Treatment Patterns and Economic Burden of Post Cataract Macular Edema

Gina Ahmadyar

A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Science

University of Washington

2022

Committee:

Ryan N. Hansen, Chair

Josh J. Carlson, Member

Program Authorized to Offer Degree:

Department of Pharmacy

University of Washington

Abstract

Treatment Patterns and Economic Burden of Post Cataract Macular Edema

Gina Ahmadyar

Chair of the Supervisory Committee:

Ryan N. Hansen

Department of Pharmacy

Background: Post cataract macular edema (PCME) is a condition that affects 0.1 – 2.3% of patients following cataract surgery and can occur in the absence of risk factors and complications. Although 80% of patients experience spontaneous resolution after 3 to 12 months, in persistent cases, it can lead to permanent vision loss if left untreated. There is currently no widely accepted therapy or standardized treatment guidelines for PCME making treatment variable across patients. PCME has also been shown to significantly increase annual Medicare spending and ophthalmology related outpatient visits per case compared to those without the complication. To date, there have been no studies conducted on the treatment patterns of PCME and few studies have been conducted to quantify the relationship between PCME and costs.

Objective: Our objective was to evaluate the treatment patterns and economic burden of PCME. We sought to achieve this objective by identifying the sequence of medications used for PCME and estimating the differences in healthcare resource utilization (HCRU) and costs among cataract surgery patients who developed PCME versus those who did not.

Methods: Our study was a retrospective claims analysis that utilized data from the IBM® MarketScan® Commercial and Medicare Supplemental databases. The patient population consisted of adult patients ages 18 years or older who underwent cataract surgery, with date of surgery serving as the index date for each patient. The population was divided based on diagnosis of PCME (cases) or no diagnosis of PCME (controls) within a year after surgery. Each case was matched to three individuals from the control group using propensity score matching conditioned on age, geographic region, presence of diabetes, type of cataract surgery, and Charlson Comorbidity Index (CCI) score. Baseline demographic and clinical characteristics were assessed during a 12-month pre-index period. Analysis of treatment patterns was performed by combining medication claims for each PCME patient and summarizing the distribution of which medications were used for each line of therapy. Economic burden was assessed by comparing the mean number and costs (sum of patient out of pocket costs and payer cost) of unique eye-related outpatient visits, optical coherence tomography (OCT) imaging scans, and ophthalmic medications between the two groups of patients using linear regression models. All models were adjusted for age, geographical region, presence of diabetes, complexity of cataract surgery, number of cataract surgeries, and CCI score category.

Results: Of the 98,050 patients who had cataract surgery and met the eligibility criteria, 2.5% (n= 2430) were diagnosed with PCME and met our prespecified criteria. Analysis of treatment patterns resulted in 27 different combinations of medications across six treatment lines. The most

common first line treatments received were topical steroid drops (30%), topical nonsteroidal anti-inflammatory drug (NSAID) drops (27%), and intraocular or periocular injectable steroids (15%). Patients in the PCME group had significantly higher amounts and costs of healthcare resource use across all categories compared to matched controls. On average they had an excess of 6 eye related outpatient office visits (95% CI: 5.7 – 6.2) which resulted in additional $3,897 (95% CI: $3,475 - $4,319) total costs. Patients also filled 3 more ophthalmology related outpatient prescription medications (95% CI: 2.8 – 3.2), adding $371 in total cost (95% CI: $332 - $410).

Conclusions: Treatment pattern results show large variability in treatments and timing of use for PCME, specifically around injectable treatments and combination therapy. Although current literature supports a stepwise treatment approach with injectable treatments reserved as last line alternatives, this was not observed. Additionally, we found significantly higher heath care resource use and financial burden for both patients and payers when comparing PCME patients to non-PMCE controls. Eye related outpatient office visits were found to be a main driver of excess economic burden for these individuals.

Table of Contents

1. Background

Cataract surgery is one of the most common ocular surgeries performed around the world. According to the American Academy of Ophthalmology, roughly 2 million cataract surgeries are performed in the United States each year and this number is expected to increase by more than 4-fold with the ageing population.[1,2] Although advances in surgical techniques have improved the safety and effectiveness of these surgeries, post-cataract macular edema can occur in the absence of complications and risk factors. Post-cataract macular edema, also known as pseudophakic cystoid macular edema (PCME) or Irvine-Gass syndrome, is believed to be caused by post-operative inflammation that results in increased capillary permeability and fluid accumulation with subsequent cystoid changes to the retina.[3]

There is currently no uniform diagnosis criteria for PCME and incidence estimates vary based on the diagnostic methods and type of cataract surgery performed.[4] Common methods for diagnosis include angiographic findings, decreased visual acuity, and optical coherence tomography (OCT). In a 2016 review, the incidence rate of uncomplicated PCME was reported to be between 0.8 – 20% for extracapsular cataract extraction and between 0.1 – 2.3% for the less invasive and more common phacoemulsification technique.[5]

PCME is self-limiting with 80% of patients experiencing spontaneous resolution after 3 to 12 months. However, in persistent cases, it can lead to permanent vision loss if left untreated.[4] Because there are no standardized treatment guidelines established to date, treatment of PCME is often variable and based on provider preference. In practice, topical non-steroidal anti-inflammatory drug (NSAID) ophthalmic drops given as monotherapy or in combination with

topical corticosteroids are often used first line. Various studies have reported favorable outcomes with topical NSAIDs compared to topical steroids, especially NSAIDs that have enhanced penetration to the posterior segment of the eye such as bromfenac and nepafenac.[5–7] Despite their effectiveness, some patients may experience inadequate response to topical therapy and require more invasive periocular or intravitreal injectable treatments.[8] Unfortunately, evidence supporting their use and which injectable therapy is most effective is limited.

Due to the large volume of cataract surgeries performed each year, PCME management can sum to substantial costs. One study found that PCME doubled ophthalmic charges and increased payments by 85% in Medicare patients.[9] Another study reported that PCME result in an excess of 5.1 follow-up ophthalmologist appointments per case compared to those without the complication.[9,10]

Despite the clinical consequences of PCME and lack of treatment consensus, to date no study has been performed assessing treatment patterns for PCME. Additionally, few studies have been done to characterize the economic consequences of PCME. Thus, the goal of this study was to use insurance claims data to depict the sequence of medications used to treat PCME and quantify the differences in healthcare resource use and costs among cataract surgery patients who develop PCME and those who did not.

.

2. Objectives

The primary objective was split into two parts: 1) to characterize the treatment patterns of PCME by recording the distributions of medications used for each line of therapy and 2) to evaluate the economic burden of PCME by comparing the mean incremental number and costs of unique eye related outpatient visits, optical coherence tomography (OCT) imaging scans, and ophthalmic medications between PCME and non-PCME patients.

3. Methods

3.1 Data Source

We used administrative claims data from the IBM® MarketScan® Commercial and Medicare Supplemental databases. This dataset represents nearly 40 million commercially insured US adults or US adults qualifying for Medicare that have commercial supplemental insurance and includes member eligibility, medical, drug, and other information. Data from the Enrollment (A), Outpatient Services (O), and Outpatient Pharmaceutical Claims (D) of these two databases were used for this analysis. Patient-level data contained in the Truven MarketScan database is de-identified and compliant with the Health Insurance Portability and Accountability Act of 1966 (HIPAA). Thus, our analysis is considered as non-human subject research by the University of Washington IRB.

3.2 Sample Selection and Study Cohorts

We performed a retrospective claims analysis to identify patients ages 18 years or older who had cataract surgery between 2014 and 2017. Cataract surgery date served as each patient's index date and was identified using Current Procedural Terminology (CPT) codes. For patients who had more than one cataract surgery claim, the date of the first claim was used as their index date. Sample enrollment was limited to patients who had at least 1 year of continuous enrollment prior to their index and at least 3 years of continuous enrolment post index. International Classification of Diseases External 9th and 10th Revision (ICD-9 and ICD-10) codes for PCME were used to separate patients into PCME and non-PCME groups. Patients in the non-PCME group were matched 3:1 to each PCME case using propensity score matching. Details of the propensity score match are included in Section 4. In the PCME group, the first PCME diagnosis date served as the event date which had to occur within one year from the index date. The number of post-operative days between the index and event date was used to determine an equivalent event date for each matched control. Patients who had a diagnosis for PCME, macular edema, or diabetic macular edema prior to their index date were excluded. A list of all procedure and diagnosis codes are included in Appendix 1-2.

3.3 Study Period

The full data set contained dates between January 1st, 2013, and December 31st, 2019. Baseline clinical and demographic data were assessed during the year prior to each patient's index date. Treatment patterns and economic burden were assessed throughout the two-year follow-up period following each patient's event date. The study timeline is provided in Figure 1.

3.4 Study Measures and Outcomes

3.4.1 Baseline Demographic and Clinical Characteristics

Baseline demographic characteristics such as age, gender, region, plan type (commercial or Medicare supplemental), and type of cataract surgery received were collected for each patient on their respective index date. Baseline clinical characteristics and comorbidities were assessed for each patient based on ICD 9 and ICD 10 codes during the pre-index period prior to cataract surgery. These included specific PCME risk factors such as diabetes, diabetic retinopathy, epiretinal membrane, retinal vein occlusion, and uveitis as well as conditions for the calculation of a Charlson Comorbidity Index (CCI) score per Quan, et al., which captures 17 clinical characteristics and comorbidities.[11] Outpatient pharmacy claims preceding each cataract surgery date were reviewed to identify PCME prophylactic treatments. Prophylactic treatments included any topical ophthalmic NSAID with or without a topical ophthalmic corticosteroid started within a week before cataract surgery. For individuals in the PCME group, time from surgery to PCME diagnosis and prevalence of persistent PCME were also recorded. Persistent PCME was defined as the same eye or bilateral diagnosis code matched laterally at 12 months or later from the first PCME diagnosis code.

3.4.2 Treatment Patterns

For treatment pattern analysis, relevant PCME related outpatient prescription medications following the PCME diagnosis event date through the two-year follow up period were reviewed. PCME related treatment was defined as treatments given until 3 months from the last outpatient service claim containing a PCME diagnosis. Included treatments consisted of medications used for PCME based on what was reported in the literature (Appendix 3).[6,12] A full list of all relevant

national drug codes (NDC) for each treatment was generated using IBM® Micromedex RedBook. Because NSAIDs such as nepafenac and bromfenac have been reported to have better efficacy than other NSAIDs, we grouped NSAID containing regimens based on their absorption level to identify any differences in treatment patterns.[7,12] Thus all regimens containing nepafenac or bromfenac were grouped as enhanced absorption (EA) NSAIDs; all others were grouped as regular NSAIDs. Additionally intravitreal and sub-tenon injected steroids were grouped together as injectable steroids. Each treatment line was identified as any new treatment course continued for at least 4-weeks. Different treatments received within two weeks of each other and continued together were considered as combination therapy and were treated as part of the same treatment line. Because injectable treatments are administered in-office, they were identified using their respective Healthcare Common Procedure Coding System (HCPCS) J code for active pharmacologic agent and CPT code for administration route. Additionally, given their long-acting nature and repeating dosing intervals, duration of pharmacologic activity was assumed to be 6 months for implant steroid and 3 months for ocular injectable steroids and vascular endothelial growth factor (VEGF) inhibitors.[13,14,15] Complete changes in therapy were considered as a new line of therapy for all agents regardless of timing.

3.4.3 Economic Burden

The economic burden of PCME was determined by comparing the mean incremental differences of healthcare resource use and costs between PCME and non-PCME patients. Both counts and costs were summed for each individual before means were estimated over the entire group to determine per patient estimates.

Healthcare resource use included the number of unique eye related outpatient office visits days, OCT scans, and ophthalmology related medications accumulated by PCME and non-PCME patients. Outpatient office visits included any visit with an eye related provider such as an optometrist and ophthalmologist or visits containing a PCME diagnosis code. Ophthalmology related medications included the number of relevant prescription medication fills and injectable treatments administered. In addition to the mean counts of each resource category, the number and percentage of patients who had at least one claim was also recorded.

Costs were categorized as patient, payer, and total costs. Patient-related costs were those incurred by the patient and consisted of the sum of the patient co-pay, co-insurance, and deductibles. Payer-related costs were total payments made by the health plan to healthcare providers and total costs were the sum of both patient and payer costs. All costs were reported in 2022 U.S. dollars using the medical care component of the Consumer Price Index for all urban consumers.[16]

3.4.4 Subgroup analysis of prophylactic users

Subgroup analysis was performed to compare both treatment patterns and economic burden between PCME patients who received prophylactic therapy and PCME patients who did not to explore potential effect modification by prophylactic therapy.

4. Statistical Analysis

Logistic regression was used to calculate propensity scores to match PCME and non-PCME patients 3:1 using the nearest neighbor method, adjusting for age, geographic region, presence of diabetes, type of cataract surgery, and CCI score.

$$P_i = p(PCME = 1 | X_{(1...n)}) \qquad P_j = p(PCME = 0 | X_{(1...n)})$$
$$Match = \min |P_i - P_j|$$

Baseline demographic characteristics were summarized for all variables using mean and standard deviation (SD) for continuous variables and frequencies and proportions for categorical variables. CCI scores were summarized as a continuous variable (mean and SD) as well as categorically (groups with scores equal to 1, 2, and 3 or more). Differences were assessed using Student's t-tests for continuous variables. For categorical variables that had counts greater than five a Chi-squared test was used, otherwise Fischer's exact test was used to compare differences between the two groups.

For treatment patterns, the frequency of each treatment regimen was recorded for each line of therapy. A Sankey diagram was also created to depict the flow of patient treatments by line of therapy.

Differences in the mean number and costs of eye related outpatient visits, OCT scans, ophthalmic prescription medications, and injectable medication claims were assessed using multivariable linear regression models that adjusted for age, geographic region, presence of diabetes, complex cataract surgery, number of cataract surgeries, and CCI score. Four models were used to summarize adjusted incremental differences in the counts of each resource use category described above. Twelve models were used to summarize adjusted incremental differences in costs of each category separately for patient, payer, and total costs.

$$E(Y_i | X_i) = ß_0 + ß_1 X_{PCME} + ß_2 X_{age} + ß_3 X_{region} + ß_4 X_{diabetes} + ß_5 X_{complexity} + ß_6 X_{num\_surg} + ß_7 X_{CCI}$$

SAS version 9.4 (SAS Institute Inc., Cary, NC) was used for constructing the analytical dataset. Baseline demographics testing and regression analyses were conducted in R studio version 1.4.1106 (Rstudio Inc., Bost, MA). A two-sided alpha with a significance level of 5% was used for all statistical comparisons.

5. Results

5.1 Baseline Characteristics

A total of 98,050 cataract surgery patients were identified who met the prespecified sample selection criteria. After assessing for PCME diagnosis, 2,430 patients (2.5%) were included in the PCME group and 7,290 were matched to form the non-PCME group (Figure 2). Table 1 summarizes the baseline demographic and clinical characteristics of the two groups. There were slightly fewer males than females in both the PCME and non-PCME group (47% and 45% respectively) and 68 years was the mean age for both groups. About 87% of patients in both groups had undergone phacoemulsification for their cataract surgery and the prevalence of complex cataract surgery was also the same for both groups (13%). The PCME group had a slightly higher mean CCI score (0.87 ± 1.39) compared to patients without PCME (0.86 ± 1.4), however, this difference along with comparisons of all characteristics listed above were not statistically significant.

A significantly higher proportion of patients in the non-PCME group had received PCME prophylaxis compared to patients in the PCME group (27.6% vs 25.5%, p value 0.04). Conversely, patients in the PCME group had a significantly higher prevalence of PCME risk factors such as diabetes, diabetic retinopathy, epiretinal membrane, retinal vein occlusion, and uveitis (p value <0.001).

Baseline characteristics were also examined for all individuals who were not matched (n = 88,330) to assess for any potential of selection bias. No observable differences were found.

In terms of PCME specific characteristics, the mean time from cataract surgery to PCME diagnosis was calculated to be 3.6 ± 2.9 months. Additionally, 12.1% of patients were found to have persistent PCME (PCME lasting longer than 12 months).

5.2 Treatment Patterns

Twenty-seven different combinations of medications across 6 lines of therapy were identified and totaled to 1942 treatment regimens (Table 2). In total 1222 patients received at least one line of therapy. Of these individuals, 411 (34%) advanced on to a second line treatment and only 47 (3.9%) received treatment beyond the fourth line. Regimens containing an EA NSAID were slightly more common than regular NSAIDs (456 vs 373). NSAIDs were given more frequently as combination therapy with a topical steroid whereas EA NSAIDs were given more frequently as monotherapy. Otherwise, no major differences between the two types were observed.

Most patients received monotherapy (83%) or dual therapy (16%) first line and this trend continued across all treatment lines. In terms of first line treatments, the most common medications given were monotherapies of topical steroids (30%), NSAIDs as a class (27%), and injectable steroids (15%). About 31% of patients received an ocular injectable containing regimen as first line treatment. For second line treatments, monotherapy of NSAIDs as a class (24%), dual therapy of any NSAID and topical steroid (19%), and topical steroid monotherapy

(18%) were the most common treatments. Over the entire cohort, 22 regimens consisted of triple therapy. Figure 3 displays the flow of patients between all lines of therapy.

5.3 Economic Burden

The PCME group accumulated more healthcare resource use in terms of counts and costs and had a higher proportion of patients with at least one claim across all categories compared to match controls. All differences were found to be statistically significant.

Roughly 97% of the PCME group had at least one eye related outpatient provider visit compared to 62% of the control group which totaled to an excess of 6 visits (95% CI: 5.7 – 6.2). 95% of the PCME group also had at least one claim for an OCT scan compared to 17% of the control group which resulted in an excess of 4.5 scans (95% CI: 4.3 – 4.7). In terms of ophthalmology related medications, the PCME group received an excess of 3 prescription medications (95% CI: 2.8 - 3.2) and 0.9 injectable medications (95% CI: 0.7 – 1.0) when compared to the control group (Table 3).

Table 4 shows that for eye related outpatient office visits, the PCME group incurred an additional $380 in patient OOP costs (95% CI: $341 - $419) and $3517 in payer costs (95% CI: $3111 - $3923) equaling to a mean adjusted incremental total difference of $3897 (95% CI: $3475 - $4319). The difference in adjusted total costs for OCT was $295 ($268 - $322) higher for the PCME group. Patients and payers also spent more on prescription and injectable medications which resulted in higher mean adjusted costs for both categories (prescription $371, 95% CI: $332 - $410; injectable $119, 95% CI: $99 - $140).

5.4 Subgroup Analysis

Subgroup analysis of treatment patterns stratified by prophylactic therapy revealed that patients who received prophylactic therapy were less likely to use injectable treatments. The most common medication regimens used across all lines of therapy, were topical steroid monotherapy (26%), topical NSAIDs as a class (20%), and dual therapy of the two (17%). Additionally, separation of the two groups revealed that the majority of patients who received triple therapy and nine of the eleven patients who advanced to a sixth treatment line were patients who did not receive prophylactic therapy. In terms of economic burden, there were no statistically significant differences in counts or costs of resources used between patients who received prophylactic therapy and those who did not (Appendix 4-7).

6. Discussion

In this retrospective claims analysis, we evaluated the treatment patterns and economic burden of post cataract macular edema to gain insight on how the condition is treated and quantify the incremental healthcare resource use and costs among cataract surgery patients who developed PCME compared to those who did not. We found variable approaches to treatment and statistically significant economic burden for both patients and payers in the PCME group.

Analysis of the treatment patterns reveals variability in the treatment of PCME. We observed EA NSAIDs being used more often and as monotherapy compared to NSAIDs which could be attributable to their enhanced efficacy. Otherwise, no major differences were found and both were analyzed together as an entire class during analysis for simplicity. The literature commonly describes a stepwise approach for the treatment of PCME as topical monotherapy, topical dual therapy, and periocular or intraocular injectables in prolonged or non-responsive cases.[6,12,17]

However, we observed monotherapy as the most common regimen across all treatment lines. Upon further inspection, we found that among first line treatments, topical agents on their own only accounted for 56% of the medications used. The other half composed of combination therapy and periocular or intraocular injectables with injectable steroids being one of the top three medications used. This was surprising given that the majority of the literature reports injectable treatments as monotherapies and last line options. We found one study by Sharma et al that supports the early initiation of intravitreal injectables. In their study they found better visual outcomes in patients who received these medications within 4-weeks of diagnosis compared to those who started later which may explain the high prevalence of early initiation that we observed.[18]

We found substantially higher healthcare resource use in both counts and the proportion of patients with at least one claim in the PCME group compared to those without the condition. Statistically significant differences were found for each category; outpatient services consisting of eye related office visits and OCT scans had the largest differences. This excess in resource use also translated to significantly higher costs for both patients and payers across all categories. Eye related outpatient visits was the main driver of additional costs incurred by PCME patients followed by outpatient prescription medications. These results demonstrate the substantial economic burden associated with PCME. When factoring the high volume of cataract surgeries performed each year, the implications of our findings are further amplified. Thus, strategies focused on preventing PCME, such as prophylactic therapy, may be valuable interventions for avoiding eye related health care resource use and providing cost savings.

In our subgroup analysis we found a statistically significant higher prevalence of prophylactic therapy in the control group compared to the PCME group and prophylactic users were less likely to receive injectable treatments and advance to a 6th treatment line. However, these differences in treatment patters were minimal and analysis of the economic burden of individuals who received prophylactic therapy compared to those who did not failed to show any significant differences. Previous studies have supported the efficacy of prophylactic therapy but are limited to short term visual outcomes.[5] Our findings suggest that although prophylactic therapy is effective at reducing the risk of PCME, it may not have as much of an effect on reducing the long term severity or burden of the condition measured by incremental healthcare resource use.

To date there have been no published studies on the treatment patterns of post cataract macular edema. In the absence of standardized treatment guidelines, prior research supports a stepwise approach to treating PCME from topical agents to injectables in cases where no response is seen after 3 months.[6,12,19] Although we did not observe this pattern in our analysis, our findings highlight the lack of treatment consensus and need for standardization. Only a small number of studies have explored the relationship between PCME and costs and all reported similar directionality of outcomes. Schmier et al, found that PCME increased Medicare payments by 85% and doubled ophthalmic charges from $5,950 to $10,410. However, their study may not be comparable to ours since it was done exclusively in Medicare patients, included inpatient costs, and only followed patients for 6 months after cataract surgery.[9] Sanders et al conducted a matched case-control study in the UK and found that PCME patients accrued an excess of 5.1 ophthalmology related visits which was slightly less than what we found and likely due to their shorter duration of follow up of 18 months.[10]

There were several limitations to our study. First, the Marketscan® database represents individuals who have Medicare supplemental or commercial insurance. This could impact the generalizability of our results for those who are ages 65 years or older which is the group that is more commonly affected by cataracts and most at risk for developing PCME. Additionally, because we used a claims data set it was not possible to confirm diagnoses or the eye being treated. This could have resulted in the misclassification of exposure or outcome of our study and induce bias to our results. An example of this could be patients who received triple therapy, as it is possible that they were receiving treatment in both eyes rather than all medications for one. Another limitation was the three years of post-index enrollment required for inclusion into the study and the long duration of follow-up used for our analysis which limited our sample size and could have led to the incorporation of treatments and resources that were no longer related to PCME. The long follow up period was chosen to account for patients who had persistent PCME and capture any potential long-term consequences of the disease which has not been previously explored in the literature. Additionally, Hunter et al. found that 26.8% of eyes with PCME did not recover 20/20 vision despite resolution of PCME within one year of diagnosis, indicating that patients may still experience clinical consequences from PCME after resolution.[20] However, this may have resulted in an overestimation of its economic burden. Lastly, given the variable dosing intervals of injectable medications and differences in pharmacologic activity, discerning if they were part of a new or previous treatment line required assumptions that may have overestimated their duration of pharmacological activity and resulted in treatments inaccurately being grouped as combination therapy.

7. Conclusion

Cataract surgery is one of the most frequently performed surgical procedures worldwide, making PCME a condition that can result in significant economic and clinical burden. Our results show that those who develop PCME following cataract surgery incur substantially higher costs and resource use compared to those who did not, demonstrating that interventions targeted at preventing PCME may be highly valuable. There was also large variability in treatment regimens used especially with combination therapy and injectable treatments highlighting the need for treatment standardization. Future studies should explore the treatment patterns and economic burden of PCME and incorporate data from sources that can confirm treatment eye such as electronic health records and look at the duration of treatments used.

8. Figures

Figure 1: Study Timeline

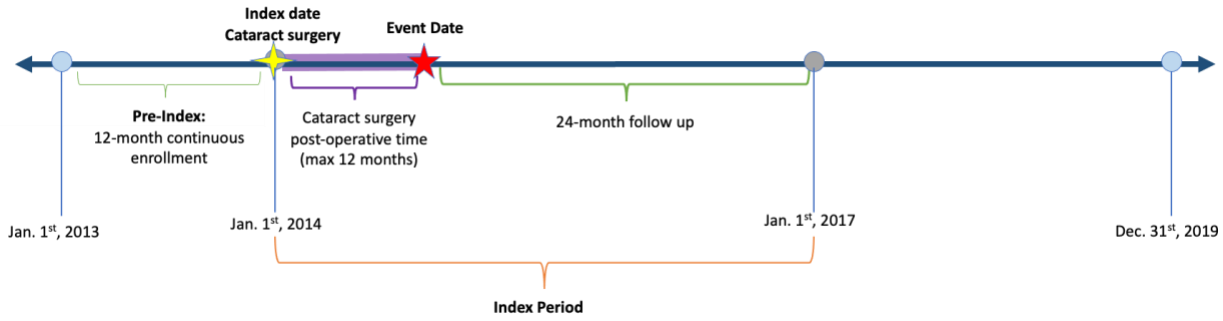


Figure 2: Sample Attrition

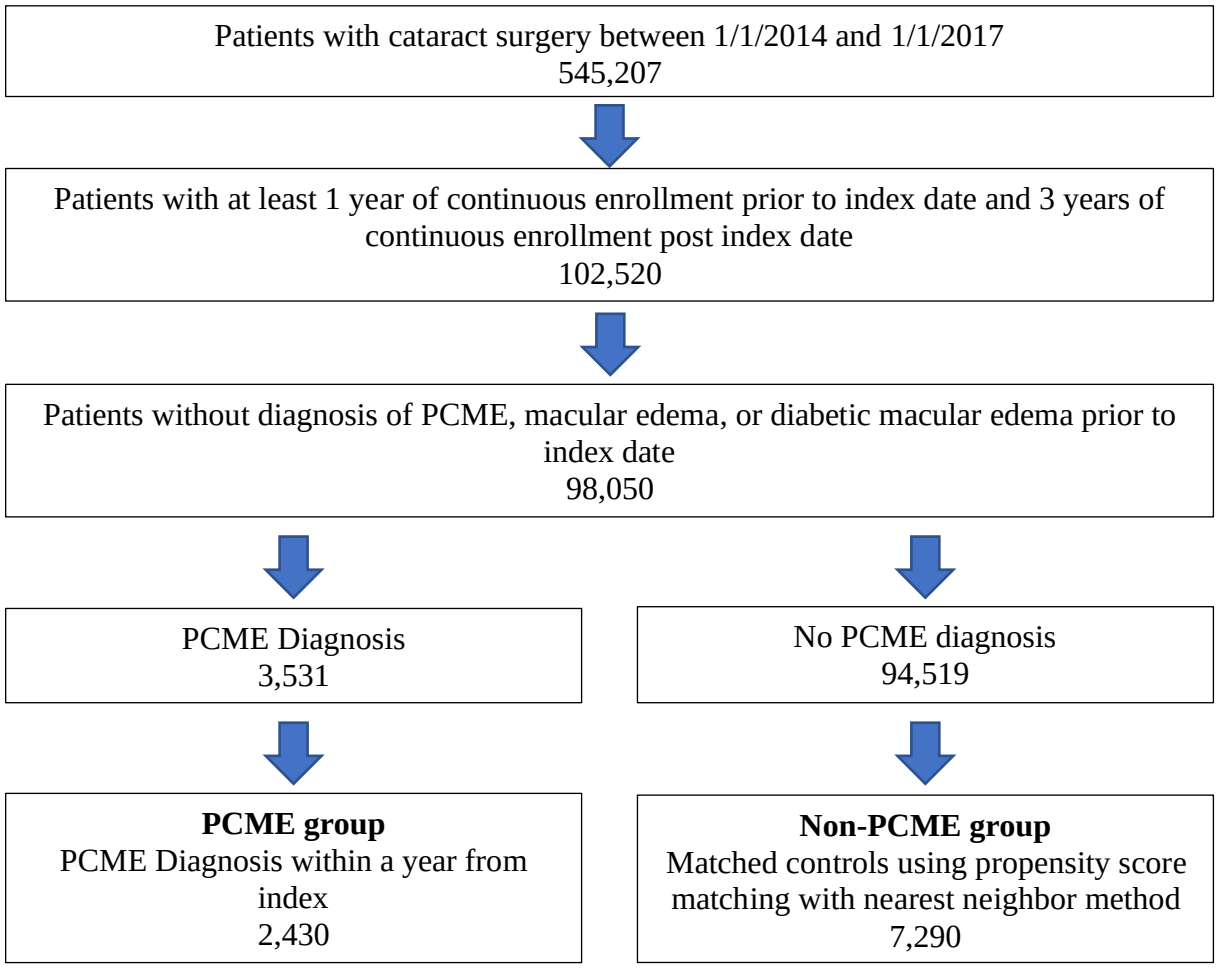
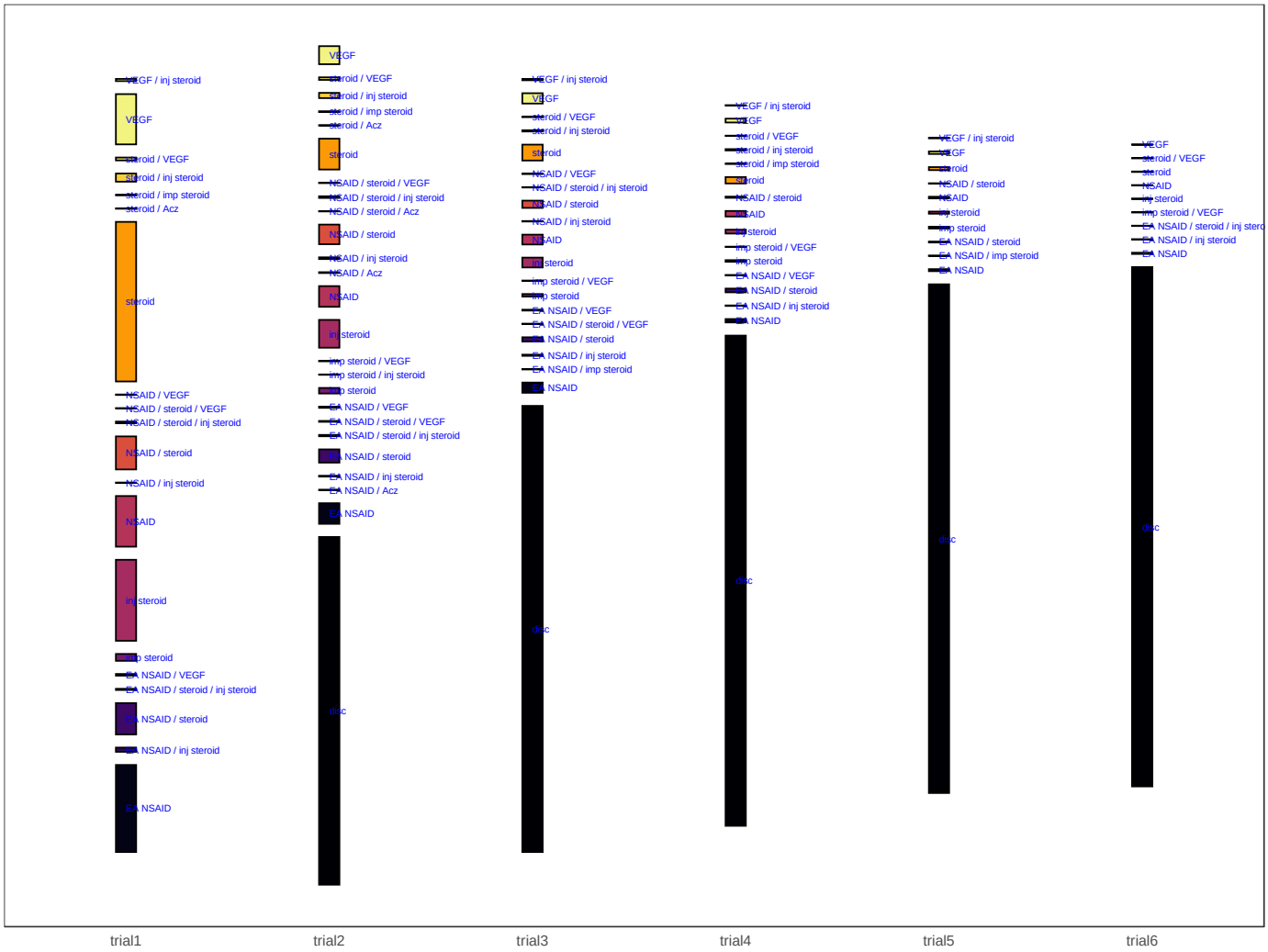


Figure 3: Sankey Diagram

Sankey Diagram: Treatment Patterns



9. Tables

Table 1. Baseline Demographic and Clinical Characteristics

	PCME (n= 2430)	**Non-PCME** (n= 7290)	**P value**
Male sex, n (%)	1138 (46.8)	3294 (45.1)	P = 0.17
Age, mean (SD)	68 (11.4)	68 (11.3)	P = 0.94
Geographic region, n (%) North central Northeast South West Unknown	 744 (30.6) 552 (22.7) 868 (35.7) 261 (10.7) 5 (0.3)	 2243 (30.8) 1661 (22.8) 2589 (35.5) 781 (10.7) 16 (0.2)	 P= 0.99
Payer, n (%) Commercial Medicare	 926 (43.1) 1504 (56.9)	 2679 (36.7) 4611 (63.3)	 P= 0.248
Type of surgery, n (%) Phacoemulsification Extracapsular Intracapsular Complex	 2102 (86.5) 1 (<0.1) 7 (0.3) 320 (13.2)	 6310 (86.6) 0 (0.1) 20 (0.3) 960 (13.2)	 P= 0.49*
Prophylactic treatment, n (%)	620 (25.5)	2015 (27.6)	P = 0.04
Months from cataract surgery to PCME diagnosis, mean (SD)	3.6 (2.9)	N/A	N/A
Persistent PCME, n (%)	295 (12.1)	N/A	N/A
Charlson comorbidity index (CCI) Score, n (%) 0 1 2 3+ Mean (SD)	 1408 (57.9) 456 (18.8) 309 (12.7) 257 (10.6) 0.87 (1.39)	 4230 (58.0) 1371 (18.8) 917 (12.6) 772 (10.6) 0.86 (1.4)	 P= 0.99 P= 0.85
PCME risk factors, n (%) Diabetes Diabetic retinopathy Epiretinal membrane Retinal vein occlusion Uveitis	 804 (33.1) 71 (2.9) 41 (1.7) 54 (2.2) 151 (6.2)	 2365 (32.4) 108 (1.5) 20 (0.3) 43 (0.6) 95 (1.3)	 P= <0.001

*Fischer's exact test

Table 2: Treatment Patterns

	Trial 1		Trial 2		Trial 3		Trial 4		Trial 5		Trial 6	
	N = 1222	(%)	N = 411	(%)	N = 182	(%)	N = 79	(%)	N = 36	(%)	N = 11	(%)
Monotherapy												
EA NSAID	203	17%	48	12%	24	13%	8	10%	5	14%	3	27%
NSAID	118	10%	48	12%	23	13%	13	16%	4	11%	1	9%
Steroid	372	30%	72	18%	37	20%	15	19%	7	19%	1	9%
Inj steroid	189	15%	65	16%	23	13%	9	11%	5	14%	1	9%
Implant steroid	16	1%	13	3%	6	3%	4	5%	4	11%	0	0%
VEGF	117	10%	42	10%	24	13%	9	11%	6	17%	1	9%
Dual therapy												
EA NSAID/ steroid	73	6%	31	8%	10	5%	9	11%	2	6%	0	0%
NSAID/ steroid	77	6%	46	11%	17	9%	3	4%	1	3%	0	0%
EA NSAID/ inj steroid	10	1%	2	0%	3	2%	1	1%	0	0%	1	9%
NSAID/ Inj steroid	1	0%	4	1%	1	1%	0	0%	0	0%	0	0%
EA NSAID/ implant steroid	0	0%	0	0%	1	1%	0	0%	1	3%	0	0%
EA NSAID/ VEGF	4	0%	3	1%	2	1%	1	1%	0	0%	0	0%
NSAID/ VEGF	1	0%	0	0%	1	1%	0	0%	0	0%	0	0%
EA NSAID/ ACZ	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%
NSAID/ ACZ	0	0%	2	0%	0	0%	0	0%	0	0%	0	0%
Steroid/ Inj steroid	19	2%	12	3%	3	2%	3	4%	0	0%	0	0%
Steroid/ implant steroid	1	0%	2	0%	0	0%	1	1%	0	0%	0	0%
Steroid/ VEGF	7	1%	6	1%	1	1%	1	1%	0	0%	1	9%
Steroid/ ACZ	1	0%	1	0%	0	0%	0	0%	0	0%	0	0%
Implant steroid/ inj steroid	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%
Implant steroid/ VEGF	0	0%	1	0%	1	1%	1	1%	0	0%	1	9%
VEGF/ inj steroid	5	0%	0	0%	3	2%	1	1%	1	3%	0	0%
Triple therapy												
EA NSAID/ steroid/ inj steroid	3	0%	3	1%	0	0%	0	0%	0	0%	1	9%
NSAID/ steroid/ inj steroid	4	0%	4	1%	1	1%	0	0%	0	0%	0	0%
EA NSAID/ steroid/ VEGF	0	0%	2	0%	1	1%	0	0%	0	0%	0	0%
NSAID/ steroid/ VEGF	1	0%	1	0%	0	0%	0	0%	0	0%	0	0%
NSAID/ steroid/ ACZ	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%

EA: enhanced absorption, inj: intravitreal or sub tenon injection, NSAID: nonsteroidal antiinflammatory drug, VEGF: Vascular endothelial growth factor

Table 3: Healthcare Resource Use

	PCME (N = 2430)		Non-PCME (N = 7290)		
	Patients with claim (%)	Mean number of claims	Patients with claim (%)	Mean number of claims	Adjusted Differences (95% CI)
Eye related outpatient visits	2357 (97%)	8.6	4513 (62%)	2.7	6.0 (5.7 - 6.2)
Imaging (OCT)	2310 (95%)	5.1	1215 (17%)	0.5	4.5 (4.3 - 4.7)
Ophthalmology related medications					
Prescription medications	1591 (66%)	3.5	1489 (20%)	0.5	3.0 (2.8 - 3.2)
Intraocular injectables	536 (22%)	1.1	147 (2%)	0.2	0.9 (0.7 - 1.0)

All p values <0.0001
Mean number of claims were calculated over each group
Models were adjusted for age, region, presence of diabetes, and CCI score

Table 4: Costs

	PCME Incremental Mean Patient Costs (95% CI)	PCME Incremental Mean Payer Costs (95% CI)	PCME Incremental Mean Total Costs (95% CI)
Eye related outpatient visits	$380 ($341 - $419)	$3517 ($3111 - $3923)	$3897 ($3475 - $4319)
Imaging (OCT)	$57 ($50 - $64)	$238 ($215 - $261)	$295 ($268 - $322)
Ophthalmology related medications			
Prescription medications	$69 ($62 - $76)	$298 ($264 - $331)	$367 ($328 - $406)
Intraocular injectables	$9 ($6 - $12)	$111 ($90 - $131)	$119 ($99 - $140)

All p values <0.0001
Patient costs were calculated as the sum of each individual's copay, coinsurance, and deductible
Models were adjusted for age, region, presence of diabetes, and CCI score

10. Appendix

Appendix 1: Diagnosis Codes		
ICD-10 Code / ICD-9 Code	Description	Rationale
H59.03, 362.53	Cystoid macular edema	Inclusion/ exclusion criteria
H35.35	Cystoid Macular degeneration	Inclusion/exclusion criteria
H35.81, 362.83	Macular edema	Exclusion criteria
E11.311, E11.321, E11.331, E11.341, E11.351, E10.311, E10.321, E10.331, E10.341, E10.351, 362.07	Macular edema associated with diabetes	Exclusion criteria
E11.319, E11.329, E11.339, E11.349, 362.01	Diabetic retinopathy	Baseline characteristic
H35.379, 362.5	Epiretinal membrane	Baseline characteristic
H34.81, 362.35	Retinal vein occlusion	Baseline characteristic
H20.01, H20.02, H20.1, H43.9, H30.02, H30.03, 364.04	Uveitis	Baseline characteristic
I21, I22, I25.2, 410, 412	Acute myocardial infarction	CCI
I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I43, I50, P29.0, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428	Congestive heart failure	CCI
I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9, 093.0, 437.3, 440, 441, 443.1-443.9, 447.1, 557.1, 557.9, V43.4	Peripheral vascular disease	CCI
G45, G46, H34.0, I60-I69, 362.34, 430-438	Cerebrovascular disease	CCI
F00-F03, F05, G30, G31.1, 290, 294.1, 331.2	Dementia	CCI
I27.8, I27.9, J68.4, J40-J47, J60-J67, J70.1, J70.3, 416.8, 416.9, 490-505, 506.4, 508.1, 508.8	Chronic pulmonary disease	CCI
M05, M06, M31.5, M32, M33, M34, M35.1, M35.3, M36.0, 446.5, 710.0-710.4, 714.0-714.2, 714.8, 725	Rheumatic disease	CCI

K25 – K28, 531-534	Peptic ulcer disease	CCI
B18, K70.0, K70.1, K70.2, K70.3, K70.9, K71.3, K71.4, K71.5, K71.7, K73, K74, K76.0, K76.2, K76.3, K76.4, K76.8, K76.9, Z94.4, 070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570, 571, 573.3, 573.4, 573.8, 573.9, V42.7	Mild liver disease	CCI
E10.0, E10.l, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9, 250.0-250.3, 250.8, 250.9	Diabetes (mild to moderate)	CCI / Baseline characteristics
E10.7, E11.7, E12.7, E13.7, E14.7, E10.2-E10.5, E11.2-E11.5, E12.2-E12.5, E13.2-E13.5, E14.2-E14.5, 250.4-250.7	Diabetes with complications	CCI/ Baseline characteristics
G04.1, G11.4, G80.1, G80.2, G81, G82, G83.0-G83.4, G83.9, 334.1, 342, 343, 344.0-344.6, 344.9	Hemiplegia or paraplegia	CCI
I12.0, I13.1, N18, N19, N25.0, N03.2-N03.7, Z49, Z94.0, Z99.2, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582, 583.0-583.7, 585, 586, 588.0, V42.0, V45.1, V56	Renal disease	CCI
C43, C88, C00-C26, C30-C34, C37-C41, C45-C58, C60-C76, C81-C85, C90-C9, 140-172, 174-195.8, 200-208, 238.6	Any malignancy, including lymphoma and leukemia, excluding malignant neoplasm of skin	CCI
C77, C78, C79, C80, 196-199	Metastatic solid tumor	CCI
I85.0, I85.1, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7, 456.0-456.2, 572.2-572.8	Moderate to severe liver disease	CCI
B20, B21, B22, B24, 0.42-0.44	HIV/AIDS	CCI

Appendix 2: Procedure Codes		
CPT Codes	Description	Rationale
66830, 66840, 66850, 66852, 66984, 66982	Phacoemulsification	Identifying type of cataract surgery received
66920, 66930, 66983	Intracapsular	Identifying type of cataract surgery received
66940	Extracapsular	Identifying type of cataract surgery received
92134	OCT	Economic Burden

Appendix 3: List of Treatments
Topical NSAIDs
Ketorolac tromethamine
Diclofenac sodium
Nepafenac
Bromfenac sodium
Flurbiprofen sodium
Topical Steroids
Prednisolone acetate
Prednisolone sodium phosphate
Dexamethasone
Dexamethasone sodium phosphate
Loteprednol etabonate
Difluprednate
Fluorometholone
Rimexolone
Medrysone
Oral carbonic anhydrase inhibitors
Acetazolamide
Injectable Steroids
Triamcinolone acetonide
Implant Steroids
Dexamethasone
Fluocinolone
Injectable VEGF inhibitor
Bevacizumab
Ranibizumab
Aflibercept
Injectable TNF inhibitor
Infliximab

Appendix 4: Treatment Patterns of Non-Prophylaxis Users

	Trial 1		Trial 2		Trial 3		Trial 4		Trial 5		Trial 6	
	N = 890	(%)	N = 296	(%)	N = 131	(%)	N = 57	(%)	N = 27	(%)	N = 9	(%)
Monotherapy												
EA NSAID	147	17%	31	10%	18	14%	7	12%	4	15%	3	33%
NSAID	92	10%	37	13%	15	11%	7	12%	3	11%	1	11%
Steroid	269	30%	54	18%	24	18%	12	21%	5	19%	1	11%
Inj steroid	144	16%	48	16%	17	13%	8	14%	3	11%	1	11%
Implant steroid	13	1%	10	3%	6	5%	4	7%	3	11%	0	0%
VEGF	84	9%	35	12%	18	14%	6	11%	5	19%	1	11%
Dual therapy												
EA NSAID/ steroid	44	5%	21	7%	8	6%	5	9%	2	7%	0	0%
NSAID/ steroid	57	6%	29	10%	10	8%	1	2%	1	4%	0	0%
EA NSAID/ inj steroid	8	1%	2	1%	2	2%	1	2%	0	0%	1	11%
NSAID/ Inj steroid	1	0%	3	1%	1	1%	0	0%	0	0%	0	0%
EA NSAID/ implant steroid	0	0%	0	0%	1	1%	0	0%	1	4%	0	0%
EA NSAID/ VEGF	2	0%	1	0%	2	2%	1	2%	0	0%	0	0%
NSAID/ VEGF	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%
EA NSAID/ ACZ	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%
NSAID/ ACZ	0	0%	2	1%	0	0%	0	0%	0	0%	0	0%
Steroid/ Inj steroid	14	2%	7	2%	3	2%	3	5%	0	0%	0	0%
Steroid/ implant steroid	1	0%	1	0%	0	0%	1	2%	0	0%	0	0%
Steroid/ VEGF	3	0%	4	1%	1	1%	0	0%	0	0%	1	11%
Steroid/ ACZ	1	0%	1	0%	0	0%	0	0%	0	0%	0	0%
Implant steroid/ inj steroid	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%
Implant steroid/ VEGF	0	0%	0	0%	1	1%	1	2%	0	0%	0	0%
VEGF/ inj steroid	4	0%	0	0%	3	2%	0	0%	0	0%	0	0%
Triple therapy												
EA NSAID/ steroid/ inj steroid	3	0%	3	1%	0	0%	0	0%	0	0%	0	0%
NSAID/ steroid/ inj steroid	2	0%	3	1%	0	0%	0	0%	0	0%	0	0%
EA NSAID/ steroid/ VEGF	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%
NSAID/ steroid/ VEGF	1	0%	0	0%	0	0%	0	0%	0	0%	0	0%
NSAID/ steroid/ ACZ	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%

EA: enhanced absorption, inj: intravitreal or sub tenon injection, NSAID: nonsteroidal antiinflammatory drug, VEGF: Vascular endothelial growth factor

Appendix 5: Treatment Patterns of Prophylaxis Users

	Trial 1		Trial 2		Trial 3		Trial 4		Trial 5		Trial 6	
	N = 332	(%)	N = 115	(%)	N = 51	(%)	N = 22	(%)	N = 9	(%)	N = 2	(%)
Monotherapy												
EA NSAID	56	17%	17	15%	6	12%	1	5%	1	11%	0	0%
NSAID	26	8%	11	10%	8	16%	6	27%	1	11%	0	0%
Steroid	103	31%	18	16%	13	25%	3	14%	2	22%	0	0%
Inj steroid	45	14%	17	15%	6	12%	1	5%	2	22%	0	0%
Implant steroid	3	1%	3	3%	0	0%	0	0%	1	11%	0	0%
VEGF	33	10%	7	6%	6	12%	3	14%	1	11%	0	0%
Dual therapy												
EA NSAID/ steroid	29	9%	10	9%	2	4%	4	18%	0	0%	0	0%
NSAID/ steroid	20	6%	17	15%	7	14%	2	9%	0	0%	0	0%
EA NSAID/ inj steroid	2	1%	0	0%	1	2%	0	0%	0	0%	0	0%
NSAID/ Inj steroid	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%
EA NSAID/ VEGF	2	1%	2	2%	0	0%	0	0%	0	0%	0	0%
NSAID/ VEGF	1	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Steroid/ Inj steroid	5	2%	5	4%	0	0%	0	0%	0	0%	0	0%
Steroid/ implant steroid	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%
Steroid/ VEGF	4	1%	2	2%	0	0%	1	5%	0	0%	0	0%
Implant steroid/ VEGF	0	0%	1	1%	0	0%	0	0%	0	0%	1	50%
VEGF/ inj steroid	1	0%	0	0%	0	0%	1	5%	1	11%	0	0%
Triple therapy												
EA NSAID/ steroid/ inj steroid	0	0%	0	0%	0	0%	0	0%	0	0%	1	50%
NSAID/ steroid/ inj steroid	2	1%	1	1%	1	2%	0	0%	0	0%	0	0%
EA NSAID/ steroid/ VEGF	0	0%	1	1%	1	2%	0	0%	0	0%	0	0%
NSAID/ steroid/ VEGF	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%

EA: enhanced absorption, inj: intravitreal or sub tenon injection, NSAID: nonsteroidal antiinflammatory drug, VEGF: Vascular endothelial growth factor

Appendix 6: Healthcare Resource Stratified by Prophylaxis Use

	PPX (N = 620)		No PPX (N = 1810)		Adjusted Differences (95% CI)
	Patients with claim (%)	Mean number of claims	Patients with claim (%)	Mean number of claims	
Eye related outpatient visits	603 (97%)	8.4	1754 (97%)	8.7	-0.4 (-1.0 - 0.3)
Imaging (OCT)	586 (95%)	5.0	1724 (95%)	5.1	0.0 (-0.4 - 0.4)
Ophthalmology related medications					
Prescription medications	431 (70%)	3.9	1160 (64%)	3.3	0.5 (-0.1 - 1.0)
Intraocular injectables	146 (25%)	1.1	390 (22%)	1.0	0.1 (-0.2 - 0.4)

PPX: prophylaxis
All p values >0.05
Mean number of claims were calculated over each group
Models were adjusted for age, region, presence of diabetes, type of cataract surgery, number of cataract surgeries, and CCI score

Appendix 7: Costs of Prophylaxis Users

	PPX Incremental Mean Patient Costs (95% CI)	PPX Incremental Mean Payer Costs (95% CI)	PCME Incremental Mean Total Costs (95% CI)
Eye related outpatient visits	$65 (-$36 - $168)	$221 (-$632 - $1074)	$287 (-$604 - $1178)
Imaging (OCT)	-$11 (-$25 - $2)	-$13 (-$66- $41)	-$24 (-$83 - $35)
Ophthalmology related medications			
Prescription medications	$7 (-$9 - $24)	$95 (-$4 - $193)	$102 (-$9 - $213)
Intraocular injectables	$10 (-$2 - $21)	$31 (-$13 - $75)	$41 (-$7 - $88)

PPX: prophylaxis
All p values >0.05
Patient costs were calculated as the sum of each individual's copay, coinsurance, and deductible
Models were adjusted for age, region, presence of diabetes, type of cataract surgery, number of cataract surgeries, and CCI score

References:

1. Congdon N, Vingerling JR, Klein BEK, et al. Prevalence of cataract and pseudophakia/aphakia among adults in the United States. *Arch Ophthalmol*. 2004;122(4):487-494. doi:10.1001/archopht.122.4.487

2. Cataract Surgery Infographic. American Academy of Ophthalmology. Published June 10, 2014. Accessed September 14, 2021. https://www.aao.org/eye-health/news/cataract-surgery-infographic

3. Erikitola OO, Siempis T, Foot B, Lockington D. The incidence and management of persistent cystoid macular oedema following uncomplicated cataract surgery—a Scottish Ophthalmological Surveillance Unit study. *Eye*. 2021;35(2):584-591. doi:10.1038/s41433-020-0908-y

4. Rotsos TG, Moschos MM. Cystoid macular edema. *Clin Ophthalmol*. 2008;2(4):919-930.

5. Grzybowski A, Sikorski BL, Ascaso FJ, Huerva V. Pseudophakic cystoid macular edema: update 2016. *Clin Interv Aging*. 2016;11:1221-1229. doi:10.2147/CIA.S111761

6. Shelsta HN, Jampol LM. PHARMACOLOGIC THERAPY OF PSEUDOPHAKIC CYSTOID MACULAR EDEMA: 2010 Update. *RETINA*. 2011;31(1):4-12. doi:10.1097/IAE.0b013e3181fd9740

7. Warren KA, Bahrani H, Fox JE. NSAIDs in combination therapy for the treatment of chronic pseudophakic cystoid macular edema. *Retina*. 2010;30(2):260-266. doi:10.1097/iae.0b013e3181b8628e

8. Lobo C. Pseudophakic Cystoid Macular Edema. *OPH*. 2012;227(2):61-67. doi:10.1159/000331277

9. Schmier JK, Covert DW, Hulme-Lowe CK, Mullins A, Mahlis EM. Treatment costs of cystoid macular edema among patients following cataract surgery. *Clin Ophthalmol*. 2016;10:477-483. doi:10.2147/OPTH.S98892

10. Sanders FWB, Lowin P, Gupta N, Roberts HW. A matched case–control study of the clinical, economic, and patient-reported outcomes of cystoid macular edema complicating phacoemulsification surgery. *J Cataract Refract Surg*. 2020;46(6):831-838. doi:10.1097/j.jcrs.0000000000000192

11. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130-1139. doi:10.1097/01.mlr.0000182534.19832.83

12. Orski M, Gawęcki M. Current Management Options in Irvine–Gass Syndrome: A Systemized Review. *Journal of Clinical Medicine*. 2021;10(19):4375. doi:10.3390/jcm10194375

13. ozurdex_pi.pdf. Accessed May 20, 2022. https://www.rxabbvie.com/pdf/ozurdex_pi.pdf

14. WPR32110-intravitreal-injection-of-triamcinolone.pdf. Accessed May 20, 2022. https://www.dbth.nhs.uk/wp-content/uploads/2017/07/WPR32110-intravitreal-injection-of-triamcinolone.pdf

15. Kosobucki BR, Freeman WR, Cheng L. Photographic estimation of the duration of high dose intravitreal triamcinolone in the vitrectomised eye. *Br J Ophthalmol*. 2006;90(6):705-708. doi:10.1136/bjo.2005.088278

16. Databases, Tables & Calculators by Subject. Accessed May 26, 2022. https://www.bls.gov/data/

17. Grzybowski A, Kanclerz P. The Role of Steroids and NSAIDs in Prevention and Treatment of Postsurgical Cystoid Macular Edema. *Curr Pharm Des*. 2018;24(41):4896-4902. doi:10.2174/1381612825666190206104524

18. Sharma A, Bandello F, Loewenstein A, et al. Current role of intravitreal injections in Irvine Gass syndrome-CRIIG study. *Int Ophthalmol*. 2020;40(11):3067-3075. doi:10.1007/s10792-020-01491-5

19. Erichsen JH, Holm LM, Forslund Jacobsen M, Forman JL, Kessel L. Prednisolone and Ketorolac vs Ketorolac Monotherapy or Sub-Tenon Prophylaxis for Macular Thickening in Cataract Surgery: A Randomized Clinical Trial. *JAMA Ophthalmology*. 2021;139(10):1062-1070. doi:10.1001/jamaophthalmol.2021.2976

20. Hunter AA, Modjtahedi SP, Long K, et al. Improving visual outcomes by preserving outer retina morphology in eyes with resolved pseudophakic cystoid macular edema. *Journal of Cataract & Refractive Surgery*. 2014;40(4):626-631. doi:10.1016/j.jcrs.2013.09.018