INDEPENDENT SCIENTIFIC ADVISORY COMMITTEE (ISAC) PROTOCOL APPLICATION FORM

PART 1: APPLICATION FORM

***IMPORTANT***

**Both parts of this application must be completed in accordance with the guidance note ‘Completion of the ISAC Protocol Application Form’, which can be found on the CPRD website (**[**https://cprd.com/research-applications**](https://cprd.com/research-applications)**).**

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| FOR ISAC USE ONLY | |
| **Protocol No. -** | **Submission date -** |

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| GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY |
| Quantifying Bias in Epidemiological Studies on the Association Between Acetaminophen and Cancer 2 |
| **Research Area** (place ‘X’ in all boxes that apply) |
| |  |  |  |  | | --- | --- | --- | --- | | Drug Safety | X | Economics |  | | Drug Utilisation |  | Pharmacoeconomics |  | | Drug Effectiveness |  | Pharmacoepidemiology |  | | Disease Epidemiology |  | Methodological | X | | Health Services Delivery |  |  |  | |
| Chief Investigator  |  |  | | --- | --- | | Title: | PhD | | Full name: | Martijn J. Schuemie | | Job title: | Senior Director | | Affiliation/organisation: | Janssen R&D | | Email address: | [mschuemi@its.jnj.com](mailto:mschuemi@its.jnj.com) | | CV Number (if applicable): | 455\_16CES | | Will this person be analysing the data? (Y/N) | Y | |
| Corresponding Applicant  |  |  |  | | --- | --- | --- | | Title: | PhD |  | | Full name: | Martijn J. Schuemie |  | | Job title: | Senior Director |  | | Affiliation/organisation: | Janssen R&D |  | | Email address: | [mschuemi@its.jnj.com](mailto:mschuemi@its.jnj.com) |  | | CV Number (if applicable): | 455\_16CES |  | | Will this person be analysing the data? (Y/N) | Y |  | |
| List of all investigators/collaborators  |  |  | | --- | --- | | Title: | PhD | | Full name: | Patrick B. Ryan | | Job title: | Vice President | | Affiliation/organisation: | Janssen R&D | | Email address: | [pryan4@its.jnj.com](mailto:pryan4@its.jnj.com) | | CV Number (if applicable): | 120\_15SL | | Will this person be analysing the data? (Y/N) | N |   [Add more investigators/collaborators as necessary by copy and pasting a new table for each investigator/collaborator] |
| Experience/expertise available List below the member(s) of the research team who have experience with CPRD data.   |  | | --- | | **Name(s):** | | Martijn Schuemie | | Patrick Ryan | |  |   List below the member(s) of the research team who have statistical expertise.   |  |  | | --- | --- | | **Name(s):** |  | | Martijn Schuemie | | | Patrick Ryan | | |  | |   List below the member(s) of the research team who have experience of handling large datasets (greater than 1 million records).   |  |  | | --- | --- | | **Name(s):** |  | | Martijn Schuemie | | | Patrick Ryan | | |  | |   List below the member(s) of the research team, or supporting the research team, who have experience of practicing in UK primary care.   |  |  | | --- | --- | | **Name(s):** |  | |  | | |  | | |  | | |
| ACCESS TO THE DATA |
| Sponsor of the study  |  |  | | --- | --- | | Institution/Organisation: | Janssen R&D | | Address: | 1125 Trenton Harbourton Road  Titusville, NJ 08560  USA | |
| Funding source for the study  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Same as Sponsor? | Yes | X | No |  |  | | Institution/Organisation: |  | | | | | | Address: |  | | | | | |
| Institution conducting the research  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Same as Sponsor? | Yes | X | No |  |  | | Institution/Organisation: |  | | | | | | Address: |  | | | | | |
| Data Access Arrangements Indicate with an ‘**X**’ the method that will be used to access the data for this study:   |  |  | | --- | --- | | Study-specific Dataset Agreement |  |  |  |  |  | | --- | --- | --- | | Institutional Multi-study Licence | X |  | | Institution Name | Janssen R&D | | | Institution Address | 1125 Trenton Harbourton Road  Titusville, NJ 08560  USA | |   Will the dataset be extracted by CPRD?   |  |  |  |  | | --- | --- | --- | --- | | Yes |  | No | X |   If yes, provide the reference number: |
| 1. **Data Processor(s):**  |  |  |  | | --- | --- | --- | | Processing | X |  | | Accessing | X | | Storing | X | | Processing area (UK/EEA/Worldwide) | | Worldwide | | Organisation name | | Janssen R&D | | Organisation address | | 1125 Trenton Harbourton Road  Titusville, NJ 08560  USA | |
| INFORMATION ON DATA |
| Primary care data (place ‘X’ in all boxes that apply)  |  |  |  |  | | --- | --- | --- | --- | | CPRD GOLD | X | CPRD Aurum |  |   **X**  Reference number (if applicable): |
| Please select any linked data or data products being requested **Patient Level Data** (place ‘**X**’ in all boxes that apply) |
| |  |  |  |  | | --- | --- | --- | --- | | ONS Death Registration Data |  |  | | | HES Admitted Patient Care |  |  |  | | HES Outpatient |  |  |  | | HES Accident and Emergency |  | NCRAS Cancer Registration Data |  | | HES Diagnostic Imaging Dataset |  | NCRAS Cancer Patient Experience Survey (CPES) data |  | | HES PROMS (Patient Reported Outcomes Measure) |  | NCRAS Systemic Anti-Cancer Treatment (SACT) data |  | | CPRD Mother Baby Link |  | NCRAS National Radiotherapy Dataset (RTDS) data |  | | Pregnancy Register |  | NCRAS Quality of Life Cancer Survivors Pilot (QOLP) |  | | Mental Health Data Set (MHDS) |  | NCRAS Quality of Life Colorectal Cancer Survivors (QOLC) |  | |
| **Area Level Data** (place ‘**X**’ in one Practice / Patient level box that may apply)   |  |  |  |  | | --- | --- | --- | --- | | **Practice level (UK)** |  | **Patient level (England only)** |  | | Practice Level Index of Multiple Deprivation |  | Patient Level Index of Multiple Deprivation |  | | Practice Level Index of Multiple Deprivation  (index other than the most recent) |  | Patient Level Index of Multiple Deprivation Domains |  | | Practice Level Index of Multiple Deprivation Domains |  | Patient Level Carstairs Index for 2011 Census |  | | Practice Level Carstairs Index for 2011 Census (Excluding Northern Ireland) |  | Patient Level Townsend Score |  | | 2011 Rural-Urban Classification at LSOA level |  | 2011 Rural-Urban Classification at LSOA level |  |   Reference / Protocol number (where applicable): |
| Are you requesting linkage to a dataset not listed above?  |  |  |  |  | | --- | --- | --- | --- | | Yes |  | No | **X** |   If yes, provide the Non-Standard Linkage reference number: |
| Does any person named in this application already have access to any of these data in a patient identifiable form, or associated with an identifiable patient index?  |  |  |  |  | | --- | --- | --- | --- | | Yes |  | No | **X** |   If yes, provide further details: |
| VALIDATION/VERIFICATION |
| Does this protocol describe an observational study using purely CPRD data?  |  |  |  |  | | --- | --- | --- | --- | | Yes | **X** | No |  | |
| Does this protocol involve requesting any additional information from GPs, or contact with patients?  |  |  |  |  | | --- | --- | --- | --- | | Yes |  | No | **X** |   If yes, provide the reference number: |

**PART 2: PROTOCOL INFORMATION**

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| **Applicants must complete all sections listed below**  **Applications with sections marked ‘Not applicable’ without justification will be returned as invalid** |
| Study Title (Max. 255 characters, including spaces) Quantifying Bias in Epidemiological Studies on the Association Between Acetaminophen and Cancer 2. |
| Lay Summary (Max. 250 words) Many studies have sought to answer the question “Does acetaminophen (paracetamol) cause cancer?”, but these studies show inconsistent results. One reason for this inconsistency could be that the study designs that were used are prone to bias. Here we aim to evaluate these designs by using a large set of ‘negative control outcomes’, things we know are not caused by acetaminophen, and determine how often the various study designs used in the past get the right answer for these negative controls (in relationship to acetaminophen).  We will evaluate two main types of study designs, so-called ‘case-control’ designs, and ‘cohort’ designs. We’ll test several variants of each. The various design choices are all based on the designs used in previously published studies.  We will execute these designs against the CPRD database to produce estimates for the negative controls, as well as several types of cancer. This will allow us to see how far off the results for the negative controls are from the truth (that there is no effect), as well as how far away the results for the cancers are from the negative controls. The results of this study could very well help explain the inconsistencies between the various studies. |
| Technical Summary (Max. 300 words) A large number of epidemiologic studies have been conducted to examine whether use of acetaminophen predisposes to the occurrence of one or more forms of cancer. There are many limitations to many of these studies, including vulnerability to channeling, protopathic bias, and uncontrolled confounding. However, the magnitude of the bias resulting from these limitation remains unknown, hampering the interpretability of the results of these studies. Recent methodological developments have focused on using large sets of negative controls – exposure-outcome pairs where no causal effect is believed to exist – to measure the operating characteristics of study designs by observing to what extent these designs produce effect size estimates in line with the truth (that there is no effect for the negative controls).  Here we aim to emulate prior studies, while including negative controls to quantify residual bias in these study designs. These prior studies mostly followed a case-control designs, although some used a cohort design. We will mimic the design choices in these prior studies as best we can, including the mechanism by which controls were selected, how exposure was defined, as well as the covariates used to adjust for potential confounding. We define 8 variants of the case-control design, and 2 variants of the cohort design.  The 37 negative controls were selected based on a lack of evidence in literature, product labels, and spontaneous reports, as well as a manual review by several clinicians. In addition to the negative controls we also include four cancer outcomes.  The negative controls will allow quantification of the error due to the limitations of these study designs. This quantification in turn can be used to help interpret study results by determining whether an observed effect size falls outside of what can be expected based solely on error (both systematic and random error). |
| Outcomes to be Measured 37 negative control outcomes: Achilles tendinitis; Atrophic vaginitis; Breath smells unpleasant; Bronchiectasis; Disorders of initiating and maintaining sleep; Ear problem; Erythema nodosum; Falls; Foot-drop; Ganglion and cyst of synovium, tendon and bursa; Hemangioma; Hydrocele; Hyperthyroidism; Impaired glucose tolerance; Impingement syndrome of shoulder region; Impotence; Incontinence of feces; Interpersonal relationship finding; Irregular periods; Irritability and anger; Joint stiffness; Loss of sense of smell; Mixed hyperlipidemia; Osteitis deformans; Panic attack; Perforation of tympanic membrane; Pes planus; Polymyalgia rheumatica; Premature menopause; Prolapse of female genital organs; Pure hypercholesterolemia; Respiratory symptom; Restless legs; Restlessness and agitation; Rosacea; Simple goiter; Skin sensation disturbance; Snapping thumb syndrome; Urinary symptoms  4 outcomes of interest: Renal cell carcinoma; Primary liver cancer; Lymphoma; Multiple myeloma |
| Objectives, Specific Aims and Rationale The purpose of this research is to quantify bias in previous observational studies evaluating the relationship between acetaminophen and cancer.  Primary objective:   * To emulate typical case-control studies performed in the past as well as the Walter et al. cohort study,1 while including negative controls to quantify residual bias in these study designs.   The definition of ‘typical case-control studies’ is based on a review of a set of published studies. Throughout this protocol we highlight the design choices in this set of studies, and the design choices we implement in our study.  Negative controls in this study are outcomes believed not to be caused or prevented by acetaminophen, and where therefore the true effect size equals 1 (no effect).  Secondary objective:   * Estimate the effect of acetaminophen on the risk of several types of cancer using the same study designs as used for the primary objective.   We aim to evaluate whether the estimates for the outcomes of interest falls inside or outside of the distribution of estimates observed for the negative control outcomes. For this we will rely on the empirical calibration framework described elsewhere.2 |
| Study Background A large number of epidemiologic studies have been conducted to examine whether use of acetaminophen predisposes to the occurrence of one or more forms of cancer. There are many limitations to many of these studies as noted earlier3, including vulnerability to channeling, protopathic bias, and uncontrolled confounding. However, the magnitude of the bias resulting from these limitation remains unknown, hampering the interpretability of the results of these studies.  Recent methodological developments have focused on using large sets of negative controls – exposure-outcome pairs where no causal effect is believed to exist – to measure the operating characteristics of study designs by observing to what extent these designs produce effect size estimates in line with the truth (that there is no effect for the negative controls). Previously, this approach has been used to show substantial bias in a comparative cohort study comparing acetaminophen to ibuprofen, even after adjustment using propensity scores.4  Because the vast majority of studies on the association between acetaminophen and cancer are case-control studies, we aim to extend this research to the case-control design. Recent work already previously explored the operating characteristics of case-control designs in general.5 In this study we will perform a similar analysis, but focusing specifically on the case-control design variants used to study the association between acetaminophen and cancer, and using negative controls outcomes for acetaminophen.  Although most studies used a case-control design, some studies applied a cohort design. Here we will use the study by Walter et al.1 as an example of such studies. This particular study linking a regional survey to a cancer registry to compare prevalent users of acetaminophen to non-users. We aim to replicate this study as closely as possible to examine its risk of residual bias.  In all these replications, we will include negative control outcomes as well as four cancer outcomes that some have suggested may be associated to acetaminophen exposure. The negative controls will allow quantification of the error due to the limitations of these study designs. This quantification in turn can be used to help interpret study results by determining whether an observed effect size falls outside of what can be expected based solely on error (both systematic and random error).  **Important:** These analyses were previously undertaken as part of a regulatory submission,6 and although those analyses were fully prespecified before execution and followed general scientific best practices, they did not undergo ISAC review. Instead, they received special exemption afterwards. We are here re-applying for the same analyses, with the goal of published the results in a peer-reviewed academic journal, and are seeking prospective ISAC approval. |
| Study Type Methodological |
| Study Design A methodological study using negative control hypotheses to quantify bias in several study designs. The designs that will be evaluated are several variants of a case-control design and a cohort design. |
| Feasibility countsCase-control designs Appendix B lists the number of cases and controls for each of the outcomes described in Section D and the analysis variants described in Section O. Also listed is the fraction of controls considered to be exposed to acetaminophen according to the various exposure status definitions described in Section 10.1.3, ranging from 31% to 63%, as well as the Minimum Detectable Relative Risk (MDRR), assuming alpha = 0.05, and a power of 80%.7 Cohort designs Following the description of ‘high use’ and ‘no use’ of acetaminophen described in Section O, and accounting for the inclusion and exclusion criteria defined in Section L, the following numbers of subjects were identified in the CPRD database, for the two analysis variants described in Section O:   |  |  |  |  | | --- | --- | --- | --- | | Analysis ID | Exclude subjects with the outcome in the 2 years following the index date | Number of subjects | | | High use | No use | | 9 | No | 5,284 | 84,551 | | 10 | Yes | 3,935 | 69,526 |   **Table 1.** Number of subjects in the exposure cohorts for the two analyses variants.  Note that the main reason for the different counts between the two analysis variants is not because those subjects experienced the outcome during the two years, but because those subjects were observed for less than two years after the index date.  The final number of subjects in the two exposure cohorts depends on the outcome that is studied, since subjects who experienced the outcome of interest were excluded for that outcome. Appendix C lists, for each analysis variant and outcome, the number of subjects in the exposure cohorts, as the number of subjects experiencing the outcome across both cohorts, and the MDRR (assuming alpha = 0.05 and power = 0.80).8 |
| Sample size considerationsCase-control designs As can be seen in Appendix B, all case-control designs have very small MDRR, ranging from 1.01 – 1.15, and will therefore be adequately powered to detect any relevant effect sizes. Cohort designs The cohort designs have less power, but still have a larger sample size than the main cohort study we aim to emulate. This study by Walter et al. reported 3,258 high-use subjects and 48,928 non-use subjects in their primary analysis (equivalent to our analysis 9).1 |
| Planned use of linked data (if applicable): None |
| Definition of the Study population Case-control studies are sometimes nested in some subpopulation of interest, for example subjects having a particular disease. However, none of the reviewed studies use nesting (as defined here). Some studies do restrict to specific genders depending on the outcome (females for breast cancer9 or ovarian cancer10, males for prostate cancer11), and/or to specific age groups. In our case-control analyses we will therefore not nest within a clinical subpopulation, but we will restrict age to 30 years and older.  Similar to the study by Walter et al.1, our cohort study will restrict to ages 50-76 at baseline, excluding people with prior history of cancer other than nonmelanoma skin cancer reported at baseline. |
| Selection of comparison group(s) or controls Most studies9-18 define controls simply as all non-cases or a random sample of non-cases, and randomly assign index dates to these controls. The index dates are often drawn from the distribution of dates observed for the cases.  Several studies19-23 select controls specifically for each case, giving controls the same index date as the case for which they were selected. Subsequently the outcome model (logistic regression) is conditioned on the matched set.  Since these two designs could have very different implications for the residual bias, we will evaluate both:   1. Sampling index dates from the distribution observed for cases, and randomly applying these to viable controls (i.e. non-cases that were observed at the index date). The size of the control group will be limited to four times the number of cases. 2. Randomly selecting up to four matched controls per case.  Matching Like most studies that match cases to controls, when performing matching we will match on:   * Age using a two-year caliper (i.e., ± 2 years) * Sex * Index date * Time observed prior to the index date, using a one-year caliper * Practice |
| Exposures, Outcomes and CovariatesExposure(s) of Interest Our exposure of interest is any drug containing the ingredient acetaminophen (concept ID 1125315). See Appendix A for a full list of the drug codes in CPRD that fall under this definition. Outcome(s) of interest We include four types of cancer which have been associated with acetaminophen use in prior studies:   * Renal cell carcinoma * Primary liver cancer * Lymphoma * Multiple myeloma   Outcome definitions will be evaluated using the PheValuator framework.24  Although hepatocellular carcinoma specifically might be of more clinical interest than the broader ‘Primary Liver Cancer’ selected here, the data does not support a finer distinction. Most primary liver cancers are coded as ‘Primary malignant neoplasm of liver’ (READ code B150.00). For this reason we define our outcome of interest as ‘Primary liver cancer’, similar to other studies performed in CPRD.25-27  The events described below as the ‘initial event cohort’ determine the date of the outcome, which will be used as the index date for cases in the case-control studies. Note that these formal definitions do not yet require a minimum prior observation time. These criteria are applied at a later stage in the analysis, as described in Sections 10.1 and 10.2. Renal cell carcinomaInitial Event Cohort People having any of the following:   * a condition occurrence of Primary renal cell carcinoma1   with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**  Limit qualifying cohort to: **earliest event per person.** End Date Strategy No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event. Cohort Collapse Strategy Collapse cohort by era with a gap size of 0 days. Concept Set Definitions  1. Primary renal cell carcinoma (See Appendix D for READ codes)  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped | | 4181357 | Malignant tumor of renal pelvis | Condition | SNOMED | NO | YES | NO | | 198985 | Primary malignant neoplasm of kidney | Condition | SNOMED | NO | YES | NO | | 196653 | Malignant tumor of kidney | Condition | SNOMED | NO | YES | NO | | 196053 | Secondary malignant neoplasm of kidney | Condition | SNOMED | YES | YES | NO |  Primary liver cancerInitial Event Cohort People having any of the following:   * a condition occurrence of Malignant neoplasms of liver1   with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**  Limit qualifying cohort to: **earliest event per person.** End Date Strategy No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event. Cohort Collapse Strategy Collapse cohort by era with a gap size of 0 days. Concept Set Definitions  1. Malignant neoplasms of liver (See Appendix D for READ codes)  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped | | 432851 | Secondary malignant neoplastic disease | Condition | SNOMED | YES | YES | NO | | 4111921 | Squamous cell carcinoma of skin | Condition | SNOMED | YES | YES | NO | | 4112752 | Basal cell carcinoma of skin | Condition | SNOMED | YES | YES | NO | | 4246127 | Malignant neoplasm of liver | Condition | SNOMED | NO | YES | NO |  LymphomaInitial Event Cohort People having any of the following:   * a condition occurrence of Malignant neoplasms of lymphoma1   with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person**.  Limit qualifying cohort to: **earliest event per person.** End Date Strategy No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event. Cohort Collapse Strategy Collapse cohort by era with a gap size of 0 days. Concept Set Definitions  1. Malignant neoplasms of lymphoma (See Appendix D for READ codes)  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped | | 432571 | Malignant lymphoma | Condition | SNOMED | NO | YES | NO | | 432851 | Secondary malignant neoplastic disease | Condition | SNOMED | YES | YES | NO | | 441235 | Large cell anaplastic lymphoma | Condition | SNOMED | YES | YES | NO | | 4003183 | T-cell lymphoma | Condition | SNOMED | YES | YES | NO | | 4038835 | Hodgkin's disease | Condition | SNOMED | YES | YES | NO | | 4040380 | Mycosis fungoides | Condition | SNOMED | YES | YES | NO | | 4082311 | B-cell chronic lymphocytic leukemia | Condition | SNOMED | YES | YES | NO | | 4111921 | Squamous cell carcinoma of skin | Condition | SNOMED | YES | YES | NO | | 4112752 | Basal cell carcinoma of skin | Condition | SNOMED | YES | YES | NO | | 4216139 | Plasmacytoma | Condition | SNOMED | YES | YES | NO |  Multiple myelomaInitial Event Cohort People having any of the following:   * a condition occurrence of Multiple myeloma1   with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person**.  Limit qualifying cohort to: **earliest event per person**. End Date Strategy No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event. Cohort Collapse Strategy Collapse cohort by era with a gap size of 0 days. Concept Set Definitions  1. Multiple myeloma (See Appendix D for READ codes)  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped | | 437233 | Multiple myeloma | Condition | SNOMED | NO | YES | NO | | 42538151 | Osteoporosis co-occurrent and due to multiple myeloma | Condition | SNOMED | YES | YES | NO |  Negative Control Outcomes Negative control outcomes are those determined a priori to have no association with the exposure of interest. We will use the same set of negative control outcomes as an earlier study.4 Briefly, in this study we identified outcomes as follows: Person counts of all potential drug-condition pairs are reviewed in observational data; this person count data helps determine which pairs are even feasible for use in calibration. Given the list of potential drug-condition pairs, the concepts in the pairs must meet the following requirements to be considered as negative controls: (1) that there is no Medline abstract where the MeSH terms suggest a negative association between the drug and the condition28, (2) that there is no mention of the drug-condition pair on a US Product Label in the “Adverse Drug Reactions” or “Postmarketing” section29, (3) there are no US spontaneous reports suggesting that the pair is in an adverse event relationship30 31, (4) that the OMOP Vocabulary does not suggest that the drug is indicated for the condition, (5) that the concepts are usable (i.e. not too broad, not suggestive of an adverse event relationship, not pregnancy related), and (6) the exact concept itself is utilized in patient level data (i.e. concepts that are not usually used within the data are usually indicative of a broad concept that has a child that is more specific).  The remaining concepts are “optimized”, meaning parent concepts remove children as defined by the OMOP Vocabulary (e.g. if both “Non-Hodgkin’s Lymphoma” and “B-Cell Lymphoma” were selected, the child concept “B-Cell Lymphoma would be removed for its parent “Non-Hodgkin’s Lymphoma”).  Once potential negative control candidates are selected, manual clinical review to exclude any pairs that may still be in a causal relationship or similar to the study outcome should be performed to select the top 50 or so concepts by patient exposure.  The 37 negative control outcomes we will be using from the prior study are as follows:   1. Achilles tendinitis 2. Atrophic vaginitis 3. Breath smells unpleasant 4. Bronchiectasis 5. Disorders of initiating and maintaining sleep 6. Ear problem 7. Falls 8. Foot-drop 9. Ganglion and cyst of synovium, tendon and bursa 10. Hemangioma 11. Hydrocele 12. Hyperthyroidism 13. Impaired glucose tolerance 14. Impingement syndrome of shoulder region 15. Impotence 16. Incontinence of feces 17. Interpersonal relationship finding 18. Irregular periods 19. Irritability and anger 20. Joint stiffness 21. Loss of sense of smell 22. Mixed hyperlipidemia 23. Osteitis deformans 24. Panic attack 25. Perforation of tympanic membrane 26. Pes planus 27. Premature menopause 28. Prolapse of female genital organs 29. Pure hypercholesterolemia 30. Respiratory symptom 31. Restless legs 32. Restlessness and agitation 33. Rosacea 34. Simple goiter 35. Skin sensation disturbance 36. Snapping thumb syndrome 37. Urinary symptoms   We will identify a negative control outcome occurrence as the first occurrence of the negative control concept or any of its descendants in any position in the patient’s record. Other Variables of Interest Other variables are captured at the index date to address potential confounding. The definition of the index date varies, as explained in Section 10. Case-control designs: Variables used for matching As will be discussed elsewhere, several studies match cases to controls. This matching is almost always done on these variables:   * Age at index date19-23 * Sex19-23 * Index date19-23 * Time observed prior to the index date19-22 * Practice, hospital or geographical area19-21 23   These variables will also be used for matching in our study. Case-control designs: Variables used in multivariable outcome models Most studies include the following variables in the outcome model (the logistic regression):   * Age at index date9-18 23   We will categorize age in five-year intervals.   * Sex10 12-17 23 * Index year9-12 15 18 * BMI (Body Mass Index)9 12 15-17 19-21   BMI will be computed from body height (measurement concept ID 3036277) and weight (measurement concept ID 3013762) recorded within one year from each other, or directly from BMI measurements (measurement concept ID 3038553). We will discretize BMI into three categories: BMI < 25, 25 <= BMI < 30, BMI >=30   * Alcohol intake9 12 17 or alcohol-related disorders21   We will identify regular drinkers as patients who self-report as regular drinkers (an observation with concept ID 40770351 and value “yes”), and patients reporting they drink more than two alcoholic beverages per week (observations with concept ID 3043872 and value > 2).   * Smoking9 12 15-21 23   We will identify smokers as those reporting smoking at least one cigarette per day (an observation with concept ID 40766929 and value >= 1), or those classified as smoker (observations with concept ID 4144271, 4052030, 4052029, 4052947, 4217594, 37395605, 4058137, 4295004, 4199818, 44802474, 4085459, 4144273, 4193014, 44806696, 44802794, 4086132, 4058136, 4190573, 4215409, 4052948, 44810930, or 4204653)   * Diabetes (medication use)12 17 21   We will identify diabetes as any exposure to a drug in ATC class A10 (drugs used in diabetes).  We will also adjust for these in our study. Note that only those variables need to be included that are not used to match cases to controls. Cohort design: Variables used in the outcome model Walter et al.1 adjusted for these variables:   * Sex * Race/ethnicity (white, Hispanic, other)   This information is not available in CRPD and will therefore not be used.   * Education   This information is not available in CRPD and will therefore not be used.   * Smoking   We will identify smokers as described in Section 8.6.2.   * Self-rated health   This information is not available in CRPD. Instead, we will include the Charlson Index (Romano adaptation)32 as indicator of overall health.   * History of rheumatoid arthritis   Defined as any occurrence of concept 80809 (Rheumatoid arthritis) or any of its descendants on or before the index date.   * History of non-rheumatoid arthritis or chronic neck/back/joint pain.   Defined as any occurrence of concept 4291025 (Arthritis) or any of its descendants, excluding concept 80809 (Rheumatoid arthritis) and any of its descendants, as well as concept 43530622 (chronic neck pain) or 4046660 (chronic back pain), or any of their descendants on or before the index date.   * History of fatigue or lack of energy   Defined as any occurrence of 439926 (Malaise and fatigue) on or before the index date.   * History of migraines or frequent headaches   Defined as any occurrence of 318736 (Migraine) or 375527 (headache disorder) on or before the index date.   * Number of first-degree relatives with a history of leukemia or lymphoma   This information is not available in CRPD and will therefore not be used. Cohort design: Variables used for descriptive statistics Descriptive analysis of the baseline covariates will be generated to provide a characterization of the exposed and unexposed cohort. The following baseline variables will be included.   * Demographics   + Gender   + Age group (5-year bands)   + Initial drug exposure month * Condition occurrence record for the concept or any of its descendants observed during 365d on or prior to cohort index * Drug exposure record for the concept or any its descendants observed during 365d on or prior to cohort index * Procedure occurrence record for the concept or any its descendants observed during 365d on or prior to cohort index * Measurement record for the verbatim concept observed during 365d on or prior to cohort index * Charlson Index - Romano adaptation, using conditions all time on or prior to cohort index * Number of distinct conditions observed in 365d on or prior to cohort index (defined as unique SNOMED condition concepts) * Number of distinct drugs observed in 365d on or prior to cohort index (defined as unique RxNorm ingredient concepts) * Number of distinct procedures observed in 365d on or prior to cohort index (defined as unique CPT4/HCPCS/ICD9P/ICD10P concepts) * Number of distinct observations observed in 365d on or prior to cohort index * Number of distinct measurements observed in 365d on or prior to cohort index (defined as unique LOINC concepts) * Number of visits observed in 365d on or prior to cohort index * Number of inpatient visits observed in 365d on or prior to cohort index * Number of ER visits observed in 365d on or prior to cohort index   An explicit head-to-head comparison between two cohorts of baseline covariates, using standardized difference as a metric to compare individual factors, will be conducted. Covariates with standardized difference > 10% will be highlighted as potential imbalanced confounding factors.  When computing a propensity score, we will exclude acetaminophen from the set of covariates, because this is the exposure the propensity model aims to predict. In addition, we will also exclude these ingredients that are contained in products containing acetaminophen: aspirin, caffeine, chlormezanone, codeine, dextromethorphan, dihydrocodeine, diphenhydramine, domperidone, isometheptene, methionine, metoclopramide, orphenadrine, oxycodone, pentazocine, phenylephrine, phenylpropanolamine, promethazine, propoxyphene, pseudoephedrine, salicylic acid, and tramadol. |
| Data/ Statistical AnalysisCase-control studiesExposure status Some studies10 13 19 21 22 set the index date to one year before the outcome, and evaluate exposure on or prior to that date, since it is not believed biologically plausible for any effect to occur within a shorter time frame. Other studies also included a ‘current use’ category, or do not distinguish between current and past use (e.g. when exposure status is ascertained using questionnaires). 9 11 12 14-17 20 23  In our study, we will evaluate using the following algorithms to define exposure status:   1. All time prior: exposed on or any time prior to the index date, where the index date is the date of the outcome (for cases). 2. One-year delay: exposed on or any time prior to the index date, where the index date is one year before the date of the outcome (for cases).  Model Specification After controls have been selected, exposure status has been ascertained, and covariates have been constructed, we will fit a logistic regression to estimate the effect size (odds ratio) and 95% confidence interval. For those analyses where controls are matched to cases this regression will be conditioned on the matched sets. The following case-control variants will be performed:  **Table 2**. Case-control design analysis variants.   |  |  |  |  | | --- | --- | --- | --- | | Analysis ID | Control selection | Exposure status | Covariate adjustment | | 1 | Sampling | All time prior | Age, sex, index year | | 2 | Sampling | All time prior | Age, sex, index year, BMI, alcohol, smoking, diabetes | | 3 | Sampling | One-year delay | Age, sex, index year | | 4 | Sampling | One-year delay | Age, sex, index year, BMI, alcohol, smoking, diabetes | | 5 | Matching | All time prior | None | | 6 | Matching | All time prior | BMI, alcohol, smoking, diabetes | | 7 | Matching | One-year delay | None | | 8 | Matching | One-year delay | BMI, alcohol, smoking, diabetes |   These eight analyses will be used to estimate odds ratios for all 37 negative controls and four outcomes of interest, resulting in 8 x (37 + 4) = 328 odds ratios and confidence intervals. Patient Characteristics Summary Descriptive analyses will be comprised of covariate balance of age group, gender, and selected variables in exposed and unexposed. Cohort studies The original study1 determined exposure status and baseline characteristics using a mailed questionnaire, with responses returned between October 2000 and December 2002. The outcome status was ascertained by linking the survey to a cancer registry, using data up to December 31, 2008, thus allowing a maximum follow-up time of approximately six to eight years. To emulate this design, while selecting the period in time with the largest number of subjects captured in CRPD, we will select a random date (the index date) for each person in the year 2008. We include every person aged 50-76 at the index date, requiring that they are observed at that date as well as the four years before. We will ascertain outcome status in the period from the index date until the end of observation.    **Figure 1.** Persons observed per month in the CPRD database. Index dates will be sampled throughout the year 2008. Exposure status Similar to Walter et al,1 our focus will be on ‘high use’, defined in the original study as >= 4 days/week for >= 4 years.1 In our analysis, we will classify subjects as ‘exposed’ if they are continuously exposed in the 4 years prior to the index date, allowing for gaps representing use of acetaminophen only 4 out of 7 days, with a minimum allowed gap of 30 days. For example, if someone received a 25-day prescription of acetaminophen, we will consider them continuously exposed if they receive the next prescription in *n* days of the first prescription start, were *n = max(25 \* 7 / 4, 25+30)* = 55 days.  Subjects will be classified as ‘unexposed’ if they were not prescribed any acetaminophen in the 4 years prior to the index date. Outcome status Outcome status will be classified based on the occurrence of the outcome during the time after the index date until the end of observation. Subjects who had the outcome prior to the index date will be excluded in the analysis for that outcome.  Similar to Walter et al.1 a separate analysis will be performed excluding those who experienced the outcome in the 2 years following the index date. Model specification The following cohort design analyses will be performed:  **Table 3**. Cohort design analysis variants.   |  |  | | --- | --- | | Analysis ID | Exclude subjects with the outcome in the 2 years following the index date | | 9 | No | | 10 | Yes |   These two analyses will be used to estimate hazard ratios for all 37 negative controls and four outcomes of interest, resulting in 2 x (37 + 4) = 82 hazard ratios and confidence intervals. Patient Characteristics Summary Descriptive analyses will be comprised of covariate balance of the variables described in Section 8.6.4.  Additionally, the propensity score will be estimated for each patient, using the predicted probability from a regularized logistic regression model, fit with a Laplace prior (LASSO) and the regularization hyperparameter selected by optimizing the likelihood in a 10-fold cross validation, using a starting variance of 0.01 and a tolerance of 2e-7. We will plot the propensity score distribution for exposed and unexposed to assess comparability. Quantification of bias We will plot the estimated odds ratios/hazard ratios and standard errors (linearly related to the width of the confidence interval). Study designs that adequately control for confounding factors should produce odds ratio estimates in line with the known true effect size (i.e., a odds ratio/hazard ratio of 1.0) for the negative control outcomes. We will compute the percentage of negative controls having a p-value below 0.05, with the expectation that for an unbiased study design this percentage should be 5%. We will fit an empirical null distribution2 to the distribution of negative control estimates and report the estimated distribution parameters. |
| Plan for addressing confounding In this study we will apply similar methods to address confounding as used in the prior studies we aim to emulate. For both the case-control studies and the cohort studies the primary mechanism is by including potential confounders in the outcome models, as described in Section O (Data/ Statistical Analysis). |
| Plans for addressing missing data Most covariates will be constructed based on the presence or absence of clinical observations, so ‘missing data’ may result in misclassification of covariates. Missing data may also result in outcome misclassification if persons with the various outcomes are not recorded as such. Missing exposure information may reduce sensitivity of exposure cohort definitions but should not bias the analysis. In all cases, the effect of misclassification due to missing data is one source of the bias that we aim to quantify in this study. |
| Patient or user group involvement None. This is a methodological study aimed at examining advanced epidemiologic principles of residual bias in the context of a specific clinical question. We do not expect patient groups would have interest or scientific knowledge to actively engage in this methodological question. |
| Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication The results of this study will be presented to the California Office of Environmental Health Hazard Assessment as part of the Proposition 65 Implementation Program. An article will be written and submitted to a peer review journal for publication.  **Conflict of interest statement:**  Johnson & Johnson is a manufacturer of acetaminophen. Drs. Schuemie and Ryan are full-time employees of Janssen R&D, a Johnson & Johnson company, and are shareholders of Johnson & Johnson. |
| Limitations of the study design, data sources, and analytic methods This is an observational study and as such is subject to the inherent bias because we were not able to randomize treatment. For example, in this data source, the drug data is based on prescriptions written, not dispensed, so we do not know if the drugs were taken and how. For those prescriptions that were repeated, the likelihood that the medication was ingested increases. Exposure attribution based on a single prescription may be seen as a limitation, however we would argue that any other measures such as dose or drug era would be similarly confounded with underlying health. |
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| List of Appendices **Appendix A**: List of drug codes used in CPRD to determine exposure to acetaminophen.  **Appendix B**: Case-control power calculations. The number of cases and controls for each of the outcomes described in Section D and the analysis variants described in Section O. Also listed is the fraction of controls considered to be exposed to acetaminophen according to the various exposure status definitions described in Section 10.1.3, ranging from 31% to 63%, as well as the MDRR, assuming alpha = 0.05, and a power of 80%.7  **Appendix C**: Cohort method power calculations. For each analysis variant and outcome, the number of subjects in the exposure cohorts, as the number of subjects experiencing the outcome across both cohorts, and the MDRR (assuming alpha = 0.05 and power = 0.80).8  **Appendix D**: List of READ codes for the four cancer outcomes used in CRPD.  **Appendix E**: An Integrated Weight of Evidence Assessment of the Carcinogenicity Hazard Potential of Acetaminophen; Information for the California Carcinogen Identification Committee |