**The Effects of Mental Health on Knee Arthroplasty Outcomes**

**Statistical Analysis Plan**

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**Document Version History**

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| 1.4 | 20/06/2024 | First signed off version |
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**1. Executive summary**

**Background**

Patients with Mental Health (MH) disorders (MHD) are at higher risk of dissatisfaction, complications and chronic pain following knee arthroplasty (TKR). Chronic pain following knee arthroplasty alone costs the NHS £33,000,000 per Anum in direct care costs. Despite MH disorders being common problem, they are often underrepresented and overlooked in perioperative guidance.

Extensive literature has identified MHD as a key risk factor for poor outcome, the next translational step, patient level prediction of individuals at high risk has proven to be difficult, predominantly due to lack of granular MH data. Little research has considered the importance of specific diagnosis, severity and chronicity of the MHD.

**Aim**

Our overall aim is to explore mental health related risk factors which may place patients at risk of poor outcomes following knee replacement surgery.

**Methodology**

To achieve our aim we will link and subsequently analyse patient data from 3 routine NHS data sources.

1.Discovery Data Service (DDS) - Holds linked patient data combining GP, Social service and Mental health records. It covers the population of North-East London (approximately 2 million people).

2.National Joint Registry (NJR) – A world leading database for patient undergoing arthroplasty in the UK. Details include arthritis, surgery, and hospital data. It also has a linked Patient Reported Outcomes Score (PROMS) database, which patients answer at 6 months pre and post op.

3.Hospital Episode Statistics (HES) - Is linked to the NJR. Provides details about patients engagement with secondary health providers, and further inpatient data.

**Statistical Analysis**

**Knee Replacement Outcomes**

Patient knee function – As recorded using the Oxford Knee score at 6 months

Surgical complication – Any re-admission to hospital during the first 6 months after surgery

Chronic pain – As recorded in the EQ5D Patient questionnaire at 6 months

**Primary Objective**

1. To estimate the prevalence and distribution of different mental health disorders diagnoses, in patients before they undertake a knee replacement within the NHS in North East London from January 2014 to January 2024.

2. Estimate the association between different mental health disorder diagnoses and knee replacement outcomes within the NHS in North East London from January 2014 to January 2024.

**Secondary Objective**

3. To estimate the level of association between severity of disease (for depression and anxiety only), and timing of diagnosis on the three outcomes of interest following knee replacements within the NHS in North East London from January 2014 to January 2024.

**Analysis Plan**

Initial analysis will describe the distribution and prevalence of mental health disorders diagnosis at the time of surgery, for patients undergoing knee arthroplasty.

Following this regression analysis will be conducted to investigate the effects of mental health disorder diagnosis, severity and timing on the outcomes of interest following knee replacement. Outcomes will be measured at 6 months taking into account baseline score and other health confounder variables.

**2. General**

**2.1 SAP scope**

The scope of this SAP is to state the variables of interest from the 3 main data sources, state the populations we intend to focus on during analysis and describe the statistical methods that will be employed to analyse the data.

**2.2 Glossary**

DDS – Discovery Data Service

NJR – National Joint registry

TKR – Total Knee Replacement

MHD – Mental Health Disorders

MH – Mental Health

OKS – Oxford Knee Score

**3. Summary of project and methods of data collection**

This project aims to explore the association between mental health disorders and poor outcomes following knee replacement. The outcomes of interest are poor patient knee function as measured by the ‘Oxford knee score’, complication rate, and the development of ‘Chronic Pain’. We will conduct a retrospective cohort study of routine electronic NHS data. Exposures of interest include mental health diagnosis, the severity of disease, and the timing of disease diagnosis. We will link data from primary care (GP and community), secondary care (hospital), and arthritis / arthroplasty specific data (held by the National Joint Registry).

All data will be taken from routine healthcare databases that record data on standard care in the UK. A description of each database to be used is in Table 1.

Table1 – Database description

|  |  |
| --- | --- |
| Discovery Data Service (DDS) | A clinical partnership programme in London, and recently expanding across the UK. The data service combines all health care monitoring systems in the NE London area, including GP, Social service and Mental health records. It covers approximately 6 million people. It has a data completeness of 95%, and contains demographics, diagnosis codes, health resource use, prescribing data and investigation results. The primary data vocabulary is snowmed CT codes. |
| National Joint Registry (NJR) | The NJR collects data on all joint replacement surgeries, surgeons, and implants in the United Kingdom. The NJR has previously been linked to the national Patient Reported Outcome Measure where patients answer questions about their joint function and general health, pre-operatively and at 6 months post operatively. It has already been proven to be representative of the UK population. It records 2 general wellbeing scores EuroQoL 5D (EQ-5D), EQ visual analogue scale (EQ VAS), in which there are questions also relating to patients Mental Health. It also containing the Oxford Knee Score (OKS), a specific score about knee joint function. |
| Hospital Episode Statistics (HES) | A nation wide ‘data product’ providing robust details about a patients engagement with any hospital in the United Kingdom. It contains information in 4 major categories – inpatient admissions, outpatient appointments, accident and emergency attendances, critical care admissions. The data controlled is NHS England , and the data is used to guide NHS leaders, government and other national bodies / regulators. |

After gaining ethical approval, data access and completing the required data protection impact assessment, we will then perform a encrypted linkage process. In this process each patient is given a pseudonymised patient number (study ID), via an online encryption software. We will then match the study ID’s across the 3 databases to collate a database with granular patient level detail about patients undergoing knee replacement in North East London and their respective mental health disorders.

Details of the data extracted about each patient is included in full in the extraction plan. This has been constructed previously and is published online. Key variables are included in section 6.1

**4. Data selection for study**

Data will be selected for the analysis in the SAP based on the following criteria;

1. Patients in the North East London area as determined by their GP location.

2. Patients with a TKR in any NE London NHS hospital from January 2014 to January 2024. These include Gateway Surgical Centre, King George Hospital, North Middlesex Hospital, Royal Free Hospital, Whips Cross University Hospital, Homerton Hospital, Royal London Hospital, Wittington Hospital, University College London Hospital, Barnet Hospital , Chase Farm Hospital, Queens Hospital, Basildon Hospital, Broomfield Hospital and Braintree Hospital.

3. Patients with linked data from the NJR and DDS.

Patients will be excluded if:

1. They had revision knee arthroplasty, partial or ‘uni’ knee replacements,

2. knee replacements performed privately

3. Data not linked across more than 1 database.

**5. Study details**

**5.1 Study Objectives**

The overall aim of the study :

To explore the relationship between mental health disorders and poor function, surgical complications and chronic pain following knee replacements in the NHS.

**5.2 Analysis objectives**

**5.2.1 Primary objectives**

The primary objectives for the statistical analysis are

1. To estimate the prevalence and distribution of different mental health disorders diagnoses, in patients before they undertake a knee replacement within the NHS in North East London from January 2014 to January 2024.

2. Estimate the association between different mental health disorder diagnoses and (i) patient knee function, (ii) surgical complication rates, and (iii) chronic pain, following knee replacements within the NHS in North East London from January 2014 to January 2024. Patient knee function will be determined by the oxford knee score (described later), Complication rate by re-admission to hospital and chronic pain by EQ5D (described later).

**5.2.2 Secondary objectives**

The secondary objectives for the statistical analysis are :

To estimate the level of association between severity of disease (for depression and anxiety only), and timing of diagnosis (relative to surgery), on patient knee function, surgical complication rates, and chronic pain, following knee replacements within the NHS in North East London from January 2014 to January 2024.

**5.3 Study design**

**Design**

A retrospective observational cohort study using electronic health records

**Setting**

Patients in the North East London area (as determined by their GP) and receiving a TKR in any NE London NHS hospital (previously listed) from January 2014 to January 2024

**Target population**

Patients undertaking a knee replacement in the NHS.

**Nature of follow-up**

6 months, when patients are requested to answer a post operative questionnaire as part of standard follow up care . The outcomes of interest will be assessed at this point.

**Endpoints**

Primary endpoints are

* + - 1. Oxford knee score reported by the patient at 6 months.
      2. Any attendance to AE or admission to hospital in the 6 months immediately following Knee replacement
      3. EQ5D questionnaire reported by the patient at 6 months

**Sample size justification**

The NJR publishes aggregate statistics on the previous 3 years (2020-2023) of operating for each hospital online. From these, the total number of knee replacements for all hospitals in North East London between Jan 2020 – Jan 2023 was 4,619. Extrapolating to 10 years equates to 15,242 knee operations. This will also be an underestimation, as COVID lockdowns occurred in 2020, led to fewer knee operations.

The NJR has a PROMS completion rate of approximately 60%, resulting in complete data sets for an expected 9,145 patients. A conservative estimate for mental health disorders in the arthroplasty population is 10%, however the true number is unknown. With this assumption 900 patients would have our exposure of interest (Mental health disorder) in comparison to 8100 control patients without mental health disorders.

The rate of poor outcomes (as defined by a poor patient score) following knee replacement is approximately 20% (ref). The true effect size of mental health disorders is unknown, however assuming a conservative estimate of 23% poor outcome in the exposure group vs 19% in the control group (effect size of -0.098) between the two groups will provide approximately 83% to test for a difference between groups at the 5% level. We therefore find that our study is adequately powered to detect relatively small but clinically meaningful differences.

**6. Analysis**

**6.1 Definition of analysis data sets**

**Primary analysis**

**How analysis set defined**

The analysis set will be all patients included in the previously constructed database.

**Variables**

**Primary Exposure**

This is the specific diagnosis of mental health disorder. This will be extracted from the discovery data service. Due to the complexity and large number of codes used to describe mental health, patients will be grouped into broad diagnostic groups. These groups are mapped to the DSM5 classifications, which are a validated grouping for MH research. The groups are

1. No MHD
2. Depression (only)
3. Anxiety (only)
4. Mixed Anxiety + Depression
5. Serious Mental Illness (SMI), includes schizophrenia, psychosis + bipolar
6. Pain Disorders (including fibromyalgia + chronic pain)
7. Addiction

**Secondary Exposures**

1. Mental Health Severity. This will be determined using Discovery Data Service data, and guided by NHS guidelines for treating MH. Severity variables will be applied to Depression and Anxiety diagnosis only.. Severity will not be applied to Chronic pain, SMI and alcohol, as the nature of these diagnosis require multiple follow ups and treatments. Severity groupings will be defined as:

1. One attendance to GP with Mental Health Disorder at any point preoperatively.
2. Multiple attendances to GP with a Mental Health Disorder at any point preoperatively.
3. Required first-line treatment at any point preoperatively. (eg = talking therapies)
4. Required second-line treatment at any point preoperatively. (eg = medication prescription)

2. Timing of diagnosis. This will be determined using Discovery Data Service data. Timing variables will be applied to Depression and Anxiety. MHD timing will be based on time from GP appointment (for MHD related complaint) to timing of surgery. Timing of diagnosis will be grouped as

1. No appointments with GP in year leading up to surgery
2. Appointment with GP in year leading up to surgery
3. Appointment with GP within 3 months leading up to surgery

**Outcomes**

Knee function – As recorded in the National Joint Registry. The oxford knee score is a validated questionnaire about patients knee function. Patients submit their score pre-operatively and 6 months post operatively. The post operative score and difference between the two scores will be analysed.

Complication Rate – As recorded in the Hospital Episode Statistics and National Joint Registry. Any attendance to AE or re-admission to hospital in the 6 months post operation.

Chronic Pain – As recorded in the National Joint Registry. The EQ5D is a validated questionnaire relating to patient health. It has questions about chronic pain included. Patients submit their score pre-operatively and 6 months post operatively. Patients reporting pain at 6 months will be considered to have chronic pain.

Confounders

Any other variables known to be associated with poor outcomes following TKR will also be included. These are;

Sex, age, ethnicity, deprivation status (IMD quintile), BMI, smoking status, frailty, medical diagnosis (including Arterial disease, cardiac disease, Stroke, Resp disease, Chronic Kidney disease, Diabetes). This data is included in the Discovery Data Service

**6.2 Definition of the analysis subgroups**

A subgroup analysis will be performed on;

* Sex (Male / Female)
* Ethnicity (White, Black African/Caribbean/British; South Asian (Bangladeshi/Pakistani/Indian); Other including Mixed and Chinese; Not Reported)
* Deprivation level (IMD Quintile)

**6.3 General principles**

**Quantifying uncertainty**

Unless stated otherwise, all statistical tests will be two-sided, and 95% confidence intervals will be used to quantify uncertainty. Where presented, P-values will be given to 2 significant digits without reference to a cut-off or reference to statistical significance. There will be no adjustments for multiple testing.

**Missing data**

The NJR has a completion rate of 97% for hospital data, and a 60% response rate for patient reported outcomes. We expect the link to the discovery data base to have a success rate above 95%, due to the nature of the GP data collected.

To allow for analysis of missing data, data for patients recorded in the NJR but not in the DDS will be monitored to mitigate potential bias. Patient demographics and PROMS outcomes will be compared between those included and excluded from the study group. It will be reported transparently including any assumptions made to ensure integrity and reproducibility. We will be unable to analyse the reverse missing patients, eg those included in the DDS and not in the NJR, due to the data collected by the DDS. Following the analysis of missing data, we will ascertain if the participants with missing outcomes are “missing at random’ (MAR) or missing not at random (MNAR). The primary analysis will be a complete case analysis. Depending on the level and type of data missing, further analysis will be performed accounting for this. Techniques we are likely to consider include multiple imputational analysis and inverse probability weighting.

**Statistical models**

**Descriptive analysis**

Descriptive analysis will include methods commonly used for such aims and be reported with adherence to 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) Guidelines. Basic summary statistics (count data and percentages) will be used to report the prevalence of medical / mental health diagnosis, demographic data and complications . Continuous scores will be reported with means and 95% Confidence intervals.

**Main Analysis**

The main analysis will use generalized linear modelling to explore the relationship between mental health variables and poor outcomes following TKR.

**Outcomes**

For patient reported outcome models a linear regression model will be used. The oxford knee score at 6 months will be used as previously described. For complication and chronic pain, outcomes will be binary and a logistic regression will be used. Complication rate and chronic pain are defined as in part 6.1.

Predictor variables of interest (Mental health diagnosis, severity and timing) will always be grouped as previously described in 6.1. For all models, confounding factors (as described in 6.1) and pre-operative oxford knee score will be adjusted for.

Model Assumptions will be tested during analysis. Linearity and Independence using scatterplots. Homoscedasticity using a goldfield-quant test. Normality of residuals using a Shapiro – wilk test.

**6.4 Software**

Analyses will be performed in R.

**6.5 Analysis**

**Part 1**

Demographic data including sex, age, ethnicity, smoking status, medical diagnosis, Outcomes, PROMS Scores, and complication rate. Counts , percentages and means with confidence intervals will be reported. Please see table 1 for example results table.

Frequency distribution plots for oxford knee score, EQ5D, EQVAS will be constructed to test for normality.

Initial analysis will describe the distribution and prevalence of mental health disorders diagnosis at the time of surgery, for patients undergoing knee arthroplasty. Diagnosis will be grouped as already previously described in section 6.2. Count and percentages will be reported. Please see table 2 for example table.

Secondary analysis will firstly describe the distribution of mental health severity. Severity will be grouped as previously described. MH Severity will be reported individually for Depression and Anxiety. Count data and percentages will be used. Please see example table 3 for example results table.

Final secondary analysis will describe the distribution of mental health diagnosis timing. Timing will be grouped as previously described. MH timing will be reported individually for Depression and Anxiety. Count data and percentages will be used. Please see example table 4 for example results table.

**Part 2**

**Primary Objective**

With the initial analysis complete, main analysis will approach the primary object exploring the relationship between mental health disorder diagnosis and poor outcomes following knee replacements. Separate regression models will be used for each of the outcomes of interest, (PROMS, Complication rate, Chronic Pain). Model details are described in section 6.3 For all regression models the coefficient estimate, standard error, z score and P value will be reported. Please see table 5 for example results table. The differing models are listed below.

2A – Linear regression model, predictor variable – mental health diagnosis, outcome – oxford knee score

2B – Logistic regression model, predictor variable – mental health diagnosis, outcome – complication rate

2C - Logistic regression model, predictor variable – mental health diagnosis, outcome – chronic pain

**Secondary Objective**

The secondary analysis will be limited those patients with depression and anxiety only. Each of the diagnosis will be considered in isolation. Exposures of interest will be the previously mentioned severity of mental health disease and timing of diagnosis. Participants will be grouped as previously described, with regression model parameters as described for the primary objective and in section 6.3. The differing models are listed below in table 6.

Table 6 - Regression models

|  |  |  |  |
| --- | --- | --- | --- |
| Analysis | GLM | Predictor | Outcome |
|  |  |  |  |
| 3A | Linear | Depression Severity | Oxford Knee |
| 3B | Linear | Anxiety Severity | Oxford Knee |
|  |  |  |  |
| 3C | Logistic | Depression Severity | Complication rate |
| 3D | Logistic | Anxiety Severity | Complication rate |
|  |  |  |  |
| 3E | Logistic | Depression Severity | Chronic Pain |
| 3F | Logistic | Anxiety Severity | Chronic Pain |
|  |  |  |  |
| 4A | Linear | Depression Timing | Oxford Knee |
| 4B | Linear | Anxiety Timing | Oxford Knee |
|  |  |  |  |
| 4C | Logistic | Depression Timing | Complication rate |
| 4D | Logistic | Anxiety Timing | Complication rate |
|  |  |  |  |
| 4E | Logistic | Depression Timing | Chronic Pain |
| 4F | Logistic | Anxiety Timing | Chronic Pain |
|  |  |  |  |

**6.6 Sensitivity Analyses**

Sensitivity analyses will be conducted to test for robustness and reliability of results.

Missing data will be tested as previously noted.

Further sensitivity analysis will consider the timing and severity criteria in the sub group analysis, with different parameters for each of the groups. Depending on the distribution of patients in the timing and severity groups, group parameters may be adjusted to allow for even distribution across the four groups.

Further sensitivity analysis will examine the impact of varying model specifications, outlier treatment and other potential sources of bias as identified during our primary analysis.

**6.7 Exploratory analysis**

Following the main analysis, further exploratory analysis may be conducted;

* The effects of mental health disorder on knee arthroplasty revision rate
* More specific investigation into chronic pain outcomes and predictors
* Considering mental health as an outcome variable

**7.0 Signatures of Approval**

The sign-off relates to the SAP version 1.0, dated dd/mm/2021

|  |  |  |  |
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**Appendix 1: Dummy Tables**

Table 1; Demographic Data

|  |  |  |
| --- | --- | --- |
| Demographic |  | Total Number (% / CI) |
|  |  |  |
| Sex | Male | N(N) |
|  | Female | N(N) |
| Mean Age |  | N(CI) |
| Ethnicity | White | N(N) |
|  | Black | N(N) |
|  | South Asian | N(N) |
|  | Other | N(N) |
| BMI |  | N(N) |
| Smoking Status | Current | N(N) |
|  | Past | N(N) |
|  | Non Smoker | N(N) |
| Medical Diagnosis | Arterial Disease | N(N) |
|  | Cardiac Disease | N(N) |
|  | Stroke | N(N) |
|  | Resp | N(N) |
|  | CKD | N(N) |
|  | Diabetes | N(N) |
| Outcomes (PROMS) | OKS | N(CI) |
|  | EQ5D | N(CI) |
|  | EQVAS | N(CI) |
| Outcomes (PROMS) | OKS | N(CI) |
|  | EQ5D | N(CI) |
|  | EQVAS | N(CI) |
| Complication Rate |  | N(N) |

Table 2 – Mental Health Diagnosis Table

|  |  |  |
| --- | --- | --- |
| Diagnosis |  | Total Number (% of TKR population) |
|  |  |  |
| No MH |  | N(N) |
| Depression (only) |  | N(N) |
| Anxiety (only) |  | N(N) |
| Mixed Anxiety and Depression |  | N(N) |
| Serious Mental Illness |  | N(N) |
| Pain Disorders |  | N(N) |
| Alcohol Addiction |  | N(N) |

Table 3 – Mental Health Severity

|  |  |  |
| --- | --- | --- |
| Severity Level |  | Total Number (% of population) |
|  |  |  |
| One attendance to GP |  | N(N) |
| Multiple attendances |  | N(N) |
| Required 1st line treatment |  | N(N) |
| Required 2nd line Treatment |  | N(N) |

Table 4 – Mental Health Timing

|  |  |  |
| --- | --- | --- |
| Timing of diagnosis |  | Total Number (% of Population) |
|  |  |  |
| 1 year + |  | N(N) |
| Within 1 year |  | N(N) |
| Within 3 months |  | N(N) |

Table 5 – Generalized Linear Model Results

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Predictor | Estimate | SE | Z | P |
|  |  |  |  |  |
| MH Diagnosis | N | N | N | N |
| Sex | N | N | N | N |
| Age | N | N | N | N |
| Deprivation | N | N | N | N |
| BMI | N | N | N | N |
| Smoking | N | N | N | N |
| Frailty | N | N | N | N |
| Medical diagnosis | N | N | N | N |
| Pre op PROMS | N | N | N | N |