

RESEARCH PROTOCOL:

Characterizing surgery for wrist arthritis and its outcomes: protocol for an OHDSI network study

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1. List of Abbreviations

BSSH	British Society for Surgery of the Hand
EHDEN	European Health Data and Evidence Network
OMOP	Observational Medical Outcomes Partnership
OHDSI	Observational Health Data Science and Informatics
PRC	Proximal row carpectomy
FCA	Four corner arthrodesis
SLAC	Scaphoid Lunate Advanced Collapse
SNAC	Scaphoid Non-union Advanced Collapse
SNOMED	Systematized Nomenclature of Medicine
AIN/PIN	Anterior intraosseous nerve/ posterior intraosseous nerve
DISI	Dorsal intercalated segmental instability

2. Responsible Parties

2.1. Investigators and Authors

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Authorship will also include those who meaningfully contribute to study design, analysis and interpretation of results during the British Society for Surgery of the Hand (BSSH) Studyathon 8-10th September 2021, and subsequently contribute to the drafting of the work for publication, approving the final version of the study. Full guidance related to how to qualify for meaningful contribution can be found on the OHDSI website: <https://www.ohdsi.org/wp-content/uploads/2021/07/OHDSI-Authorship-Guidance.pdf>. The Responsible Parties involved in this protocol take accountability for the overarching protocol, package development, providing assistance to sites running the analysis and ensuring site-specific governance is adhered to in all publications generated from this protocol.

2.2 Sponsor

This study will be undertaken by Observational Health Data Science and Informatics (OHDSI), an open collaboration.[1]

DPA receives partial support from the National Institute for Health Research Oxford Biomedical Research Centre and Senior Research Fellowship. **GH** receives grant funding from the US National Institutes of Health and contracts from Janssen Research and Development. **PBR** is an employee of Janssen Research and Development and shareholders in Johnson & Johnson. **KK** receives consulting fees from the National Institutes of Health outside of this submitted work.

Participating data owners will be responsible for self-reporting any grants funding the conversion and maintenance of their OMOP CDM. A full list of disclosures will be generated once final authorship is established during the study-a-thon. Disclosures will be reported in accordance with publication policies of journals papers are submitted to. No other disclosures reported.

3. Abstract

In this study we will describe the baseline demographic and clinical characteristics of individuals who undergo surgical management of wrist arthritis, in addition to the incidence of serious adverse outcomes following surgery.

4. Amendments and Updates

Number	Date	Section of study protocol	Amendment or update	Reason

5. Rationale and Background

Wrist arthritis is clinically defined as the presentation of progressive wrist pain, altered joint mechanics and instability. It predominantly occurs at the radiocarpal joint, but also affects the midcarpal joint, and has a varied aetiology, including primary osteoarthritis, inflammatory arthritis, and posttraumatic degenerative change.[2-4] Rarely, wrist arthritis can be generated through idiopathic avascular necrosis of the lunate (Kienbock's disease) or scaphoid (Preiser's disease).[5, 6] Posttraumatic arthritis at the radiocarpal joint can be divided into scapholunate advanced collapse (SLAC) and scaphoid nonunion advanced collapse (SNAC).[7] SLAC arthritis is the more common cause of posttraumatic wrist arthritis and occurs following injury to the scapholunate ligament causing chronic diastasis between the scaphoid and lunate bones. The dissociation between the scaphoid and the lunate generates radiocarpal and midcarpal instability, leading to abnormal force transmission across these joints, causing a DISI (dorsal intercalated segmental instability) deformity. SNAC occurs following chronic non-union of a scaphoid fracture, and follows a similar pattern of radiocarpal and midcarpal instability which can also lead to arthritis.[8, 9]

Early in the disease process degenerative wrist disease can be treated with wrist denervation with or without radial styloidectomy, or with motion sparing techniques such as a proximal row carpectomy or partial wrist fusion (arthrodesis).[10-27] As the arthritis progresses, more involved techniques such as total wrist joint arthrodesis or arthroplasty (replacement) may be required.[28, 29] There is some debate as to whether procedures such as PRC should be limited to those who do not have inflammatory conditions, or who are younger than 35-40 years of age.[30-32] Wrist arthritis is relatively rare compared to other conditions, and is currently treated using a heterogeneous group of surgical options without consensus.[32-36] In this sense, this condition lends itself to multicentre observational research.

Conducting multicentre research using data sources mapped to the Observational Medical Outcomes Partnership (OMOP) common data model (CDM) provides a unique opportunity to compare populations and healthcare systems, allowing for robust analyses to be performed in a timely manner across a network of sites.[37]

This OHDSI study will be formulated alongside and informed by a systematic review undertaken within the BSSH study-a-thon to ensure the most up to date knowledge from the literature is used to inform study design alongside clinical and scientific expertise.

6. Objective

The primary objective of this study is to describe the baseline demographic and clinical characteristics of individuals undergoing surgery for wrist arthritis, in addition to the occurrence of adverse outcomes following surgery. This will be explored overall and if sufficiently sampling exists, to also examine treatments and outcomes by sex, age and surgical subtype.

7. Methods

7.1 Data Sources

This study is a multinational cohort study describing the baseline characteristics, treatments and outcomes of 3 cohorts, namely:

1. All patients with wrist arthritis who have undergone surgical management
2. Subgroups based upon of type of surgery undertaken
3. Subgroups based upon aetiology of wrist arthritis

We intend to solicit participation from a variety of healthcare settings in multiple geographies. Our project includes a UK general practice EHR database, multiple U.S. (New York City, San Francisco, Baltimore) health systems databases, and one Spanish EHR database will test the operability of the analysis package at their sites (**Table 1**). Should more data partners wish to participate, this analysis could extend to any additional databases that are formatted to the Observational Medical Outcomes Partnership-Common Data Model (OMOP-CDM). These analyses will reflect the clinical experience of patients from the US and the United Kingdom and any other country participating in this study. We welcome those with data mapped to the OMOP-CDM to join us in executing this study if they are willing to participate.

The study will be conducted using data from real world data sources that have been mapped to the OMOP- CDM in collaboration with the Observational Health Data Sciences and Informatics (OHDSI) and European Health Data and Evidence Network (EHDEN) initiatives. The OMOP-CDM (<https://github.com/OHDSI/CommonDataModel/wiki>) includes a standard representation of health care experiences (such as information related to drug utilization and condition occurrence), as well as common vocabularies for coding clinical concepts, and enables consistent application of analyses across multiple disparate data sources.[38]

Table 1. Participating Data sources mapped to the OMOP CDM

Data source	Source population	Sample size	Data type	Longitudinal history
CPRD	UK General Practice	≈ 13 million	National primary care dataset with conditions, prescriptions, vaccinations, measurements, observations and referrals as well as mortality data	1989
Columbia University Irving Medical Center	Patients of the Columbia University Irving Medical Center (New York City, USA)	≈ 6 million	General practice electronic health records, outpatient specialist electronic health records, inpatient hospital electronic health records, hospital billing/summary	1989 (1978 for diagnoses)
Stanford Medicine Research Data Repository (STARR)	Patients of Stanford University (San Francisco Bay Area, USA)	≈ 3 million	General practice electronic health records, outpatient specialist electronic health records, inpatient hospital electronic health records, hospital billing/summary	2008
The Information System for Research in Primary Care (SIDIAP)	General population in Catalonia, Spain	≈ 8 million	Electronic health records from primary care partially linked to inpatient data. SIDIAP is also linked to pharmacy dispensations and primary care laboratories. Healthcare is universal and tax-payer funded in the region, and primary care physicians are gatekeepers for all care and responsible for repeat prescriptions.	2006
Johns Hopkins University of California Health Data Warehouse (UCHDW)	<i>tbc</i> Population of California represented by the patients of UC-San Francisco, UC-Davis, UC-San Diego, UC-Irvine, UC-Los Angeles and UC-Riverside, including a small fraction of patients outside of California receiving care in any of the UC affiliated hospital.	<i>tbc</i> ≈ 7 million	<i>tbc</i> UC-Wide inpatient hospital electronic health records, outpatient specialist electronic health records and general practice electronic health records including hospital billing records and summaries. UC self-funded employee health plan claims, and UC-wide electronic health records linked with California death registry.	<i>tbc</i> 2012

7.2 Study design

The study will be an observational cohort study based on routinely-collected health care data which has been mapped to the OMOP-CDM. Cohorts of individuals undergoing surgery for wrist arthritis will be identified. Characteristics of these individuals at their index date will be described. Treatments and outcomes of these individuals after their index date will be described.

7.3 Target cohorts

Persons in the main target cohort for *all surgically managed wrist arthritis* will:

- have a record of a first surgery for wrist arthritis (index event)

Persons in secondary target cohorts:

For cohorts by surgical intervention:

#1 PRC

- have a record of a first proximal row carpectomy (index event)

#2 PWA – partial wrist arthrodesis (will capture RSL, RL, other midcarpal fusions)

- have a record of a first partial wrist arthrodesis (index event)

#3 Total Wrist fusion

- have a record of a first wrist fusion (index event)

#4 Radial styloidectomy

- have a record of a first Radial styloidectomy (index event)

#5 Wrist (AIN/ PIN) denervation

- have a record of a first wrist denervation (index event)

#6 – wrist arthroplasty

- have a record of any form of wrist arthroplasty (including total wrist and pyrocarbon interposition if identifiable) (index event)

#7 – wrist arthroscopy

- have a record of wrist arthroscopy (index event)
- have a record of SLAC, SNAC, Kienbocks disease, Preisers disease, Rheumatoid arthritis or crystalline deposition any time prior to and including the date of index event

For cohorts by disease aetiology:

#8 SLAC

- have a record of a first surgery for wrist arthritis (index event)
- have a record of SLAC any time prior to and including the date of the index event

#9 SNAC

- have a record of a first surgery for wrist arthritis (index event)
- have a record of SNAC any time prior to and including the date of the index event

#10 Idiopathic

- have a record of a first surgery for wrist arthritis (index event)
- have a record of Kienbocks or Preisers disease any time prior to and including the date of the index event

#11 Rheumatoid arthritis

- have a record of a first surgery for wrist arthritis (index event)
- have a record of rheumatoid arthritis any time prior to and including the date of the index event

#12 Crystalline deposition (gout, pseudogout)

- have a record of a first surgery for wrist arthritis (index event)
- have a record of gout or pseudogout any time prior to and including the date of the index event

These cohorts will all be identified without any requirement for prior observation time, and also with the added restriction of having a minimum of 365 days of prior observation time available in order to assess how large proportion of subjects fall ill without previous healthcare encounters, and if their inclusion in analyses would change results or conclusions.

7.4 Follow-up

Different index dates will be used for each of the cohorts above:

Target Cohort #1:

Index event: first surgery for wrist arthritis
Follow-up: 30 days after the index event.

Target Cohort #2:

Index event: first surgery for wrist arthritis
Follow-up: 90 days after the index event.

If follow up allows Target Cohort #3:

Index event: first surgery for wrist arthritis
Follow-up: 365 days after the index event.

If follow up allows Target Cohort #4:

Index event: first surgery for wrist arthritis
Follow-up: 1825 days after the index event.

7.5 Stratifications

Each target cohort will be analysed in full and stratified on factors based on the following pre-index characteristics, all stratum are pending meeting minimum reportable cell counts (as specified by data owners) and where possible, may include:

- Follow-up time: overall, with full 30 days follow-up, without full 30 days follow-up
- Sex (Male vs. Female)
- Those with another type of specified hand surgery prior to index procedure (eg denervation prior to arthrodesis)
- All reportable age groups as well as specifically:
 - Young age (Age ≥ 35)
 - Elderly (Age ≥ 65). If sample size allows, results will be reported stratified in the following age categories: 65-84 years, and ≥ 85 years, or in finer age strata (65-69, 70-74, 75-79, 80-84, ≥ 85 years)

7.6 Features of interest

May include:

Pre-index characteristics

These features will be described as assessed in two different time windows: the last 30 days (-1 to -30 days) and the year (-1 to -365 days) pre-index:

Demographics:

- Age: calculated as year of cohort start date – year of birth and with 5 year groupings
- Sex
- Race
- Measures of comorbidity (such as Charlson comorbidity index or isolated comorbidities of interest)

Concept-based:

- Condition groups (SNOMED + descendants), ≥ 1 occurrence during the interval
- Drug era groups (ATC/RxNorm + descendants), ≥ 1 day during the interval which overlaps with at least 1 drug era

Cohort-based: (to be added if relevant from lists)

Post-index characteristics

These features will be described in two different time windows: at index date (day 0) and in the 30 days from index date (0 to 30 days). As time elapses, additional windows of time will be investigated (eg. in the 90 days from index date [0 to 90 days]) and where possible for some surgical outcomes up to 1 and 5 years following surgery. The characteristics will include:

Concept-based:

- Condition groups (SNOMED + descendants), ≥ 1 occurrence during the interval
- Drug era start groups (ATC/RxNorm + descendants), ≥ 1 drug era start during the interval

Cohort-based Medical outcomes:

- Acute kidney injury (AKI) diagnosis during hospitalization
- Acute kidney injury (AKI) using diagnosis codes and change in measurements during hospitalization
- Acute myocardial infarction events
- Angina during hospitalization
- Bleeding during hospitalization
- Bradycardia or heart block during hospitalization
- Cardiac arrhythmia during hospitalization
- Cardiovascular-related mortality
- Death
- Deep vein thrombosis events
- Renal/Dialysis during hospitalization
- Heart failure during hospitalization
- Hemorrhagic stroke (intracerebral bleeding) events
- Hospitalization episodes
- Intensive services during hospitalization
- Ischemic stroke events
- Mechanical ventilation during hospitalization
- Persons with chest pain or angina
- Pneumonia during hospitalization
- Pneumonia episodes
- Pulmonary Embolism events
- Sepsis during hospitalization
- Stroke (ischemic or hemorrhagic) events
- Supraventricular arrhythmia during hospitalization
- Total cardiovascular disease events
- Transient ischemic attack events
- Venous thromboembolic (pulmonary embolism and deep vein thrombosis) events
- Ventricular arrhythmia or cardiac arrest during hospitalization

Cohort-based Surgical outcomes:

- Wound infection requiring antibiotics
- Wound infection requiring surgical management
- Deep surgical site infection including septic arthritis
- Neurovascular injury
- Tendon injury
- Fracture
- Prominent metalwork
- Reoperation

- Non-union

7.7 Analysis: Characterizing cohorts

All analyses will be performed using code developed for HADES (Health Analytics Data-to-Evidence Suite), formerly known as the OHDSI Methods library.[39] The code for this study can be found at <https://github.com/oxford-pharmacoepi/BSSHStudyathon2021>. A diagnostic package, built off the OHDSI Cohort Diagnostics (<https://ohdsi.github.io/CohortDiagnostics/>) library, is included in the base package as a preliminary step to assess the fitness of use of phenotypes on your database. If a database passes cohort diagnostics, the full study package will be executed. Baseline covariates will be extracted using an optimized SQL extraction script based on principles of the FeatureExtraction package (<http://ohdsi.github.io/FeatureExtraction/>) to quantify Demographics (Gender, Prior Observation Time, Age Group), Condition Group Eras and Drug Group Eras (at and within 30 days after index date, at index date, within 30 days before index date, and within 365 days before index date). Additional cohort-specific covariates will be constructed using OMOP standard vocabulary concepts.

At the time of executing Feature Extraction, the package will create a data frame in which individuals' age and sex will be extracted. Individuals' medical conditions, procedures, measurements and medications will be summarized 1) over the year prior to their index date (-365d to -1d), 2) over the 30 days before index date (-30d to -1d), 3) at index date (0d), and 4) at and over the 30 days after index date (0d to 30d). Number and proportion of persons with feature variables during time-at-risk windows will be reported by target cohort and specific stratifications. Standardized mean differences (SMD) will be calculated when comparing characteristics of study cohorts, with plots comparing the mean values of characteristics for each of the characteristics (with the color indicating the absolute value of the standardized difference of the mean).

7.8 Logistics of Executing a Federated Analysis

Sites will run the study analysis package locally on their data coded according to OMOP-CDM. Only aggregate results will be shared with the study coordinator. Result files will be automatically staged into a ZIP file that can be transmitted using the OhdsiSharing R Library (<http://ohdsi.github.io/OhdsiSharing/>) or through a site's preferred SFTP client using a site-specific key provisioned by the OHDSI Study Coordinator. Local data stewards are encouraged to review study parameters to ensure minCellCount function follows local governance. At a minimum, it is encouraged to keep this value to >5 to avoid any potential issues with re-identification of patients. An example of tables and figures can be seen in Section 13. (Note: covariates are constructed using controlled ontologies from the OMOP standard vocabularies though some labels may be replaced with publication-friendly labels due to space restrictions of the submitting journal.)

8. Sample Size and Study Power

The study package will be designed to suppress any analyses which have less than 5 unique persons. This parameter is configurable and can be adjusted by the analyst executing the

package, should their institution require a different threshold. This means that each data owner will only generate results for target-stratum-feature pairs that meet this minimum threshold. This study is descriptive in nature and not designed for causal inference. Only cohorts or stratified sub-cohorts with a minimum sample size of 140 subjects were characterized. This cut-off was deemed necessary to estimate with sufficient precision the prevalence of a previous condition or 30-day risk of an outcome affecting $\geq 10\%$ of the study population.

9. Strengths and Limitations

9.1 Strengths

To our knowledge, this is one of the world's largest observational sets of analyses of secondary health data investigating the surgical management of wrist arthritis. We aim to run a multi-country, multi-centre characterization study to understand baseline covariates, treatments and outcomes observed in wrist arthritis, and to identify the potential difference in surgical subtypes undertaken in different patient groups. Where possible, we aim to compare the trends in outcomes from surgery based upon surgical subtype undertaken and disease aetiology. This study uses the OMOP common data model and standard vocabularies to encourage interoperability and portability of phenotypes utilized in this analysis. Using the collaboration between data scientists, epidemiologists and clinical surgeons, the aim is to generate robust phenotypes for surgical subtypes, surgical disease aetiology and for serious adverse outcomes following surgery that will be of use to the OHDSI open science community in future. The use of a federated study model will ensure no movement of patient-level data from institutions participating in this analysis. This is critically important to ensure the protection of patient privacy in the secondary use of routinely collected patient data. Data custodians will remain in control of the analysis run on these data.

9.2 Limitations

This study focuses upon a condition that includes the potential for many different surgical treatments and condition aetiology. This may show temporal, and geographical variability that represents true surgical practice, or may also be related to surgeon preference rather than disease incidence and demographic variability between sites. The different disease aetiologies that may lead to surgeries being undertaken may vary, and therefore there is a risk of confounding by indication. Similarly, availability of devices used for some surgeries may not be universally available, although this is less likely in the US and UK datasets currently included. The case definition may inherently vary over calendar time and may require, as time continues, adjustment for known issues in case classification. This may be particularly prominent in procedure occurrence in US data sources due to the ICD9-10 conversion in October 2015.

Medical conditions for comorbidity or representing serious adverse events may be underestimated as they will be based on the presence of condition codes, with the absence of such a record taken to indicate the absence of a disease. Meanwhile, medication records indicate that an individual was prescribed or dispensed a particular drug, but this does not necessarily mean that an individual took the drug as originally prescribed or dispensed. Our

study could be subject to exposure misclassification with false positives if a patient had a dispensing but did not ingest the drug, but may also be subject to false negatives for non-adherent patients who continued their medication beyond the days supply due to stockpiling. Medication use estimates on the date of hospitalization is particularly sensitive to misclassification, and may conflate baseline concomitant drug history with immediate treatment upon admission. Observed differences may be explained by changes in clinical practice or data capture procedures over time, rather than by differences in the individuals themselves. This is likely a particular relevant drawback for any comparison of medication use.

10. Protection of Human Subjects

The study uses only de-identified data. Confidentiality of patient records will be maintained at all times. Data custodians will remain in full control of executing the analysis and packaging results. There will be no transmission of patient-level data at any time during these analyses. Only aggregate statistics will be captured. Study packages will contain minimum cell count parameters to obscure any cells which fall below allowable reportable limits. All study reports will contain aggregate data only and will not identify individual patients or physicians.

11. Management and Reporting of Adverse Events and Adverse Reactions

This study will provide a descriptive summary of individuals at time of surgery for wrist arthritis. The main focus is upon adverse events within the first 90 days following surgery, and those events over five years following surgery are outside the scope of the study.

12. Plans for Disseminating and Communicating Study Results

All results will be posted on a freely available and accessible website such as the OHDSI website (evidence.ohdsi.org) after completion of the study. Results are aimed for publication in a clinically focused peer reviewed scientific journal to inform future shared patient and clinician decision making regarding the role of surgery in wrist arthritis. The results will also be presented at the OHDSI and BSSH in-person events.

13. References

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