Master Statistics and Data Science

Proposal for the Thesis Project

MSc Statistics and Data Science

Leiden University

**Period of the project**

*Carrying out the project will account for 30 ECTS, which is equivalent to 21 weeks of 40 hours.*

* Intended period of the project: Feb 4th - July 15th
* Intended date for the Midterm Progress Meeting: May 1st

**Student**

Name: Yixiao Tang

Student number: s3855422

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**Daily Supervisor**

Name: Jan H.N. Lindeman

e-mail: [j.h.n.lindeman@lumc.nl](mailto:j.h.n.lindeman@lumc.nl)

Institute: Leiden University Medical Center (Depts. Vascular and Transplantation Surgery)

Function:

**Internal supervisor**

*A second supervisor from the master of Statistics and Data Science is needed when the daily supervisor is no staff member of the departments/Institutes of the master.*

Name: Hein Putter

e-mail: h.putter@math.leidenuniv.nl

Institute: Mathematics Institution

Function:

**EMOS (European Master in Official Statistics)**

project (no)

**Intended independent reader (to be filled in by Statistics and Data Science supervisor)**

*Each thesis is judged independently by a second member of the Statistics and Data Science organizations. The independent reader is not involved in the research of the project and has no direct hierarchical relation with the supervisor(s).*

Name:

e-mail:

Institute:

Function:

# 1 Summary

## 1.1 Title and abstract (max 150 words)

**Reevaluating Composite Endpoints in Cardiovascular Trials: Integrating QUALY and Restricted Mean Survival Time**

Cardiovascular diseases (CVD) remain a leading global cause of morbidity and mortality, highlighting the need for improved treatments. Lipid-lowering therapies are central to managing cardiovascular risk, with evolocumab demonstrating significant LDL cholesterol reduction and a decrease in major cardiovascular events in the FOURIER trial. However, traditional time-to-event analyses of composite endpoints face challenges such as competing risks, non-proportional hazards, and equal weighting of events with differing clinical impacts.

This study proposes a novel approach by integrating Quality-Adjusted Life Years (QALYs), commonly used in health economic evaluations, to assign weighted values to outcomes based on their impact on quality of life. Additionally, Restricted Mean Survival Time (RMST) will be employed as a more relevant and quantitative measure for evaluating composite endpoints. Using data from the FOURIER trial, this methodology aims to provide a more precise and clinically meaningful analysis of cardiovascular outcomes.

## 1.2 ECTS Justification for the preparation of the Thesis Proposal (max 500 words)

*The investment for the study and writing of this thesis proposal should be 4 ECTS. Please clarify how many hours were spent on the activities needed for the writing of this thesis proposal.*

*Write down here your justification of your hours for this thesis proposal, know that you can also include hours spent on further improvement of academic skills (For example presentation workshop / writing workshop or module etc.).*

# 2 DESCRIPTION OF THE PROPOSED RESEARCH PART OF THE THESIS PROJECT

*Write a concise proposal of a maximum of 1200 words. This should contain:*

## 2.1 The Research Problem

The FOURIER trial demonstrated evolocumab's effectiveness, but traditional methods of analyzing its outcomes—primarily time-to-event analysis of composite endpoints—have several limitations. These include:

1. **Competing risks**: Traditional analyses often fail to account for competing events that may preclude the occurrence of the primary event.
2. **Non-proportional hazards assumption**: Many cardiovascular trials face issues with hazard ratios that vary over time, reducing the reliability of proportional hazard models.
3. **Equal weighting of events**: Composite endpoints treat all events (e.g., nonfatal myocardial infarction, stroke, cardiovascular death) equally, despite their differing impacts on patients' quality of life.

## 2.2 Research aims

This study aims to address the limitations of traditional composite endpoint analyses in cardiovascular trials by:

1. **Developing a QALY-based weighting way** for evaluating composite endpoints, incorporating the impact of each event on patients' quality of life.
2. **Applying the principles of Restricted Mean Survival Time (RMST)** as a quantitative and clinically relevant outcome measure for composite endpoints in cardiovascular trials.
3. **Testing this novel methodology** using data from the FOURIER trial to assess its feasibility and effectiveness in providing a more comprehensive evaluation of evolocumab's impact on cardiovascular outcomes.

## 2.3 Research plan

The research will use extracted data from the report of the FOURIER trial and conduct the following parts:

Establish a reconstructed dataset of the Fourier trial with longitidual follow up (multiple primary events possible)

**Weighting Events Using QALYs**:  
Assign QALY weights to each type of clinical event (e.g., nonfatal myocardial infarction, stroke, cardiovascular death) based on their relative impact on quality of life. The weights will be determined by consulting existing literature and expert opinion.

NB you can also apply QUALYs for a cost-effective analysis: clinical benefit: QUALY’s only, Cost effectiveness: QUALY’s + Costs converted into QUALY’s

**Outcome Analysis with Restrict Mean Survival Time (RMST)**:  
Use the principles of RMST to qualitatively estimate survival benefits of evolocumab group to placebo group. Compare RMST-based findings with traditional hazard ratio analyses to highlight differences and advantages.

## 2.4 Expected Results/end product:

## QALY-weighted Restrict Mean Survival Time Estimation of the FOURIER trial.

## 2.5 Reference list

1. Sabatine, M. S., Giugliano, R. P., Keech, A. C., Honarpour, N., Wiviott, S. D., Murphy, S. A., Kuder, J. F., Wang, H., Liu, T., Wasserman, S. M., Sever, P. S., & Pedersen, T. R. (2017). Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *The New England Journal of Medicine*, *376*(18), 1713–1722. <https://doi.org/10.1056/NEJMoa1615664>
2. Erviti, J., Wright, J., Bassett, K., Ben-Eltriki, M., Jauca, C., Saiz, L. C., Leache, L., Gutiérrez-Valencia, M., & Perry, T. L. (2022). Restoring mortality data in the FOURIER cardiovascular outcomes trial of evolocumab in patients with cardiovascular disease: a reanalysis based on regulatory data. BMJ Open, 12(12), e060172–e060172. <https://doi.org/10.1136/bmjopen-2021-060172>
3. D’Agostino, J. (2000). Debate: The slippery slope of surrogate outcomes. *Current Controlled Trials in Cardiovascular Medicine*, *1*(2), 76–78. <https://doi.org/10.1186/CVM-1-2-076>
4. Wouters OJ, Naci H, Samani NJ.QALYs in cost-effectiveness analysis: an overview for cardiologists.Heart 2015;101:1868-1873.<https://doi.org/10.1136/heartjnl-2015-308255>
5. McCaw, Z. R., Yin, G., & Wei, L.-J. (2019). Using the Restricted Mean Survival Time Difference as an Alternative to the Hazard Ratio for Analyzing Clinical Cardiovascular Studies. *Circulation (New York, N.Y.)*, *140*(17), 1366–1368. <https://doi.org/10.1161/CIRCULATIONAHA.119.040680>
6. DOLAN, P., METCALFE, R., MUNRO, V., & CHRISTENSEN, M. C. (2008). Valuing lives and life years: anomalies, implications, and an alternative. *Health Economics, Policy and Law*, *3*(3), 277–300. <https://doi.org/10.1017/S1744133108004507>
7. Kim, D. H., Uno, H., & Wei, L. J. (2017). Restricted Mean Survival Time as a Measure to Interpret Clinical Trial Results. JAMA cardiology, 2(11), 1179–1180. <https://doi.org/10.1001/jamacardio.2017.2922>

# 3 ACTIVITIES TO GET EXPERIENCE AS A WORKING STATISTICIAN/DATA SCIENTIST IN A POSSIBLE FUTURE WORKING ENVIRONMENT

*Formulate, together with your supervisor(s), three concrete working activities in which you will participate during your thesis project. One of these activities should involve developing communication skills. A list of possible activities can be found on Brightspace and in the information for supervisors, but it is allowed to formulate other activities. Give for each of the activity a short description and a short motivation for choosing the activity.*

Addresses the limitations of established methodology

Clinical Question

Collaboration with a clincial department and working with clinical data

## 3.1 Activity 1

* Short description of the activity (max 150 words)
* Motivation for choosing the activity (max 150 words)
* What do you expect to gain from the activity? What skills to you want to improve?

## 3.2 Activity 2

* Short description of the activity (max 150 words)
* Motivation for choosing the activity (max 150 words)
* What do you expect to gain from the activity? What skills to you want to improve?

## 3.3 Activity 3 (developing communication skills)

* Short description of the activity (max 150 words)
* Motivation for choosing the activity (max 150 words)
* What do you expect to gain from the activity? What skills to you want to improve?
* Presentation for clinicians

# 4 WORK PLAN AND SUPERVISION

## 4.1 Supervision

*Describe the arrangements regarding the type and frequency of meetings between student and daily supervisor(s) and on roles and responsibilities. If there is a second supervisor from Statistics & Data Science, also describe type and frequency of communications between the second supervisor, the daily supervisor and the student.*

**Daily Supervisor (Jan)**: Provide guidance on cardiovascular research aspects, review drafts, and ensure the research adheres to clinical relevance.

**Internal Supervisor (Hein)**: Offer expertise on statistical methods, and ensure methodological rigor.

**Student(Yixiao)**: Conduct literature reviews, data analyses, and manuscript preparation, seeking insights from supervisors.

We plan to have weekly meetings every Tuesday from 11 am to 12 am to update progress, problems encountered, and action plans for next week.

## 4.2 Time Schedule

*Carrying out the thesis project should take 30 EC (exclusive 4 EC to write this proposal). Present a feasible time schedule of your activities. Note that 30 EC corresponds to 21 weeks full time work. Make a detailed plan (week by week) so that at each supervisor-student meeting, it can be discussed if things are still going as planned, and if not, how to tackle that. Be aware that writing takes time. Indicate what elements can be cut / reduced if necessary.*

**February**

Week 1-4: Conduct literature reviews. Begin exploratory analyses of the extracted FOURIER dataset.

**March**

Week 5-8: Implement QALY-based weighting for composite endpoints

**April**

Week 9-12: Conduct RMST analyses and compare results with traditional methods.

**May**

Week 13-16: Interpret results and draft initial sections of the manuscript. Share drafts with supervisors for feedback. (Midterm Progress Meeting in between)

**June**

Week 17-20: Refine the manuscript based on feedback. Prepare visualizations and presentations for dissemination.

**July**

Week 21: Finalize manuscript and submit for review.

## 4.3 Infrastructure

*Describe the arrangements offered to the student to facilitate the students’ work progress (For example, guest employment, a desk, shared office, computer, access to a computing server)*

## 4.4 Other Courses / Activities:

*- What courses (how many ECTS) still need to be obtained during the thesis project before graduation. Please adapt your time schedule to incorporate this.*

*- Are there other reasons that may make it impossible to spend ±21 consecutive weeks on the thesis project*

# 5 AGREEMENT PAGE

The supervisors and student hereby declare that they agree to the arrangements in this proposal.

* The supervisors and student hereby declare that they have applied, and will apply good scientific practices, that follow the University Academic Integrity Regulations and the Ethical Guidelines from Statistical Practice . When in conflict with each other, the University Academic Integrity Regulations should be followed.
* The supervisors hereby declare that they are aware that all supervisors, the independent reader, and the board of examiners and panel member of independent audits should be able to assess the complete thesis. Furthermore all supervisors and independent reader should be able to view the corresponding programming code.
* The student hereby declares that he has provided the supervisor with the Documentation for Supervisors
* The student hereby declares that both this proposal, and its resulting thesis, will be free of plagiarism (cf. Rules and Regulations of the Board of Examiners).

**Name Signature Date**

**Student Yixiao Tang**

**Supervisor 1 Jan Lindeman**

**Supervisor 2 Hein Putter**

This signed proposal should be submitted to the Thesis Committee by uploading it in Brightspace. In case of problems please contact thesis@stat.leidenuniv.nl.