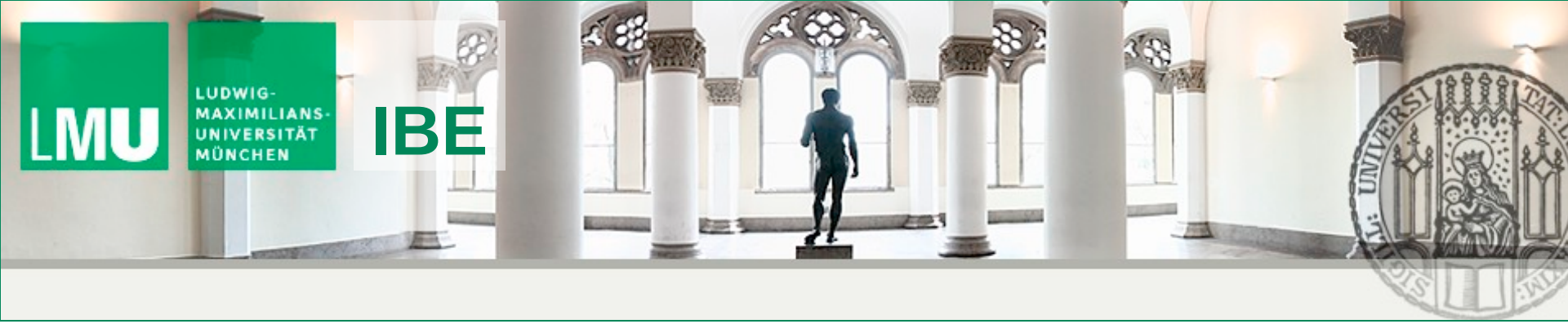

Research Skills: SS 2016
Study Protocol

Prof. Dr. Eva Grill, MPH

Amanda Phillips, MSc

Department of Medical Informatics, Biometry, and Epidemiology

Ludwig Maximilians University Munich

RS Schedule SS 2016

April 4th
09:15 – 15:00

Good Epidemiologic Practice

Study Protocol

Group Work/ Presentations

June 8
9:00 – 17:00

How to create a questionnaire

Dr. Anne Quante

Presentation Skills

Today‘s Schedule

09:15 – 10:30	Lecture
10:30 – 12:30	Group Work
12:30 – 13:15	Lunch
13:30 - 15:00	Presentations/Discussion

Picture: https://pbs.twimg.com/media/B8xF2DWCMAAlpxJ.png

→ PICO

→ Pubmed

???? SS 2016

→ Endnote, Pubmed, Plagiarism

* → How to critically read a paper

* → Presentation Skills

Study Protocol
Good Epidemiologic Practice

July 12

Interpreting Research (Group work)
Preparing a Study Protocol (Group Work)
Presentation practice (Group Work)

Picture:
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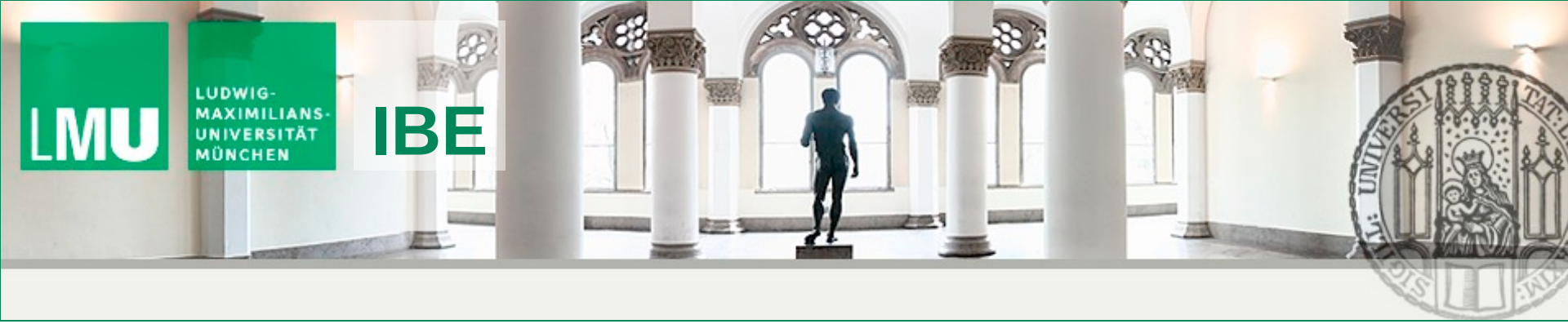

Good Epidemiologic Practice

Guidelines and Recommendations
to Assure

Good Epidemiologic Practice (GEP)

Long Version

German Society for Epidemiology
(DGEpi)

In Collaboration with the
German Association for Medical Informatics, Biometrics, and Epidemiology
(GMDS),
German Association for Social Medicine and Prevention
(DGSMP)
German Region of the International Biometrics Association
(DR-IBS)

Online: http://dgepi.de/fileadmin/pdf/GEP_LL_english_f.pdf

Introduction

- German Research Foundation (DFG) assembled international commission in 1997
- March 1998 the German Epidemiology Foundation (DAE) authorized Working Group
- In 2000 Guidelines and Recommendations to Assure Good epidemiological Practice (GEP) were available

Guidelines and Recommendations

- Addresses the **planning, preparation, execution, analysis and evaluation processes of research**
- Based on widely accepted **standards**
- Should establish standards of **quality research**
- Help to **eliminate fraud, ensure transparency**, and **promote trust** within scientific community
- Define **framework** to be used to its fullest **benefit, extent, and application**

Purpose of Epi Research

- **To investigate the determinants of health as well as causes, incidence, progression and outcomes of diseases in human populations, or rather in well-defined population groups.**

- Epi studies are primarily observational and therefore are to be differentiated from randomized intervention studies in clinical research

Guideline 1: Ethics

- Epidemiological research must be conducted in accordance with **ethical principles**
- and must respect **human dignity** as well as **human rights**

Guideline 2: Research Question

- The **planning** of every epidemiological study requires explicit and operating research questions that are to be **formulated as specifically and precisely as possible**
- The **selection of the study population** must be **justified** on the basis of the main research question

Guideline 3: Study Protocol

- An epidemiological study is based on a **detailed and binding study protocol**, in which the study elements are defined in **writing**

Study Protocol

- The study protocol should include:
  - Research question(s) and working hypotheses
  - Study design
  - Target population and study population
  - Sample size of the study and it's rationale
  - Sampling procedure and recruitment methods for study participants
  - Definition of, measurement methods and survey procedures for the dependent variables (outcome variables)
  - Independent variables (risk factors)
  - Potential confounders and effect modifiers
  - Data collection and storage methods
  - Analysis strategy, including statistical models
  - Quality assurance methods
  - Methods to ensure data protection and safety and compliance with ethical principles
  - Timeline with predefinition of accountability

Guideline 4: Biological Sample Banks

- In many epidemiological studies, the creation of a **biological sample bank** is both necessary and reasonable. The **documented consent** of all probands is required for this as well as for all **current and intended future uses** of the collected samples

Guideline 5: Quality Assurance

- In epidemiological studies, an accompanying **quality assurance** of all **relevant instruments and procedures** is to be guaranteed

Guideline 6: Data mgmt. and Documentation

- A **detailed concept** is to be developed **in advance** for the compilation and management of **all data collected** during the study, including the **editing, plausibility, verification, and coding of data**, as well as the provision of data for transfer

Guideline 7: Analysis

- The analysis of epidemiological studies should be carried out using **adequate methods and without unreasonable delays**.
- The data underlying the results are to be **kept for a minimum of 10 years** in a complete **reproducible form**

Guideline 8: Data Protection

- In the planning and conduct of epidemiological studies, compliance with applicable **data protection regulations** are to be respected in order to **protect the right** to informational self-determination

Guideline 9: Contractual Conditions/Frameworks

- The conduct of an epidemiological study presumes certain defined **legal and financial conditions.**

- Therefore, **legally binding agreements** are to be sought between **contractor (sponsor) and consignee (researcher**), as well as between **all partners of research collaborations**

Guideline 10: Interpretation

- The interpretation of the results of an epidemiological study is the **duty of the author(s) of the publication.**
- The basis of every interpretation is a **critical discussion of methods, data, and results** of one's own research in the context of existing evidence.
- All publications should be subjected to an **external review**

Guideline 11: Communication and Public Health

- Epidemiological studies, which by nature concern the **translation of results into real effects on health**, should strive to adequately involve the **affected population groups**, and to report a qualified **risk-communication to the interested public**

Study Protocol

BMC Ear, Nose and Throat Disorders

BioMed Central

Study protocol

Open Access

An evaluation of the cost-effectiveness of booklet-based self-management of dizziness in primary care, with and without expert telephone support

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This article is available from: http://www.biomedcentral.com/1472-6815/9/13

Study protocol: What?

- Describes every step of a study
  - identification of the problem
  - application of the results

- Answers relevant questions
  - ✓ Public health problem: Important?
  - ✓ Study question: relevant to the problem?
  - ✓ Objectives: consistent with the study question?
  - ✓ Study design: achieves objectives?
  - ✓ Power of the study: sufficient?
  - ✓ Public health impact of the findings?

Study protocol: Why?

- To check if the objectives can be achieved
- To check the feasibility of the study
- Prevents failure to collect crucial information
- Lays down the rules for all partners
- To obtain approval of ethical committee(s)
- Application for funds
- Makes it much easier to write article

Study protocol: How to start ?

- Get good examples
- Get ideas from similar published studies
- Use a checklist of items to include
- Get the requested format
  (grant application)
- Share ideas with colleagues

1. Protocol outline (condensed)

- Title: a statement of long-term goals/conclusions
- Abstract: simple, accurate, interesting, to the point
  - Keywords
- Research Plan
  - Objectives(5%)
  - Background & Significance(10-15%)
  - Pilot Data
  - Methods/Approach (55-60%)
- Budget

Protocol outline

1. Presentation
2. Background and significance
3. Objectives/Aims and research questions
4. Methods
   - Study design
   - Definitions and measurement procedures
   - Study procedures (sampling and recruitment/screening)
   - Data Analysis Plan
5. Safety Monitoring Plan (Quality Assurance)
6. Ethical considerations
7. Project management
8. Timetable
9. Resources
10. References
11. Appendices

1.Presentation

- Title
- Date
- Investigators
- Main centres
- Research Team (Steering committee)
- Summary (abstract) of the protocol

1.Presentation

- Abstract
  - Current situation (literature)
  - We have a problem
  - It is an important problem
  - This was already done to solve that problem..
  - This is the topic that is still unknown
  - And this is our goal to help resolve the unknown

Abstract

Background: Dizziness is a very common symptom that often leads to reduced quality of life, anxiety and emotional distress, loss of fitness, lack of confidence in balance, unsteadiness and an increased risk of falling. Most dizzy patients are managed in primary care by reassurance and medication to suppress symptoms. Trials have shown that chronic dizziness can be treated effectively in primary care using a self-help booklet to teach patients vestibular rehabilitation exercises that promote neurological adaptation and skill and confidence in balance. However, brief support from a trained nurse was provided in these trials, and this model of managing dizzy patients has not been taken up due to a lack of skills and resources in primary care. The aim of this trial is to evaluate two new alternative models of delivery that may be more feasible and cost-effective.

Methods/Design: In a single blind two-centre pragmatic controlled trial, we will randomise 330 patients from 30 practices to a) self-help booklet with telephone support from a vestibular therapist, b) self-help booklet alone, c) routine medical care. Symptoms, disability, handicap and quality of life will be assessed by validated questionnaires administered by post at baseline, immediately post-treatment (3 months), and at one year follow-up. The study is powered to test our primary hypothesis, that the self-help booklet with telephone support will be more effective than routine care. We will also explore the effectiveness of the booklet without any support, and calculate the costs of treatment in each arm.

Discussion: If our trial indicates that patients can cost-effectively manage their dizziness in primary care, then it can be easily rolled out to relieve the symptoms of the many patients in primary care who currently have chronic, untreated, disabling dizziness. Treatment in primary care may reduce the development of psychological and physical sequelae that cause handicap and require treatment. There is also the potential to reduce the cost to the NHS of treating dizziness by reducing demand for referral to secondary care for specialist assessment and treatment.

Trial Registration: ClinicalTrials.gov trial registration ID number: NCT00732797

2. Background and significance

- Statement of the current situation, study justification
  - ✓ Describe importance
  - ✓ Describe why
  - ✓ Describe questions
  - ✓ Describe how
- Review relevant literature and current knowledge
  - – Critical evaluation of this knowledge and how you will enhance this knowledge

Background

Dizziness has a prevalence of up to 25% in the community [1-4], and 1 in 10 working age adults report some degree of handicap due to dizziness [3]. Dizziness is a more severe problem for older people; more than 1 in 5 people aged over 60 have current dizziness that has led to significant disability, medical consultation or medication use [5]. Dizziness is also associated with falls, fear of falling and loss of independence in older people [6,7].

The most common cause of dizziness in primary care is peripheral vestibular disorder, and serious sinister pathology in patients with no other symptoms is very rare [2,8-12]. Most patients are therefore managed in primary care [1,9,13,14] by reassurance and medication for symptomatic relief [9,11,13,15,16]. However, living with chronic dizziness often entails avoiding all physical activities and situations that might provoke dizziness, leading to clinically significant limitations in physical functioning, reduced quality of life, emotional distress, loss of fitness, unsteadiness and lack of confidence in balance (especially as patients get older), and vulnerability to falling [17-20].

3. Objectives/Aims and research questions

VERY IMPORTANT PART OF RESEARCH PROPOSAL!

- **S**pecific - not “focus on ….”
- To **m**easure something (prevalence, incidence, risk increase…)
- **A**ction oriented – “in order to ….”
- **R**elevant
- **T**ime specified

Main objective

- Focussed, conceptualized and realistic
- Must be achieved

Secondary objectives

- Of interest, but not essential

Specific research questions (Think about PICO!)

Rationale and aims

Despite the consensus that VR is the treatment of choice for patients with dizziness of peripheral vestibular origin [23,27], few eligible patients are currently offered VR. Only 2% to 13% of dizzy patients seen by GPs eventually receive VR, of whom around 70% are seen in ENT [1,13].

…

- Hypothesis 1: Provision of a self-help booklet teaching VR exercises, with up to one hour of telephone support from a vestibular therapist, will be a) more effective than routine care in reducing symptoms (and therefore also disability and handicap) in dizzy patients in primary care, and b) less costly than routine care of dizzy patients.

- Hypothesis 2: Provision of a self-help booklet teaching VR exercises, without any other support, will be a) more effective than routine care in reducing symptoms (and therefore also disability and handicap) in dizzy patients in primary care, and b) less costly than routine care of dizzy patients.

Protocol outline

1. Presentation
2. Background and significance
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4. Methods
   - Study design, study population, sample size
   - Definitions and measurement procedures
   - Study procedures (sampling and recruitment/screening)
   - Data Analysis Plan
5. Safety Monitoring Plan (Quality Assurance)
6. Ethical considerations
7. Project management
8. Timetable
9. Resources
10. References
11. Appendices

4. Methods

- At least 50% of the total proposal length!
- Study design
  - ✓ Which design?
    (cohort, case-control, cross-sectional…)
  - ✓ Why?
- Study population
  - ✓ selection and definition
  - ✓ appropriateness for study objectives
  - ✓ accessibility, follow up, representativeness
  - ✓ How will the participants be recruited?
  - ✓ Inclusion/exclusion criteria

4. Methods

- Sampling design
  - ✓ Frame: district, household, persons,…
  - ✓ method: cluster, stratified, representative…
  - ✓ Randomization?
- Sample size
  - ✓ sample size and power calculations
  - ✓ feasibility

4. Methods

Data required

- Selection and definition
  - ✓ exposures: potential risk factors, protective factors, confounding factors
  - ✓ outcomes: definition of a case, definition of a control

  example:

  smoking: definition, quantification, categories

  lung cancer: case definition, definition of a control
- Items to be measured and how (scales used)

4. Methods

Data collection

- How?
  - ✓ Interview, observation, record review
- By whom?
  - ✓ interviewers: selection, training
  - ✓ level of supervision
- Tools?
  - ✓ questionnaires, recording materials (forms)
  - ✓ questionnaires: self or interviewer administered, face to face or telephone interview
- Blind data collection?
- Procedures for taking samples

4. Methods

Data handling

- Data coding
  - ✓ during data collection, afterwards?
  - ✓ by whom?
- Data processing
  - ✓ manually, by computer
  - ✓ software, hardware
  - ✓ data entry:
    - during the study, afterwards?
    - order of entry screen and structure of data base
    - single entry, double entry?

4. Methods

Data analysis

- Validation and data cleaning
  - ✓ timing: during study or later
- Data analysis plan
  - ✓ structured in terms of the specific objectives
  - ✓ dummy tables
  - ✓ from general to specific

Primary and secondary analysis

Statistical analysis will be carried out by LY and MM at the end of the trial who will both be blind to participants' group allocation. The main analysis will compare patients randomised to the self-help booklet with telephone support versus patients randomised to routine care. The analysis will be performed on the primary outcome symptom score (the Vertigo Symptom Scale - Short Form) at 3 months after randomisation, using ANCOVA (analysis of covariance) adjusted for symptom score at baseline. Continuous outcomes on the secondary outcome measures will also be evaluated using ANCOVA. All continuous outcome variables will be checked for the assumption of normality. If the assumption is not met, bias corrected and accelerated bootstrap methods will be used to construct confidence intervals. Binary outcomes will be compared between the two groups using logistic regression. All analyses will be adjusted for the level of the relevant outcome variable at baseline. All analyses will also be adjusted for any confounding variables that may differ by chance between the two groups at baseline. These analyses will be repeated for outcome at 12 months. Further secondary outcome analyses will repeat the above, comparing outcomes between patients randomised to the self-help booklet without any other support versus patients randomised to routine care.

Why a data analysis plan ?

- Prevents collection of data that will not be used
- Prevents failure to collect crucial information
- Better estimates of sample size for analysis of sub groups

4. Methods

Pilot studies, pre-testing

- No study should ever proceed without a test
- Describe how to test
  - ✓ Feasibility of sampling
  - ✓ Data collection, measurement methods
  - ✓ Questionnaire

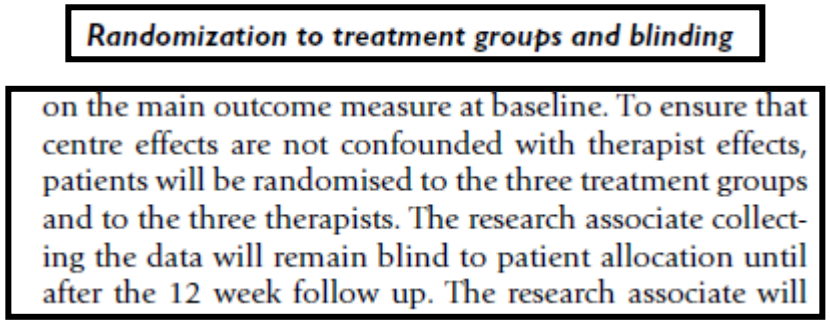
Methods/Design
Design overview

This design was chosen so it can be compared with a previous successful trial [42], and if found to be effective, these models of delivery can be easily rolled out through the NHS across the region and the UK.

4. Methods

Validity (limitations, weaknesses)

- Identification of potential sources of biases
  - ✓ confounding
  - ✓ selection bias
  - ✓ information bias
- How to deal with them
  - ✓ In design
  - ✓ In analysis



Randomization to treatment groups and blinding

on the main outcome measure at baseline. To ensure that centre effects are not confounded with therapist effects, patients will be randomised to the three treatment groups and to the three therapists. The research associate collecting the data will remain blind to patient allocation until after the 12 week follow up. The research associate will

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5. Safety Monitoring Plan (Quality Assurance)

- Definition of adverse events
- Subject safety procedures
- Reporting of adverse events
- Review of safety information during study
- Risks/Benefits of participants

Potential benefits and adverse effects

The trial has several anticipated benefits as well as predictable risks and inconveniences for patients taking part. Previous research has shown that chronic dizziness can be treated effectively using the self-help booklet, although we cannot guarantee that the self-help will be effective for all patients. Benefits may also include feeling that they have helped a medical research project. We hope the results will be used to review current primary care services for people with dizziness and this may result in improved services though there is no guarantee of this. Risks and inconveniences include the time and effort required to carry out the self-help exercises and complete the questionnaires (approximately 20-25 minutes for each stage of the trial). In addition to this, the self-help exercises require patients to deliberately make themselves dizzy in a controlled manner. Although some people may find this unpleasant, the exercises cannot cause any damage to their balance system.

6. Ethical considerations

- Informed consent
- Confidentiality, anonymity?
- Data storage and protection
- Ethical review committee
- Data protection inspectorate

Ethical approval and data protection

The trial will be conducted, analysed and reported in accordance with the ethical principles described in the Declaration of Helsinki, ICH Guidelines for Good Clinical Practice, and the CONSORT Statements. Ethical approval for the trial has been given by the Southampton and South West Hampshire (B) REC, reference number 08/H0504/31. R&D and data protection approval has also been obtained from the relevant geographical areas. Indemnity cover is provided by the University of Southampton. All patients will receive an information sheet about the trial, and written consent will be obtained from all patients before entering into the trial. Consent will include permission to access relevant sections of participants' medical records, to audio-tape the telephone support sessions, and to inform participants' GPs of their participation in the trial. Participants are informed that they remain free to withdraw from the trial at any time.

7. Project management

- Participating institutes and persons
- Responsibilities and tasks of each partner
- Quality assurance
  - ✓ compliance with protocol
  - ✓ problem identification
  - ✓ distribution and maintenance of material
- Data ownership

Trial management

Each centre team will meet monthly, and the whole team will meet 4 times a year. Because of the geographical dispersion of the team, for rapid communication between meetings email will be most efficient. The research associate will circulate a monthly update to review progress relative to the project plan, highlighting any issues that need to be addressed. Each team member will consult the other team members immediately by email and/or phone on any issues that arise.

Trial steering committee

Management of the project will be overseen by a steering group including members who are independent of the research team (including the Director and Research Trustee of the Ménière's Society, and a neuro-otological

Reporting and dissemination

We will disseminate the findings of the research to three key populations: lay people with dizziness (who need to be informed about the availability and effectiveness of treatment); primary care professionals (particularly GPs), who could implement provision of VR in primary care; and clinicians currently treating dizziness in secondary care, who could provide expert support for treatment in primary care. We will disseminate our findings to lay peo-

8. Timetable

Planning/organisation of the study

- questionnaire design, recruitment, purchases
- permission
- obtain funding

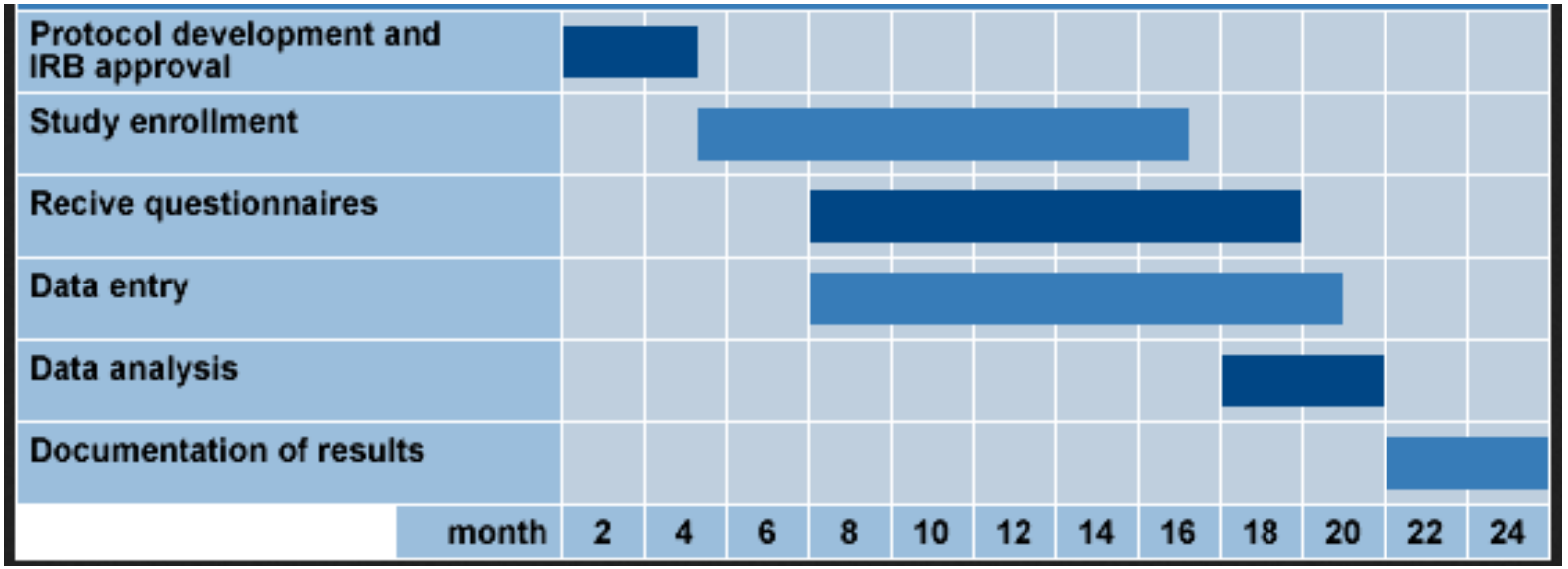
“Pilot study”

- testing of methods and questionnaires
- adjust procedures as result of pilot

Final study

- data collection
- analysis
- presentation of results and write up

Example Timetable



Picture credit: https://www.aofoundation.org/Structure/research/clinical-research/case/doing/therapeutic-cohort-study/Pages/part-2.aspx

9. Resources

- Specify
  - ✓ available sources
  - ✓ requested sources
- Keep budget
  - ✓ reasonable
  - ✓ detailed
  - ✓ well justified

Acknowledgements
This trial is funded by a grant from the National Institute of Health Research (NIHR) Research for Patient Benefit Programme (RfPB). Reference number: PB-PG-0107-12069.

10. References

- Limit number of references to key articles
- Follow recommended style of target journal

11. Appendices

- (Methodological appendices)
- Questionnaires
- Variable list with definitions
- Introductory letters to study participants
- Forms for informed consent

…..

Preparing a Proposal

- Outline, write, edit
- Write the complete draft, then edit
- Think about the perspective of the reviewer
  - Comes from a different research field
  - Not much time
  - Protocol must be self explanatory
- Obtain necessary permissions/funding on time

Submitting a Proposal

- The optimal order/flow (discuss with colleagues)
- Deadlines
- Online submission or by Mail
  - Computer problems
  - Backups
  - Post stamp date on envelope
- Are attachments accepted?
- Notice of acceptance

Problems

- Unrealistic amount of work
- Lack of focus on previous literature
- Lack of original ideas
- Poor justification
  - ✓ why is it important to answer this question?
  - ✓ what impact does it have on public health?
- **Poorly formulated objectives! Unspecific.**
- Inappropriate analysis
- Inadequate description

http://www.ninds.nih.gov/funding/write_grant_doc.htm#problems

Study Protocol: Exercise

- Groups
- Draw Card
- Prepare Presentation (max. 10 minutes)
  - Study Protocol Exercise Sheet
  - Be precise and brainstorm ideas
  - No need for extensive research and literature review (for time purposes)
  - Be able to defend your study proposal
  - Be able to defend your methods and why they were chosen
- One group presents, one group reviews

Resources and References

- www.epinorth.org/dav/8FC335F7AD
- Guyatt, G. Preparing a research protocol to improve its chances for success. In: Haynes RB, Sackett DL, Guyatt GH, Tugwell P, (eds.) Clinical Epidemiology. Philadelphia: Lipincott³ p. 429 – 439
- http://dgepi.de/fileadmin/pdf/GEP_LL_english_f.pdf
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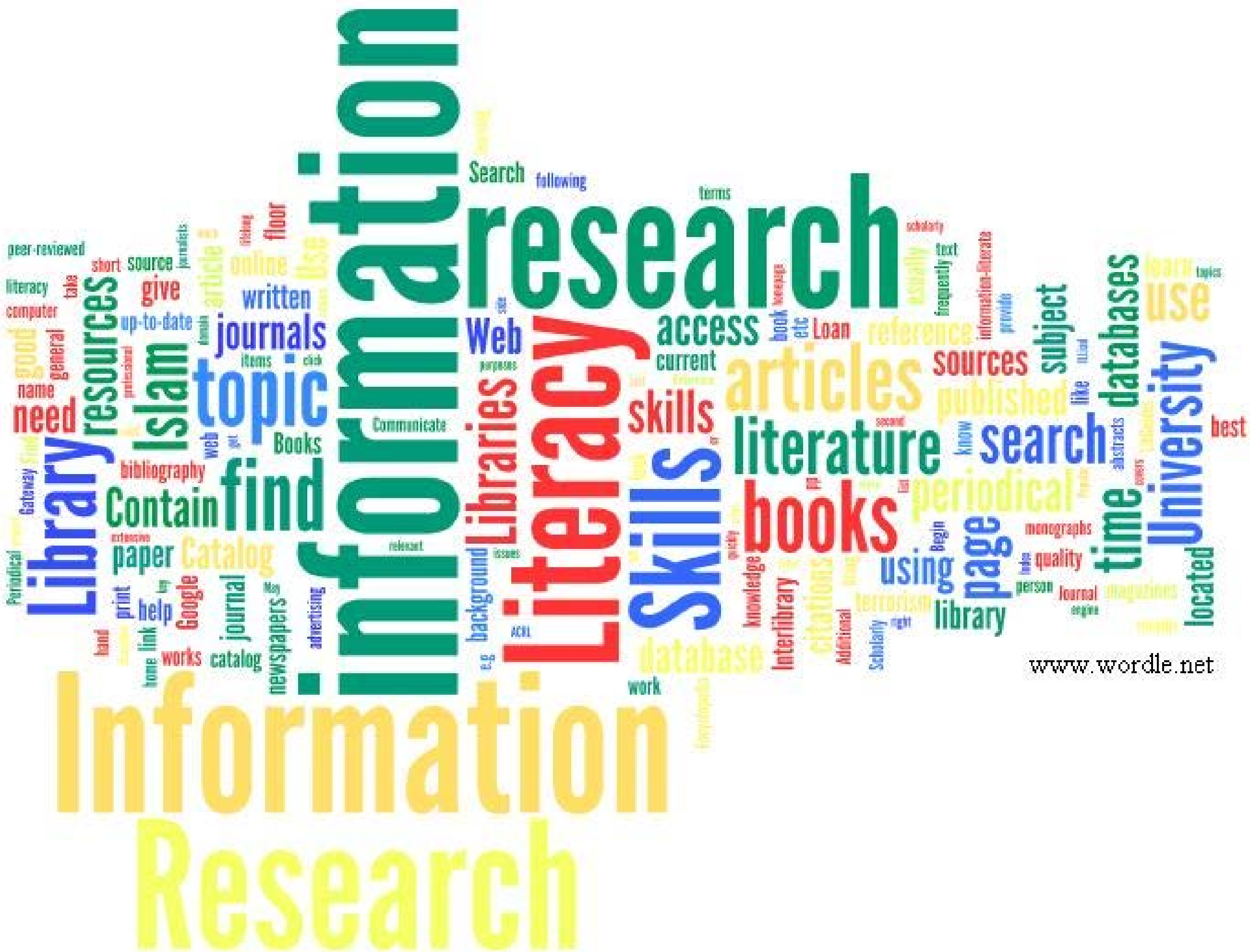
- Yardley L, Kirby S, Barker F, Little P, Raftery J, King D, et al. An evaluation of the cost-effectiveness of booklet-based self-management of dizziness in primary care, with and without expert telephone support. BMC Ear Nose Throat Disord. 2009;9:13. PubMed PMID: 20098640. Pubmed Central PMCID: PMC2810289. Epub 2010/01/26. eng.


information
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