# Research plan
# General research internship
# Master Biomedical Sciences

(to Board of Examiners)

**Name student: Gwen Van de Wall**
**Start date internship: 11-01-2021**

| **OSIRIS code:** | MED-BMS30GEN | MED-BMS36GEN | MED-BMS42GEN | MED-BMS48GEN |
|---|---|---|---|---|
| **Tick if applicable:** | **X** | | | |

**Background / context of the enquiry:**

Return on investment in the pharmaceutical industry continues to decline and is now at an all-time low (1). This impairs the development of new treatments due to lowered interest of companies to invest in this research. Many treatments that show promising results in preclinical development do not pass clinical tests. More than 50% of preclinical research is not reproducible (2). A significant part of this irreproducibility may be explained by poor animal-to-human translation. Animal-to-human translational success is defined as the replication of statistically positive, negative or neutral effects from preclinical animal models in clinical trials. Using animal models to predict safety or efficacy in humans if the overall translation success is low humans is not ethical, nor does it promote responsible research and innovation. Out of all compounds showing promising results in animal models, only 5-20% (3) become registered treatments after clinical trials. This is not in line with the 3R principles (Reduction, Replacement and Refinement) (4).

Currently, the value of animal models is evaluated mechanistically; researchers assess the construct, face and predictive validity of an animal model. This type of evaluation is generally non-systematic, and the results are synthesized in a binary manner, either successful or unsuccessful. This evaluation aids in understanding the model's strengths and limitations but has limited value in terms of assessing predictability. Animal-to-human predictability, i.e. translational success, can also be evaluated probabilistically (5,6). Probabilistic studies result in more objective success rates, which are suitable for comparisons between research fields and between animal models.

Several studies have emphasized the importance of experimental design for translational success (1,3,7). If translational success rates show substantial variation between medical research fields, future analyses of the experimental designs used in these fields may identify factors involved in successful translation. Therefore, it is important to first assess possible differences in translational success between medical research fields. Preliminary data from my literature review suggested that translational success rates could be higher in cancer research compared to neuroscience and pharmacology. This data also showed first evidence that translation in neuroscience is probably not lower compared to other fields, even though this was long thought be the case (8).

**Research question:**

The overarching research question is: "How can the reliability of laboratory animal studies be improved?", with a focus on animal-to-human translation. In this internship, the following underlying research question will be investigated: "How do translational success rates differ between medical research fields?"

Based on preliminary research, I hypothesize that I will be able to detect differences in translational success between several research fields.

**Experimental design (research techniques / material / analysis):**

From anecdotal evidence it seems that the translational success rate is high for rheumatoid arthritis (9) and low in the neurosciences (8). Other researchers have reported overall success rates of clinical trials from 5 to 20% in different research fields (3). In this internship, I will analyze the success rates of clinical trials from public registries.

To investigate the differences between research fields I will determine the fraction of phase-2 clinical trials with a positive outcome for different research fields as a proxy for translational success. If the results of the pre-clinical trials are not sufficiently discussed by the clinical trials, these papers will be accessed as well. The choice to primarily focus on phase-2 clinical trials is based on the relative comparability with animal models. Phase-1 trials are mostly performed in healthy volunteers and only relevant for adverse events, while this study will address both efficacy and safety. Phase-3 and Phase-4 trials would not allow for a fair comparison as they are performed at a later stage and

use a different experimental design than the average laboratory animal study.

To retrieve the phase-2 clinical trials, the WHO trial register will be used. This trial register includes data from most large clinical trial registries and has the option to export the search results to .xml or .csv. I will export all registered phase-2 trials for further analysis.

Trials with the status "recruiting" will be excluded from the analysis. These are still recruiting participants and are thus ongoing, which means the results are not yet available. I will categorize all other trials into medical research fields according to the international classification of disease (ICD-10) (10). Low-level categories will be pooled to higher level categories where necessary, to create clusters containing at least 100 trials. For example, Alzheimer's disease with late onset (G30.1) could be pooled to Alzheimer's disease (G30), which can be further pooled to other degenerative disease of the nervous system (G30-G32), or even to disease of the nervous system (G00-G99).

To prevent bias, I will only retrieve trial results after this categorization. Exporting all registered phase-2 trials from the WHO database has previously been successfully piloted. On 06-08-2019, the WHO listed 2273 phase 2 trials, with over 2000 not recruiting. At the start of this internship, the number of registered trials will have increased. In another pilot study, retrieval of the results was successful for the majority of registered trials. I will calculate percentages of successful trials per field based on the trials for which results are available. While part of the non-recruiting trials will not have the results available, there is nevertheless a decent number of registered studies to work with.

After the fraction of phase-2 trials with a positive outcome has been calculated for the clusters with sufficient data, data will be visualized and statistically analysed using R. The results will be combined with my literature review into a manuscript for publication in a scientific journal.

**References**


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**Learning objectives**

**General learning objectives**

The student

1 is able to describe the motive for the study, its relevance and its scientific medical context

2 can search, critically appraise and systematically review relevant literature

3 a can specify a research question or hypothesis which relates to findings discussed in relevant scientific literature

b is able to describe a study design which addresses the research question

4 is able to plan, organise and carry out an empirical study
5 is able to systematically analyse data
6 is able to clearly describe the results and summarise these in tables and figures
7 is able to address measurement errors and other limitations of collected data
8 is able to critically reflect upon results, design and interpretation
9 can write a concept scientific article (in English) which complies with the academic standards:
a contents: coherent, all inclusive and balanced
b presentation: style, appearance, lay out, word choice, references
10 is able to give a concise oral presentation (in English) about the study for colleagues and discuss this afterwards.

**Specific learning objectives**

*In addition to the general objectives of each general research internship, the student will learn specifically:*

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|---|---|
| 1. | How to consult clinical trial registers. |
| 2. | How to implement the international classification of disease (ICD-10). |
| 3. | How to accurately describe thought processes on paper. |
| 4. | How to present data, and how to transfer knowledge to others on a higher level. |

**Work-plan / timetable (in weeks):**

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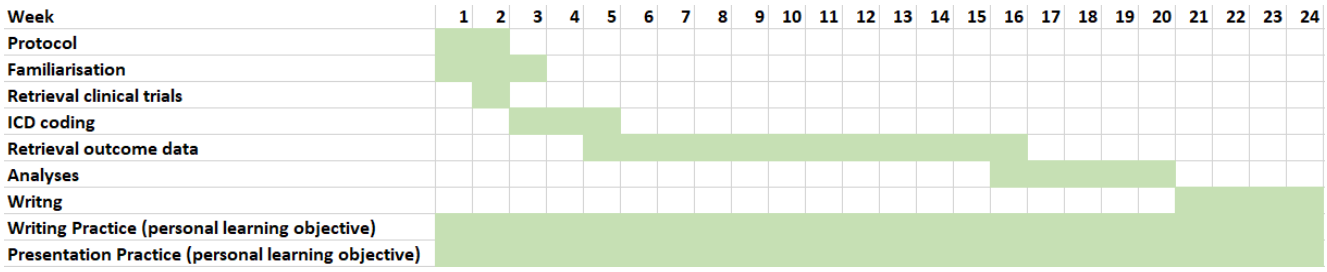
|---|---|
| week 1: | Writing the research protocol and getting familiar with used techniques and databases |
| Week 2: | Writing the research protocol and getting familiar with used techniques and databases and retrieving clinical trials from the WHO database |
| Week 3-5: | Getting familiar with used techniques and databases Classifying clinical trials with ICD-10 codes. |
| week 5-8: | Collecting outcome data from retrieved clinical trials |
| week 9-12 | Collecting outcome data from retrieved clinical trials |
| Week 13-16 | Collecting outcome data from retrieved clinical trials and performing statistical analyses on this data |
| Week 17-20 | Performing statistical analyses on collected data. |
| Week 21-24 | Writing of the manuscript for publication and the internship report. |

Gantt Chart for further clarification of the timetable




**Note: do not exceed 3 pages for description**