Government of **Western Australia**
Department of **Health**

Form DS001

For Office Use Only	
Draft#	EOI2015.59
HREC#	2016/53
DL#	201612.01

DEPARTMENT OF HEALTH WESTERN AUSTRALIA

APPLICATION FOR DATA

All applications for unit record data *(including linked data requests)* should be made on this application form. All applications for projects requiring Department of Health (DOH) data and ethics approval by the Department of Health WA Human Research Ethics Committee (DOH HREC) should complete this application form ***plus*** the WA Health Ethics Application Form (For Research Conducted Within WA Health) **or** Western Australian-Specific Module with the National Health Ethics Application Form v2.0.

This form is also used to provide details of requests that involve the **use** of DOH data collections, not involving the release of data, where HREC approval is required.

PLEASE CHECK WHICH IS APPLICABLE:
(double click on box and select "checked")

☐ **DRAFT APPLICATION**

This step must be completed before applying to DOH HREC. Signatures and signed Confidentiality Agreements are not needed for a draft application.

Email your electronic copy to DataServices@health.wa.gov.au Please include:

- Application for Data form
- Data Services forms
- Variable lists for all datasets requested
- Research protocol
- Other supporting documentation

☒ **APPLICATION FOR DATA (FINAL COPY) WHERE DOH HREC APPROVAL IS REQUIRED**

Refer to submission Instructions on DOH HREC website for requirements. **This Application for Data form is to be completed in addition to the relevant WA Health ethics application forms if applying for DOH HREC approval.**

☐ **APPLICATION FOR DATA (FINAL COPY) WHERE DOH HREC APPROVAL IS NOT REQUIRED**

Post one copy of the signed Application for Data form, Data Services forms, Variable lists, Research protocol and other documentation (including current ethics approval and signed confidentiality agreements) to:

Send to: **Project Manager**
Data Linkage Branch
Department of Health
1st Floor, C Block
189 Royal Street
EAST PERTH WA 6004

☐ **APPLICATION FOR DATA AMENDMENT / UPDATE FOR AN EXISTING PROJECT**

To be used for projects where last approval was granted more than one year ago. Should be completed in conjunction with the relevant amendment form.

1. PROJECT TITLE

Investigating **M**edication re-**P**urposing to reduce **R**isk of **OV**arian and **E**ndometrial cancer study (The IMPROVE study)

2. CONTACT DETAILS

2.1 Principal Investigator

This must be the person who has overall responsibility for the management of the project and must <u>not</u> be a student. The Principal Investigator must read and sign the legal declarations at the end of this form.

Name & Title:	Dr Susan Jordan			
Position:	Senior Research Fellow			
Organisation:	The QIMR Berghofer Medical Research Institute			
Address:	Locked Bag 2000, PO Royal Brisbane Hospital, Herston. 4029			
Phone:	**(w):**	(07) 38453576	**(m):**	0438690215
	(h):		**Fax:**	(07) 38453503
Email:	Susan.jordan@qimrberghofer.edu.au			

2.2 Project Contact

This should be the person to be contacted for queries regarding this project *(if same as above please write "as above")*.

Name & Title:	As above			
Organisation:				
Address				
Phone:	**(w):**		**(m):**	
	(h):		**Fax:**	
Email:				

2.3 Student Details

If a student will be involved in this project please provide the student's following information:

Student Name:	N/A			
Organisation:				
Degree Course:				
Supervisor:				
Phone:	**(w):**		**(m):**	
	(h):		**Fax:**	
Email:				

2.4 Student training and experience

If a student will be involved in this project please describe the student's training and experience in the research methodology and research ethics. Describe the supervision to be provided and the proportion of work to be carried out by the student.

N/A

3. ORGANISATION RESPONSIBLE FOR APPLICATION

3.1 List all the locations where the research will be conducted and data analysed (please specify department at institutions).

Population Health Department, QIMR Berghofer Medical Research Institute, Queensland

Centre for Population Health Research, Curtin University, WA

School of Public Health, University of Queensland

Centre for Big Data research in Health, University of NSW, New South Wales

Secure Unified Research Environment (SURE) (Sax Institute, Sydney)

3.2 As the requestor of this information, please indicate the type of organisation/institution that you are from:

☐ Department of Health (DOH)/WA Health
☐ A State department or agency other than DOH (e.g. other Government Department, Public University)
☒ A non-governmental organisation? (e.g. Private Hospital, Medical Research Institute, Private University)
☐ A Commonwealth department or agency
☐ Other, please specify below:

3.3 Do you believe this project has a conflict of interest? If yes, please provide details below.

☐ YES ☒ NO

☐ Commercially
☐ Financially
☐ Intellectually
☐ Other, please specify below:

3.4 Has this project received funding? Please provide details below.

☐ YES ☒ NO

This project will be submitted as a project grant proposal to the NHMRC, Cancer Australian and state based cancer registries in the 2016 round.

4. PROJECT SUMMARY

4.1 Please provide a lay summary *(approximately 50-100 words)* of your project in plain language.

This summary should be written with the general public audience in mind, rather than researchers or medical professionals. Avoid the use of overly technical terms, abbreviations and medical jargon. This summary may be published on the DOH HREC and/or Data Linkage WA website unless you tick 'NO' to question 4.2.

Endometrial and ovarian cancers are the 5th and 9th most commonly diagnosed cancers in Australian women respectively and ovarian cancer the 6th most common cause of cancer death. (AIHW, 2014) While much is known about the risk factors for these cancers, few are readily modifiable. In fact, a recent analysis undertaken by our group showed that only ~ 7% of ovarian cancers and 33% of endometrial cancers could be attributed to modifiable exposures.[1] Given the substantial burden that these cancers place on women and our health services, increasing the opportunities for prevention is a priority. Recent evidence suggests that a number of commonly used medications may have chemopreventive actions in addition to their use in treating chronic disease. The overall objective of this project is therefore to investigate associations between specific chronic disease medications and gynaecological cancer risk and survival in order to identify new potential avenues for gynaecological cancer prevention and treatement.

4.2 In the interest of maintaining public confidence in research, this information about the project may appear on the DOH HREC and/or Data Linkage WA website after the project is approved. If you DO NOT agree to the publication of this information online, please tick the box below.

☐ NO

If NO, please explain:

5. OUTLINE OF PROJECT

Please provide a detailed outline (approximately one to two pages) of your project including the background, aims, design and methodology of the project.

5.1 Background:
Please provide background information on the research topic and provide references where appropriate.

There is a great need to find better ways to prevent cancer and some studies suggest the promising potential for existing chronic disease medications to be re-purposed for this indication. However, in the area of gynaecological cancer there is a dearth of high-quality, large scale observational studies to assess associations and aid translation into clinical practice. Indeed, this was highlighted by a group of eminent ovarian cancer researchers in a recent Nature Reviews publication.[2] "Repurpos(ing) drugs with low-toxicity profiles as preventive agents" was one of their recommended research priorities for reducing incidence and improving outcomes in ovarian cancer.
Such associations can be examined in traditional case-control and cohort studies, but these methods have limitations. For example, self-report of medication use may not be reliable; there is limited information on duration of medication use; recall bias can be problematic; and there are often small numbers of both exposed participants and cancer cases. Large data linkage studies can overcome these problems although one limitation can be the lack of sufficient information on potential confounders.
The aim of this study is to assess associations between medication use and cancer incidence and survival using national routinely collected medication data (Pharmaceutical Benefits Scheme) and nationally routinely collected outcome data (Cancer Registries and National Death Index). Potential confounding of associations will be assessed using a subset of these data linked to more detailed historical health information collated by the Western Australian (WA) Data Linkage Branch.
The proposed project will focus on three groups of medications for which there is some evidence that suggests potential to reduce gynaecololgical cancer incidence and/or improve survival amongst women with these cancers.

1. Osteoporosis medications (Bisphosphonates and raloxifene)
Bisphosphonates are medications that reduce bone resorption and are used commonly in the general population to treat osteoporosis. In vitro and in vivo experiments have also suggested that these compounds have anti-cancer activities, influencing cancer growth and development via mechanisms such as anti-angiogenesis, inhibition of cell proliferation, effects on immune pathways and increasing cell apoptosis.[3]
Thus there is interest in this class of medications for both cancer prevention and treatment.
Risk reduction: Several studies,[4-6] although not all,[7] have indicated a link between bisphosphonate use and reduced endometrial cancer risk in the order of 40-50%. For ovarian cancer, one small case-control study reported a non-significant reduced risk of ovarian cancer with bisphosphonate use (Odds ratio (OR)=0.58);[5] while another study showed risk reduction associated only with one specific type of bisphosphonate (residronate, OR=0.62).[7]
Survival: data suggest that use of bisphosphonates by women with early-stage breast cancer improves survival, particularly amongst those who are post-menopausal at diagnosis.[8] There are also *in vitro* data that suggest the potential for bisphosphonates to inhibit ovarian cancer metastases,[9] but no studies appear to

have assessed associations between bisphosphonate use and survival in women with ovarian or endometrial cancer. This study will assess these relationships.

Raloxifene is also used for the treatment of osteoporosis, particularly in women who are at higher risk of breast cancer. It is a selective oestrogen receptor modulator (SERM), that acts as an oestrogen agonist in bone but an oestrogen antagonist in breast and probably endometrium.[10] Its effects on the ovary are less established. Some observational studies suggest that it may reduce endometrial cancer risk[11,12] and one study (based on 16 case of ovarian cancer) found a non-significant reduction in risk (RR=0.5) of ovarian cancer amongst raloxifene users.[13] Thus, additional evidence is required to clarify this drug's relationships with gynaecological cancers.

While study results are suggestive of preventive potential for osteoporosis medications, an alternative explanation is confounding by indication. Both ovarian and endometrial cancers are hormonally-related (for e.g., menopausal oestrogen therapy increases risk of both cancers), so it may be that reported associations with osteoporosis medications reflect underlying low oestrogen levels associated with osteoporosis rather than the use of the drugs themselves. To clarify this issue it is important that we also examine the association between osteoporotic fracture and gynaecological cancers amongst women who have *not* taken bisphosphonates or raloxifene. Linking with WA health data will allow for these relationships to be assessed.

2. Hypertension medications

Beta-blockers are commonly used for treatment of hypertension and other cardiovascular diseases. Pre-clinical studies suggest that adrenergic stimulation can increase the growth and progression of cancer cells (reviewed in[14]) and thus blockade of adrenergic stimulation might reduce their invasive potential. Two studies have reported improved overall and disease-specific survival of women with ovarian cancer who were treated with beta-blockers after diagnosis compared to non-users of these drugs.[14,15] In one of these, the effect was seen mainly among women using non-selective beta-blockers (overall survival 90 vs 38 months in users versus non-users).[14] However, another study undertaken using linked data from Denmark[16] did not confirm these associations. We could find no studies that have investigated associations between beta-blocker use and endometrial cancer survival however one study reported a non-significant reduced risk of developing endometrial cancer amongst propranolol (non-selective beta-blocker) users compared to non-users.[17] Given the widespread use of these drugs and their well-established safety profile, clarifying their potential for improving gynaecological cancer outcomes could have significant clinical application.

3. Simple analgesics (aspirin, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs))

A larger number of studies have investigated associations between the use of simple analgesic medications and both ovarian and endometrial cancer incidence, however, the evidence is inconsistent. For ovarian cancer paracetamol use has been associated (in large studies) with risk reductions in the order of 30-50%[18,19] although not consistently.[20] Similarly, use of aspirin has been associated with reduced ovarian cancer risk in pooled and meta-analyses[20,21] but whether this association is limited to low-dose aspirin requires clarification as does the association with non-aspirin NSAIDs. Fewer studies have investigated these associations in endometrial cancer but there is some suggestion that aspirin, but not paracetamol or non-aspirin NSAIDs, use is associated with reduced endometrial cancer risk.[22] The evidence for associations between use of simple analgesics and survival in either of these cancers is limited, but promising pre-clinical data suggest this should be an avenue of investigation. While many of these medications are bought over- the-counter rather than on prescription, it is likely that many regular (daily) users will receive these medications on prescription, particularly those who hold concession cards. In 2014 there were over 10 million prescriptions for paracetamol, over 2 million for aspirin and over 6 million for NSAIDs recorded by the PBS.

The proposed linkage study will address gaps in evidence by capitalising on recent changes facilitating the use of national PBS data for research and the emerging potential for cross-jurisdictional linkage. As such this linkage study will be at the forefront of population-based chemoprevention research and will contribute essential evidence to enhance cancer control in Australia.

5.2 Aims:

The aims should reflect the datasets, time frames and variables requested.

The aim of the project is to investigate the associations between

a. bisphosphonates and raloxifene
b. selective β-blockers
c. aspirin, paracetamol, non-steroidal anti-inflammatory drugs - NSAIDs

and i) incident endometrial and ovarian cancer

ii) cancer-specific and overall survival amongst women with endometrial and ovarian cancer.

5.3 Design:
Please describe the project design.

We will conduct a retrospective cohort study to assess the associations described above

5.4 Methodology:
The methodology should outline the data extraction process and contain detailed information of what methods will be used in the data analysis.

The overall study will examine associations between medication use and cancer incidence and survival using locally and nationally linked data (see below – section 11.2). For the subset of women from Western Australia (WA), we are requesting that the data be linked both nationally (to national collections) and locally (to WA health datasets – see below). Linked data from WA will provide access to historical health information which will enable adequate capture of important potentially confounding factors that can be used in the analysis of associations between medication use and cancer outcomes.

The focus of this application is the local (WA) linkage and the process for enabling linkage at a national level. For the WA linkage we aim to use data from a large cohort of women from WA, selected from the Electoral Roll, linked locally to hospital morbidity, Emergency Department, Birth and Midwives Notifications records.

The WA Study Cohort:

The WA Electoral Roll – The Electoral Roll will be used to define the WA Study Cohort. All women on the Roll (excluding silent electors) from January 1st 2002 will be included in the cohort and those who join (or re-join) the roll after January 2002 until latest date available will also be included. Flags for those who have left the state and moved off the roll will be used to determine periods at risk. For women who have no other information, the midpoint of their 5-year year-of-birth category will be used to estimate age, and postcode will be used (where possible) as an indicator of socioeconomic status.

The WA Study Cohort would be linked to locally to HMDS, EDDC, Birth Registrations and MNS data.

Local linkage:
The Hospital Morbidity Data System – these data will be used to identify women from the study cohort who have had particular procedures or diagnoses that we will consider in our analyses as confounders. We would like information about the specified procedures or diagnoses (Principal, Co-diagnoses and/or Additional Diagnoses) whether they have occurred *before or after* an individual appears on the Electoral Roll for the first time (including, for example, women who had gynaecological procedures or births before the age of 18) to avoid misclassification bias. It is also likely that some of these exposures (e.g. hysterectomy) could have occurred many years in the past and we wish to capture that information. We also wish to develop a comorbidity score for included women because data that we (and others) have published show that having comorbidities is associated with cancer-specific survival and is likely also to be strongly associated with some of the medications we are investigating. We will therefore need to adjust for a comorbidity score particularly in our analyses of survival.

We are requesting all linked hospital records rather than only records related to specific conditions in order to extract all useful information from the data. Our reasons for requesting all the hospital records are as follows:

- Excluding certain conditions may mean that worthwhile usable information is lost. Useful information that is not immediately apparent includes co-morbidities that are listed on an admission with an apparently irrelevant principal diagnosis. For example tobacco use is associated with endometrial cancer and some types of ovarian cancer as well as with conditions that could lead to the use of the medications of interest. Tobacco use could be recorded on a range of admissions: it could appear as a principal or co-diagnosis as a mental and behavioural disorder (F17.1), a family history (Z81.2), as environmental tobacco exposure (Z58.7), as deposits on teeth (K03.6). Therefore, by retaining all admissions rather than selecting specific ones, it may be possible to extract a range of useful information on potential risk factors and confounders. Whilst we will focus on known endometrial/ovarian cancer risk factors (parity, infertility, endometriosis, socio-economic status, oophorectomy, salpingectomy, tubal ligation, hysterectomy) we will also make use of co-morbidities listed in the various datasets to derive indicators of, for example, tobacco consumption and obesity (indicated by e.g. bariatric surgery, type 2 diabetes). In doing so we recognise that the data on these variables may be incomplete. Nevertheless inclusion of these variables as confounding factors should improve the accuracy of the estimates of risk for the exposures of interest.
- Data that are as complete as possible are required to construct a comorbidity score to use in adjustment of survival analyses

- We also intend to construct propensity scores to investigate the possibility of confounding by indication. For example, it may be that it is not bisphosphonates per se that reduce risk of these hormonally responsive cancers. Rather it may be the fact that women treated with these have osteoporosis as a result of having relatively low oestrogen levels and that it is the low oestrogen levels rather than the bisphosphonates that reduce risk of endometrial and ovarian cancers. Having extensive covariate information will help us to validly construct these propensity scores.

Emergency Department Data Collection – these data will be used to identify those who have a hip, pelvis, wrist, ankle, vertebral body or humerus fracture between 2002 and present who are not admitted to hospital. These data (along with admissions data) will be used to assess associations between fracture and future cancer risk among women who have and have not used bispohosphonates.

Midwives Notifications – this data set will be used to determine the numbers of births (live or stillborn) that included women have had, including any births women may have had before age 18 years (before joining the Electoral Roll). We will adjust for numbers of births as a potential confounding factor. We are interested in when births occur in relation to exposures and outcomes so will need temporal information on births from the individual MNS records rather than just those associated with a woman's last birth.

Birth Registrations –we would like information from this data set about births that individual women had before the MNS began in 1980. We would like this information going back to 1950 and understand that the linkages for around this time may be incomplete. We will conduct sensitivity analyses to estimate the effects of missing birth information on our study estimates.

National Linkage:
The WA Study Cohort would be linked nationally to PBS, Australian Cancer Registry and the National Death Index data (from 2002 to most recently available) (see below and section 11.2). Personal identifiers including names and full date of birth of the women on the WA Electoral Roll cohort (after permission has been obtained from the Electoral Commission) as well as a national project-specific person key (NPSK) would be provided to the AIHW for the purposes of linking the WA Electoral Roll cohort with the Nationally linked data set. The study investigators would be provided with access to final linked data sets (through SURE - see section 12) with all personal identifiers removed. The investigators would also be provided with access to the de-identified linked health data from WA with the same national project-specific person key (NPSK) to enable merging of the national data set with the WA data set.

National Study Cohort
For *risk* analyses:
We will ask the AIHW to construct a cohort of women who:
- Are eligible for PBS benefits who are aged 18 years or over on 01/07/2002 or who turn 18 or become eligible for PBS benefits after this date
- who have no diagnosis of invasive cancer prior to 01/07/2002

From this sampling frame two groups of women would be selected
1. all of those who have had at least one script supplied for the medication of interest ('users') between 01/07/2002 and the date of linkage
2. a comparison group who have never had a script supplied for the medication of interest ('non-users')

this second group will comprise either
- *all* women who meet this criterion; or
- *a random sample* of women who meet this criterion, matched with users (2:1) on year of birth and state (of residence).

Group definitions will be subject to further refinement after consultation with the Commonwealth data custodian(s).
For survival analyses:
Cohorts of all women diagnosed with invasive ovarian cancer or invasive endometrial cancer after 01/07/2002 up until 30/06/2015 (To allow minimum 2 years follow-up to mid-2017) will be included.

Statistical Analysis
Survival:
Women will enter the study on the date of diagnosis of an invasive cancer and will remain in the study (contributing person-time) until the earliest of: date of death or end of follow-up (the date of linkage).
We will initially define women as ever vs. never users of the medication in question (beta-blockers, bisphosphonates, analgesics) and will classify follow-up time as unexposed prior to first meeting the criterion for being a medication user. Several definitions of users will be explored, e.g.: one prescription; continuous prescriptions representing 6-12 months of use; or continuous prescriptions representing >5 years of use. After meeting this criterion, subsequent time in the study will be classified as exposed. We will further classify

never users into those who have/have not used alternative osteoporosis/ antihypertensive/analgesic medications, allocating their follow-up time as exposed and unexposed accordingly. We will also evaluate the impact of duration of use (exposure accumulation), allowing the exposure to vary over time according to medication use during each time period, intensity of use (drug dosage) and time since last exposure (recency) as well as considering medication use during pre- and post-diagnosis periods separately.
We will use Cox proportional hazards regression to estimate hazard ratios for survival (overall, all-cancer and cancer-specific) associated with medication use compared to (i) use of alternative osteoporosis/ antihypertensive/analgesic medications and (ii) no use. We will explore several methods to account for concurrent use of two types of antihypertensive medications, including: adjusting for use of alternative medications; and further classifying person-time among users as sole beta-blocker use, or beta-blocker use combined with alternative anithypertensives. Statistical models will be adjusted for age and potential confounders including tumour morphology (including histologic subtype and tumour differentiation), chemotherapy and hormone treatment.
Note: analyses for beta-blockers (and other anithypertensives) and analgesics will be restricted to concessional beneficiaries.

Risk:

We will calculate person-years at risk for each woman in the study. Women will enter the study on the latest of: 01/01/2002, the date they were first registered in the Medicare registrations database, or their 18th birthday. Using ACD data, we will exclude women with a diagnosis of invasive cancer prior to this date. Women will remain in the study (contributing person-time) until the earliest of: date of cancer diagnosis, death, or end of follow-up (the date of linkage).
We will initially define women as ever vs. never users of the medication of interest, classifying person-years at risk into homogenous exposure categories as described for survival analyses. We will use Poisson regression to estimate incidence rate ratios for cancer (ovarian, endometriall) associated with the medication use compared to non-use. Statistical models will be adjusted for age and we will conduct sensitivity analyses among concessional beneficiaries to assess the effects of potential confounders including use of hormonal contraceptives and menopausal hormone therapy.
For the women from WA we will also assess the strength of association between the medication of interest and each potential confounder (parity, tubal ligation, hysterectomy, unilateral oophorectomy, endometriosis, diabetes, obesity, etc) as well as the strength of association between confounders and the cancer of interest. Where power permits we will adjust models for these potential confounders. Where appropriate we will also use quantitative bias techniques to estimate the potential size of overall (national) risk estimates taking into consideration the likely effects of confounding as determined using the WA data.

We will subsequently evaluate the impact of factors such as duration and recency of use of the medication in question.

6. PROJECT DURATION

6.1 This period should cover all data analysis, e.g.: data collection through to report writing. Please note that delivery of linked data can take several months depending on the complexity of the request.

Anticipated Start Date:	January 2017
Anticipated Finish Date:	January 2020

6.2 Does your project have any deadlines you would like to make us aware of?

Please note that while we will endeavour to deliver your data within the required timeframe, project complexity and existing workloads may result in delays.

☐ YES ☒ NO

If yes, please provide details and the date you would require data by:

7. PERSONNEL

Please list all personnel and describe their qualifications, expertise, role in the project and indicate whether they require access to data. If multiple positions are held across organisations, list the employing institution relevant for this data application.

Project personnel who are not WA Public Sector employees, must sign a Declaration of Confidentiality (available at http://www.health.wa.gov.au/healthdata/HREC/index.cfm)

Please note that all projects requesting linked data must have at least one team member based at a

WA institution.			
Title, Full Name, Qualifications, Employing Institution, Email Address *eg: Prof Albert Smith, MBBS, University of Western Australia, asmith@uwa.au*	**Expertise and role in the project**	**Access to data required**	**Confidentiality Agreement submitted**
Dr Susan Jordan, MBBS, PhD, QIMR Berghofer Medical Research Institute, QLD Susan.jordan@qimrberghofer.edu.au	Chief investigator- with specific expertise in cancer aetiology and women's health. Dr Jordan will coordinate the project and will oversee and contribute to data analysis interpretation of results and contribution to manuscript preparation.	☒ Yes ☐ No	☐ Yes ☐ No
Dr Louise Stewart, BSc, PhD Curtin University, WA louise.m.stewart@curtin.edu.au	Investigator with experience in data linkage and ovarian cancer epidemiology. Dr Stewart will contribute to data analysis, interpretation of results and contribution to manuscript preparation.	☒ Yes ☐ No	☐ Yes ☐ No
Dr Nirmala Pandeya, MSc, PhD University of Qld n.pandeya1@uq.edu.au	Investigator with extensive statistical experience, experience in cancer epidemiology and in data linkage. Dr Pandeya will contribute to data analysis, interpretation of results and contribution to manuscript preparation	☒ Yes ☐ No	☐ Yes ☐ No
Professor Sallie Pearson, PhD University of NSW Sallie.pearson@unsw.edu.au	Investigator with extensive experience in pharmacoepidemiolgy, particularly in the use of PBS data in data linkage projects. Prof Pearson will advise on PBS data analysis, interpretation of results and contribution to manuscript preparation	☒ Yes ☐ No	☐ Yes ☐ No
A/Professor Anna Ferrante, PhD Curtin University, WA A.Ferrante@curtin.edu.au	Data Linkage Coordinator from PHRN Centre for Data Linkage. Extensive experience and expertise in data linkage, specifically in the WA context. A/Prof Ferrante will act as data linkage coordinator for the project and in particular will help facilitate the cross-jurisdictional linkage.	☐ Yes ☒ No	☐ Yes ☐ No
A/Professor Katrina Spilsbury, PhD Curtin University, WA katrina.spilsbury@curtin.edu.au	Statistician with extensive experience and expertise in the analysis of complex, linked data, specifically in	☒ Yes ☐ No	☐ Yes ☐ No

	the WA context. Will advise and assist with data analysis interpretation of results and contribution to manuscript preparation		

8. ETHICS REVIEW & APPROVALS

8.1 Does your project require review by the DOH HREC?

DOH HREC information links:

- Applicant External to WA Health
- Applicants Internal to WA Health

☒ YES ☐ NO

8.2 Does your project require approval by any other ethics committee?

This could include WA Health ethics committees and/or external ethics committees. DOH Research Development Unit information links:

- WA Health Research Governance Policy and Procedures 2012
- WA Health Research Ethics

☒ YES ☐ NO

If yes, list the other committees that must approve this application and the current status of applications for approval. Please attach a copy of each approval granted.

QIMR Berghofer Medical Research Institute Human Research Ethics Committee (HREC)

Curtin University HREC

AIHW HREC

DoH (Commonwealth) HREC

8.3 Does your project require any other approvals?

☒ YES ☐ NO

If yes, list the other approvals required and the current status of applications for approval. Please attach a copy of each approval granted.

Approval from each state-based cancer registry (this is a requirement to access data held by the Australian Cancer Database held by the AIHW) – application has not yet been made.
Approval from WA Electoral Commissioner (for release of name-identified data for national linkage) – application has not yet been made.

9. PROJECT DATA

Data Services

9.1 Complete the following table to indicate the data services you are seeking.

Complete the corresponding data service form for each service requested. See http://www.datalinkage-wa.org.au/forms All required data service forms must be attached to your application.

DATA SERVICE		REQUEST
Extraction	Data extraction from one or more data collections	☒
Linkage	New data to be linked to one or more core data sets	☐

Geocoding	New addresses to be assigned a geocoded point or area	☐
Sample Selection	Sample of population to be selected from the Electoral Roll or other dataset	☐
Genealogical Data	Family relationships or data for related individuals	☐
Study Recruitment	Use of DOH data to contact persons for research purposes	☐
Indigenous Status Flag	The Indigenous status flag can be included in record level health data provided for data linkage projects or extracts from single health data sets. A validated algorithm is used to create this flag for each individual with one or multiple data records held in one or multiple WA government administrative data sets. Data recipients must note that their project could receive data for an individual where data sets provided report an Indigenous Status of NO but an Indigenous status flag of YES. The Indigenous status flag indicates what a person may identify as over all available collections/records which may be different to what is reported in a specific record or collection.	☐
Survival Risk Ratios	A Survival Risk Ratio is a derived measure of injury severity. It is calculated for each injury ICD code, and is a number between zero and one. It is calculated as a proportion of patients who survived that injury, out of the total number who were diagnosed with it.	☐

Data Collections

9.2 Complete the table below to indicate which data collections you need and the year span required. It is strongly recommended that you discuss your request with the relevant Data Custodians before applying for data.

If applying for an extraction of data, please complete the variable list for each dataset requested. See http://www.datalinkage-wa.org.au/forms

If the variable list you require is not available on the website please contact Data Services (dataservices@health.wa.gov.au)

For other datasets please attach a separate word document outlining the details (Dataset name, data custodian and/or contact details, data variables you are requesting)

DATA SET		**SELECT**	**FROM** *e.g.: Jan 1984*	**TO** *e.g.: most recent*
Midwives Notification System	(since 1980)	☒	Jan 1980	Most recent
Hospital Morbidity Data System	(since 1970)	☒	Jan 1970	Most recent
Mental Health Information System	(since 1966)	☐		
WA Cancer Registry	(since 1982)	☐		
Emergency Department Data Collection	(since 2002)	☒	Jan 2002	Most recent
Birth Registrations	(since 1974)	☒	Jan 1950	Dec 31st 1979
Mortality Register	(since 1969)	☐		
Electoral Roll	(since 1988)	☒	Jan 2002	Most recent
WA Register of Developmental Anomalies (Birth Defects)		☐		
WA Register of Developmental Anomalies (Cerebral Palsy)		☐		
WA Notifiable Infectious Diseases Database		☐		

Other datasets	(please list below)	☐		

10. PRIVACY AND CONSENT

Personal Information

Personal information is information about an individual where the identity of the individual or institution is apparent or can be reasonably ascertained from the information itself.

Information is also personal information if it is reasonably possible for the person receiving the information to identify the individual by using other information that they already hold.

Note: If you tick yes to any of the items in question 10.4, you must answer yes to this question.

Applicants are advised to read the Practice Code for the Use of Personal Health Information.

10.1 Are you applying for the release of personal information from a DOH data collection?

☐ YES ☒ NO

10.2 If the answer is yes please explain below why non-identifiable information cannot be used. How will privacy be maintained?

10.3 If the answer is no please explain how privacy will be maintained.

We do not believe that the identity of an individual can be reasonably ascertained from the information that we are requesting. The information provided to researchers will not include names, dates of birth or addresses and the number of pieces of information about individuals would not be sufficient to identify them.

The listed researchers are also not in the possession of any other information that can be used to identify the individuals.

All researchers with access to data will sign and abide by the DOH Confidentiality Agreement

Personal Information Variables

10.4 Please indicate below ("Yes" or "No") whether you need any of the listed information in your data extract. This does not apply to data provided for linkage, nor to the use of data by DOH to contact people.

Participant / Patient names?	☐ YES	☒ NO
Participant / Patient addresses?	☐ YES	☒ NO
Participant / Patient full date of birth (NB: ddmmyyyy **not** mmyyyy)?	☐ YES	☒ NO
Patient identifiers (UMRN)?	☐ YES	☒ NO
Clinician or health service provider identifications?	☐ YES	☒ NO
Individual hospital or healthcare institution identifications?	☐ YES	☒ NO
Geo-coded points (longitude and/or latitude)	☐ YES	☒ NO

Consent

10.5 Please indicate below whether consent will be sought from the participants for the use and disclosure of the information about them from the DOH data collections.

☐ YES ☒ NO

10.6 If consent will be sought explain the consent process, i.e. how participants or those deciding for them will be informed about project or, whether or not they choose to participate. (Attach copies of all contact letters, information sheets and consent forms that will be used.)

10.7 If consent will not be sought from the participants explain why it is impracticable to obtain the consent of the individual to the data collection, use or disclosure of their information? Tick one or more of the following and provide details in the box below.

- ☒ The size of the population involved in the research.
- ☒ The proportion of individuals who are likely to have moved or died since the health information was originally collected.
- ☒ The risk of introducing potential bias into the research.
- ☐ The risk of creating additional threats to privacy.
- ☐ The risk of inflicting psychological, social or other harm by contacting individuals.
- ☒ The difficulty of contacting individuals directly when there is no existing or continual relationship between the organisation and the individuals.
- ☒ The difficulty of contacting individuals indirectly through public means.
- ☐ Other

Please provide details:

Given the age span of the included population of women, many will have died. Further, many will have moved over time and will be difficult to locate. Finally, seeking consent will result in much less than 100% participation by those alive and contactable. Together, these introduce the potential for serious bias in participation in our study and hence in the research results.

11. OTHER SOURCES OF INFORMATION FOR THE PROJECT

11.1 Indicate the other sources of information that will be used in this project.

- ☐ Information will be collected directly from the participant.
- ☐ Information will be collected from another person (e.g. carer, parent, Doctor) about the participant.
- ☒ Information will be collected from an existing record or data collection held by an individual or organisation other than the DOH.
- ☐ Information will be used that you or your organisation have previously collected for another purpose.
- ☐ Other DOH data collections.
- ☐ Other

11.2 Describe the source of the information, the information that will be collected from each source and specify whether your project involves the matching of records from different sources. Attach a separate word document outlining the details. (Dataset name, data custodian contact name, phone number and email address and data variables you are seeking).

*** Please Note - if the data custodian is named as a researcher on the application form, the next tier or authority above must be listed below and provide written approval for release of data.**

Australian Cancer Database: all diagnoses of cancer for included women from January 1982 until date of data linkage (estimated mid-2017). We are interested in incident diagnoses of ovarian and endometrial cancer after 2002 but will need to exclude women with prior diagnoses of invasive cancer so will need to know about all other cancer diagnoses. Requested data fields cover demographics, diagnosis details, and tumour characteristics.
PBS and Medicare Registrations: data on supply of any scripts for: beta-blockers and other antihypertensive drugs (for comparison), paracetamol, NSAIDs, aspirin, bisphosphonates, raloxifene and

other osteoporosis drugs (for comparison) and hormones and chemotherapy drugs, for comparison and adjustment for confounding, from 01/07/2002 to the date of linkage (estimated mid-2017); Requested fields cover Medicare registration details and dispensing details for each script.
National Death Index: all deaths of women in the study cohort from 01/07/2002 until the date of linkage (estimated mid-2017).Requested fields cover date/cause of death and age at death.

Personal identifiers from the above datasets will not be released to the researchers, but will be used within AIHW and the WA Department of Health in order to link the Study Cohort. These personal identifiers include names, sex, and full date of birth.

12. SECURITY PLAN

12.1 Please provide a detailed Security Plan for the protection of the information provided by DOH, or the information to be received from persons contacted as a result of DOH's actions. The Security Plan should specify the measures that will be taken to protect the information from misuse, loss or unauthorised access during the research project. (See *Practice Code for the Use of Personal Health Information from the Department of Health Data Collections*)

Technological Security:

Data Security at SURE

The investigators will access and analyse the project data through SURE. The remote environment is accessible over encrypted Internet and AARNet connections. A virtual project workspace hosted by SURE will be established for this project, with access restricted to the investigators listed on the ethics application. Access to virtual project workspaces requires a username, password and a onetime access code provided by a physical token (Yubikey). Prior to logging into SURE, a series of endpoint check are run on a user's local computer. These checks ensure that minimum security requirements are met, including the presence of up-to-date antivirus software and the installation of important updates to the local computer's operating system. There are strong security controls in SURE to protect the privacy and confidentiality of data files. Within SURE, a user cannot access the internet or email, there is no print function, there is no ability to copy data to removable media, and all files move into or out of SURE by passing through the Curated Gateway. All inbound data files uploaded to the Curated Gateway for use in SURE are reviewed by a member of the SURE operations team (who is subject to the same restrictions as a SURE user) for compliance with ethics committee approval and data custodian requirements. Files other than data files are reviewed by the study's chief investigator prior to being accepted for use in SURE. Outbound files uploaded to the Curated Gateway for use outside SURE are reviewed by the study's chief investigator. All files that pass through the Curated Gateway are logged and may be subject to audit by the Sax Institute, the organisation operating the SURE service.

Physical Security:

As SURE is a remote access computing environment, it will be accessed physically from both the **QIMR BERGHOFER Medical Research Institute** (CIs Jordan and Pandeya) and **Curtin University** (CIs Stewart and Spilsbury). Access to SURE is restricted to the investigators listed on the ethic application and all inbound files uploaded to the Curated Gateway for use in SURE are reviewed by a member of the SURE operations team for compliance with ethics and data custodian requirements.

• Within the SURE facility, all data and files are stored on servers housed in a data centre called Global Switch, which is located in Sydney and listed on the Australian Government Data Centre Facilities Panel. The servers are stored in locked cabinets dedicated to SURE. Premises-wide security measures include 24 hour staffed security surveillance, intruder resistance at all levels and strict physical access controls including access control lists. Regular backups of data stored in the SURE facility are made using two processes. First, disk-to-disk backups are made at the SURE facility. Additionally, data is copied off in encrypted form to tapes that are rotated offsite. Data taken offsite is strongly encrypted using 256bit Advanced Encryption Standard.

Transport:

The data set created by the WA Data Linkage branch will be released to the research team via secure online transfer (either MyFT or the PHRN SUFEX service – https://sufex.org.au).

Data from the Electoral Roll cohort will also be transferred to the AIHW for national linkage using the PHRN secure file transfer service, SUFEX https://sufex.org.au.

Any other data transfers will be undertaken using the PHRN secure file transfer service, SUFEX https://sufex.org.au.

12.2 Does your security, retention and disposal plan comply with the DOH '*Practice Code for the Use of Personal Health Information*'?

☒ YES ☐ NO

12.3 If no, please explain why not:

13. RETENTION AND DISPOSAL PLAN

13.1 Please describe the proposal for the retention and disposal of the information provided by DOH, or the information to be received from persons contacted as a result of DOH's actions. See the *Practice Code for the Use of Personal Health Information from the Department of Health Data Collections* for DOH requirements. The Information Retention and Security Plan should specify the period of retention of the data after the completion of the project and the measures to be taken to secure the information during that period. It should also specify the date by which the information will be returned or destroyed.

Data destruction through SURE

Electronic files containing the health data for analysis will be stored on a Virtual Project Workspace within the Secure Unified Research Environment (SURE) facility and the access period shall be from study commencement in 2017 to study completion (anticipated to be 2020). Upon completion of the project, files stored on the virtual project workspace within the SURE facility will be archived to tape and stored at a secure facility in an encrypted format. In accordance with the joint NHMRC/ARC Australian Code for the Responsible Conduct of Research (2007), these archived files will be stored for five years after the completion of the project. This time period represents the likely time that interest and discussion will persist following publication of the findings of the projects. At the end of this data retention period, the tapes holding the archived data files will be physically destroyed. Therefore the expected destruction date is 2025. Archiving, storage and destruction will be performed by staff of the SURE facility.

Data destruction/ return date:	31 December 2025

14. ANALYTICAL TOOLS

14.1 Optional - for our planning purposes only, if known could you please describe the software packages and analytical tools you will use for this project e.g. SPSS, SAS, Excel.

Analytical tools within SURE include SAS, SPSS and STATA.

15. DISSEMINATION OF RESULTS

15.1 Please explain how results will be disseminated, e.g. report, publication, thesis.
Please note that all draft reports, publications and presentations must be sent to the Data Custodians and/or Data Linkage Branch for comment (see declarations in section 16).

The results will be published in peer-reviewed journals and presented at local and international conferences.
15.2 Please describe how confidentiality of participants will be maintained in the dissemination of results.
We will not have access to individual identifying information. All the results will be published in aggregate form and the numbers of people involved in the study would preclude identification of the individual circumstances of individuals

16. GOVERNANCE

Head of Department / School / Research Organisation

Please tick the boxes to indicate that you have read and understand each clause.

I/ we certify that:

- ☐ **I/we are familiar with this project and endorse its undertaking.**
- ☐ **The resources required to undertake this project are available.**
- ☐ **The researchers have the skill and expertise to undertake this project appropriately or will undergo appropriate training as specified in this application.**
- ☐ **I/we warrant that I/we are authorised to make this application and to bind the institution below in relation to the obligations arising out of the submission of this application.**
- ☐ **The conduct of the project has been approved by : *(see below)***

I/we certify that	

(name of institution)

accepts the legal and ethical responsibility for the conduct of this project and have adequate indemnity insurance to cover the conduct of this project and indemnifies the Minister for Health, the State of Western Australia, the Department of Health and their officers, servants, agents and contractors for any loss or damage they suffer through any breach in the conduct of this project.

FULL NAME *(PRINTED)*:	
POSITION:	
ORGANISATION:	

SIGNATURE *	**DATE**

*** Please Note - if the Principal Investigator is the Head of Department / School / Research Organisation the next tier or authority above is required to sign the indemnity form. This section cannot be signed by a member of the project team.**

17. DECLARATIONS AND SIGNATURES

17.1 Applicant / Principal Investigator

Please tick the boxes to indicate that you have read and understand each clause.

I certify that;

- ☐ **All information in this application is truthful and as complete as possible.**
- ☐ **The project will be conducted in accordance with the ethical and research arrangements of the organisations involved.**
- ☐ **I have consulted any relevant legislation and regulations, and the project will be conducted in accordance with these.**
- ☐ **I recognise that unit record data from DOH is confidential information and that I am responsible for ensuring that the information will be kept confidential.**
- ☐ **The information provided for this project by DOH will only be used for the project outlined in this application.**
- ☐ **The project will be conducted in accordance with the protocol and conditions approved for this project and in accordance with the provisions of the DOH *Practice Code for the Use of Personal Health Information.***
- ☐ **I will make available all resulting draft manuscripts, reports or other presentation based on the analysis of linked data in this application to the relevant Data Custodians and thereby allowing DOH the opportunity to review and respond within 14 days (2 weeks).**
- ☐ **I will provide the Data Linkage Branch and/or Data Custodians with an electronic copy of all publications of results of analysis as they become publicly available.**
- ☐ **I will acknowledge the Data Linkage Branch and/or DOH in any publications, reports or presentations resulting from this application.**

FULL NAME *(PRINTED)*:	
SIGNATURE	**DATE**

17.2 Supervisor/s of student/s

Please tick the boxes to indicate that you have read and understand each clause.

I /we certify that:

- ☐ **I/we will provide appropriate supervision to the student to ensure that the project is undertaken in accordance with the undertakings above.**
- ☐ **I/we will ensure that any necessary training is provided to enable the project to be undertaken skilfully and ethically.**

FULL NAME *(PRINTED)*:	
SIGNATURE	**DATE**

References

1. Whiteman DC, Webb PM, Green AC, et al. Cancers in Australia in 2010 attributable to modifiable factors: summary and conclusions. Australian and New Zealand journal of public health 2015;39:477-84.
2. Bowtell DD, Bohm S, Ahmed AA, et al. Rethinking ovarian cancer II: reducing mortality from high-grade serous ovarian cancer. Nature reviews Cancer 2015;15:668-79.
3. Gronich N, Rennert G. Beyond aspirin-cancer prevention with statins, metformin and bisphosphonates. Nature reviews Clinical oncology 2013;10:625-42.
4. Alford SH, Rattan R, Buekers TE, Munkarah AR. Protective effect of bisphosphonates on endometrial cancer incidence in data from the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial. Cancer 2015;121:441-7.
5. Rennert G, Rennert HS, Pinchev M, Lavie O. The effect of bisphosphonates on the risk of endometrial and ovarian malignancies. Gynecol Oncol 2014;133:309-13.
6. Newcomb PA, Passarelli MN, Phipps AI, et al. Oral bisphosphonate use and risk of postmenopausal endometrial cancer. J Clin Oncol 2015;33:1186-90.
7. Vinogradova Y, Coupland C, Hippisley-Cox J. Exposure to bisphosphonates and risk of common non-gastrointestinal cancers: series of nested case-control studies using two primary-care databases. Br J Cancer 2013;109:795-806.
8. Mathew A, Brufsky AM. The use of adjuvant bisphophonates in the treatment of early-stage breast cancer. Clinical advances in hematology & oncology : H&O 2014;12:749-56.
9. Sawada K, Morishige K, Tahara M, et al. Alendronate inhibits lysophosphatidic acid-induced migration of human ovarian cancer cells by attenuating the activation of rho. Cancer Res 2002;62:6015-20.
10. Martinkovich S, Shah D, Planey SL, Arnott JA. Selective estrogen receptor modulators: tissue specificity and clinical utility. Clin Interv Aging 2014;9:1437-52.
11. DeMichele A, Troxel AB, Berlin JA, et al. Impact of raloxifene or tamoxifen use on endometrial cancer risk: a population-based case-control study. J Clin Oncol 2008;26:4151-9.
12. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. Jama 1999;281:2189-97.
13. Neven P, Goldstein SR, Ciaccia AV, Zhou L, Silfen SL, Muram D. The effect of raloxifene on the incidence of ovarian cancer in postmenopausal women. Gynecol Oncol 2002;85:388-90.
14. Watkins JL, Thaker PH, Nick AM, et al. Clinical impact of selective and nonselective beta-blockers on survival in patients with ovarian cancer. Cancer 2015;121:3444-51.
15. Diaz ES, Karlan BY, Li AJ. Impact of beta blockers on epithelial ovarian cancer survival. Gynecol Oncol 2012;127:375-8.
16. Johannesdottir SA, Schmidt M, Phillips G, et al. Use of ss-blockers and mortality following ovarian cancer diagnosis: a population-based cohort study. BMC Cancer 2013;13:85.
17. Chang PY, Huang WY, Lin CL, et al. Propranolol Reduces Cancer Risk: A Population-Based Cohort Study. Medicine 2015;94:e1097.
18. Bonovas S, Filioussi K, Sitaras NM. Paracetamol use and risk of ovarian cancer: a meta-analysis. British journal of clinical pharmacology 2006;62:113-21.
19. Baandrup L, Friis S, Dehlendorff C, Andersen KK, Olsen JH, Kjaer SK. Prescription use of paracetamol and risk for ovarian cancer in Denmark. J Natl Cancer Inst 2014;106:dju111.
20. Trabert B, Ness RB, Lo-Ciganic WH, et al. Aspirin, nonaspirin nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: a pooled analysis in the Ovarian Cancer Association Consortium. J Natl Cancer Inst 2014;106:djt431.
21. Baandrup L, Faber MT, Christensen J, et al. Nonsteroidal anti-inflammatory drugs and risk of ovarian cancer: systematic review and meta-analysis of observational studies. Acta obstetricia et gynecologica Scandinavica 2013;92:245-55.
22. Neill AS, Nagle CM, Protani MM, Obermair A, Spurdle AB, Webb PM. Aspirin, nonsteroidal anti-inflammatory drugs, paracetamol and risk of endometrial cancer: a case-control study, systematic review and meta-analysis. Int J Cancer 2013;132:1146-55.

Extraction

For Office Use Only	
EOI#	2015.59
DL#	

Please specify the data to be extracted, listing all data sets and specific detail around selection of a cohort or cases and controls. Any date limits should also be given. If you require assistance with completing this form, please email DataServices@health.wa.gov.au.

Please note: DOHWA HREC approval is required for any personal health information*.

*Personal health information is information or opinions that relate to the health of a person where the identity of a person is apparent or can reasonably be ascertained from the information. For a more detailed explanation see the *Practice Code For the Use of Personal Health Information*. All project personnel who will have access to personal health information provided by the DOHWA must enter into a Confidentiality Agreement. Please contact the Manager or Project Manager of the Data Linkage Branch or the DOHWA HREC Executive Officer if you are unsure of the criteria for "personal health information".

1. COHORT/CASE GROUP

Cohort Description
Please provide a description of your cohort and how your study population is defined. E.g. all people living in Bunbury who were diagnosed with lung cancer between 1995 and 2005, defined through the WA Cancer Registry
The cohort: all women on the Electoral Roll at Jan 1 2002 and all those women who enrolled to vote subsequent to that date up until latest available at time of linkage
For quoting purposes please provide an estimate of how many people there will be in your cohort.
~800,000
Disease and Procedure Codes
If your cohort is to be selected from specific disease or procedure groupings, please specify the version of ICD codes you require (i.e. ICD9, ICD10), and whether they should be applied only to the principal disease/procedure code or to any of the multiple codes within a record. For the time periods and versions of ICD codes used in WA please see http://www.datalinkage-wa.org.au/sites/default/files/HMDS_ICD_DRG.pdf **Please attach an Excel spreadsheet of all the specific ICD codes you require. Please note that the DLB cannot provide or check ICD codes.** E.g. ICD10, diagnosis codes for lung cancer. See attached spreadsheet.
N/A
Geographical areas

If your cohort is to be restricted to a specific residential or service area, please specify the relevant postcodes or CDs that define the area required. **Please attach an Excel spreadsheet of the postcodes or CDs you require.** *SEIFA and ARIA codes are available for Emergency, Death, Hospital and Midwives data. If you require SEIFA or ARIA codes, please select this in the variable lists for each dataset (Module 4).* E.g. People residing in Bunbury. See attached spreadsheet of postcode and collection districts.
N/A

Service data extraction

Please specify the datasets you require, the time period and any restrictions on which records you need.

WA Cancer Registry: Please refer to the variable list for record scope. If you require specific exclusions please list them in the comments section of that form.

Midwives Notification System, Birth Registrations & WA Register of Developmental Anomalies: Please specify below whether you need records for the birth of a person, records where they are the parent or both.

***Attach variable lists (Module 3).**

Dataset E.g. Hospital Morbidity	**Time period** E.g. Jan 1995 – most recent	**Restrictions** E.g. I wish to analyse comorbidities. Please extract all records for 5 years before and all after the index admission.
Hospital Morbidity Data System	Jan 1970 – most recent	We wish to have all hospital data to enable us to adjust for potential confounders and by extracting all useful information from the data. In addition to adjusting for specific diseases or procedures, we wish to construct comorbidity scores and propensity scores to include in our analyses.
Midwives Notification System	Jan 1980 – most recent	We wish to have records linked where the woman from the cohort is the biological mother (not the child) including births to woman who were younger than 18.
Electoral Roll	Jan 2002 – most recent	Women only
Birth Register	Jan 1950 to Dec 31 1979	We would like information about births that women on the electoral roll cohort may have had prior to the beginning of the MNS in 1980.
Emergency Department Data Collection	Jan 2002 – most recent	these data will be used to identify those who have a hip, pelvis, wrist, ankle, vertebral body or humerus fracture between 2002 and present who are not admitted to hospital