

Independent Scientific Advisory Committee for MHRA database research Instructions on Content of Protocols for research using GPRD data

These instructions are intended to identify issues that are essential for ISAC's scientific evaluation of the proposed research. We welcome feedback from researchers on the instructions, which are based on the Guidelines for Good Pharmacoepidemiology Practices developed by the International Society for Pharmacoepidemiology; http://www.pharmacoepi.org/resources/guidelines_08027.cfm

Prior to developing the protocol, it is suggested that it may be helpful to talk to staff within the GPRD Group about the feasibility of the proposed research. This may be particularly important for researchers with limited experience of either the GPRD or of UK primary health care.

When submitting your protocol to ISAC, you will be required to complete a checklist (as part of the application form) to confirm that you have covered the issues identified in these instructions; protocols that do not comply may be returned to investigators.

Issues to be covered in the protocol

Lay Summary of Research (Max 200 words)

Please provide a simple overview of your proposed research including purpose, background, methodology, possible results and their significance.

Objectives, Specific Aims, and Rationale

Include:

- (i) A description of the knowledge/information to be gained from the study (research objectives)
- (ii) A list of the measurements to be made, and any hypotheses to be tested (specific aims). The protocol should distinguish between a priori research hypotheses and hypotheses that are generated based on knowledge of the source data.
- (iii) An explanation of how achievement of the specific aims will further the research objectives (rationale).

Background

Explain the reason for the study and include any other essential background information, e.g. the findings of similar studies and other related research.

Study Type

Specify whether the study will be hypothesis generating, hypothesis testing or both.

Hypothesis Generating

Hypothesis generating studies are often descriptive studies that aim to reveal patterns associated with a specific condition or event without an emphasis on pre-specified hypotheses. Thus, the emphasis of hypothesis generating studies is on estimation. Some quantities that can be estimated

in hypothesis generating studies are the prevalence and incidence of a disease, the resources required to treat a disease or utilization patterns of a product.

Hypothesis Testing

Hypothesis testing studies in epidemiology involves the use of data to make statistical decisions about the causal factors of a disease or the degree of exposure to an agent or product and its relationship with disease. Hypothesis testing studies are therefore intended to provide results by examining pre-stated questions (hypotheses) using predefined statistically valid plans.

Study design

Describe the overall research design, strategy, and reasons for choosing the proposed study design. Research designs include, for example, case-control, cohort, cross-sectional, nested case-control, or hybrid designs.

Study population

Define the source and study population, in terms of persons, place, time period, and listing the criteria which will be used to select the study population from the GPRD, e.g. exclusion, inclusion criteria. The rationale for the inclusion and exclusion criteria (including any age limits) and their impact on the number of subjects available for analysis should be described. If any sampling from a base population is undertaken, provide details of sampling methods. Include information describing the study period, i.e. total calendar time to be investigated and the observational period, i.e. information on the exposure window of interest. An estimate of the expected number of relevant patients in the GPRD should be included.

Selection of comparison group(s) or controls

If applicable, describe and give justification for the procedure for control selection.

Sample size/ power calculations

Where possible, please provide detailed justification of the sample size/power calculation needed to detect an effect within the proposed study population. This is especially important for those studies evaluating rarer exposures and/or outcomes.

Exposures, Outcomes, and Covariates

Describe the strategies and data sources for determining the main exposures, key health outcomes, and all other variables relevant to the study objectives including all key covariates considered to be potential confounding variables and effect modifiers, using validated measurements whenever possible. Include operational definitions for each important exposure, health outcome, and key covariates (both clinical and non-clinical).

Data sources might include, for example, questionnaires, hospital discharge files, abstracts of primary clinical records, administrative records such as eligibility files, prescription drug files, biological measurements, exposure/work history record reviews, or exposure/disease registries.

An operational definition is one that can be implemented independently using the data available in the proposed study. For example "PCP episode" is not an operational definition; a better description would be "a record of a Read or OXMIS code indicating a PCP episode as listed in Annex X". Operational definitions will not always be limited to a clinical code set; in defining patients with a particular condition, test results or therapy may need to be considered.

It is recognised that considerable effort is often put into the development of code lists. Given the nature of the coding system, it is advised that where possible, a clinician with experience of UK primary care is involved in the process. The logic and procedure used to develop the code list, including appropriate QA steps, should be outlined in the protocol. While code lists may be included as annexes to the protocol, ISAC will not review these in any detail.

Comment on how the exposure, outcome, or covariate of interest is going to be ascertained, e.g. whether it is intended to obtain additional clinical information from the GP to validate the clinical outcome(s) defined by OXMIS, Read codes or MedDRA clinical terms. Similarly, non-clinical exposure, outcomes, and covariates of interest, e.g. new prescription, blood pressure measurement or electrocardiogram also require operational definitions.

Data /Statistical Analysis

Outline the methodology to be used for data management and the statistical approaches to be used in data analysis. This should include the data management and statistical software programs and hardware to be used in the study. Mention of approaches to address potential problems of misclassification, bias, confounding and missing data should be given. Also state whether sensitivity analyses will be undertaken and the provisions to account for reverse causality where this is felt to be a potential issue. Analysis should be represented according to whether the study is hypothesis generating or testing or both.

Hypothesis Generating

Descriptive statistics are used to describe the basic features of the data in a hypothesis generating study. They provide simple summaries about the sample and the measures. Together with simple graphics analysis, descriptive statistics form the basis of virtually every quantitative analysis of data. Hypothesis generating analysis includes measures of disease frequency such as prevalence and incidence estimation and time trend analysis.

Hypothesis Testing

Hypothesis Testing is basically an assumption that is made about the population parameter. Hypothesis testing analysis includes parametric and non-parametric tests of comparison such as ANOVA, Regression Analysis, and Survival Analysis etc.

Patient or user group involvement

It is expected that many studies will benefit from the involvement of patient or user groups in their planning and refinement stages, and/or in the interpretation of results and plans for further work. This is particularly, but not exclusively true of studies with interests in the impact on quality of life. Where possible, please provide some indication of whether patients/users group will be engaged in any of the aforementioned ways. Please see the '**Patient Involvement**' statement from the ISAC on incorporating patient/user group involvement in your study.

Limitations of the study design, data sources, and analytic methods

At a minimum, issues relating to bias and confounding, misclassification, random error and generalisability, and should be considered. The likely success of efforts taken to reduce errors

should be discussed.

Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

There is an ethical obligation to disseminate findings of potential scientific or public health importance (e.g., results pertaining to the safety of a marketed medication). Authorship should follow guidelines established by the International Committee of Medical Journal Editors (<http://www.icmje.org/>). The Consolidated Standards of Reporting Trials (CONSORT) statement (<http://www.consortstatement.org/Statement/revisedstatement.htm>) refers to randomized studies, but provides useful guidance applicable to nonrandomized studies as well.

Points to remember

Please

1. Be succinct where possible, you should aim for no more than 5 sides of A4, excluding annexes.
2. Use annexes to list all codes used for the definition of exposure(s) and outcome(s)
3. Number pages

Extended role of the new committee

In addition to GPRD research protocols, ISAC is responsible for the scientific review of research protocols seeking to use data from the Yellow Card Scheme*. The GPRD Group supports this extended role of the committee however; we are conscious of the importance of keeping the nature and content of GPRD research protocols confidential within the GPRD Group, which is separate from the regulatory function of the MHRA.

For this reason, though the same committee will be reviewing the protocols for both data sources, administrative/Secretariat support for the two aspects of ISAC's work will be provided by entirely distinct groups of staff within the MHRA. Staff of the GPRD Group will form the Secretariat support for GPRD protocols, with responsibility for receiving, logging, and distributing protocols for review as well as liaising with applicants, including the provision of feedback from the committee. ISAC meetings will also have separate sessions for the discussion of GPRD and Yellow Card protocol-related issues; the only MHRA staff permitted to attend the sessions for GPRD protocol-related matters will be staff from the GPRD Group. This will ensure that, as at present, knowledge of the nature of research that applicants propose to conduct using GPRD remains confidential to the GPRD Group and to ISAC members, who will be required to sign confidentiality agreements.

The MHRA's Vigilance and Risk Management of Medicines (VRMM) division will provide equivalent support to ISAC for Yellow Card protocols; such protocols will remain confidential to relevant staff in VRMM and to ISAC members.

On occasion, it is possible that a research protocol proposal will propose the use of data from both the Yellow Card Scheme and from GPRD; such protocols will be seen by relevant staff from both the GPRD Group and the VRMM Division and will remain confidential to these staff and to ISAC members.

*The Yellow Card Scheme is the UK's spontaneous reporting scheme to which notifications

of suspected adverse drug reactions can be made by healthcare professionals and, more recently, patients; the MHRA is responsible for the operation of this Scheme.

Ethical review for GPRD Protocols

The GPRD Group has obtained ethical approval from a Multi-centre Research Ethics Committee (MREC) for all purely observational research using GPRD data; namely, studies which do not include patient involvement (which is the vast majority of GPRD studies). ISAC will be responsible for reviewing protocols for scientific quality, but may recommend that study-specific MREC approval is sought if ethical issues arise in relation to an individual study. Separate MREC approval will be required for any study which includes any form of direct patient involvement.

National Research Register

The National Research Register (NRR) is a register of ongoing and recently completed projects funded by, or of interest to, the UK National Health Service. ISAC **strongly** recommends that UK researchers using GPRD and Yellow Card data consider registering as NRR data providers, in order that others engaged in research within the UK can be made aware of current works. Registration with the NRR is **entirely voluntary** and will not replace information on ISAC approved protocols published in summary minutes or in the ISAC Annual Report

ISAC Secretariat (GPRD protocols)

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