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| **Title of Study or Project:** | PCRC 168 - Use of Total Intravenous Anesthesia versus Inhaled Anesthesia in Elective Non-cardiac Surgery |
| **Primary Institution:** | Washington University School of Medicine & University of Michigan |
| **Primary Author:** | Bethany Pennington, PharmD, BCPS & Allison Janda, MD |
| **Co-Authors:** | Douglas Colquhoun, MB ChB, MSc, MPH; Stephen Gregory, MD; Michael L Burns, MD PhD**,** Graciela Mentz, PhD; Elizabeth Jewell, MS; Nan Lin, PhD; Sachin Kheterpal, MD, MBA; Michael Avidan, MBBCh, FCA SA |
| **Statisticians:** | Graciela Mentz, PhD; Elizabeth Jewell, MS; Nan Lin PhD |
| **Type of Study:** | ☑ Retrospective Observational |
| **Data Source(s):** | MPOG Database |
| **IRB Number and Status:** | HUM00211733/pending |
| **Hypotheses/Aims:** | We propose to analyze the patterns of TIVA use in patients undergoing elective non-cardiac surgery across MPOG centers and to understand potential sources of variation in practice patterns.**Aim 1:** *i)* Identify variables associated with TIVA use *ii)* Determine the strengths of the associations observed *iii)* Explore the relative contribution of each level to variation in TIVA use accounting for the nested structure of the data *Hypothesis:* Institution, clinician, and patient/case level variables are associated with TIVA use, with institution and clinician being more strongly associated with choice of TIVA than patient/case variables.**Aim 2:** Describe the frequency, variation and duration of administration of agents used during TIVA and inhaled-volatile based anesthetic techniques. *Hypothesis:* This is a descriptive aim only.**Aim 3**: Describe the frequency, variation and duration of administration of agents used during TIVA and inhaled-volatile based anesthetic techniques in homogenous surgical subgroups.*Hypothesis:* This is a descriptive aim only |
| **Number of Patients/Participants:** | Based on the availability of pertinent perioperative data, we expect approximately 1.9 million cases will meet eligibility criteria. |
| **Power Analysis:** | If the true population level use of TIVA ranges between 5% and 90%, we will need a sample of at least 48,265 patients to estimate descriptive statistics with a margin of error of 1%. For the multilevel modeling techniques, an estimation of 20 patients nested in 20 providers nested in 20 institutions would be adequate. |
| **Proposed statistical test/analysis:** | We will use Generalized linear mixed models to estimate the variation in the use of TIVA attributable to institution-, clinician- and patient-levels (Aim 1)). We will use descriptive statistical approaches regarding the frequency, variation and duration of administration of agents used during TIVA and inhaled-volatile based anesthetic techniques (Aim 2 & Aim 3). |

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| **Resources (Brief summary of resources for data collection, personnel, financial):** | Statistical analysis will be conducted by Graciela Mentz at the University of Michigan and Nan Lin, within the Computational Medicine and Bioinformatics Department and Anesthesiology Department at Washington University School of Medicine, with the support of all co-investigators. |

# TITLE PAGE

Use of Total Intravenous Anesthesia versus Inhaled Anesthesia in Elective Non-cardiac Surgery

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# Introduction

In conducting a general anesthetic, technique selection may result in differential impact on common patient-centered, adverse postoperative experiences including nausea and vomiting, delirium, delayed neurocognitive recovery, acute and persistent pain, depressive symptoms, impaired physical functionality, accidental falls, and worse overall quality of life [1–6.](https://paperpile.com/c/2j5oZF/ijfg%2BwsJy%2BxMi4%2BMXvm%2Bqie4%2BJfjo) Propofol TIVA and inhaled volatile-based anesthesia may drive completely different patient experiences. [7](https://paperpile.com/c/2j5oZF/U06d) The decision to use an inhaled agent versus an intravenous agent is usually made by the clinician administering the anesthetic agent. Outside of narrow indications in specific clinical situations, anesthetic care may be safely and successfully conducted using either of these approaches.

Practice patterns regarding general anesthesia vary in the literature [8](https://paperpile.com/c/2j5oZF/WzyR) and have not been rigorously explored. Previous studies have suggested clinicians feel dissuaded from TIVA use due to the burdensome set up [9](https://paperpile.com/c/2j5oZF/k5EJ), lack of familiarity with clinical evidence [10](https://paperpile.com/c/2j5oZF/pGUP), and inadequate education and training [11,12.](https://paperpile.com/c/2j5oZF/1Ufs%2BgjSQ) The lack of evidence that patient recovery and adverse outcomes are more favorable with one technique over the other may also impact a clinician’s decision to primarily use their preferred technique. It is recognized that institutional preferences of anesthesia clinicians and patient specific factors may influence the decision to use one technique or another but this has not yet been evaluated thoroughly. Recognizing factors that may predict TIVA practice patterns is valuable. In addition, the variation of agents used within TIVA and Inhaled volatile- based techniques in the United States has not been well described.

We therefore seek to perform a retrospective observational trial to evaluate predictors of TIVA use across US medical centers. The primary aim of this study is to assess whether certain variables (institution, clinician and patient/case) are associated with TIVA use and to determine the strength of the associations. In addition, we plan to describe the variation of agents selected and duration of administration of agents used within TIVA and inhaled-volatile based techniques. This information will provide a further understanding of general anesthetic practices in the US and aid in the selection for site inclusion into the Trajectories of Recovery after Intravenous propofol versus inhaled VolatilE anesthesia (THRIVE) Trial.

# Methods

*Study Design*

This is a retrospective observational study which will follow the RECORD extension of the STROBE reporting guidelines.[13](https://paperpile.com/c/2j5oZF/7h3i) Study outcomes and statistical methods were established and will be presented and approved at a multicenter peer-review committee prior to extraction of data and data analysis. This study was approved by the University of Michigan Institutional Review Board (HUM00211733, Ann Arbor, Michigan). As no care interventions were involved and all protected health information except date of service and extremes of age were removed prior to analysis, patient consent was waived. A revised finalized proposal will be registered on Open Science Framework prior to inferential analyses of the study data.

*Study Population*

The study population includes patients in the MPOG database from January 1, 2016 - December 31, 2021 undergoing elective, non-cardiac surgery.

# Inclusion Criteria

* Adult patients (≥18 years) undergoing elective non-cardiac surgical procedures from

January 1, 2016 - December 31, 2021 with a case duration lasting ≥ 60 minutes.

* General anesthesia with a tracheal tube or laryngeal mask airway [Technique Code 1,2 or 3 from Anesthesia Technique: General Phenotype]

# Exclusion Criteria

* Procedures for which no TIVA, halogenated anesthetic gas, or nitrous oxide gas was documented
* Emergency surgery (ASA E Modifier)
* Obstetrics cases
* Lung, Liver or heart transplantation
* Cardiac surgeries
* Cardiopulmonary bypass used
* [Location Tags:](https://phenotypes.mpog.org/Location%20Tags)
	+ Facility Type - Office-based anesthesia
	+ OB-GYN - Labor and Delivery
	+ OB-GYN - Obstetric Operating Room
	+ OB-GYN-IVF-only room
	+ Other-Pediatric
	+ Radiology-MRI
	+ Service Specific Room-Cardiac OR
* [Body Region](https://phenotypes.mpog.org/Body%20Region): Other Procedures, Obstetrics, or Radiologic Procedures
* Non-operative procedures and MRIs
* ASA Class 5 or 6
* Organ harvest (Anesthesia CPT 01990)
* Absence of an actual or predicted anesthesia CPT
* Active [*Propofol Infusion*](https://phenotypes.mpog.org/propofol%20infusion)prior to:
	+ [Patient in room](https://phenotypes.mpog.org/Patient%20In%20Room%20Date%21Time); if not available then
	+ 5 minutes after Anesthesia Start
* Patient arrived to the operating room already intubated (phenotype)
* Patient not extubated prior to departure from the operating room (phenotype)

*Data source*

Data will be obtained from the Multi-Center Perioperative Outcomes Group (MPOG) dataset after the MPOG peer-review research committee’s approval. Data acquisition through uploads of electronic medical record systems from each participating institution, data storage, and secure transfer has been previously described.[14,15](https://paperpile.com/c/2j5oZF/K9nm%2ByGQ8)

Primary outcome

*Aim 1: i) Identify variables associated with TIVA use ii) Determine the strengths of the associations observed iii) Explore the relative contribution of each level to variation in TIVA use accounting for the nested structure of the data.*

The primary outcome of interest, **TIVA**, is defined as: administration of only intravenous anesthetic agents with no administration of volatile anesthetic agents or nitrous oxide gas between anesthesia start and anesthesia end, as documented in the anesthesia record.

Using a multi-level statistical model (full details below) we will estimate the variation contribution of TIVA use which emerges from institution-, clinician- and patient/case-level variables. See “candidate variables of interest” below for additional information.

*Hypothesis:*

We hypothesize that institution, clinician, and patient/case variables are associated with TIVA use, with institution and clinician variables being more strongly associated with choice of TIVA than patient variables.

*Aim 2: Describe the frequency, variation, and duration of administration of agents used during TIVA and inhaled-volatile based anesthetic techniques*

This descriptive aim seeks to determine the frequency of TIVA (as defined above) and Inhaled anesthesia use. **Inhaled anesthesia** is defined as the administration of an inhaled anesthetic (either a volatile anesthetic agent or nitrous oxide gas) at any time between anesthesia start and anesthesia end, as documented in the anesthesia record.

Inhaled techniques will be further categorized into the following subgroups (a-e) (see Figure 1):

1. Any Nitrous oxide PLUS propofol infusion administration
2. Any Halogenated gas PLUS propofol infusion administration
3. Any Halogenated gas with nitrous oxide PLUS propofol infusion administration
4. Any Halogenated gas with nitrous oxide and NO propofol infusion administration



*Figure 1 - Venn diagram illustrating the relationships between potential anesthetic combinations and groupings proposed in our analysis.*

The authors recognize that a substantial proportion of anesthetics may include a combination of agents (in parallel or in overlapping sequence), including propofol, volatile agents and/or nitrous oxide. In this aim, we seek to describe the variation in selection and duration of agents used in both TIVA and each Inhaled subgroup.

For TIVA and each Inhaled subgroup we will describe:

* The amount of time in minutes from anesthesia start to anesthesia end that propofol and/or an inhaled agent was administered.
* Fraction of time that propofol and/or an inhaled agent is administered over the total case duration
* Administration opioid or non-opioid analgesic anesthetic agents (e.g. remifentanil, fentanyl, sufentanil, ketamine, dexmedetomidine, lidocaine)
* Phase of case in which these medications were in use:
	+ Post Induction - 10min after airway management (ETT or LMA placement)
	+ Mid Case - in 10 min period around midpoint of Procedure Start to Procedure End
	+ Emergence - in 10 min period prior to extubation

*Aim 3: Describe the frequency, variation, and duration of administration of agents used during TIVA and inhaled-volatile based anesthetic techniques in homogenous surgical subgroups*

To explore practice patterns amongst homogenous surgical subgroups, we will repeat the analysis proposed in Aim 2 in specific surgery subgroups. The surgical groups will be identified based upon anesthesia CPT code. We have selected procedure types which represent commonly performed procedures in which anesthesia care may be accomplished by a range of anesthetic techniques (TIVA versus subcategories of Inhaled described in Aim 2).

Specifically we propose to examine cases within the existing study population in the following anesthesia CPT groups:

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| **Group** | **Anesthesia CPT’s** | **Summarized Description** |
| Head and Neck (Minor) Surgery | 00160, 00162, 00164, 00100,00170, 00172, 00174, 00176,00120, 00124, 00126, 00103,00190, 00322 | Minor Procedures on Head (ears, sinuses, eyelid, face, neck inc thyroid) |
| Intracranial Neurosurgery | 00210, 00211, 00212, 00214,00215, 00216, 00218, 00220 | Intracranial surgery including removal of tumor, vascular lesions or evacuation of blood or fluid collections |
| Spine (Major) | 00600, 00604, 00620, 0062500626, 00630, 00632, 00635,00670 | Open major spine procedures, posterior approaches (all levels) |
| Orthopedic Knee/Hip Replacement | 01214, 01215, 01402 | Hip and Knee Replacement, inc revision. |

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| --- | --- | --- |
| Orthopedic Knee/Hip Soft Tissue | 01320, 01360, 01382, 0139201400, 01202 | Hip/Knee Arthroscopic/Open non-soft tissue procedures |
| Major Vascular | 00770, 00350, 00880, 00882 | Suprainguinal vascular (not intra-thoracic) |
| Major Abdominal | 00752, 00754, 00756, 00790,00792, 00794, 00796, 00797,00832, 00840, 00844, 00848,00866, 00904, 00862, 00864,00865, 00908, 00860, 00846,00851, 00928 | Major Abdominal Procured including ventral hernias, laparoscopic procedures, gastric bypass procedure, colon resection, urologic or gynecological procedures. |

*Secondary outcome(s), if applicable*

Not Applicable

Exposure Variable

Not Applicable

*Covariates*

Predictor variables for the assessed outcome of TIVA will include:

# Patient/Case level variables:

* + age, sex, race, BMI, ASA status, surgical procedure type by body region, extent defined by Base Units (from Anesthesia billing), duration of surgery, year of procedure, Elixhauser comorbidities (hypertension, coronary artery disease, congestive heart failure, arrhythmia, valvular heart disease, pulmonary circulation disorders, diabetes, neurologic disorders, renal failure, liver disease, obesity, psychotic disorders, depression, and chronic pulmonary disease), history of alcohol use, history of drug abuse, first\* anesthesia attending ID, institution ID, CRNA signed in upon arrival to procedure\*\* (Yes/No), and anesthesiology resident signed in upon arrival to procedure room\*\* (Yes/No).

# Clinician-level variables:

* + Attending anesthesiologist annual case volume (among cases meeting study inclusion/exclusion criteria, and defined by anesthesiologist attending at start of case)\*\*\*

# Institution-level variables:

* + Institution annual case volume (among cases meeting study inclusion/exclusion criteria)
	+ Academic vs. Non-Academic Institutions

*\* First anesthesia attending ID defined as the attending signed in to case 2 minutes after Anesthesia Start; more details/rationale described in* [*Starting Provider MPOG Phenotype*](https://phenotypes.mpog.org/Starting%20Provider)

*\*\* Defined by* [*Patient In Room Date/Time MPOG Phenotype;*](https://phenotypes.mpog.org/Patient%20In%20Room%20Date%21Time) *if not available, then* [*Case Start*](https://phenotypes.mpog.org/Case%20Start)[*Phenotype*](https://phenotypes.mpog.org/Case%20Start)

\*\*\*Defined as the total case volume of a given attending ID number as the primary provider per year for those years where the attending ID was an attending at that institution.

*Statistical analysis*

Exploratory Data Analysis (EDA) techniques such as histograms, QQ-plots, box-plots, scatterplots and basic descriptive (means, medians, IQR) will be used to assess the distribution of all relevant variables. In addition, these techniques will also be used to explore the most informative transformations of the covariates, confounders and relevant predictors considered in the analysis. Outlier values will be discarded if outside of the valid ranges as described in MPOG phenotypes.

Continuous measures will be summarized in terms of means and standard deviation if the distribution is symmetric or medians and interquartile range if not. Binary and categorical measures will be summarized using a percentage and displayed as a contingency table. Tests of differences of means, medians or proportions will be done using ANOVA F-test, Wilcoxon rank sum or logistic regression types of approaches respectively.

Generalized linear mixed models will be used to account for hierarchical data and to estimate marginal associations of patient, clinician, and institution level factors with TIVA use. The proportion of variation attributable to each level will be estimated using intraclass correlation coefficients (ICC).[16](https://paperpile.com/c/2j5oZF/a0UBY). GLMs with logic-links will be used to estimate relevant predictor effects. If institutions with extremes of use or low case volumes prevent model convergence, they will be included for the descriptive analysis, but will be excluded from the logistic modeling.

Variance at institutional, clinician and patient levels will be assessed using variance partition coefficients (VPCs) such as intraclass correlation coefficients (ICCs) and median odds ratios (MORs) depending on whether the outcome is continuous or binary.[16](https://paperpile.com/c/2j5oZF/a0UBY) The ICC characterizes the proportion of variation attributable to cluster levels (i.e. institution and clinician levels) and can be used to ascertain the validity of a multilevel approach to modeling the data observed: for example, if less than 5% of the total variability is explained by upper-level units, then limited empirical support exists for a multilevel analysis and a robust analytical method such as Generalized Estimating Equations (GEE) will be used. For those practice patterns with over 5% of total variability attributed to upper-level units (institution or clinician) we will utilize the proposed generalized linear mixed models approach (GLMM). The goal of this analysis is to describe the proportion of total variance in a given practice pattern or outcome that is attributable to that factor or level.

To assess the relationship of patient, clinician or institutional factors to the choice of TIVA versus Inhaled practice patterns we will use multilevel analysis or GEE whenever appropriate. The use of a multilevel analysis or GEE will be highly dependent on the ultimate number of upper level units (institutions) with high-quality data in our cohort, using estimates of needing at least 20 upper level units for unbiased multilevel models.[17](https://paperpile.com/c/2j5oZF/x8doy)3,14 To select variables for inclusion in our multilevel model, we will include variables with clinical relevance to choice of TIVA versus Inhaled administration and will use the least absolute shrinkage and selection operator (LASSO) technique for selecting variables for inclusion to avoid over-fitting. Due to multiplicity of outcomes of interest, we will consider the Benjamini–Hochberg method for p-value adjustment[.18](https://paperpile.com/c/2j5oZF/2tY4) This method controls the False Discovery Rate (FDR) using sequential modified Bonferroni correction for multiple hypothesis testing.

The secondary aim will be analyzed separately. To understand the timing of administration of differing anesthetic agents, the intraoperative period will be divided into periods of time (phases of care) described above. We will describe the composition of the subgroups defined above in terms of administration in a binary form, as well as describe the duration of use, and timing of use within the case.

*Pre-specified Sensitivity / Subgroup / Secondary outcome analyses (optional)*

Not Applicable

*Power analysis*

Descriptive studies power analysis and sample size determination are based on the accuracy of the prevalence estimates. In order to estimate the true proportion of specific anesthetic administered, p, within a 1% margin of error we use the 95%CI for the sample proportion. The formula for the 95%CI is for the sample proportion is:

pˆ ± 1.96\*SE(pˆ)

SE(pˆ) is the standard error of the sample proportion. The formula for SE(pˆ) has the square root of n, the sample size, in the denominator (SE(pˆ) = √ [ pˆ(1 − pˆ)/n]). Therefore, as the sample size gets bigger, SE(pˆ) gets smaller, the 95%CI gets narrower, and we get a more precise estimate of the true population prevalence of TIVA use. Table 2 outlines estimated sample sizes needed for p=5-95% with a margin of error from 1 to 10%. Preliminary data from MPOG DataDirect suggests a population size of in excess of 1.9 million cases will be available within MPOG for this analysis across the defined study period. Based on this data we expect that where, p=5-95% with an estimated n= 1,900,000 available cases, we will be able to estimate the true population level TIVA use with margin of error within 1%.

Additionally, based on simulation studies for multilevel models, a minimum of 20 units per level are required for unbiased, robust multilevel modeling.[17](https://paperpile.com/c/2j5oZF/x8doy) Therefore, for the multilevel

modeling techniques, an estimation of 20 patients nested in 20 providers nested in 20 institutions would be adequate. We expect that over 40 institutions will be included in this study. Finally, using Monte-Carlo simulations, Chen et al, in 2017 demonstrated that Bayesian approach tend to require smaller samples than the classical frequentist approach. Thus, we anticipate adequate sample size for our primary as well as sensitivity analysis based on the estimated sample sizes outlined above.

# Table 2. Estimated sample sizes with variable sample proportions and margin of error.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Required Margin of Error** | **p=0.05** | **p=0.10** | **p=0.50** | **p=0.60** | **p=0.70** | **p=0.80** | **p=0.90** | **p=0.95** |
| 1% | 9376 | 17536 | 48265 | 46345 | 40583 | 30980 | 17536 | 9376 |
| 2% | 2409 | 4446 | 12126 | 11646 | 10206 | 7806 | 4446 | 2409 |
| 3% | 1100 | 2004 | 5416 | 5203 | 4563 | 3496 | 2004 | 1100 |
| 4% | 635 | 1143 | 3061 | 2941 | 2581 | 1981 | 1143 | 635 |
| 5% | 418 | 741 | 1968 | 1891 | 1661 | 1278 | 741 | 418 |
| 6% | 298 | 521 | 1373 | 1320 | 1160 | 894 | 521 | 298 |
| 7% | 224 | 388 | 1013 | 974 | 856 | 661 | 388 | 224 |
| 8% | 175 | 301 | 779 | 749 | 659 | 509 | 301 | 175 |
| 9% | 143 | 240 | 618 | 594 | 524 | 405 | 240 | 143 |
| 10% | 118 | 198 | 503 | 484 | 426 | 330 | 198 | 118 |

p = sample proportion of cases involving TIVA administered.

Sample sizes conservatively assume 25% loss of cases from sample due to missing data

*Handling of missing or invalid data*

Missing data patterns will be assessed and the percent of missing data will be determined. If missing data is larger than 10 percent, multiple imputation techniques will be used to complete that data in order to estimate unbiased statistical parameters.

*Preliminary Data*

Based on data obtained during the THRIVE funding application process, representative data from 2019 across 21 sites was obtained (notably, this was intentionally performed for only sites expressing interest in THRIVE and is therefore fewer than the total number of sites we plan to include in our study). The number of general anesthetics conducted in adult patients undergoing non-cardiac surgery and the incidence of “TIVA” and “Inhaled” using similar definitions to those proposed in the analysis is presented below (Table 1).

|  |  |  |
| --- | --- | --- |
| **Site** | **Eligible General Anesthetics N =** | **Technique (%)** |
| **Inhaled** | **TIVA** |
| A | 11,019 | 9,961 | 90.4% | 1,058 | 9.6% |
| B | 20,440 | 17,783 | 87.0% | 2,657 | 13.0% |
| C | 21,879 | 18,575 | 84.9% | 3,304 | 15.1% |
| D | 15,630 | 15,396 | 98.5% | 234 | 1.5% |
| E | 21,126 | 17,260 | 81.7% | 3,866 | 18.3% |
| F | 20,230 | 18,531 | 91.6% | 1,699 | 8.4% |
| G | 27,543 | 22,861 | 83.0% | 4,682 | 17.0% |
| H | 36,561 | 29,651 | 81.1% | 6,910 | 18.9% |
| I | 29,693 | 27,644 | 93.1% | 2,049 | 6.9% |
| J | 34,397 | 33,812 | 98.3% | 585 | 1.7% |
| K | 17,753 | 17,025 | 95.9% | 728 | 4.1% |
| L | 25,896 | 23,773 | 91.8% | 2,123 | 8.2% |
| M | 25,025 | 24,925 | 99.6% | 100 | 0.4% |
| N | 25,597 | 21,578 | 84.3% | 4,019 | 15.7% |
| O | 28,204 | 25,948 | 92.0% | 2,256 | 8.0% |
| P | 15,689 | 14,967 | 95.4% | 722 | 4.6% |
| Q | 27,032 | 25,491 | 94.3% | 1,541 | 5.7% |
| R | 18,346 | 7,210 | 39.3% | 11,136 | 60.7% |
| S | 9,577 | 9,366 | 97.8% | 211 | 2.2% |
| T | 26,499 | 22,259 | 84.0% | 4,240 | 16.0% |
| U | 18,313 | 17,800 | 97.2% | 513 | 2.8% |
| **Total** | **476,449** | **421,816** | **88.5%** | **54,633** | **11.5%** |

*Table 1: Data from 21 MPOG sites in 2019 describing the incidence of TIVA and Inhaled anesthetics as a proportion of adult non-cardiac general anesthetics performed.*

Preliminary data from MPOG DataDirect suggests a population size of in excess of 1.9 million cases will be available for this analysis across the defined study period.

*Areas for discussion*

The study team would appreciate the discussion of the PCRC group regarding:

1. Necessity/utility in quantifying dose/degree of exposure to the anesthetic agents (eg MAC, propofol dose etc)
2. Defining which parts of the case to quantify the time of TIVA/inhaled administration.
3. Relevant subgroups for Aim 3.

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# Query Specification

*See separate query spec document*

**RECORD Statement**

# The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

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| --- | --- | --- | --- | --- | --- | --- |
|  | **Item No.** | **STROBE items** | **Page #** | **RECORD items** | **Page #** |  |
| **Title and abstract** |
|  | **1** | **(a) Indicate the study’s design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done****and what was found** | **2&3** | **RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.** | **2&3** |  |
|  |  |  | **RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.** |  |
|  |  |  | **RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.** |  |
| **Introduction** |
| **Background rationale** | **2** | **Explain the scientific background and rationale for the investigation being reported** | **3** |  | **3** |  |
| **Objectives** | **3** | **State specific objectives, including any prespecified hypotheses** | **3&4** |  | **3&4** |
| **Methods** |
| **Study Design** | **4** | **Present key elements of study design early in the paper** | **4** |  | **4** |  |

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| **Setting** | **5** | **Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection** | **4** |  | **4** |
| **Participants** | **6** | 1. ***Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls**

***Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants**1. ***Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed**

***Case-control study* - For matched studies, give matching criteria and the number of controls per case** | **4&5** | **RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.****RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.****RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.** | **4&5** |
| **Variables** | **7** | **Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.** | **6&7** | **RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.** | **6&7** |
| **Data sources/ measurement** | **8** | **For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group** | **6&7** |  | **6&7** |

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| **Bias** | **9** | **Describe any efforts to address potential sources of bias** | **8** |  | **8** |
| **Study size** | **10** | **Explain how the study size was arrived at** | **9&10** |  | **9&10** |
| **Quantitative variables** | **11** | **Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why** | **6-9** |  | **6-9** |
| **Statistical methods** | **12** | 1. **Describe all statistical methods, including those used to control for confounding**
2. **Describe any methods used to examine subgroups and interactions**
3. **Explain how missing data were addressed**
4. ***Cohort study* - If applicable, explain how loss to follow-up was addressed**

***Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy**1. **Describe any sensitivity analyses**
 | **8-10** |  | **8-10** |
| **Data access and cleaning methods** |  | **..** | **8-10** | **RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.****RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.** | **8-10** |

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| **Linkage** |  | **..** | **6** | **RECORD 12.3: State whether the study included person- level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.** | **6** |  |
| **Results** |
| **Participants** | **13** | 1. **Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed)**
2. **Give reasons for non- participation at each stage.**
3. **Consider use of a flow diagram**
 | ***N/A for PCR C*** | **RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.** | ***N/A for PCR C*** |  |
| **Descriptive data** | **14** | 1. **Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders**
2. **Indicate the number of participants with missing data for each variable of interest**
3. ***Cohort study* - summarise follow-up time (*e.g.*, average and total amount)**
 | ***N/A for PCR C*** |  | ***N/A for PCR C*** |
| **Outcome data** | **15** | ***Cohort study* - Report numbers of outcome events or summary measures over time*****Case-control study* - Report numbers in each exposure category, or summary measures of exposure*****Cross-sectional study* - Report numbers of outcome events or summary measures** | ***N/A for PCR C*** |  | ***N/A for PCR C*** |

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| **Main results** | **16** | 1. **Give unadjusted estimates and, if applicable, confounder- adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included**
2. **Report category boundaries when continuous variables were categorized**
3. **If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period**
 | ***N/A for PCR C*** |  | ***N/A for PCR C*** |  |
| **Other analyses** | **17** | **Report other analyses done— e.g., analyses of subgroups and interactions, and sensitivity analyses** | ***N/A for PCR C*** |  | ***N/A for PCR C*** |
| **Discussion** |
| **Key results** | **18** | **Summarise key results with reference to study objectives** | ***N/A for PCR C*** |  | ***N/A for PCR C*** |  |
| **Limitations** | **19** | **Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias** | 13 | **RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.** | 13 |
| **Interpretation** | **20** | **Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence** | ***N/A for PCR C*** |  | ***N/A for PCR C*** |

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| **Generalisabil ity** | **21** | **Discuss the generalisability (external validity) of the study results** | ***N/A for PCR C*** |  | ***N/A for PCR C*** |  |
| **Other Information** |
| **Funding** | **22** | **Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based** | **TBD** |  | **TBD** |  |
| **Accessibility of protocol, raw data, and programming code** |  | **..** | **6****and TBD** | **RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.** | **6****and TBD** |

**\*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.**