Clinical Trial Design for the Investigation of Palofenac to Reduce Cholesterol

MATH335 Medical Statistics Individual Project

ABSTRACT – This report outlines the proposal for a Phase III Trial to evaluate the efficacy of Palofenac, administered through an oral tablet, in reducing LDL cholesterol in patients with elevated LDL cholesterol despite receiving statin therapy.

I. Introduction

Cardiovascular diseases (CVD) have emerged as the main cause of mortalities across the globe since the beginning of the millennium. In 2021, CVD accounted for 13% of all fatalities, as well as impacting hundreds of millions of people (The World Health Organisation 2024). Low-Density Lipoprotein (LDL) cholesterol has been found to have a significant effect on the risk of CVD in patients (Stanciulescu et al. 2023). As such, statin therapy, first discovered in 1970 by Endo (1992), has been used as a first line of response to reduce LDL levels in high risk CVD patients. Studies have found that whilst statins might be insufficient for some patients, combination therapy with other treatments can be more effective (Brautbar & Ballantyne 2011), with notable treatments such as alirocumab and inclisiran. This study seeks to investigate the effectiveness of a new, orally-administered drug, Palofenac, in reducing cholesterol in patients who have elevated LDL cholesterol, despite also receiving statin treatment.

II. Methodology

A. Administrative Responsibilities

Given Palofenac's high promise of efficacy in Phase I and II trials, this study aims to conduct a Phase III trial. There are several parties involved to ensure the proper execution of the trial. There will be persons involved in collection and uploading of participant's data onto the secure database. There will be persons tasked with the statistical analysis of results, as well as therapists to regularly assess patient's mental wellbeing. Finally, an independent ethics committee will be assigned to evaluate the trial design and ensure clinical equipoise.

B. Patient Selection

Patients are recruited according to a strict set of criteria and from medical practices across the North-West of England. Any person who meets all criteria points can apply to participate in the trial. To apply, persons should fill out an online questionnaire to submit patient consent and determine patient suitability. This questionnaire will ask for confidential patient information, such as age, sex, ethnicity, weight, height, UK Postcode, email address, as well as test each of the criteria and finally obtain patient consent. All applicants that receive trial approval should meet the following criteria exactly;

- Has a QRISK2[1] $\geq 20\%$, high CVD risk determined by a medical professional, or equivalent
- Has been taking statins for a period of time ≥ 1 year
- Has a baseline LDL cholesterol level ≥ 70 mg/dl
- Not pregnant or breastfeeding
- No other serious or life threatening health conditions
- Aged 18 years or above

All applicants meeting all of the above criteria will be considered for the trial if their application was made during the 3-month recruitment period. A medical professional will go through all applicants and sort into a group of valid applicants and non-valid applicants. All valid applications will be

[1]QRISK2 calculates the risk of a person developing a heart attack or stroke over the next 10 years. A patient with QRISK2 $\geq 20\%$ is considered to be in a high CVD risk category. It is based on a clinically-approved algorithm that outputs probabilities grouped into three risk categories. It was produced by Hippisley-Cox et al. (2017) and is widely used by the NHS in the UK NHS (2024)

considered and if the number of valid applications exceeds the sample size then random selection will be used to allocate applicants into successful and unsuccessful groups. All successful applicants will receive an email confirming their enrolment on the trial. If enrolment numbers are lower than the required sample size then an extension on the recruitment period will be considered, as well as a review on the geographical limits.

C. Trial Design

The study will conduct a randomised, triple-blind, parallel-group[2], Phase III trial (Ray et al. 2020, Kastelein et al. 2017). Stratified randomisation will be used to allocate patients to receive Palofenac or a placebo, where patients will be assigned depending on their age, concomitant therapy and baseline LDL cholesterol level. Past research indicates that these factors all may influence LDL cholesterol levels, so using stratified randomisation will reduce potential confounding. The age stratum will be < 65 and ≥ 65 in years. The concomitant therapy stratum will be participants who have received statin and participants who have received high-intensity statin. The baseline LDL cholesterol stratum will be $<$ 130 mg/dL and $\geq$ 130 mg/dL. This gives eight strata, with randomisation taking place within each stratum. Participants, physicians, monitoring groups and data analysts will all be blind to the treatment allocation. Labelling treatment arms as participants receiving Palofenac as Group 1 and those receiving a placebo as Group 2 will also facilitate the triple-blind environment for reducing the risk of bias. A parallel group trial was selected to account for the long trial period, of 6 months or longer, to reduce risk for participants with high CVD risk, and to reduce potential carry-over effect of Palofenac. Using between-subject comparison, an estimate of the treatment effect can be determined as well as reducing the risk of unblinding.

D. Treatment Schedule

Participants in both treatment arms, Group 1 and Group 2, will follow the same treatment schedule. As illustrated in Table I, the total trial period will be 6 months, with LDL cholesterol (in mg/dl) tested at 3 month intervals. After recruitment has ended and participant groups finalised, a test for LDL cholesterol (in mg/dl) will be conducted at the Baseline by a physician, as well as at Test 1 and Test 2. Participants will then self-administer an oral tablet once-daily from the Baseline until Test 2. Physicians will give each participant 3-months worth of daily tablets at each testing appointment; Baseline, Test 1, and Test 2, checking that the participant has administered every day during Period 1 and Period 2. It is crucial to the efficacy of results that each patient correctly administers their allocated tablet and attends their testing appointment, any deviations should be recorded and reported. The oral tablet will contain Palofenac for Group 1, whereas Group 2 will administer a sugar tablet as a placebo. The placebo tablet will mimic the colour, size, and packaging of the Palofenac tablet to ensure blindness. Participants will be monitored for adverse effects throughout the trial with monthly check-up calls with a physician and additional health testing at Baseline, Test 1, and Test 2 appointments, as well as reporting any serious adverse events to the clinical trial convenors. The conclusion of Test 2 marks the end of the trial.

E. Sample Size Calculation

The sample size should be sufficiently large to provide a reliable answer to the primary objective of the trial. Carefully following European Medicines Agency (1998), the proposal of the hypotheses comes foremost;

- H_0: There is no difference in LDL cholesterol reduction between Group 1 and Group 2
- H_1: There is a difference in LDL cholesterol reduction between Group 1 and Group 2

With this basis set, the type-I error rate is set to 5%, $\alpha = 0.05$, and the type-II error rate is set to 10%, $\beta = 0.1$. For the purposes of calculating an approximate two sample t-test, data from the placebo arm of a previous study on a similar patient population is utilised alongside the following method to calculate sample size (Titman 2025);

$$n = \frac{1}{r(1-r)} \frac{(\Phi^{-1}(1-\alpha/2) + \Phi^{-1}(1-\beta))^2}{\Delta^{*2}} \sigma^2 \tag{1}$$

Assuming equal distribution between Group 1 and Group 2, $r = 0.5$. The clinically relevant difference,

[2]Whilst a cross-over trial was considered, this would place more burden on participants, come at a higher monetary cost, and take over a year to ensure no carry-over effects. Thus, a parallel group trial was selected as the optimum design.

$\Delta^* = 10$ is a standard aim for reduction in LDL cholesterol levels from Baseline to Test 2. This study employed methods from Chen et al. (2013) to determine $\sigma = 48$ from the previous study sample, calculated from the standard error of differences between Baseline and Month 6 LDL cholesterol levels. A summary of the previous study's data is included in Table II. The approximate sample size n is therefore;

$$\begin{aligned} n &= \frac{1}{0.25}\frac{(\Phi^{-1}(0.975) + \Phi^{-1}(0.9))^2}{10^2}(48)^2 \\ &= 968.3641 \\ &\approx 970 \end{aligned} \tag{2}$$

Aiming to allocate 485[3] participants to each treatment group; $n_1, n_2 = 485$.

III. Results

A. Patient Testing and Monitoring

Before the trial commences, a group of physicians will be recruited, trained, and given strict guidelines to follow for appointments, check-up calls, and data entry. Patients will have three formal physician appointments at Baseline, Test 1 and Test 2. During each appointment, the patient will be measured for their LDL cholesterol levels via a blood test, complete a questionnaire on side effects, their vitals checked by the physician, their weight measured, and checking all tablets have been administered, recalling that both the physician and the patient are blind to the treatment. Results will be recorded on an online-form to be approved and submitted by the physician. Five monthly check-up calls between the patient and physician will require an interview-style format to ensure any adverse side effects are detected and reported, as well as ensuring tablets have been administered as required. The physician will subsequently submit an online-form to either confirm everything is normal or report otherwise. Data from this is uploaded in the same way as appointments above.

[3]To validate this value further, using `power.t.test(delta =10, sd=48, sig.level=0.05, power=0.9)` in `R` computes $n = 485.1444$ for each treatment group. Given that the approximate sample size is generally an underestimate of the former, this is considered to be valid (Titman 2025).

B. Data Handling

The online-forms discussed in Section III-A will load the data onto a cloud database, a secure SQL Azure database or similar, which is only accessible to statisticians after the conclusion of the treatment period. All additional data, such as patient's application details and their assigned treatment group, will be stored in the same secure database. Physicians can only upload data and not access it. The only individuals allowed to access this data will be the statisticians, after the conclusion of the treatment period to ensure triple-blindness. After all analysis has been conducted, the data will be anonymised and published via a reputable medical journal. All data handling and security will strictly follow the UK compliance regulatory guidelines.

C. Handling of Protocol Deviation

Any protocol deviations should be reported and recorded appropriately, ensuring that statisticians are aware of every circumstance. In anticipation of protocol deviations, potential events have been drawn up below;

1) *Violations of Patient Eligibility:* There is a risk that applicants are enrolled despite not meeting all eligibility criteria, either due to sharing misinformation or a classification mistake. This could also extend to the stratified randomisation. Solutions to this include an audit on applications before the trial commences, two physicians checking approved applications, or elimination of patients from the trial.
2) *Non-Compliance with Treatment Schedule:* There is a risk that participants do not correctly self-administer their allocated treatment, including missing or incorrect treatment days and not reporting. Signing an agreement to ensure they are bound to administering daily and monthly check-in calls will help to prevent this.
3) *Violations of Patient Confidentiality:* The risk of confidential patient information being leaked can be prevented by limiting access to the database to only statisticians after the end of the trial. This database is fully secure and is cloud-only, never stored on hard-drives or on paper.

4) *Failure to Attend:* Missing any of the test appointments, without prior confirmation, is detrimental to the trial. Solutions include the check-up calls as a reminder, sending a text-message on the day before and day-of the appointment, and providing incentives to attend.
5) *Patient Withdrawal:* The risk of a participant dropping out from the trial can be limited by providing check-up calls as well as flexible appointment times and locations.
6) *Loss of Samples:* As is general practice with blood samples, they will be sent to a laboratory to undertake testing. If the samples get lost or contaminated then this renders the test invalid. Ensuring strict labelling and handling protocols are upheld, as well as taking two blood samples at each patient's blood test, will limit these events.

D. Ethical Considerations

With triple blinded trials, informed patient consent of treatment should be obtained so that all patients have consented to Palofenac. They should be aware of a control group but not necessarily the method of control. Since all patients will also be taking statins, a placebo control group will not adversely affect those patients. An independent review on the trial should be conducted prior to commencement by a Research Ethics Committee. Blindness can be broken in the case of serious adverse events, but this knowledge should be limited only to the patient and physician involved and reported to the clinical trial convenors.

E. Analysis

Statistical analysis on results will be conducted through two independent samples t-tests and Confidence Intervals (CI) using the Intention-To-Treat (ITT) population, extending to the Per Protocol (PP) population if there are more than $n/100$ non adherers. Defining the endpoint to be LDL cholesterol levels (in mg/dl) at the Baseline minus LDL cholesterol levels (in mg/dl) at Test 2 allows objective measurements for the impact of Palofenac. Positive differences imply the treatment reduced LDL levels, negative differences imply the treatment increased LDL levels. Results will be analysed at a 5% Significance Level (α) and using a 95% CI. The difference between the treatment groups, D, is the true Treatment Effect (TE) and will be tested for significance.

1) Two-Sample T-Test: Let μ_1 denote mg/dl mean difference for Group 1 and μ_2 denote mg/dl mean difference for Group 2. The hypothesis is

$$H_0 : D = \mu_1 - \mu_2 = 0 \; vs \; H_1 : D = \Delta \neq 0$$

and the estimate TE is $\hat{D} = \hat{X}_1 - \hat{X}_2$. The Test Statistic is calculated under H_0 as

$$T = \frac{\hat{D}}{SE(\hat{D})} \sim t_{n-2}$$

where $SE(\hat{D}) = S\sqrt{(1/n_1) + (1/n_2)}$ is the estimated TE's standard error with

$$S^2 = 1/(n-2) \sum_{i \in 1,2} \sum_{j=1}^{n_i} (X_{ij} - \bar{X}_i)^2$$

and n is as stated in Section 2. It is assumed standard variance, independent data and normal distributions hold. From the above, a p-value will be yielded and a conclusion on significance made at the 5% level by a statistician.

2) Confidence Interval: For direct assessment of effect sizes a calculation of the 95% CI will be conducted. Using the corresponding values in Section III-E1, the 95% CI is calculated using

$$\hat{D} \; \pm \; t_{n-2,1-\alpha/2} S \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}.$$

The statistician will use inference at $\alpha = 0.05$ to determine its significance and conclude on the hypothesis set.

IV. Conclusion

The primary aim of this study is to evaluate the efficacy of Palofenac as a treatment alongside statins in high risk CVD patients. If this study is proves successful then it could facilitate regulatory approval of Palofenac and distribution among high risk CVD patients. This study was provided with a limited sample of a placebo arm of a previous study on a similar patient population. Due to this, the estimate of the standard deviation, σ in Equation 2, is predicted to be an over-estimate of the true population value. To improve the sample size approximation, it would be preferred either to have a sample dataset with at least 1000 participants (Chen et al. 2013), or to conduct a population study at the recruitment stage.

APPENDIX

TABLE I
TRIAL TIMELINE

Time, t (in months)	Treatment Period
$t = 0$	Baseline
$0 < t < 3$	Period 1
$t = 3$	Test 1
$3 < t < 6$	Period 2
$t = 6$	Test 2

TABLE II
SUMMARY OF PLACEBO ARM IN PREVIOUS STUDY

Baseline	Month 3	Month 6
Min. : 70.0	Min. : 42.00	Min. : 38.00
1st Qu.: 81.0	1st Qu.: 82.25	1st Qu.: 74.75
Median : 97.0	Median :103.00	Median :104.00
Mean :109.2	Mean :117.21	Mean :117.59
3rd Qu.:125.0	3rd Qu.:143.75	3rd Qu.:147.00
Max. :268.0	Max. :256.00	Max. :270.00

Output from `summary()` in `R`

REFERENCES

Brautbar, A. & Ballantyne, C. M. (2011), 'Pharmacological strategies for lowering ldl cholesterol: statins and beyond', *Nature Reviews Cardiology* **8**(5), 253–265.

Chen, H., Zhang, N., Lu, X. & Chen, S. (2013), 'Caution regarding the choice of standard deviations to guide sample size calculations in clinical trials', *Clinical Trials* **10**(4), 522–529.

Endo, A. (1992), 'The discovery and development of hmg-coa reductase inhibitors.', *Journal of lipid research* **33**(11), 1569–1582.

European Medicines Agency (1998), 'Harmonisation; guidance on statistical principles for clinical trials'.

Hippisley-Cox, J., Coupland, C. & Brindle, P. (2017), 'Development and validation of qrisk3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study', *bmj* **357**.

Kastelein, J. J., Kereiakes, D. J., Cannon, C. P., Bays, H. E., Minini, P., Lee, L. V., Maroni, J. & Farnier, M. (2017), 'Effect of alirocumab dose increase on ldl lowering and lipid goal attainment in patients with dyslipidemia', *Coronary Artery Disease* **28**(3), 190–197.

NHS (2024), 'Cardiovascular risk score (qrisk2) and the use of statins'.
URL: *https://www.albanyhousemedicalcentre.co.uk/health information/cardiovascular-risk-score-qrisk2-and-the-use-of-statins/*

Ray, K. K., Wright, R. S., Kallend, D., Koenig, W., Leiter, L. A., Raal, F. J., Bisch, J. A., Richardson, T., Jaros, M., Wijngaard, P. L. et al. (2020), 'Two phase 3 trials of inclisiran in patients with elevated ldl cholesterol', *New England journal of medicine* **382**(16), 1507–1519.

Stanciulescu, L. A., Scafa-Udriste, A. & Dorobantu, M. (2023), 'Exploring the association between low-density lipoprotein subfractions and major adverse cardiovascular outcomes—a comprehensive review', *International Journal of Molecular Sciences* **24**(7), 6669.

The World Health Organisation (2024), 'The top 10 causes of death'.
URL: *https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death*

Titman, A. (2025), 'Math335: Medical statistics: study design and data analysis'.