Methods and results

TODO(Patrick): think more deeply about regression to the mean and this will affect our claims. Reference: https://www.reviewofoptometry.com/ce/considerations-in-iop-measurement

Follow the procedures in PRISMA 2009.

10. Data extraction

An undergraduate assistant manually extracted data from the tables of the identified studies. In one case where the data of interest was not cited in the main study (ref Liu et al.), the data was extracted from figures using a graphical data extraction tool (WebPlotDigitizer, http://arohatgi.info/WebPlotDigitizer/; ref Cochrane Review).

The data tables were spot-checked by M.M. against the primary studies. Data was also audited for self-consistency by P.M. – e.g. ensuring that differences in IOP post-surgery were consistent with pre- and post-surgery IOP measurements, that number of eyes tracked did not increase through follow-up, etc. The full extent of these automated checks (unit tests) can be viewed at (ref github link).

The data for OAG studies was also cross-verified against Table 1 of Thomas et al (ref). We rejected one study from meta-analysis because the SD numbers could not be relied on (reported range too large for reported SD; ref Jacobi et al.). The full extracted data can be accessed at (ref Github link).

11 & 13. Data items & summary measures

We extracted the following columns from the primary sources:

```
extracted.data <- read.column.names()
kable(data.frame(extracted.data))
```

extracted.data

Journal, Volume (Page)
Author
Study Type
Year
MIGs (Y or N)
Wash Out
Wash out baseline
Baseline wash out SD
Wash out IOP period
Wash out IOP
Wash out SD
Types of MIGS (if any)
Age (Mean)
Age (Std Dev)
% Male
% Female
% OAG
% ACG
% NTG

% PXG
acuteangleclosure
Note on Type of Glaucoma
PreOpEyes
PreOpIOPMean
PreOpIOPStdDev
Eyes6mo
MeanIOP6mo
MeanIOPsd6mo
IOPchangemean6m
IOPchangesd6mo
Eyes12mo
MeanIOP12mo
MeanIOPsd12mo
IOPchangemean12m
IOPchangeSD12mo
LastPeriodofEyes
TimeofLastPostOp
LastPeriodIOPMean
LastPeriodIOPStdDev
LastPeriodAbsIOPChangeMean LastPeriodAbsIOPChangeStd
RxPreOpMean
RxPreOpStdDev
RxPostOpMean
RxPostOpStdDev
VisualAcuityPreOpMean
VisualAcuityPreOpStdDev
VisualAcuityPostOpMean
VisualAcuityPostOpStdDev
Notes

> TODO(Marisse): transform this to a table, group similar measurements together.

The main metric of interest for our meta-analysis was the IOP change at the final follow-up period (12 months or longer). In complementary analyses, we performed meta-analyses separately for 6 month, 12 month, and > 12 month follow-ups; the results differed by less than 1 mm per period. and in a complementary multivariate meta-analysis we found even these small differences shrinked further when taking into account missing follow-up and serial correlation.

> TODO(Marisse): decide whether you want to include the information in that last paragraph in the methods or in the results.

Some studies used washout in at least some time periods to measure the effect of surgery separately from the effect of medication. When both pre- and post-surgery IOP were reported with washout, these are the values we used (refs Pfeiffer, Vold); this is indicated by an asterisk in the main results. When washout was used in only some periods, we used non-washouted values across time periods, for consistency. The only exception was (ref Azuara—Blanco 2016), where IOP was measured with washout in the pre-period but not in the post period, due to study design. We indicate this study with a double asterisk.

Many studies did not report IOP drop directly, but rather only absolute IOP in the pre-period and at the follow-up period. Assuming full follow-up, the IOP drop is simply the difference of these measurements, while the SD (σ) of the IOP drop is estimated by:

$\sigma^2_{drop} = \sigma^2_{pre} + \sigma^2_{post} - 2r\sigma_{pre}\sigma_{post}$

r, the correlation between the pre-and-post measurements, was set to the median of the correlations in the studies reporting the full set of metrics (r = 0.35).

```
df <- read.data(impute.change = FALSE)
rs <- with(df, (PreOpIOPStdDev ** 2 + LastPeriodIOPStdDev ** 2 - LastPeriodAbsIOPChangeStdDev ** 2) / (
quantile(rs, .5, na.rm=TRUE)
```

```
##      50%
## 0.306774
```

Many studies reported several arms corresponding to different severities, treatments and subtypes. For phacoemulsification studies, we aggregated the data to obtain one arm per glaucoma subtype (ACG, OAG, PXG, acute) per study.

After this step, the total number of arms and eyes per subtype was as follows:

```
df_ <- df %>% filter(!is.na(LastPeriodAbsIOPChangeMean)) %>% group_by(subtype) %>%
  dplyr::summarize(
    n.total = n(),
    n.prospective = sum(StudyType == 'Prospective'),
    n.retrospective = sum(StudyType == 'Retrospective'),
    PreOpEyes = sum(PreOpEyes),
    FinalPeriodEyes = sum(LastPeriodEyes))

df_ <- df_ %>% rbind(., summarize(df_,
                                  subtype="(all)",
                                  n.total=sum(n.total),
                                  n.prospective=sum(n.prospective),
                                  n.retrospective=sum(n.retrospective),
                                  PreOpEyes=sum(PreOpEyes),
                                  FinalPeriodEyes = sum(FinalPeriodEyes)))

kable(df_)
```

subtype	n.total	n.prospective	n.retrospective	PreOpEyes	FinalPeriodEyes
ACG	5	4	1	215	213
acute	1	1	0	43	43
OAG	11	6	5	662	577
PXG	2	1	1	52	50
(all)	19	12	7	972	883

The full list of studies is as follow:

```
df_ <- df %>% filter(!is.na(LastPeriodAbsIOPChangeMean)) %>%
  arrange(subtype, Year, study.name) %>%
  dplyr::select(
    study.name,
    Year,
    StudyType,
    subtype,
    PreEyes=PreOpEyes,
    PreIOPMean=PreOpIOPMean,
    PreIOPSD=PreOpIOPStdDev,
    TimeofLastPostOp)
kable(df_, digits = 1)
```

study.name	Year	StudyType	subtype	PreEyes	PreIOPMean	PreIOPSD	TimeofLastPostOp
Hayashi et al. (2001)	2001	Prospective	ACG	74	21.4	3.9	24 mo
Mierzejewski et al. (2008)	2008	Retrospective	ACG	25	19.5	5.2	14.5 +/- 4.4 mo
Tham et al. (2013)	2013	Prospective	ACG	26	24.1	4.1	24 mo
Dada et al. (2015)	2015	Prospective	ACG	44	27.1	1.6	12 mo
Moghimi et al. (2015)	2015	Prospective	ACG	46	22.3	6.3	12 mo
Jacobi et al. (2002)	2002	Prospective	acute	43	40.5	7.6	10.2 +/- 3.4 mo
Hayashi et al. (2001)	2001	Prospective	OAG	68	20.7	5.4	24 mo
Leelachaikul et al. (2005)	2005	Retrospective	OAG	58	16.5	3.8	18 mo
Mathalone et al. (2005)	2005	Retrospective	OAG	58	17.0	4.6	24 mo
Damji et al. (2006)	2006	Prospective	OAG	29	18.5	3.5	24 mo
Shingleton et al. (2006)	2006	Retrospective	OAG	55	18.4	3.4	36 mo
Shoji et al. (2007)	2007	Retrospective	OAG	35	16.7	1.4	36 mo
Mierzejewski et al. (2008)	2008	Retrospective	OAG	52	18.4	4.8	14.4 +/- 4.1 mo
Fea et. al (2010)	2010	Prospective	OAG	21	17.3	3.0	15 mo
Samuelson et al. (2011)	2011	Prospective	OAG	117	18.0	3.0	12 mo
Iancu et al. (2014)	2014	Prospective	OAG	38	23.8	2.3	12 mo
Vold et al. (2016)*	2016	Prospective	OAG	131	24.5	3.0	24 mo
Damji et al. (2006)	2006	Prospective	PXG	29	19.8	2.9	24 mo
Mierzejewski et al. (2008)	2008	Retrospective	PXG	23	21.0	3.5	15.1 +/- 2.1 mo

```
df_ <- df %>% filter(!is.na(LastPeriodAbsIOPChangeMean)) %>%
  arrange(subtype, Year, study.name) %>%
  dplyr::select(
    study.name,
    PostEyes=LastPeriodEyes,
    PostIOPMean=LastPeriodIOPMean,
    PostIOPSD=LastPeriodIOPStdDev,
    PostIOPChangeMean=LastPeriodAbsIOPChangeMean,
    PostIOPChangeSD=LastPeriodAbsIOPChangeStdDev)
kable(df_, digits = 1)
```

study.name	PostEyes	PostIOPMean	PostIOPSD	PostIOPChangeMean	PostIOPChangeSD
Hayashi et al. (2001)	72	14.5	2.6	-7.2	3.5
Mierzejewski et al. (2008)	25	14.4	4.4	-5.1	4.8
Tham et al. (2013)	26	15.9	3.9	-8.4	6.0
Dada et al. (2015)	44	13.2	1.1	-14.3	1.8
Moghimi et al. (2015)	46	14.0	3.7	-8.3	6.8
Jacobi et al. (2002)	43	17.8	3.4	-22.7	3.2
Hayashi et al. (2001)	50	15.2	3.8	-5.3	4.8
Leelachaikul et al. (2005)	54	15.2	3.7	-1.6	4.2
Mathalone et al. (2005)	24	15.1	3.2	-1.9	4.9
Damji et al. (2006)	24	NA	NA	-1.5	4.2
Shingleton et al. (2006)	55	NA	NA	-1.4	3.3
Shoji et al. (2007)	20	15.6	3.4	-1.0	3.0
Mierzejewski et al. (2008)	52	14.4	4.0	-4.0	4.0
Fea et. al (2010)	21	15.7	1.1	-1.6	3.2
Samuelson et al. (2011)	123	NA	NA	-1.0	3.3
Iancu et al. (2014)	38	21.6	2.4	-1.9	3.9
Vold et al. (2016)*	116	19.3	3.3	-5.4	3.9
Damji et al. (2006)	27	NA	NA	-3.1	4.1
Mierzejewski et al. (2008)	23	14.4	3.0	-6.6	3.9

12 & 15. Risk of bias

A major source of bias is loss of follow-up. Retrospective and prospective studies have different potential patterns of lossiness. Most retrospective studies reported the IOP before and after surgery *for the same set of eyes*, which leaves the possibility that some eyes received surgery and were lost in follow up, which is very hard to quantify. Prospective studies are less problematic in this regard, as the number of eyes lost in follow-up is known.

In the main text, we present the results of the analysis under a missing completely at random (MCAR) assumption, which does do not attempt to correct for these biases.

In a supplementary analysis, we verify the robustness of the results by considering the results of including just the prospective studies, which are less subject to bias. We also consider how our results would change if the eyes lost to follow up showed overall worse outcomes than in the measured eyes. We consider what would happen if these eyes had 0 change in IOP compared to the pre-period, or a 5 mm Hg increase compared to the observed eyes. However, because the loss of follow-up in the prospective group was rather mild (table below), the results were not very sensitive to this form of loss, except in the case of PXG, where only two prospective studies have been performed, and they both had significant loss in follow up.

```
df <- read.data()
df <- filter.data(df, 'prospective')

df_ <- df %>% filter(subtype != 'acute', !is.na(LastPeriodEyes))
frac <- (df_$PreOpEyes - df_$LastPeriodEyes)/ df_$PreOpEyes
frac.range <- data.frame("fraction with loss"=mean(frac > 0),
           "mean loss"=mean(frac),
           "SD loss"=sd(frac),
           "min loss"=min(frac),
           "max loss"=max(frac),
           check.names=FALSE)
kable(frac.range, digits=2)
```

fraction with loss	mean loss	SD loss	min loss	max loss
0.4	0.06	0.11	-0.05	0.41

Small studies often show larger magnitude effects because of the so-called file drawer problem: the tendency of negative results from small-scale studies to never get published (ref). We used standard funnel plot based methods to verify this was the case. In fact, the data shows an unusual, opposite trend: the larger studies tended to show the largest effects, an effect we attribute to washout. We discuss this in detail in the main results.

A final, important source of bias is the lack of a true control group. It would very difficult to create a true control – sham surgery – and unethical to not subject patients to any treatments.

> TODO(Marisse): Find the best estimate for the average change in IOP over a year for patients that have glaucoma and don't change medications. This could be from a meta-analysis of the change in IOP in placebo arms of drug trials, for instance. I thought I saw something like that in a paper > TODO(Marisse): think of other ways we could address this confound

14. Synthesis of results

We used standard random-effects meta-analysis for continuous outcomes (ref `meta` package in R; ref book) throughout the text. We used multivariate meta-analysis (package `mvmeta`; ref book) to summarize the

temporal trend in IOP.

15. Additional analyses

TODO(Patrick): explain the washout and medication stuff.