, missing pattern) using 500 simulations. Based on this analysis, if the missing at random (MAR) pattern for instance with probability P1, with ρ = 0.1, the sample size increases from 229 to 419 as φ increases from 0 to 1, an 83% increase. In case of a higher correlation (ρ = 0.5), the sample size increases by 31%, from 490 to 641. However if missing is Monotone missing (MM) with probability P2 and the correlation structure (AR (1)), the required sample sizes are 439, 551, and 677, for correlation ρ = 0.1, 0.25, and 0.5, respectively. In other word, a sample size under MM is always larger than that under RM. Similarly, higher correlation leads to increasing the sample size.

If, as we expect, the delay rate is 35% amongst those with typical symptoms, a sample size of 2410 will give 80% power to detect a difference of 5 percentage points (i.e. a rate of 40% amongst those with atypical presentation). However, by increasing the missing in the delay variable to rate to 37% amongst those with typical symptoms, a sample size of 970 will give 80% power to detect a difference of 8 percentage points (i.e. a rate of 45% amongst those with atypical presentation). However, as we will have access to 3years of data (approximately 240,000 observations) sample size is not an issue.

Dissemination and Outputs

The end product of this study is information for use in developing and evaluating interventions aimed at reducing patient delay in calling emergency services when symptoms of ACS present. As such, the study is of value only if the findings are successfully transferred. We view this as having two elements. The first is knowledge transfer to others in the business of reducing patient delay; the

main examples are clinicians, charities (such as the British Heart Foundation) and social-marketing bodies. The second is for our research group to develop and test interventions aimed at reducing delay.

The detailed final report to HS&DR will form the basis for a publication in an open-access peer-reviewed journal. We will also undertake local, national and international conference presentations. This activity will disseminate the findings to clinicians, researchers and policy makers and, to a lesser extent, charities and social-marketing bodies. Dissemination to the latter, however, will also involve the presentation of findings in briefing papers and bite-sized summaries. We will maintain a project website throughout the project with both public and professional domains.

In terms of the second element, future development and testing our own interventions, our relationship with patient and user groups is essential. We have, at present, a partnership with a patient group based in Sheffield; the team also has links with groups in London, South East England and South West England. The Centre for Health and Social Care Research in Sheffield, which is hosting this project, also has extensive experience of using social marketing companies. As such, we are well placed to disseminate findings to these bodies and to formulate campaigns with them.

Much has been done to reduce delay once the patient with ACS arrives at the hospital (7), and quality of such care in the NHS in England has improved markedly over recent years as shown in the MINAP annual public reports. The remaining hurdle is to improve accessibility to high-quality, effective NHS care by reducing the delay in patients with symptoms of ACS contacting the emergency services. This research is the first phase in a thorough evaluation of patient delay and the subsequent development of interventions to reduce it. The potential benefit of a successful campaign to reduce delay is immense; but in the UK there is little data on which to ground one. This project will begin that process. It makes new and innovative use of MINAP data to show the factors associated with delay and the interplay between those factors. These results are of immediate import to those concerned with designing interventions aimed at reducing delay. As we do not yet know these results, we cannot predict the nature of the impact. However, if it were shown that, for example, particular ethnic groups were liable to lengthy delay then it would seem reasonable to target interventions at those groups. The research team behind this project aims to use the findings in this way in future research proposals/interventions. We also aim to run a full evaluation of interventions including the effect on NHS usage.