TITLE PAGE

PASS information

Title	
Protocol version identifier	1.3
Date of last version of protocol	1/12/2020
EU PAS register number	**The risk of musculoskeletal adverse outcomes after treatment with endocrine blocking treatments for breast cancer**
Active substance	Tamoxifen (L02BA01), Aromatase Inhibitor (Exemestane L02BG06, Letrozole L02BG04; Anastrozole L02BG03, vorozole L02BG05)
Medicinal product	Tamoxifen, Aromatase Inhibitor
Research question and objectives	The objective is to evaluate the comparative risk of musculoskeletal side effects of tamoxifen versus aromatase inhibitors
Country(-ies) of study	To be confirmed. Provisionally included: United Kingdom, Germany, Spain, and the United States of America
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1. TABLE OF CONTENTS

The study protocol should include a table of contents. The following table of contents can be used if this guidance serves as a template (select the table of content and press "F9" to update the page numbers).

2. LIST OF ABBREVIATIONS

Ca	Cancer
AI	Aromatase inhibitor
EXE/ SAIs	Exemestane/ Steroidal AIs
NSAIs	Non-steroidal AIs
TMX	Tamoxifen
CTS	Carpal tunnel syndrome
OA	Osteoarthritis
THR	Total hip replacement
TKR	Total knee replacement

3. RESPONSIBLE PARTIES

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5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason

7 RATIONALE AND BACKGROUND

Large randomised control trials (RCT)s have shown significant improvement in breast cancer survival and time to recurrence with the use of aromatase inhibitors (AI) for post-menopausal women.[1-3] As two thirds of breast cancer is thought to be hormone receptor positive, AIs have produced a significant impact on survivorship. Aromatase inhibitors prevent the peripheral production of oestrogen by preventing androgens

converting into oestrogens. Two main forms exist: non-steroidal reversible inhibitors such as letrozole and anastrozole, and steroid irreversible inhibitors such as exemestane.[4-6] Tamoxifen was the traditional treatment of choice for oestrogen inhibition prior to the introduction of AIs, and is still widely used in pre-menopausal women.

Five year survivorship from breast cancer has now increased to over 90%, leading to an increasing interest in understanding the adverse outcomes associated with treatment.[7] AIs are known to be associated with musculoskeletal side effects.[8] Osteoporosis and increased fracture risk have been observed in AI users, especially in prolonged duration of treatment and when compared to tamoxifen.[9-13] Recent work in Catalonia has also shown increased fracture risk associated with AI use, but that this risk can be reduced through bisphosphonate use.[14]

Several large trials have investigated musculoskeletal symptoms as secondary outcomes to disease-free survival and recurrence. A higher incidence of carpal tunnel syndrome (CTS), hand pain and numbness associated with median nerve compression at the wrist was found in the ATAC, IBIS II and IES breast cancer trials.[15-17] Increased incidence of CTS with AI has been found in a retrospective case series of electronic health records from Tunisia, but has otherwise not been investigated in observational data.[18] Tendinopathy has also been reported in the literature to occur following AI use, but only in case reports or small case series.[19,20]

Arthralgia is a commonly reported side effect with AI use that has been reported to be as high as 50%.[8,21] Again, trials have investigated the incidence side effects, reporting increased incidence of joint symptoms (defined as arthralgia, arthrosis, arthritis or joint disorder) with the use of AIs compared to tamoxifen. Symptoms occur especially within the first year of use, and especially prominent in those women using hormone replacement therapy (HRT) prior to breast cancer treatment.[22] To date, RCTs have not investigated if AI use is associated with the development of osteoarthritis (OA).

There is biological plausibility for the mechanism by which AIs may cause musculoskeletal symptoms. Reduction in oestrogen associated with AI use has been shown to be associated with reduced bone mineral density.[11,12] Tenosynovial changes have been seen on MRI for women taking AIs that may explain development of CTS.[22] The role of oestrogen has been well documented in osteoarthritis, with animal models noting cartilage degradation after ovariectomy, and a relationship also documented in women following oophorectomy.[23,24] Aromatase has been found in cartilage for oestrogen production *in situ.*[25] In humans, reduced expression of aromatase has been found in tissue taken from patients with hip osteoarthritis in comparison to those with hip fracture.[26]

With the advent of digitalisation of healthcare, the ability to undertake large scale observational studies has increased. The OHDSI (Observational Health Data Sciences and Informatics) community aims to improve healthcare research through facilitating international collaboration between observational datasets. Designing the study in accordance with the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) will enable the study to be replicated within the OHDSI community

in a distributed fashion, with the same analytic code applied across sites and no need to share patient-level data. This study is designed to be informative about the risks of musculoskeletal adverse outcomes associated with breast cancer treatment in the individual countries, but also within a worldwide community of data partners.

8. RESEARCH QUESTION AND OBJECTIVES

The aim of this study is to assess the comparative risk of musculoskeletal adverse events in post menopausal women taking of tamoxifen (TMX) versus Aromatase Inhibitors (AI) used in the treatment of breast cancer. Secondly if sufficiently powered, this study aims to assess the comparative risk of musculoskeletal adverse events in those taking non-steroidal AIs (NSAIs) versus steroidal AIs (SAIs), and to compare the anatomical location of and incidence of surgically treated musculoskeletal adverse events.

9. RESEARCH METHODS

9.1. STUDY DESIGN

2 studies will be undertaken

1. A new user cohort study estimating the risk of musculoskeletal events following the use TMX compared to AIs in a multinational, multi-database network.
2. A new user cohort study estimating the risk of musculoskeletal events following the use of NSAIs versus SAIs will also be undertaken if sufficient patients are identified.

9.2. SETTING

Participants from at least 2 European countries (United Kingdom, and Spain) and the United States of America are proposed for inclusion. Additional databases will be analysed using the same analytical packages as they join the distributed data network.

Electronic health records and administrative claims from primary care and secondary care will be utilised.

The study will be conducted using data from a large network of real world data sources previously mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) in collaboration with the Observational Health Data Sciences and Informatics (OHDSI) and European Health Data and Evidence Network (EHDEN) initiatives.

9.2.1. STUDY PERIOD

The study period, when index events and outcomes of interest can be observed, will start from 01/01/2006 and end at the latest available date for all data sources in 2020.

9.2.2. STUDY POPULATION: INCLUSION/EXCLUSION CRITERIA

Participants will be identified using pre-specified concept sets reviewed by a core team of clinicians, epidemiologists, vocabulary experts, and health data scientists with extensive expertise in the use of the OMOP CDM and the OHDSI tools.

New user exposure cohorts

Exposure cohorts will be defined where first identified treatment initiation is the index event and includes the following criteria:

- History of Breast cancer: Have a condition occurrence indicating breast cancer any time before within the past 365 days or on the same day as the index event *(+breast surgery for cancer if appears necessary to identify cases following cohort diagnostics)*
- Female sex
- Be aged 55 years or over at index event
- Have at least 365 days of continuous observation time prior to index event.
- No history of secondary malignancy

Concept ID	Concept name	Domain	Excluded?
4112853	Malignant tumour of breast	Condition	
432851	Secondary malignant neoplastic disease	condition	X

AI cohort (Target)
Index event is defined as the first recorded dispensing/prescription of AI in a patient's history; inferred persistent exposure by allowing up to 30 day gaps between dispensing/prescription records.
The patient should also have no occurrences of tamoxifen use prior to or after the index event.

SAI (target subgroup)
Index event is defined as the first recorded dispensing/prescription of SAI in a patient's history; all other restrictions of main cohort apply (including prior use of NSAI)

NSAI (target subgroup)
Index event is defined as the first recorded dispensing/prescription of NSAI in a patient's history; all other restrictions of main cohort apply (including prior use of SAI)

Tamoxifen cohort (comparator)
Index event is defined as the first recorded dispensing/prescription of TMX in a patient's history; inferred persistent exposure by allowing up to 30 day gaps between dispensing/prescription records.
The patient should also have no occurrences of AI use prior to or after the index event

9.2.3. FOLLOW UP

Cohort studies

The index date is defined by the first dispensing/prescription as described in the cohort definitions above (Section 9.2.2.) Cohort exit is defined by the end of observation, death, or occurrence of a specified outcome, each outcome considered within an individual analysis. Two periods of follow-up will be considered for two types of analyses for the serious adverse effect outcomes:

In an *intention-to-treat analysis*, the analysis follow-up starts 1 day after the index date and continues up until the first of: outcome of interest, date of death (where available), loss to follow-up, or 30 days after the index date. Patients are required to have at least 1 day of follow-up.

In an *on-treatment analysis*, the analysis follow-up starts 1 day after the index date and continues until the first of: discontinuation/switching/combined therapy of index therapy plus a lag time of 30 days, outcome of interest, date of death (where available), loss to follow-up. Patients are required to have at least 1 day of follow-up.

9.3. VARIABLES

9.3.1.- EXPOSURES

Two active comparator analyses will be conducted. First, AI (target) will be compared to TMX (comparator). Second, NSAI (target) versus SAI (comparator).
Concept IDs for the AI ingredients are below:

Target drug group	**Concept ID**	**Concept name**
Aromatase Inhibitors	21603838	Aromatase inhibitors
	45803469	anastrozole 1mg/1 ORAL TABLET
	45629142	anastrozole 1mg/1 ORAL TABLET
	45633960	anastrozole 1mg/1 ORAL TABLET
	45636441	anastrozole 1mg/1 ORAL TABLET
	45671055	anastrozole 1mg/1 ORAL TABLET
	45678497	anastrozole 1mg/1 ORAL TABLET
	45703064	anastrozole 1mg/1 ORAL TABLET
	45782425	anastrozole 1mg/1 ORAL TABLET

Concept IDs for the SAI ingredients are below:

Target drug group	**Concept ID**	**Concept name**
	21603844	Exemestane

Concept IDs for the NSAI ingredients are below:

Target drug group	**Concept ID**	**Concept name**
	21603843	Vorozole
	21603842	Letrozole
	21603841	Anastrozole

Concept IDs for the Tamoxifen ingredients are below:

Concept ID	**Concept name**
21603831	Tamoxifen; oral
45661594	tamoxifen citrate 20mg/1 ORAL TABLET
45688368	tamoxifen citrate 10mg/5mL ORAL LIQUID [soltamox]
45778750	tamoxifen citrate 10mg/1 ORAL TABLET, FILM COATED

45777985	tamoxifen citrate 10mg/1 ORAL TABLET
45666144	tamoxifen citrate 10mg/1 / 20mg/1 ORAL TABLET, FILM COATED
45624491	tamoxifen citrate 10mg/1 / 20mg/1 ORAL TABLET, FILM COATED
45690920	tamoxifen citrate 10mg/1 / 20mg/1 ORAL TABLET
45781760	tamoxifen citrate 10mg/1 / 20mg/1 ORAL TABLET
42807178	TAMOXIFEN CITRATE - tamoxifen citrate tablet, film coated
35902966	TAMOXIFEN CITRATE - tamoxifen citrate tablet, film coated
44337470	TAMOXIFEN CITRATE - tamoxifen citrate tablet, film coated
42801523	TAMOXIFEN CITRATE - tamoxifen citrate tablet, film coated
44337587	TAMOXIFEN CITRATE - tamoxifen citrate tablet, film coated
42805848	TAMOXIFEN CITRATE - tamoxifen citrate tablet, film coated
44361432	TAMOXIFEN CITRATE - tamoxifen citrate tablet, film coated
45631182	TAMOXIFEN CITRATE - tamoxifen citrate tablet, film coated
45665346	TAMOXIFEN CITRATE - tamoxifen citrate tablet, film coated
45683541	TAMOXIFEN CITRATE - tamoxifen citrate tablet, film coated
46301876	TAMOXIFEN CITRATE - tamoxifen citrate tablet, film coated
36159385	TAMOXIFEN CITRATE - tamoxifen citrate tablet
36155001	TAMOXIFEN CITRATE - tamoxifen citrate tablet
42694028	TAMOXIFEN CITRATE - tamoxifen citrate tablet
44339136	TAMOXIFEN CITRATE - tamoxifen citrate tablet
42801939	TAMOXIFEN CITRATE - tamoxifen citrate tablet
44356917	TAMOXIFEN CITRATE - tamoxifen citrate tablet
42806296	TAMOXIFEN CITRATE - tamoxifen citrate tablet
45650672	TAMOXIFEN CITRATE - tamoxifen citrate tablet
45628249	TAMOXIFEN CITRATE - tamoxifen citrate tablet
45661189	TAMOXIFEN CITRATE - tamoxifen citrate tablet
45698114	TAMOXIFEN CITRATE - tamoxifen citrate tablet
46244741	TAMOXIFEN CITRATE - tamoxifen citrate tablet
45672512	SOLTAMOX - tamoxifen citrate liquid
42804940	SOLTAMOX - tamoxifen citrate liquid
45697402	NOLVADEX - tamoxifen citrate tablet
21603831	Tamoxifen; oral
45661594	tamoxifen citrate 20mg/1 ORAL TABLET
45688368	tamoxifen citrate 10mg/5mL ORAL LIQUID [soltamox]
45778750	tamoxifen citrate 10mg/1 ORAL TABLET, FILM COATED
45777985	tamoxifen citrate 10mg/1 ORAL TABLET
45666144	tamoxifen citrate 10mg/1 / 20mg/1 ORAL TABLET, FILM COATED
45624491	tamoxifen citrate 10mg/1 / 20mg/1 ORAL TABLET, FILM COATED
45690920	tamoxifen citrate 10mg/1 / 20mg/1 ORAL TABLET
45781760	tamoxifen citrate 10mg/1 / 20mg/1 ORAL TABLET
42807178	TAMOXIFEN CITRATE - tamoxifen citrate tablet, film coated
35902966	TAMOXIFEN CITRATE - tamoxifen citrate tablet, film coated

44337470	TAMOXIFEN CITRATE - tamoxifen citrate tablet, film coated
42801523	TAMOXIFEN CITRATE - tamoxifen citrate tablet, film coated
44337587	TAMOXIFEN CITRATE - tamoxifen citrate tablet, film coated
42805848	TAMOXIFEN CITRATE - tamoxifen citrate tablet, film coated
44361432	TAMOXIFEN CITRATE - tamoxifen citrate tablet, film coated
45631182	TAMOXIFEN CITRATE - tamoxifen citrate tablet, film coated
45665346	TAMOXIFEN CITRATE - tamoxifen citrate tablet, film coated
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44339136	TAMOXIFEN CITRATE - tamoxifen citrate tablet
42801939	TAMOXIFEN CITRATE - tamoxifen citrate tablet
44356917	TAMOXIFEN CITRATE - tamoxifen citrate tablet
42806296	TAMOXIFEN CITRATE - tamoxifen citrate tablet
45650672	TAMOXIFEN CITRATE - tamoxifen citrate tablet
45628249	TAMOXIFEN CITRATE - tamoxifen citrate tablet
45661189	TAMOXIFEN CITRATE - tamoxifen citrate tablet
45698114	TAMOXIFEN CITRATE - tamoxifen citrate tablet
46244741	TAMOXIFEN CITRATE - tamoxifen citrate tablet
45672512	SOLTAMOX - tamoxifen citrate liquid
42804940	SOLTAMOX - tamoxifen citrate liquid
45697402	NOLVADEX - tamoxifen citrate tablet

Exposure assessment

As described in the cohort definitions (Section 9.2.2), exposure commences on the first dispensing/prescription record with at least 365 days of prior observation period to increase confidence that the exposure is incident, and to have sufficient lookback to assess patient comorbidities and prior medication use, and history of cancer. Exposure interval gaps of ≤30 days between drug dispensing/prescription records will be allowed and inferred as persistent exposure. In the study, drug discontinuation will also be considered if a patient switches from one study drug to another, or when a concomitant second study drug is added, with switching defined as an overlap of 30 days or more between two different drugs. Patients who switch from target exposure to comparator exposure, or vice versa, will contribute follow-up time to the exposure cohort that they entered first.

9.3.2.- OUTCOMES

Outcome identification and validation

The proposed code lists for the identification of the study population (codes for the identification of CTS, OA or tendinopathy diagnosis) and for the study outcomes were created by clinicians with experience in the management of using ATLAS™, and reviewed by 3 clinicians and 1 epidemiologist.

Face validity for each of the outcome cohorts will be reviewed by exploring age- and sex-specific incidence rates compared to previous clinical knowledge and/or existing literature.

Negative control outcomes

A list of negative control outcomes will also be assessed for which there is no causal relationship with choice of TMX or AI medication after a diagnosis of breast cancer. These outcomes were identified using a semi-automatic process based on data extracted from literature, product labels and spontaneous reports followed by manual review by 2 clinicians.[27] The list is available in Annex 2.

9.3.3.- Covariates

Cohort studies

The following consistently extracted set of baseline patient characteristics will be constructed for inclusion as potentially confounding covariates in the regularized, logistic regression PS model.[28] From this large set of typically tens of thousands of covariates, key predictors of exposure classification will be selected for the propensity score (See Section 9.7.). Note that not all data sources necessarily include data for all covariates. Covariates to be included:

- Demographics (age in 5-year bands, sex, race, ethnicity, index year, index month)
- All conditions occurrence records aggregated to SNOMED clinical finding level during the following lookback windows:
    - in 365 days prior to and including index date
    - in 30 days prior to and including index date
- All drug exposure records aggregated to RxNorm ingredient level and ATC classes during the following lookback windows:
    - in 365 days prior to and including index date
    - in 30 days prior to and including index date
    - persistent exposure that overlaps index date
- All procedure occurrence records during the following lookback windows:
    - in 365 days prior to and including index date
    - in 30 days prior to and including index date
- Measurements (including laboratories) within, above, and below normal range during the following lookback window:
    - in 365 days prior to and including index date
- Device exposure records during the following lookback windows:
    - in 365 days prior to and including index date
    - in 30 days prior to and including index date
- Comorbidity or risk scores including:
    - Charlson
    - DCSI
    - CHADS2
    - CHADS2VASc

9.4. DATA SOURCES

This study will aim to be conducted using routinely collected data from different data sources that participate in the OHDSI and/or EHDEN initiatives.

These databases will provide representative clinical information as collected in actual practice conditions in different European and US healthcare settings. Further databases will be added

as they are made available to this initiative, checking the feasibility of each database for inclusion using cohort diagnostics prior to inclusion.[29]

The databases have been proposed based upon their participation in the OHDSI and EHDEN initiatives after mapping to the OMOP common data model. Where possible, data will be accessed remotely by participants from data partner institutions in EHDEN (SIDIAP, CPRD) and from study investigators at IQVIA (IMRD, IQVIA US Ambulatory EMR, IQVIA Disease Analyser Germany EMR, and IQVIA Hospital US Charge Master, US LRxDx Open Claims). Participating databases are detailed in the table below, and include electronic medical records and claims from Europe and the US.

All analyses will be conducted in a federated manner using tools previously validated and tested in a number of studies conducted by the OHDSI community.

Table 9.4: Overview of the considered databases (further databases may be added

Database name	Abbreviation	Population	Patients (millions)	Data History	Data capture process and short database description
IQVIA Disease Analyzer Germany	DAGermany	Germany (General population)	37M	1992 –	Anonymized patient records collected from Patient Management software used by general practitioners and selected specialists to document patients' medical records within their office-based practice during a visit.
IQVIA US Ambulatory EMR	AmbEMR	USA (General population)	49M	2006 –	General practice EHR, Outpatient specialist EHR - Dataset consists of longitudinal, de-identified ambulatory electronic health records data
IQVIA US LRxDx Open Claims	OpenClaims	USA (General population)	654M	2010 –	Pre-adjudicated claims at the anonymized patient level collected from office-based physicians and specialists via office management software and clearinghouse switch sources for the purpose of reimbursement.
Clinical Practice Research Datalink	CPRD	UK (General population)	13M	1995 –	De-identified patient data from a network of clinical practitioners' practices across the UK. Primary care data are linked to a range of other health related data to provide a longitudinal, representative UK population health dataset.
The Information System for Research in Primary Care	SIDIAP	Spain-Catalonia (80% of general population)	7.7M	2006 –	Electronic health records from primary care partially linked to inpatient data. SIDIAP is also linked to a pharmacy dispensations and primary care laboratories. Healthcare is universal and taxpayer funded in the region, and primary care physicians are gatekeepers for all care and responsible for repeat prescriptions.

9.5. STUDY SIZE

Since this study will be undertaken using routinely collected data, all patients meeting the eligibility criteria above will be included. No *a priori* sample calculation was performed; instead, a minimum detectable relative risk (MDRR) will be calculated for each target-comparator-outcome analysis in each of the available databases. Analyses are required to have >0 events observed during follow-up in both target or comparator cohorts in order to produce an estimate and standard error. Given at least 1 event is observed, a large MDRR in a single data source could contribute an underpowered estimate to a meta-analytic estimate provided adequate study diagnostics criteria are met (See Section 9.7.)

9.6. DATA MANAGEMENT

All data extraction and curation will be conducted using the ATLAS tool, an open source software platform by the OHDSI community, as well as the OHDSI Methods Library within

HADES (Health Analytics Data-to-Evidence Suite), a set of R packages developed and maintained by the OHDSI community.[30]

The process will follow the steps described here:

1. Define concept set expressions that consist of the source codes used to record clinical observations in disparate data sources
2. Define the target and comparator exposure cohorts used as input to subsequent analytic routines
3. Ascertain outcome populations
4. Review of cohort diagnostics for study feasibility and clinical face validity (e.g. cohort sizes, age and sex-specific incidence rates, index event source code prevalence, clinical characteristics)

9.7. DATA ANALYSIS

Comparative Cohort analysis

The comparative safety of AI study in subjects with breast cancer will be assessed through a comparative cohort analysis, compared against TMX as an active comparator. The comparative safety of NSAI versus TMX therapy will also be compared against SAI therapy in subjects with breast cancer if sufficient patients are present in the datasets. Individuals with a history of the outcome occurring prior to the index will be excluded from the analyses; all outcomes to be analysed in independent models.

Analyses will use the CohortMethod package (https://ohdsi.github.io/CohortMethod/). This analytic package uses a large-scale propensity score constructed through the Cyclops package (https://ohdsi.github.io/Cyclops), based on many baseline covariates derived from the data, including all drugs, condition, and procedures observed prior to the treatment initiation, as well as summary scores such as the Charlson Comorbidity Index.[31]

We will consider alternative approaches to Propensity score (PS) adjustment (stratification, 1:1 matching, 1: many matching) and will choose our primary method of adjustment on the basis of study diagnostics (prior to observing any results), with the alternative methods then run as a sensitivity analysis. The PS will be estimated using a large-scale regularized logistic regression fitted with a Laplace prior (LASSO) and with the optimal hyperparameter determined through 10-fold cross validation. The predictor variables included will be based on all observed patient characteristics and covariates available at each data source and extracted as described above (See Section 9.3.3). We will exclude all covariates that occur in fewer than 0.1% of patients within the target and comparator cohorts prior to PS model fitting for computational efficiency. We will compute and plot the propensity score distribution and assess covariate balance expressed as the standardized difference of the mean for every covariate before and after propensity score adjustment. We will consider any standardized difference > 0.1 to indicate non-negligible imbalance between exposure cohorts.[32]

We compare the target cohort with the comparator cohort for the hazards of outcome during the follow-up periods by applying a univariate Cox proportional hazards model conditioned on the PS adjustment with treatment allocation as the sole explanatory variable.

A sensitivity analysis assessing the competing risk of mortality upon the risk of musculoskeletal adverse side effects in women who are new users of TMX versus AI in the treatment of breast cancer will also be undertaken.

EVIDENCE EVALUATION

In addition to the design-specific diagnostics, such as the covariate balance computed for the comparator cohort design, we will estimate overall residual bias in all designs using negative controls. An assessment of negative control outcomes (Annex 3) will be used to assess whether there is residual confounding after propensity score adjustment. An empirical null distribution will be fitted to the effect size estimates of the negative controls, allowing for quantification of residual bias and calibration of hazard ratios, confidence intervals, and p-values. If there is evidence of residual confounding and there is a sufficient number of control events, estimates will be calibrated.

Study diagnostics (power, propensity score distribution, covariate balance, empirical null distribution) will be evaluated by clinicians and epidemiologists to determine which database-target-comparator-outcome-analysis variants will produce unbiased estimates. Database-target-comparator-analysis variants with 0 outcomes in the time-at-risk window or contained analyses with baseline covariate with standardized mean difference>0.1 after stratification will be excluded from analysis. Study diagnostics for all database-target-comparator-outcome-analysis will be provided as part of study, regardless of which effect estimation results are unblinded. The main models will be adjusted for unbalanced PS-variables at baseline.

All analysis code will be completed and version controlled at https://github.com/ohdsi-studies/MusculoskeletalAEsAfterAIs prior to unblinding estimation results. All study diagnostics will be made available for exploration at https://evidence.ohdsi.org/MusculoskeletalAEsAfterAIs

All the proposed analyses will be conducted for each database separately, with estimates combined in fixed effects meta-analysis methods where I2 is <=40%. No meta-analysis will be conducted where I2 for a given drug-outcome pair is >40%.

9.8. LIMITATIONS OF THE RESEARCH METHODS

Selection bias

Selection bias might arise as the consequence of including subjects with a specific period of time available in the data. Attrition tables will be provided to report on the impact of such exclusion criteria.

Information bias

Information bias may occur due to the incorrect identification of exposure, outcomes or co-variates. With regards to exposure, misclassification may occur due to the patient not fulfilling the prescription (primary non-adherence) or in relation with non-compliance. Hence an overestimate of utilization of the study drugs can happen, expectedly leading to non-differential misclassification.

In addition, lack or incomplete recording of safety events may lead to misclassification of the proposed safety endpoints.

Confounding

As confounding by indication may produce differences in baseline characteristics between the comparator and target cohorts, we will use several methods to deal with confounding:

1. Restriction: comparative studies will be conducted only in subjects previously diagnosed with breast cancer *(+breast surgery for cancer if appears necessary after cohort diagnostics*), are female, aged 55 or over and using any of the drugs of interest as a first line treatment.

In addition, we will trim the <5% and >95% percentiles of the preference score to maximise equipoise in the study population.

2. Propensity score adjustment to reduce risk of confounding due to observed confounding and confounding by indication.
3. Negative control outcome analyses will be used to identify any residual unobserved confounding in the propensity score analyses. If this analysis suggests the presence of relevant unresolved confounding then further analyses will not be completed.

10. PROTECTION OF HUMAN SUBJECTS

For this study, participants from numerous healthcare databases will be studied. The use of the OMOP common data model and OHDSI tools will enable the federated analysis of these different databases without changing access rights to patient-level data.
All the data partners will receive Institutional Review Board (IRB) approval or exemption.
SIDIAP analysis will be approved by the Clinical Research Ethics Committee of the IDIAPJGol and CPRD analysis approved by ISAC, with the associated project codes to be included in final write-ups. Other databases used (IQVIA Open Claims, IQVIA Ambulatory EMR, IQVIA Disease Analyzer Germany, etc) are commercially available, syndicated data assets that are licensed by contributing authors for observational research. These assets are de-identified commercially available data products that could be purchased and licensed by any researcher. The collection and de-identification of these data assets is a process that is commercial intellectual property and not privileged to the data licensees and the co-authors on this study. Licensees of these data have signed Data Use Agreements with the data vendors which detail the usage protocols for running retrospective research on these databases. All analyses performed in this study were in accordance with Data Use Agreement terms as specified by the data owners. As these data are deemed commercial assets, there is no Institutional Review Board applicable to the usage and dissemination of these result sets or required registration of the protocol with additional ethics oversight. Compliance with Data Use Agreement terms, which stipulate how these data can be used and for what purpose, is sufficient for these commercial entities. Further inquiry related to the governance oversight of these assets can be made with the respective commercial entities: IQVIA (iqvia.com). At no point in the course of this study were the authors of this study exposed to identified patient-level data. All result sets represent aggregate, de-identified data that are represented at a minimum cell size of >5 to reduce potential for re-identification.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

According to the new guidelines for good pharmacovigilance practice (EMA/873138/2011) there is no requirement for expedited reporting of adverse drug reactions from studies with secondary use of data (such as electronic health care databases). All the identified adverse events/reactions will be summarized in the resulting manuscript/s and/or interactive web-based report of all conducted analyses.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Dissemination activities will be of a scientific nature (articles in scientific journals, presentations at conferences, etc.) but will also include explanation to a lay audience using social media. Our aim is for these studies to be made available as soon as possible in order to support treatment decisions for women with breast cancer, and to inform both clinical and research colleagues.

13. REFERENCES

1. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005; **365**(9453): 60-2.
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ANNEX 1. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: The risk of musculoskeletal adverse outcomes after treatment with endocrine blocking treatments for breast cancer

EU PAS Register® number: **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.1 Start of data collection[1]	☒	☐	☐	9.2.1
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☐	☐	☒	
1.1.6 Final report of study results.	☐	☐	☒	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	8
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2
4.2.2 Age and sex	☒	☐	☐	
4.2.3 Country of origin	☒	☐	☐	
4.2.4 Disease/indication	☒	☐	☐	
4.2.5 Duration of follow-up	☒	☐	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.2.2 & 9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.2.2
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.2.2
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.2.2
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.2.2 & 9.3.1

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.2
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.7
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.8
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.8

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.3

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.3 & 9.7
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	9.3
10.3 Are descriptive analyses included?	☐	☐	☒	
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.8

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☐	☒	
11.2 Are methods of quality assurance described?	☒	☐	☐	9.7
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.7

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	9.8
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.6

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☐	☐	☒	

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Updated for protocol version 1.5 to note amendments made

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Jennifer Lane

Date: 1/12/2020

Signature: JCElane

ANNEX 2: OUTCOME LIST

Note- Provisional cohort definitions to be confirmed following cohort diagnostics

CTS outcomes

Concept ID	Name / Description	Concept ID to be Excluded
380094	Carpal tunnel syndrome	
760925	Bilateral carpal tunnel syndrome	
762150	Carpal tunnel syndrome of left wrist	

762151	Carpal tunnel syndrome of right wrist	
4235010	Neuroplasty and transposition of median nerve at carpal tunnel	
4234291	Transposition of median nerve at carpal tunnel	
4204075	Exploration of carpal tunnel	
4082236	Injection of carpal tunnel	
4066890	Endoscopic carpal tunnel release	
4041195	Neurolysis of carpal tunnel	
4014640	Neuroplasty of median nerve at carpal tunnel	

OA outcomes

Concept ID	Name / Description	Concept ID to be Excluded
2005962	Injection of therapeutic substance into joint or ligament	
2102900	Arthrocentesis, aspiration and/or injection, small joint or bursa (eg, fingers, toes); without ultrasound guidance	
2102901	Arthrocentesis, aspiration and/or injection, intermediate joint or bursa (eg, temporomandibular, acromioclavicular, wrist, elbow or ankle, olecranon bursa); without ultrasound guidance	
2102912	Arthrocentesis, aspiration and/or injection, major joint or bursa (eg, shoulder, hip, knee, subacromial bursa); without ultrasound guidance	
2105941	Arthroscopy, shoulder, diagnostic, with or without synovial biopsy (separate procedure) (Deprecated)	
2617368	Arthroscopy, knee, surgical, for removal of loose body, foreign body, debridement/shaving of articular cartilage (chondroplasty) at the time of other surgical knee arthroscopy in a different compartment of the same knee	
2721113	Arthroscopy, knee, surgical for harvesting of cartilage (chondrocyte cells)	
4010250	Diagnostic arthroscopy of knee with synovial biopsy	
4028987	Arthroscopy	
4031174	Injection of hip joint	
4085220	Arthroscopy of shoulder	
4144525	Injection of joint of ankle	
4165243	Diagnostic arthroscopy of wrist with synovial biopsy	
4329662	Arthroscopy planned	
4335029	Injection of steroid into joint	
4335030	Injection of facet joint	
4337874	Injection of sacroiliac joint	
38001298	Arthroscopy	
40481840	Arthroplasty	
42739910	Arthroscopy, knee, surgical, implantation of osteochondral graft(s) for treatment of articular surface defect; autografts (Deprecated)	
42739911	Arthroscopy, knee, surgical, implantation of osteochondral graft(s) for treatment of articular surface defect; allografts (Deprecated)	
45888005	Endoscopy/Arthroscopy Procedures on the Musculoskeletal System	
46271492	CT guided injection of joint	
75036	Localized, primary osteoarthritis of the hand	
79904	Localized, secondary osteoarthritis of the hand	
762330	Osteoarthritis of first carpometacarpal joint of right hand	
4144996	Generalized osteoarthritis of the hand	

4327181	Interphalangeal osteoarthritis	
4343918	Osteoarthritis of finger joint	
36713098	Osteoarthritis of joint of left hand	
2005659	Arthroscopy, hand and finger	
2106073	Arthroscopy, metacarpophalangeal joint, surgical; with debridement	
4002377	Hand injection	
4114318	Arthrodesis of finger	
4114320	Arthrodesis of thumb	
4305812	Arthroplasty of hand	
4306149	Metacarpocarpal arthrodesis	
45888185	Arthrodesis, interphalangeal joint, with or without internal fixation	
45888520	Arthrodesis, carpometacarpal joint, thumb, with or without internal fixation	
45889047	Arthrodesis, metacarpophalangeal joint, with or without internal fixation	
2105999	Arthroscopy, hip, diagnostic with or without synovial biopsy (separate procedure)	
2106000	Arthroscopy, hip, surgical; with removal of loose body or foreign body	
2106001	Arthroscopy, hip, surgical; with debridement/shaving of articular cartilage (chondroplasty), abrasion arthroplasty, and/or resection of labrum	
2106012	Arthroscopy, hip, surgical; with synovectomy	
4031174	Injection of hip joint	
4034298	Interposition arthroplasty of the hip	
4162099	Prosthetic arthroplasty of the hip	
4203771	Total replacement of hip	
4207134	Arthroscopy of hip with removal of foreign body	
4233308	Arthroscopy of hip with synovectomy	
4234038	Arthroscopy of hip with removal of loose body	
4288878	Arthroscopy of hip	
4306618	Arthroplasty of hip with bone graft	
40484624	Prosthetic arthroplasty of bilateral hips	
40756992	Arthroscopy, hip, surgical; with labral repair	
40757047	Arthroscopy, hip, surgical; with acetabuloplasty (ie, treatment of pincer lesion)	
40757126	Arthroscopy, hip, surgical; with femoroplasty (ie, treatment of cam lesion)	
45889893	Arthroscopy, hip, surgical	
1570329	Osteoarthritis of hip	
1570330	Unilateral primary osteoarthritis of hip	
1570331	Unilateral osteoarthritis resulting from hip dysplasia	
1570332	Unilateral post-traumatic osteoarthritis of hip	
4079749	Osteoarthritis of hip	
4114591	Oligoarticular osteoarthritis, unspecified, of the pelvic region and thigh	
4115379	Localized, primary osteoarthritis of the pelvic region and thigh	
4116588	Osteoarthritis NOS, of hip	
4149045	Localised osteoarthritis, unspecified, of the pelvic region and thigh	
4149048	Osteoarthritis NOS, pelvic region/thigh	
4266903	Osteoarthritis, Hip	
35208766	Bilateral primary osteoarthritis of hip	
35208767	Bilateral osteoarthritis resulting from hip dysplasia	
35208769	Other bilateral secondary osteoarthritis of hip	
35208770	Other unilateral secondary osteoarthritis of hip	
35208771	Osteoarthritis of hip, unspecified	
36684455	Osteoarthritis of bilateral hip joints	
36713109	Osteoarthritis of left hip joint	
36713110	Osteoarthritis of right hip joint	
37395586	Osteoarthritis of hip co-occurrent and due to dysplasia	

40320325	Osteoarthritis of hip	
40400697	Localised osteoarthritis, unspecified, of the pelvic region and thigh	
40400724	Hip osteoarthritis NOS	
40440091	Osteoarthritis NOS, of hip	
45437062	Hip osteoarthritis NOS	
45443644	Localised, secondary osteoarthritis of the pelvic region and thigh	
45443649	Osteoarthritis NOS, of hip	
45450329	Oligoarticular osteoarthritis, unspecified, of the pelvic region and thigh	
45453633	Localised osteoarthritis, unspecified, of the pelvic region and thigh	
45470615	Osteoarthritis NOS, pelvic region/thigh	
45490472	Localised, primary osteoarthritis of the pelvic region and thigh	
45527231	OSTEOARTHRITIS HIP	
45553095	Unilateral osteoarthritis resulting from hip dysplasia, right hip	
45572372	Unilateral osteoarthritis resulting from hip dysplasia, left hip	
45572373	Unilateral post-traumatic osteoarthritis, left hip	
45577163	Unilateral primary osteoarthritis, unspecified hip	
45577164	Unilateral primary osteoarthritis, left hip	
45586889	Unilateral primary osteoarthritis, right hip	
45601349	Unilateral post-traumatic osteoarthritis, unspecified hip	x
45606126	Unilateral osteoarthritis resulting from hip dysplasia, unspecified hip	X
46273178	Osteoarthritis of hip due to dysplasia	X
36713111	Osteoarthritis of right knee joint	
36717036	Osteoarthritis of left knee joint	
2617368	Arthroscopy, knee, surgical, for removal of loose body, foreign body, debridement/shaving of articular cartilage (chondroplasty) at the time of other surgical knee arthroscopy in a different compartment of the same knee	
2721113	Arthroscopy, knee, surgical for harvesting of cartilage (chondrocyte cells)	
4010250	Diagnostic arthroscopy of knee with synovial biopsy	
4034299	Prosthetic unicompartmental arthroplasty of knee	
4078547	Arthroplasty of knee	
4103962	Injection of knee joint	
4205229	Arthroscopy of knee	
40481441	Injection of both knee joints	
42739910	Arthroscopy, knee, surgical, implantation of osteochondral graft(s) for treatment of articular surface defect; autografts (Deprecated)	
42739911	Arthroscopy, knee, surgical, implantation of osteochondral graft(s) for treatment of articular surface defect; allografts (Deprecated)	
45887571	Arthroscopy, knee, surgical	
45888521	Arthroplasty, knee, tibial plateau	
45888673	Arthroplasty, femoral condyles or tibial plateau(s), knee	
45889826	Arthroplasty, patella	
45890558	Arthroplasty, knee, condyle and plateau	
80180	Osteoarthritis	
73840	Localized, primary osteoarthritis of the shoulder region	
77631	Localized, secondary osteoarthritis of the shoulder region	
759879	Osteoarthritis of right glenohumeral joint	
759880	Osteoarthritis of bilateral glenohumeral joints	
759882	Osteoarthritis of left glenohumeral joint	
4035440	Osteoarthritis of acromioclavicular joint	
4160051	Osteoarthritis of glenohumeral joint	
36713099	Osteoarthritis of joint of left shoulder region	
36713103	Osteoarthritis of joint of right shoulder region	
4034665	Arthroplasty of shoulder	

4128362	Injection into shoulder joint	
37116646	Prosthetic total arthroplasty of right shoulder	
37118674	Prosthetic total arthroplasty of left shoulder	
44789351	Injection of acromioclavicular joint	
45888310	Arthroplasty, glenohumeral joint	

Tendinopathy outcomes

Concept ID	Name / Description	Concept ID to be Excluded
80187	Medial epicondylitis	
81379	Lateral epicondylitis	
761175	Bilateral medial epicondylitis of elbows	
762267	Lateral epicondylitis of left humerus	
762282	Medial epicondylitis of left humerus	
762283	Medial epicondylitis of right humerus	
37109275	Lateral epicondylitis of right humerus	
42872415	Tendinitis of elbow or forearm	
2759787	Release Right Elbow Bursa and Ligament, Open Approach	
2759788	Release Right Elbow Bursa and Ligament, Percutaneous Approach	
2759789	Release Right Elbow Bursa and Ligament, Percutaneous Endoscopic Approach	
2759790	Release Right Elbow Bursa and Ligament, External Approach	
2759791	Release Left Elbow Bursa and Ligament, Open Approach	
2759792	Release Left Elbow Bursa and Ligament, Percutaneous Approach	
2759793	Release Left Elbow Bursa and Ligament, Percutaneous Endoscopic Approach	
2759794	Release Left Elbow Bursa and Ligament, External Approach	
2760001	Release Right Upper Extremity Bursa and Ligament, Open Approach	
2760002	Release Right Upper Extremity Bursa and Ligament, Percutaneous Approach	
2760003	Release Right Upper Extremity Bursa and Ligament, Percutaneous Endoscopic Approach	
2760004	Release Right Upper Extremity Bursa and Ligament, External Approach	
2760005	Release Left Upper Extremity Bursa and Ligament, Open Approach	
2760006	Release Left Upper Extremity Bursa and Ligament, Percutaneous Approach	
2760007	Release Left Upper Extremity Bursa and Ligament, Percutaneous Endoscopic Approach	
2760008	Release Left Upper Extremity Bursa and Ligament, External Approach	
4164520	Tennis elbow injection	
4171769	Golfer's elbow injection	
42735672	Fasciotomy, lateral or medial (eg, tennis elbow or epicondylitis) (Deprecated)	
42735673	Fasciotomy, lateral or medial (eg, tennis elbow or epicondylitis); with extensor origin detachment (Deprecated)	
42735674	Fasciotomy, lateral or medial (eg, tennis elbow or epicondylitis); with annular ligament resection (Deprecated)	
42735675	Fasciotomy, lateral or medial (eg, tennis elbow or epicondylitis); with stripping (Deprecated)	

42735676	Fasciotomy, lateral or medial (eg, tennis elbow or epicondylitis); with partial ostectomy (Deprecated)	
45888216	Tenotomy, elbow, lateral or medial (eg, epicondylitis, tennis elbow, golfer's elbow)	
77963	Achilles tendinitis	
761381	Tendonitis of left ankle	
761382	Tendonitis of right ankle	
4137530	Tendinitis of foot	
4180849	Peroneal tendinitis	
36684347	Tendinitis of ankle	
36685042	Tendinitis of right flexor hallucis longus	
45763856	Insertional Achilles tendinopathy	
45763857	Non-insertional Achilles tendinopathy	
2760053	Release Right Ankle Bursa and Ligament, Open Approach	
2760054	Release Right Ankle Bursa and Ligament, Percutaneous Approach	
2760055	Release Right Ankle Bursa and Ligament, Percutaneous Endoscopic Approach	
2760056	Release Right Ankle Bursa and Ligament, External Approach	
2760057	Release Left Ankle Bursa and Ligament, Open Approach	
2760058	Release Left Ankle Bursa and Ligament, Percutaneous Approach	
2760251	Release Left Ankle Bursa and Ligament, Percutaneous Endoscopic Approach	
2760252	Release Left Ankle Bursa and Ligament, External Approach	
2760253	Release Right Foot Bursa and Ligament, Open Approach	
2760254	Release Right Foot Bursa and Ligament, Percutaneous Approach	
2760255	Release Right Foot Bursa and Ligament, Percutaneous Endoscopic Approach	
2760256	Release Right Foot Bursa and Ligament, External Approach	
2760257	Release Left Foot Bursa and Ligament, Open Approach	
2760258	Release Left Foot Bursa and Ligament, Percutaneous Approach	
2760259	Release Left Foot Bursa and Ligament, Percutaneous Endoscopic Approach	
2760260	Release Left Foot Bursa and Ligament, External Approach	
2761442	Reattachment of Right Lower Leg Tendon, Open Approach	
2761444	Reattachment of Left Lower Leg Tendon, Open Approach	
4072039	Repair of tendo achilles	
4114321	Injection for plantar fasciitis	
45890228	Repair, primary, open or percutaneous, ruptured Achilles tendon	
761187	Bilateral trigger thumbs	
4173776	Tendinitis of wrist	
4307423	Tendinitis of hand	
4344264	Triggering of digit	
40481598	Tendinitis of flexor carpi ulnaris	
40482085	Tendinitis of flexor carpi radialis	
40482901	Tendinitis of extensor carpi ulnaris	
2103904	Repair, tendon or muscle, upper arm or elbow, each tendon or muscle, primary or secondary (excludes rotator cuff)	
2759795	Release Right Wrist Bursa and Ligament, Open Approach	
2759796	Release Right Wrist Bursa and Ligament, Percutaneous Approach	
2759797	Release Right Wrist Bursa and Ligament, Percutaneous Endoscopic Approach	
2759798	Release Right Wrist Bursa and Ligament, External Approach	
2759799	Release Left Wrist Bursa and Ligament, Open Approach	

2759800	Release Left Wrist Bursa and Ligament, Percutaneous Approach	
2759801	Release Left Wrist Bursa and Ligament, Percutaneous Endoscopic Approach	
2759802	Release Left Wrist Bursa and Ligament, External Approach	
2759803	Release Right Hand Bursa and Ligament, Open Approach	
2759804	Release Right Hand Bursa and Ligament, Percutaneous Approach	
2759805	Release Right Hand Bursa and Ligament, Percutaneous Endoscopic Approach	
2759806	Release Right Hand Bursa and Ligament, External Approach	
2759997	Release Left Hand Bursa and Ligament, Open Approach	
2759998	Release Left Hand Bursa and Ligament, Percutaneous Approach	
2759999	Release Left Hand Bursa and Ligament, Percutaneous Endoscopic Approach	
4167169	Decompression of tendon of hand	
4198683	Injection into tendon of hand	
44807555	Release of first extensor compartment of wrist	
193293	Pes anserinus tendinitis	
438843	Non-traumatic rupture of patellar tendon	
4001467	Semimembranosus tendinitis	
4002147	Pes anserinus tendinitis and bursitis	
4002148	Biceps femoris tendinitis	
4149245	Rupture of patellar tendon	
4178642	Tendinitis of knee	
36683408	Tendinitis of left pes anserinus tendon	
36683409	Tendinitis of right pes anserinus tendon	
36686994	Bilateral patellar bursitis	
42535182	Tendinitis of right quadriceps tendon	
42539205	Tendinitis of left quadriceps tendon	
2760045	Release Right Knee Bursa and Ligament, Open Approach	
2760046	Release Right Knee Bursa and Ligament, Percutaneous Approach	
2760047	Release Right Knee Bursa and Ligament, Percutaneous Endoscopic Approach	
2760048	Release Right Knee Bursa and Ligament, External Approach	
2760049	Release Left Knee Bursa and Ligament, Open Approach	
2760050	Release Left Knee Bursa and Ligament, Percutaneous Approach	
2760051	Release Left Knee Bursa and Ligament, Percutaneous Endoscopic Approach	
2760052	Release Left Knee Bursa and Ligament, External Approach	
4072040	Repair of patellar tendon	
4229423	Suture of infrapatellar tendon, primary	
40483559	Arthroscopic excision of infrapatellar fat pad	
79116	Disorder of tendon of shoulder region	
437966	Calcium deposits in tendon	
4000968	Biceps tendinitis	
4115237	Deltoid tendinitis	
4215217	Traumatic or non-traumatic rupture of tendon	
37108980	Bilateral rotator cuff arthropathy of shoulder	
2102895	Injection(s); single tendon sheath, or ligament, aponeurosis (eg, plantar fascia)	

2103888	Tenotomy, open, elbow to shoulder, each tendon	
2754416	Destruction of Right Shoulder Tendon, Open Approach	
2754417	Destruction of Right Shoulder Tendon, Percutaneous Approach	
2754418	Destruction of Right Shoulder Tendon, Percutaneous Endoscopic Approach	
2754419	Destruction of Left Shoulder Tendon, Open Approach	
2754420	Destruction of Left Shoulder Tendon, Percutaneous Approach	
2754421	Destruction of Left Shoulder Tendon, Percutaneous Endoscopic Approach	
2754694	Division of Right Shoulder Tendon, Open Approach	
2754695	Division of Right Shoulder Tendon, Percutaneous Approach	
2754696	Division of Right Shoulder Tendon, Percutaneous Endoscopic Approach	
2754697	Division of Left Shoulder Tendon, Open Approach	
2754698	Division of Left Shoulder Tendon, Percutaneous Approach	
2754699	Division of Left Shoulder Tendon, Percutaneous Endoscopic Approach	
2758185	Repair Right Shoulder Tendon, Open Approach	
2758186	Repair Right Shoulder Tendon, Percutaneous Approach	
2758187	Repair Right Shoulder Tendon, Percutaneous Endoscopic Approach	
2758188	Repair Left Shoulder Tendon, Open Approach	
2758189	Repair Left Shoulder Tendon, Percutaneous Approach	
2758190	Repair Left Shoulder Tendon, Percutaneous Endoscopic Approach	
2758464	Replacement of Right Shoulder Tendon with Autologous Tissue Substitute, Open Approach	
2758465	Replacement of Right Shoulder Tendon with Synthetic Substitute, Open Approach	
2758466	Replacement of Right Shoulder Tendon with Nonautologous Tissue Substitute, Open Approach	
2758467	Replacement of Right Shoulder Tendon with Autologous Tissue Substitute, Percutaneous Endoscopic Approach	
2758468	Replacement of Right Shoulder Tendon with Synthetic Substitute, Percutaneous Endoscopic Approach	
2758469	Replacement of Right Shoulder Tendon with Nonautologous Tissue Substitute, Percutaneous Endoscopic Approach	
2758470	Replacement of Left Shoulder Tendon with Autologous Tissue Substitute, Open Approach	
2758471	Replacement of Left Shoulder Tendon with Synthetic Substitute, Open Approach	
2758472	Replacement of Left Shoulder Tendon with Nonautologous Tissue Substitute, Open Approach	
2758473	Replacement of Left Shoulder Tendon with Autologous Tissue Substitute, Percutaneous Endoscopic Approach	
2758474	Replacement of Left Shoulder Tendon with Synthetic Substitute, Percutaneous Endoscopic Approach	
2758475	Replacement of Left Shoulder Tendon with Nonautologous Tissue Substitute, Percutaneous Endoscopic Approach	
2759444	Resection of Right Shoulder Tendon, Open Approach	
2759445	Resection of Right Shoulder Tendon, Percutaneous Endoscopic Approach	
2759446	Resection of Left Shoulder Tendon, Open Approach	
2759447	Resection of Left Shoulder Tendon, Percutaneous Endoscopic Approach	
2760389	Excision of Right Shoulder Tendon, Open Approach, Diagnostic	
2760390	Excision of Right Shoulder Tendon, Open Approach	
2760391	Excision of Right Shoulder Tendon, Percutaneous Approach, Diagnostic	
2760392	Excision of Right Shoulder Tendon, Percutaneous Approach	
2760393	Excision of Right Shoulder Tendon, Percutaneous Endoscopic Approach, Diagnostic	
2760394	Excision of Right Shoulder Tendon, Percutaneous Endoscopic Approach	
2760395	Excision of Left Shoulder Tendon, Open Approach, Diagnostic	

2760397	Excision of Left Shoulder Tendon, Percutaneous Approach, Diagnostic	
2760398	Excision of Left Shoulder Tendon, Percutaneous Approach	
2760399	Excision of Left Shoulder Tendon, Percutaneous Endoscopic Approach, Diagnostic	
2760400	Excision of Left Shoulder Tendon, Percutaneous Endoscopic Approach	
2760932	Extirpation of Matter from Right Shoulder Tendon, Open Approach	
2760933	Extirpation of Matter from Right Shoulder Tendon, Percutaneous Approach	
2760935	Extirpation of Matter from Left Shoulder Tendon, Open Approach	
2760936	Extirpation of Matter from Left Shoulder Tendon, Percutaneous Approach	
2760937	Extirpation of Matter from Left Shoulder Tendon, Percutaneous Endoscopic Approach	
2761404	Reattachment of Right Shoulder Tendon, Open Approach	
2761405	Reattachment of Right Shoulder Tendon, Percutaneous Endoscopic Approach	
2761406	Reattachment of Left Shoulder Tendon, Open Approach	
2761407	Reattachment of Left Shoulder Tendon, Percutaneous Endoscopic Approach	
2761654	Release Right Shoulder Tendon, Open Approach	
2761655	Release Right Shoulder Tendon, Percutaneous Approach	
2761656	Release Right Shoulder Tendon, Percutaneous Endoscopic Approach	
2761657	Release Right Shoulder Tendon, External Approach	
2761658	Release Left Shoulder Tendon, Open Approach	
2761659	Release Left Shoulder Tendon, Percutaneous Approach	
2761660	Release Left Shoulder Tendon, Percutaneous Endoscopic Approach	
2761661	Release Left Shoulder Tendon, External Approach	
4001864	Shoulder injection	
4129863	Repair of complete shoulder cuff avulsion, chronic	
4211092	Arthroscopy of shoulder with lysis and resection of adhesions with manipulation	
4259564	Arthroscopy of shoulder with biceps tenodesis	
4301750	Anesthesia for tenotomy, elbow to shoulder, open	
44789352	Injection for supraspinatus tendinitis	
45763950	Extracorporeal shockwave lithotripsy for calcific tendinitis of shoulder	
45888308	Tenotomy, shoulder area	
193293	Pes anserinus tendinitis	
761291	Tendinitis of left hip	
761292	Tendinitis of right hip	
761298	Tendinitis of bilateral gluteal tendons	
761381	Tendonitis of left ankle	
761382	Tendonitis of right ankle	
4002147	Pes anserinus tendinitis and bursitis	
4147145	Tendinitis	
4312400	Tendinitis of hip	
36685042	Tendinitis of right flexor hallucis longus	
36685043	Tendinitis of left flexor hallucis longus	
37108976	Tendinitis of right rotator cuff	
37117797	Tendinitis of left rotator cuff	
45763856	Insertional Achilles tendinopathy	
45763857	Non-insertional Achilles tendinopathy	
2006196	Lysis of adhesions of muscle, tendon, fascia, and bursa	
2006203	Injection of locally acting therapeutic substance into other soft tissue	
2103618	Arthrotomy, acromioclavicular joint or sternoclavicular joint, including biopsy and/or excision of torn cartilage	
2103634	Acromioplasty or acromionectomy, partial, with or without coracoacromial ligament release	

2103681	Tenotomy, shoulder area; single tendon	
2103692	Tenotomy, shoulder area; multiple tendons through same incision	
2103888	Tenotomy, open, elbow to shoulder, each tendon	
2103904	Repair, tendon or muscle, upper arm or elbow, each tendon or muscle, primary or secondary (excludes rotator cuff)	
2759779	Release Right Shoulder Bursa and Ligament, Open Approach	
2759780	Release Right Shoulder Bursa and Ligament, Percutaneous Approach	
2759781	Release Right Shoulder Bursa and Ligament, Percutaneous Endoscopic Approach	
2759782	Release Right Shoulder Bursa and Ligament, External Approach	
2759783	Release Left Shoulder Bursa and Ligament, Open Approach	
2759784	Release Left Shoulder Bursa and Ligament, Percutaneous Approach	
2759785	Release Left Shoulder Bursa and Ligament, Percutaneous Endoscopic Approach	
2759787	Release Right Elbow Bursa and Ligament, Open Approach	
2759788	Release Right Elbow Bursa and Ligament, Percutaneous Approach	
2759789	Release Right Elbow Bursa and Ligament, Percutaneous Endoscopic Approach	
2759790	Release Right Elbow Bursa and Ligament, External Approach	
2759791	Release Left Elbow Bursa and Ligament, Open Approach	
2759792	Release Left Elbow Bursa and Ligament, Percutaneous Approach	
2759793	Release Left Elbow Bursa and Ligament, Percutaneous Endoscopic Approach	
2759794	Release Left Elbow Bursa and Ligament, External Approach	
2759795	Release Right Wrist Bursa and Ligament, Open Approach	
2759796	Release Right Wrist Bursa and Ligament, Percutaneous Approach	
2759797	Release Right Wrist Bursa and Ligament, Percutaneous Endoscopic Approach	
2759798	Release Right Wrist Bursa and Ligament, External Approach	
2759799	Release Left Wrist Bursa and Ligament, Open Approach	
2759800	Release Left Wrist Bursa and Ligament, Percutaneous Approach	
2759801	Release Left Wrist Bursa and Ligament, Percutaneous Endoscopic Approach	
2759802	Release Left Wrist Bursa and Ligament, External Approach	
2759803	Release Right Hand Bursa and Ligament, Open Approach	
2759804	Release Right Hand Bursa and Ligament, Percutaneous Approach	
2759805	Release Right Hand Bursa and Ligament, Percutaneous Endoscopic Approach	
2759806	Release Right Hand Bursa and Ligament, External Approach	
2759997	Release Left Hand Bursa and Ligament, Open Approach	
2759998	Release Left Hand Bursa and Ligament, Percutaneous Approach	
2759999	Release Left Hand Bursa and Ligament, Percutaneous Endoscopic Approach	
2760000	Release Left Hand Bursa and Ligament, External Approach	
2760001	Release Right Upper Extremity Bursa and Ligament, Open Approach	
2760002	Release Right Upper Extremity Bursa and Ligament, Percutaneous Approach	
2760003	Release Right Upper Extremity Bursa and Ligament, Percutaneous Endoscopic Approach	
2760004	Release Right Upper Extremity Bursa and Ligament, External Approach	
2760005	Release Left Upper Extremity Bursa and Ligament, Open Approach	
2760006	Release Left Upper Extremity Bursa and Ligament, Percutaneous Approach	
2760007	Release Left Upper Extremity Bursa and Ligament, Percutaneous Endoscopic Approach	
2760008	Release Left Upper Extremity Bursa and Ligament, External Approach	

2760037	Release Right Hip Bursa and Ligament, Open Approach	
2760038	Release Right Hip Bursa and Ligament, Percutaneous Approach	
2760039	Release Right Hip Bursa and Ligament, Percutaneous Endoscopic Approach	
2760040	Release Right Hip Bursa and Ligament, External Approach	
2760041	Release Left Hip Bursa and Ligament, Open Approach	
2760042	Release Left Hip Bursa and Ligament, Percutaneous Approach	
2760043	Release Left Hip Bursa and Ligament, Percutaneous Endoscopic Approach	
2760044	Release Left Hip Bursa and Ligament, External Approach	
2760045	Release Right Knee Bursa and Ligament, Open Approach	
2760046	Release Right Knee Bursa and Ligament, Percutaneous Approach	
2760047	Release Right Knee Bursa and Ligament, Percutaneous Endoscopic Approach	
2760048	Release Right Knee Bursa and Ligament, External Approach	
2760049	Release Left Knee Bursa and Ligament, Open Approach	
2760050	Release Left Knee Bursa and Ligament, Percutaneous Approach	
2760051	Release Left Knee Bursa and Ligament, Percutaneous Endoscopic Approach	
2760052	Release Left Knee Bursa and Ligament, External Approach	
2760053	Release Right Ankle Bursa and Ligament, Open Approach	
2760054	Release Right Ankle Bursa and Ligament, Percutaneous Approach	
2760055	Release Right Ankle Bursa and Ligament, Percutaneous Endoscopic Approach	
2760056	Release Right Ankle Bursa and Ligament, External Approach	
2760057	Release Left Ankle Bursa and Ligament, Open Approach	
2760058	Release Left Ankle Bursa and Ligament, Percutaneous Approach	
2760251	Release Left Ankle Bursa and Ligament, Percutaneous Endoscopic Approach	
2760252	Release Left Ankle Bursa and Ligament, External Approach	
2760253	Release Right Foot Bursa and Ligament, Open Approach	
2760254	Release Right Foot Bursa and Ligament, Percutaneous Approach	
2760255	Release Right Foot Bursa and Ligament, Percutaneous Endoscopic Approach	
2760256	Release Right Foot Bursa and Ligament, External Approach	
2760257	Release Left Foot Bursa and Ligament, Open Approach	
2760258	Release Left Foot Bursa and Ligament, Percutaneous Approach	
2760259	Release Left Foot Bursa and Ligament, Percutaneous Endoscopic Approach	
2760260	Release Left Foot Bursa and Ligament, External Approach	
2760265	Release Left Lower Extremity Bursa and Ligament, Open Approach	
2760266	Release Left Lower Extremity Bursa and Ligament, Percutaneous Approach	
2760268	Release Left Lower Extremity Bursa and Ligament, External Approach	
2761442	Reattachment of Right Lower Leg Tendon, Open Approach	
2761444	Reattachment of Left Lower Leg Tendon, Open Approach	
2761649	Tendons, Release	
4046271	Release of tendon	
4046739	Release of tendon sheath	
4072039	Repair of tendo achilles	
4072040	Repair of patellar tendon	
4073814	Injection into bursa	
4075155	Decompression of tendon sheath	
4085220	Arthroscopy of shoulder	
4087578	Decompression of tendon or tendon sheath	
4114321	Injection for plantar fasciitis	
4164520	Tennis elbow injection	
4167169	Decompression of tendon of hand	
4171769	Golfer's elbow injection	

4198683	Injection into tendon of hand	
4209151	Repair of musculotendinous cuff of shoulder	
4222614	Bursectomy	
4229423	Suture of infrapatellar tendon, primary	
4234723	Injection of tendon sheath	
4320946	Injection of therapeutic substance into tendon	
4321084	Injection of ligament	
4328010	Injection of tendon using ultrasound guidance	
4343474	Excision of calcific deposit from rotator cuff	
36716648	Subacromial steroid injection	
40483559	Arthroscopic excision of infrapatellar fat pad	
44792138	Arthroscopic decompression of subacromial joint	
44793145	Steroid injection for tenosynovitis	
44807555	Release of first extensor compartment of wrist	
45763950	Extracorporeal shockwave lithotripsy for calcific tendinitis of shoulder	
45889314	Repair of ruptured musculotendinous cuff (eg, rotator cuff) open	
45890228	Repair, primary, open or percutaneous, ruptured Achilles tendon	

ANNEX 3: NEGATIVE CONTROL OUTCOME LIST

Provisional cohort definitions to be confirmed following cohort diagnostics

Concept ID	Concept Name
31317	Dysphagia
42709838	Cellulitis of lower limb
435796	Dehydration
257011	Acute upper respiratory infection
201620	Kidney stone
78162	Peripheral vertigo
433163	Deficiency of macronutrients
195590	Urethral stricture
314754	Wheezing
438624	Complication of renal dialysis
255302	Spontaneous pneumothorax
201606	Crohn's disease
439935	Abnormal posture
4295287	Hypercoagulability state
4103642	Amputated toe
439795	Minimal cognitive impairment
375292	Perforation of tympanic membrane
196454	Colostomy and enterostomy malfunction
435516	Lipoprotein deficiency disorder
4201390	Colostomy present
440072	Hypogammaglobulinemia
76725	Anal fissure
377572	Noise effects on inner ear
443585	Abrasion and/or friction burn of multiple sites
434490	Chill
4090353	Incompetent urethral closure mechanism
432596	Immune defect

434327	Cannabis abuse
439035	Otosclerosis
381302	Obstruction of Eustachian tube
4303805	Allergic reaction to bite and/or sting
438391	Amino acid transport disorder
437092	Physiological development failure
443702	Abnormal response to nerve stimulation
374801	Foreign body in ear
377873	Lid lag
434872	Infection by Trichomonas
25518	Sickle cell trait
433111	Effects of hunger
437448	Exhaustion due to excessive exertion
436409	Abnormal pupil
434916	Amphetamine or psychostimulant dependence, continuous
4051630	Malingering
440193	Wristdrop
4080568	Problem behavior
372329	Dissociated deviation
4163735	Hemochromatosis
434063	Jaw to cranial base anomaly
440053	Infestation by insect
4002572	Uncomplicated sedative, hypnotic AND/OR anxiolytic withdrawal
4210746	Localized amyloidosis