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Template for Research Protocols in Advanced Epidemiology, PBHL P601 Spring 2013

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Title Page

The title page should include the research title and any subtitle. The title should be scientifically or clinically appealing. In addition, this is followed by the protocol version and date of last revision or update, names of all authors in the group that is assigned to design the project, affiliations and contact information. Since the assignment will be a team work, the affiliation for the whole group will be as it shown in the following is an example.

The Correlation between Obesity and Asthma

Is Newly Diagnosed Asthma among Obese Adults a Consequence of Obesity or a Manifestation of Respiratory Symptoms of Obesity?

Version 1

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Table of Contents

To enhance readability, a structured table of contents should be included. The table of contents should be similar to the list on page 1 of this guidance document. This should be on a separate page and can extend to more than one page.

List of Tables

A list of tables that support the protocol should be included in this section and should be on a separate page. Tables should be referenced in the order they appear in the text and should be numbered according to the section they appear in. This might include tables supporting the information in the background section or the methods. At a minimum, the team is expected to include the following tables:

Table 3.1. Variable definitions.

Table 3.2. Shell table for descriptive statistics, e.g. characteristics of study sample.

Table 3.3. Shell table for inferential statistics, e.g. incidence rates and associations.

List of Figures

Listing figures should follow the same rules pertinent to tables. At a minimum, the team is expected to include the following figures:

Figure 3.1. Study follow up.

Figure 3.2. Study profile.

Figure 3.3. Shell figure for sample disposition, e.g. exclusion and final sample.

Abstract

A stand-alone one page summary of the protocol should be included as synopses for the rationale and significance for proposing this research study; research questions and objectives, including primary and secondary objectives; study design, setting and populations, and data source and study variables. The author can adopt the structure of a journal article that is relevant to the field of knowledge related to the research study. Since this is a proposal with no anticipated results, the abstract can be structured into Background, Objectives, Methods, and expected results.

1. Background

The background section should include a description of the problem which stimulated the design of the proposed study. It should present a critical review of what is already known about the topic and what gaps in knowledge the proposed study intends to fill. Also, the section should include the findings from similar studies and the expected contribution to the field by the proposed study.

2. Study Objectives

Primary and secondary broad objectives of the study can be included in this section, which are related to the research question and operationalized later in the specific aims and hypotheses sections. The following is an example of a study objective:

"…to assess asthma-related morbidity and mortality in patients exposed to inhaled long-acting beta-agonist (LABA) bronchodilators as monotherapy and inhaled corticosteroids (ICS) combination therapy in the UK…" Ali AK dissertation; 2012.

2.1. Research Question(s)

The question(s) the proposed study intends to answer should include the target population, exposures and primary outcomes. Research questions can be of descriptive nature or analytical nature. It is important to give considerable thoughts to construct sound research questions as the first step in research studies. This is because well structured questions determine study design, define study population, guide sampling, determine data source, guide data collection and analysis plan, translate into measurable exposures and outcomes, and guide interpretation and extrapolation of findings. Below is an example of a research question:

"Research Question No. 1: is there a difference in the incidence of asthma-related morbidity in terms of asthma-related hospitalizations between asthmatic patients exposed to inhaled LABA monotherapy and ICS/LABA combination therapy in the UK?"

Ali AK dissertation; 2012.

2.2. Specific Aim(s)

Study objectives are achieved by accomplishing specific aims which are translated from the proposed research questions. Each research question should be followed with a specific aim and corresponding hypotheses. Specific aims usually start with infinitive phrases that begin with “to”. When the study intends to answer more than one question with more than one aim, I recommended specifying each aim separately. The following is an example:

“Specific Aim No. 1: to examine the association between LABA monotherapy and asthma morbidity rates compared with ICS/LABA combination therapy in asthmatic patients in the UK” Ali AK dissertation; 2012.

2.3. Hypotheses

Hypotheses are usually the theoretical and statistical constructs for the specific aims. They usually follow the aims, and should be distinguished for each specific aim. This statement should define what your study will target. The following are examples of a hypothesis for the previous specific aim:

“Hypothesis No. 1: there is no difference in asthma morbidity rates between inhaled LABA monotherapy and ICS/LABA combination therapy in asthmatic patients in the UK

“Hypothesis No. 2: at there is a difference in asthma morbidity rates between inhaled LABA monotherapy and ICS/LABA combination therapy in asthmatic patients in the UK

3. Methods

This section is probably the most important part of a study proposal. The choice of study designs, analytical strategies and other methodological issues are critical parts in epidemiological studies. This section can be divided into the following subsections:

3.1. Research Ethics

A statement about study review and approval by independent ethics and review board is recommended to be included. At the earlier stages of submitting the proposal, the authors can state that the research proposal will follow due process of review by the Institutional Review Board (IRB) at the institution where the study will be conducted, e.g. The IRB at Indiana University Research Protection Program (HRPP). Note that some studies may not require IRB approval and some require varying levels of review. This level of detail should be captured here.

3.2. Study Type and Design

State the type of study and the proposed epidemiological approach to address study objectives. Highlight the strengths and weaknesses of the adopted design with justifications for selecting the proposed approach given the research question(s).

3.3. Data Source

From every research study, data will be generated and subsequently translated to conclusions that might have public health impacts. The authors should discuss the source of the data, the strengths and limitations, how the data was collected/generated, and any procedure for data linkage to other sources or data validation. Reasons why this particular data source is deemed appropriate to answer the research questions should be stated.

3.4. Study Population and Setting

In terms of person, place and time, this section should elaborate on what the units of analyses are, sampling method, and should include inclusion and exclusion criteria with rationale for every criterion. The impact of inclusion/exclusion criteria on the sample size for analysis. Internal and external validity should be discussed in this section. Study duration, selection of comparison groups, and types of comparison groups should be stated as well. In case of utilizing databases, e.g. electronic medical records or healthcare insurance claims, how the patients are identified in these databases and whether there is a potential for misclassification and selection bias should be considered. Study profile graph can be included in this section (e.g. Figure 3.2.)

3.5. Variable Definition

This section is important to guide the implementation of statistical analysis plan. Identified independent (exposure), dependent (outcome), and covariates (confounders or effect modifiers) should be stated within the corresponding section, and the process

of identifying each variable should be discussed, especially ways to prevent misclassification bias, measurement bias, and confounding. The choice of confounders and effect modifiers should be justified. I recommend including a variable definition table (e.g. Table 3.1.) which facilitates the processes of reviewing, development and completion of the protocol. An example is below:

Domain	Variable	Values
Exposure	Bronchodilator	0: ICS/LABA 1: LABA
Outcome	Asthma-hospitalization	0: No 1: Yes
Comorbidity	Weight status, BMI (kg/m^2)	0: <18.5 (normal) 1: 18.5-24.9 (underweight) 2: 25.0-29.9 (overweight) 3: 30 + (obese) 9: Unknown
Comedication	Antibiotics	0: No 1: Yes
Demographics	Age (years)	13-65
	Sex	0: Female 1: Male
Asthma severity	Oral corticosteroids	0: Not prescribed 1: Prescribed
	Number of asthma drug classes prescribed	>0
	Inhaled short-acting beta-agonists	0: Not prescribed 1: Prescribed

Ali AK dissertation; 2012.

3.5.1. Exposures

How the exposures are identified, what are the comparison groups, and how misclassification bias is minimized or prevented should be discussed.

3.5.2. Outcomes

What are the outcomes of interest and how they are measured and whether they are clinical end points or surrogate outcomes should be discussed.

3.5.3. Covariates

Why these factors are deemed important covariates and which are confounders and which are effect modifiers should be discussed. In addition, the possibility of residual confounding should be stated and whether these covariates minimize such confounding or not.

3.6. Sample Size and Power Calculations

Whenever possible a power calculation and sample size determination is encouraged to be included.

3.7. Statistical Analysis Plan

Formulating a statistical analysis plan is a crucial part of the protocol and should mirror the epidemiological approach. I recommend dividing the section into the following parts:

3.7.1. Data Management

Include how the data will be procured, where it will be stored, and what statistical analysis software will be employed to conduct data cleaning and analysis. I also recommend mentioning the type of statistical testing and the level of type-1 error that is specified. For example: *"…two-sided tests with alpha=0.05 a priori level of statistical significance are used throughout the analysis procedures…"* Ali AK dissertation; 2012.

3.7.2. Descriptive Statistics

This part includes types of statistical tests that will be applied to compare baseline characteristics of the comparison groups by describing the frequencies and patterns of patients, exposures and outcomes. Appropriate tests should be used for each data type, e.g. Chi-square test for categorical data, and t-test for continuous data. In addition, Use descriptive measures that are consistent with data type, e.g. proportions and 95% confidence intervals to describe categorical data, and means and standard deviations to describe continuous data. Types of graphs used for the description should also be mentioned, e.g. bar graphs and pie charts for categorical data, and histograms and scatter plots for continuous data. The interpretation of the statistical significance of the differences between exposure groups in terms of baseline variables should be discussed here, e.g. what would a p-value of 0.05, <0.05 and >0.05 means? In addition, I recommend including shell tables for the expected results corresponding to characteristics of units of analyses, e.g. patients (e.g. Table 3.2.).

3.7.3. Inferential Statistics

This part includes the procedures that intend to answer the research questions by testing the hypotheses for corresponding specific aims. Usually, this part aims to test associations between exposures and outcomes after controlling for potential and actual confounders and other covariates. Authors should discuss the strengths and limitations of every statistical test. I recommend providing an operationalized annotations and mathematical equations to support this part. In addition, identified measures of associations should be stated and an overview of the interpretation of the estimated results should be discussed, e.g. what would a relative risk of 1.30 means, what would an odds ratio of 0.40 means, and how a 95% confidence interval be interpreted? Furthermore, Shell tables for expected results from relevant analyses should be included here (e.g. Table 3.3.).

3.7.4. Sensitivity Analyses

Sensitivity analyses can be applied to evaluate the uncertainty of study results to changes in study parameters, e.g. changing inclusion/exclusion criteria.

4. Study Limitations

The weaknesses and limitations of the proposed study should be discussed in this section and I recommend dividing it into the following parts. Although the limitations might be stated in the corresponding parts in the methods section, the authors can restate them here to facilitate readability and grading when this document is used as part of a teaching course.

4.1. Study Design

4.2. Statistical Analyses

4.3. Data Source

5. Discussion

This section should include a description of the potential impact of the proposed study and any necessary follow-up in order to address the research problem identified.

Author Contributions

Individual contribution and responsibilities for every section or part of the protocol should be listed in table format, e.g.

	Author Contribution	Remarks
Abstract	Zac George, James Michael	
Background	All	Consulted with Dr. Ali
Study Objectives	James Michael	
Study Type and Design	James Michael	
Data Source	Zac George, James Michael	
Study Population and Setting	Jane Smith	
Variable Definition	Amy Thomas	
Statistical Analysis Plan	James Michael, Jane Smith	
Study Limitations	Daniel Smith, Jane Smith	
Expected Findings	All	
Tables	James Michael, Jane Smith	
Figures	Amy Thomas	

List of References

Any source of information referred to in the protocol should be listed in numerical or alphabetical order according to bibliography citation conventions to allow easy retrieval.

Additional Resources

- International Society for Pharmacoepidemiology. Guidelines for Good Pharmacoepidemiology Practices. *Pharmacoepidemiology and Drug Safety*. 2008;17(2):200-208.

- Berger ML et al. Good Research Practices for Comparative Effectiveness Research: Defining, Reporting and Interpreting Nonrandomized Studies of Treatment Effects Using Secondary Data Sources: The ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report—Part I. *Value in Health.*2009;12(8):1044-1052.

- Cox E et al. Good Research Practices for Comparative Effectiveness Research: Approaches to Mitigate Bias and Confounding in the Design of Nonrandomized Studies of Treatment Effects Using Secondary Data Sources: The ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report—Part II. *Value in Health*.2009;12(8):1053-1061.

- Johnson ML et al. Good Research Practices for Comparative Effectiveness Research: Analytic Methods to Improve Causal Inference from Nonrandomized Studied of Treatment Effects Using Secondary Data Sources: The ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report—Part III. *Value in Health*. 2009;12(8):1062-1073.

- von Elm E et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies. *Journal of Clinical Epidemiology.* 2008;61:344-349. Checklist: www.strobe-statement.org.

- Moher D et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *British Journal of Medicine.* 2009;339:332-336. Checklist: www.prisma-statement.org.

- Stoup DF et al. Meta-Analysis of Observational Studies in Epidemiology: A Proposal for Reporting. *Journal of American Medical Association.* 2000;283:2008-2012.

- Chan AW et al. SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. *Annals of Internal Medicine.* 2013 [Epub Ahead of Print]. Checklist: www.spirit-statement.org.

- Enhancing the Quality and Transparency of Health Research (EQUATOR) Network Initiative. List of Reporting Guidelines by Study Type and Guideline Source: http://www.equator-network.org/resource-centre/library-of-health-research-reporting.

- The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. *Guide on Methodological Standards in Pharmacoepidemiology.* Revision 1. EMA/95098/2010. London, UK: European Medicines Agency. July 2012.

- Gliklich RE, Dreyer NA, eds. *Registries for Evaluating Patient Outcomes: A User's Guide.* AHRQ Pub. No. 07-EHC001-1. Rockville, MD: Agency for Healthcare Research and Quality. April 2007.