```
/*Evaluation of FLuorometholone as Adjunctive MEdical Therapy for Trachomatous Trichiasis Surgery: The FLAME Randomized Controlled Clinical Trial*/
/*purpose: Comparison of safety outcomes between randomized treatment groups*/
/*Note: raw datasets in SAS library 'in' corresponds to the shared data file in xlsx format, their relationship are as below:
in.eligibility - EL
in.EYEEXAM_W4 - WE
in.EYEEXAM_M6 - month 6 record in ME
in.EYEEXAM_m12 - month 12 record in ME
in.EYEPAIN_M12 - month 12 record in EP
in.HEALTHREVIEW_W4 - week 4 record in FR
in.HEALTHREVIEW_M6 - month 6 record in FR
in.HEALTHREVIEW_M12 - month 12 record in FR
in.SURGERY - SI
in.ae - AE*/

/*set up SAS library, TLF path, TLF title, format catalog which will be used in later analysis*/
%include "setup.sas";
libname in "&_root_in";
libname fm "&_root_fm";
libname data "&_root_data";
%let TLF_path = &_root_output\tb5_safety_endpoints.rtf;
%let TLF_title = Table 5: Comparison of safety outcomes between randomized treatment groups;

OPTIONS FMTSEARCH=(fm.fmsurgery fm.fmexamm6 fm.fmexamw4 fm.fmelig fm.fmprimary fm.fmfu fm.fmeyepain);
option mprint;

/*set up variable format for visualization*/
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proc format;
        value gf  0 = "Placebo" 1 = "FML";
        value ynf 0 = "No" 1 = "Yes";
        value yno 1='No' 2='Yes';
        value absevf 1='Mild'
                                2='Moderate'
                                3='Severe';
        value absevo 1='Mild'
                                2='Moderate'
                                3='Severe';
        value aef 0='No'
                        1='Yes, not serious'
                        2='Yes, serious';
        value aeo 1='No'
                        2='Yes, not serious'
                        3='Yes, serious';
        value pval (default=8)
                low - <0.00095 = '<0.001'
                0.00095 - <0.0095 = [8.3]
                0.0095 - <0.045 = [8.2]
                0.045 - <0.0495 = [8.3]
                0.0495 - <0.04995 = [8.4]
                0.04995 - <0.05 = '~<0.05'
                0.05 = '0.05'
                0.05< - <0.05005 = '~>0.05'
                0.05005 - <0.0505 = [8.4]
                0.0505 - <0.055 = [8.3]
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                0.055 - 0.99 = [8.2]
                0.99< - high = [8.2];
run;

/* combine covariate used for analysis;*/
data fas;
        set data.fas;
        if reye_eligibel=1 then do; eye='OD'; output; end;
        if leye_eligibel=1 then do; eye='OS'; output; end;
run;

data eligibility_;
length eye $10.;
set in.eligibility;
eye='OD'; eliopmedian=eliopmedian_r; eltt_u=eltt_ru;output;
eye='OS'; eliopmedian=eliopmedian_l; eltt_u=eltt_lu;output;
run;
data EYEEXAM_W4;
set in.EYEEXAM_W4;
run;
data EYEEXAM_M6;
set in.EYEEXAM_M6;
run;
data EYEEXAM_m12;
set in.EYEEXAM_m12;
run;
data EYEPAIN_M12;
```

```
set in.EYEPAIN_M12;
run;
data HEALTHREVIEW_W4;
set in.HEALTHREVIEW_W4;
run;
data HEALTHREVIEW_M6;
set in.HEALTHREVIEW_M6;
run;
data HEALTHREVIEW_M12;
set in.HEALTHREVIEW_M12;
run;
%proc_reshape(indata=WORK.EYEEXAM_W4,memname="EYEEXAM_W4",outdata=EYEEXAM_W4_);
%proc_reshape(indata=WORK.EYEEXAM_M6,memname="EYEEXAM_M6",outdata=EYEEXAM_M6_);
%proc_reshape(indata=WORK.EYEEXAM_M12,memname="EYEEXAM_M12",outdata=EYEEXAM_M12_);
%proc_reshape(indata=WORK.EYEPAIN_M12,memname="EYEPAIN_M12",outdata=EYEPAIN_M12_);
%proc_reshape(indata=WORK.HEALTHREVIEW_W4,memname="HEALTHREVIEW_W4",outdata=HEALTHREVIEW_W4_);
%proc_reshape(indata=WORK.HEALTHREVIEW_M6,memname="HEALTHREVIEW_M6",outdata=HEALTHREVIEW_M6_);
%proc_reshape(indata=WORK.HEALTHREVIEW_M12,memname="HEALTHREVIEW_M12",outdata=HEALTHREVIEW_M12_);

proc sql;
create table data.tbl5_data_1 as
select r.subjid, r.eye, r.treat,
        case when a.mecornealscar in (1,2,3,4,5,6,7) then 1
                when a.mecornealscar=0 then 0 end as mecornealscar_c,
        a.meovercorrection,a.mecontour,
        a.menotchpre,a.menotchloc_1,a.menotchloc_2,a.menotchloc_3,a.menotchsev,
        a.meotherpre,a.meotherloc_1,a.meotherloc_2,a.meotherloc_3,a.meothersev,
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```
        a.melidclos,a.megranuloma,
        epcare + epsleep + ephousework + eppaidwork + epsocial as total_score,
        median(weiopsc1,weiopsc2,weiopsc3) as iop_w4,
        median(e.meiop1,e.meiop2,e.meiop3) as iop_m6,
        median(a.meiop1,a.meiop2,a.meiop3) as iop_m12,
        case when calculated iop_w4>=30 or calculated iop_w4-eliopmedian>=10 then 1
                when .<calculated iop_w4<30 and .<calculated iop_w4-eliopmedian<10 then 0 end as iop_elevation_w4,
        case when calculated iop_w4-eliopmedian>=10 or calculated iop_m6-eliopmedian>=10 or calculated iop_m12-
eliopmedian>=10 then 1
                when calculated iop_w4^=. or calculated iop_m6^=. or calculated iop_m12^=. then 0 end as
iop_elevation_m12,
        case when g.frsurgtype=3 or h.frsurgtype=3 or i.frsurgtype=3 then 1
                when (g.frsurgtype in (1,2,4,5) or g.frsurg=0) or (h.frsurgtype in (1,2,4,5) or h.frsurg=0) or (i.frsurgtype in
(1,2,4,5) or i.frsurg=0) then 0 end as cata_surg,
        /*to meet requirement of HIPAA, name (sisiname2) and certification (sisicert2) of surgeon is removed from the public
shared dataset*/
        sisicert2,sisiname2,
        /*for surgeon that only have a small number of surgery (<50), cluster them into 1 group*/
        case when sisicert2 in (/*surgeon license removed*/) then 'Other'
        else sisicert2 end as sisicert3
from fas as r
left join EYEEXAM_M12_ as a on r.subjid=a.subjid and r.eye=a.eye
left join EYEPAIN_M12_ as b on r.subjid=b.subjid and r.eye=b.eye
left join eligibility_ as c on r.subjid=c.subjectid and r.eye=c.eye
left join EYEEXAM_W4_ as d on r.subjid=d.subjid and r.eye=d.eye
left join EYEEXAM_M6_ as e on r.subjid=e.subjid and r.eye=e.eye
left join HEALTHREVIEW_M12_ as g on r.subjid=g.subjid and r.eye=g.eye
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left join HEALTHREVIEW_M6_ as h on r.subjid=h.subjid and r.eye=h.eye
left join HEALTHREVIEW_W4_ as i on r.subjid=i.subjid and r.eye=i.eye
left join in.surgery as j on r.subjid=j.subjid;
quit;

proc sql;
create table data.tbl5_data_3 as
select r.subjid, r.treat,
        case when aeaerm>1 then 2
                when aeaerm=1 then 1
                else 0 end as related_ae,
        /*to meet requirement of HIPAA, name (sisiname2) and certification (sisicert2) of surgeon is removed from the public
shared dataset*/
        sisicert2,sisiname2,
        /*for surgeon that only have a small number of surgery (<50), cluster them into 1 group*/
        case when sisicert2 in (/*surgeon license removed*/) then 'Other'
        else sisicert2 end as sisicert3
from data.fas as r
left join (select distinct subjid,max(aeaer) as aeaerm from in.ae(where=(aerel in (3,4))) group by subjid) as a
on r.subjid=a.subjid
left join in.surgery as s on r.subjid=s.subjid;
quit;

* descriptive statistics, hypothesis test and model building;
%stat_char(input=data.tbl5_data_1,output=tab_1,unit=eye,variable=mecornealscar_c,min=1,max=2,cohort=treat,ref=Placeb
o,questionlabel=Cornea opacity in study eye at 1
```

year,tab_order=**1**,value_label=ynf,order_label=yno,id=subjid,self_denom=**1**,N=**1**,gee_binomial=**1**,gee_multinomial=**0**,reverse=**0**,chi=**0**,fisher=**0**,surgeon=**1**,surgeon_cluster=**0**,surg_bar=**0**,diffs=**1**,event=**1**);
%***stat_char***(input=data.tbl5_data_1,output=tab_2,unit=eye,variable=meovercorrection,min=**1**,max=**2**,cohort=treat,ref=Placebo,questionlabel=Overcorrection in study eye at **1**
year,tab_order=**2**,value_label=ynf,order_label=yno,id=subjid,self_denom=**1**,N=**1**,gee_binomial=**1**,gee_multinomial=**0**,reverse=**0**,chi=**0**,fisher=**0**,surgeon=**0**,diffs=**1**,event=Yes);

%***stat_char***(input=data.tbl5_data_1,output=tab_3,unit=eye,variable=mecontour,min=**1**,max=**2**,cohort=treat,ref=Placebo,questionlabel=Eyelid contour abnormality in study eye at **1**
year,tab_order=**3**,value_label=ynf,order_label=yno,id=subjid,self_denom=**1**,N=**1**,gee_binomial=**1**,gee_multinomial=**0**,reverse=**0**,chi=**0**,fisher=**0**,surgeon=**1**,surgeon_cluster=**1**,surg_bar=**0**,diffs=**1**,event=Yes);
%***stat_char***(input=data.tbl5_data_1,output=tab_4,unit=eye,variable=menotchpre,min=**2**,max=**2**,cohort=treat,ref=Placebo,questionlabel=Eyelid notching in study eye at **1**
year,tab_order=**4**,value_label=ynf,order_label=yno,id=subjid,self_denom=**1**,N=**1**,gee_binomial=**1**,gee_multinomial=**0**,reverse=**0**,chi=**0**,fisher=**0**,surgeon=**1**,surgeon_cluster=**1**,surg_bar=**0**,diffs=**1**,event=Yes);
%***stat_char***(input=data.tbl5_data_1,output=tab_5,unit=eye,variable=meotherpre,min=**2**,max=**2**,cohort=treat,ref=Placebo,questionlabel=Other eyelid contour abnormalities in study eye at **1**
year,tab_order=**5**,value_label=ynf,order_label=yno,id=subjid,self_denom=**1**,N=**1**,gee_binomial=**1**,gee_multinomial=**0**,reverse=**0**,chi=**0**,fisher=**0**,surgeon=**0**,diffs=**1**,event=Yes);

%***stat_char***(input=data.tbl5_data_1,output=tab_6,unit=eye,variable=melidclos,min=**1**,max=**2**,cohort=treat,ref=Placebo,questionlabel=Lid closure defect in study eyes at **1**
year,tab_order=**6**,value_label=ynf,order_label=yno,id=subjid,self_denom=**1**,N=**1**,gee_binomial=**0**,gee_multinomial=**0**,reverse=**0**,chi=**0**,fisher=**2**,diffs=**1**,event=Yes,riskcol=**2**);
*%stat_char(input=data.tbl5_data_1,output=tab_7,unit=eye,variable=megranuloma,min=1,max=2,cohort=treat,ref=Placebo,quuestionlabel=Granuloma in study eyes at 1

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year,tab_order=7,value_label=ynf,order_label=yno,id=subjid,self_denom=1,N=1,gee_binomial=1,gee_multinomial=0,reverse=
0,chi=0,fisher=0,surgeon=0,diffs=1,event=Yes);
%stat_char(input=data.tbl5_data_1,output=tab_7,unit=eye,variable=megranuloma,min=1,max=2,cohort=treat,ref=Placebo,q
uestionlabel=Granuloma in study eyes at 1
year,tab_order=7,value_label=ynf,order_label=yno,id=subjid,self_denom=1,N=1,gee_binomial=0,gee_multinomial=0,reverse=
0,chi=0,fisher=2,surgeon=0,diffs=1,event=Yes,riskcol=2);
%stat_num(input=data.tbl5_data_1,output=tab_8,variable=total_score,cohort=treat,ref=Placebo,questionlabel=,tab_order=8,
id=subjid,gee_linear=1,surgeon=1,diffs=1);
data tab_8;
        length answerlabel $200;
        set tab_8;
        if index(upcase(answerlabel),'MEAN')>0 then do; answerlabel='Pain score in study eyes at 1 years: Mean (SD)~{unicode
A7}'; output; end;
run;

*%stat_char(input=data.tbl5_data_1,output=tab_9,unit=eye,variable=iop_elevation_w4,min=1,max=2,cohort=treat,ref=Placeb
o,questionlabel=IOP elevation in study eyes at week
4*,tab_order=9,value_label=ynf,order_label=yno,id=subjid,self_denom=1,N=1,gee_binomial=1,gee_multinomial=0,reverse=0,
chi=0,fisher=0,surgeon=0,diffs=1,event=1);
%stat_char(input=data.tbl5_data_1,output=tab_9,unit=eye,variable=iop_elevation_w4,min=1,max=2,cohort=treat,ref=Placeb
o,questionlabel=IOP elevation in study eyes at week
4*,tab_order=9,value_label=ynf,order_label=yno,id=subjid,self_denom=1,N=1,gee_binomial=0,gee_multinomial=0,reverse=0,
chi=0,fisher=2,surgeon=0,diffs=1,event=1,riskcol=2);
*%stat_char(input=data.tbl5_data_1,output=tab_10,unit=eye,variable=iop_elevation_m12,min=1,max=2,cohort=treat,ref=Pla
cebo,questionlabel=IOP elevation >=10 mmHg from baseline in study eyes within one
year,tab_order=10,value_label=ynf,order_label=yno,id=subjid,self_denom=1,N=1,gee_binomial=1,gee_multinomial=0,reverse
=0,chi=0,fisher=0,surgeon=0,diffs=1,event=1);
```

%***stat_char***(input=data.tbl5_data_1,output=tab_10,unit=eye,variable=iop_elevation_m12,min=**1**,max=**2**,cohort=treat,ref=Placebo,questionlabel=IOP elevation >=**10** mmHg from baseline in study eyes within one year,tab_order=**10**,value_label=ynf,order_label=yno,id=subjid,self_denom=**1**,N=**1**,gee_binomial=**0**,gee_multinomial=**0**,reverse=**0**,chi=**0**,fisher=**2**,surgeon=**0**,diffs=**1**,event=**1**,riskcol=**2**);

*%stat_char(input=data.tbl5_data_1,output=tab_11,unit=eye,variable=cata_surg,min=1,max=2,cohort=treat,ref=Placebo,questionlabel=Any incidence of cataract surgery in study eyes by one year,tab_order=11,value_label=ynf,order_label=yno,id=subjid,self_denom=1,N=1,gee_binomial=1,gee_multinomial=0,reverse=0,chi=0,fisher=0,surgeon=0,diffs=1,event=1);
%***stat_char***(input=data.tbl5_data_1,output=tab_11,unit=eye,variable=cata_surg,min=**1**,max=**2**,cohort=treat,ref=Placebo,questionlabel=Any incidence of cataract surgery in study eyes by one year,tab_order=**11**,value_label=ynf,order_label=yno,id=subjid,self_denom=**1**,N=**1**,gee_binomial=**0**,gee_multinomial=**0**,reverse=**0**,chi=**0**,fisher=**2**,surgeon=**0**,diffs=**1**,event=**1**,riskcol=**2**);
*%stat_char(input=data.tbl5_data_3,output=tab_13,unit=pat,variable=related_ae,min=1,max=3,cohort=treat,ref=Placebo,questionlabel=Any incidence of adverse events attributed to study treatment by one year,tab_order=13,value_label=aef,order_label=aeo,id=subjid,self_denom=1,N=1,gee_binomial=0,gee_multinomial=0,reverse=0,chi=1,fisher=0,diffs=1,riskcol=2);
%***stat_char***(input=data.tbl5_data_3,output=tab_13,unit=pat,variable=related_ae,min=**1**,max=**3**,cohort=treat,ref=Placebo,questionlabel=Any incidence of adverse events attributed to study treatment by one year,tab_order=**13**,value_label=aef,order_label=aeo,id=subjid,self_denom=**1**,N=**1**,gee_binomial=**0**,gee_multinomial=**0**,reverse=**0**,chi=**0**,fisher=**2**,diffs=**1**,riskcol=**2**);

```
data temp_notch;
        set data.tbl5_data_1;
        where menotchpre = 1;
run;
proc sql noprint;
```

```
select count(*) into :t0_eye
                from temp_notch
                where treat = 0;
select count(*) into :t1_eye
                from temp_notch
                where treat = 1;
quit;
%put &t0_eye;
%put &t1_eye;
%stat_char(input=temp_notch,output=tab_4_1,unit=eye,variable=menotchloc_1,min=2,max=2,cohort=treat,ref=Placebo,que
stionlabel=Location,tab_order=4.1,value_label=ynf,order_label=yno,id=subjid,gee_binomial=0,gee_multinomial=0,reverse=0,
chi=0,fisher=0);
%stat_char(input=temp_notch,output=tab_4_2,unit=eye,variable=menotchloc_2,min=2,max=2,cohort=treat,ref=Placebo,que
stionlabel=,tab_order=4.2,value_label=ynf,order_label=yno,id=subjid,gee_binomial=0,gee_multinomial=0,reverse=0,chi=0,fis
her=0);
%stat_char(input=temp_notch,output=tab_4_3,unit=eye,variable=menotchloc_3,min=2,max=2,cohort=treat,ref=Placebo,que
stionlabel=,tab_order=4.3,value_label=ynf,order_label=yno,id=subjid,gee_binomial=0,gee_multinomial=0,reverse=0,chi=0,fis
her=0);
%stat_char(input=temp_notch,output=tab_4_4,unit=eye,variable=menotchsev,min=1,max=3,cohort=treat,ref=Placebo,questi
onlabel=Severity,tab_order=4.4,value_label=absevf,order_label=absevo,id=subjid,gee_binomial=0,gee_multinomial=0,revers
e=0,chi=0,fisher=0);

data tab_4;
        set tab_4(in=a) tab_4_1(in=b) tab_4_2(in=c) tab_4_3(in=d) tab_4_4(in=e);
        if a and index(answerlabel,'Yes')>0 then answerlabel='  Presence (%)';
        if b and index(answerlabel,'Yes')>0 then answerlabel='  Lateral';
        if c then answerlabel='    Central';
```

```
        if d then answerlabel='    Medial';
        if b or e then answerlabel='  '||answerlabel;
run;
proc datasets;
delete tab_4_1 tab_4_2 tab_4_3 tab_4_4;
quit;

data temp_other;
        set data.tbl5_data_1;
        where meotherpre = 1;
run;
proc sql noprint;
select count(*) into :t0_eye
                from temp_other
                where treat = 0;
select count(*) into :t1_eye
                from temp_other
                where treat = 1;
quit;
%put &t0_eye;
%put &t1_eye;
%stat_char(input=temp_other,output=tab_5_1,unit=eye,variable=meotherloc_1,min=2,max=2,cohort=treat,ref=Placebo,questionlabel=Location,tab_order=5.1,value_label=ynf,order_label=yno,id=subjid,gee_binomial=0,gee_multinomial=0,reverse=0,chi=0,fisher=0);
%stat_char(input=temp_other,output=tab_5_2,unit=eye,variable=meotherloc_2,min=2,max=2,cohort=treat,ref=Placebo,questionlabel=,tab_order=5.2,value_label=ynf,order_label=yno,id=subjid,gee_binomial=0,gee_multinomial=0,reverse=0,chi=0,fisher=0);
```

```
%stat_char(input=temp_other,output=tab_5_3,unit=eye,variable=meotherloc_3,min=2,max=2,cohort=treat,ref=Placebo,ques
tionlabel=,tab_order=5.3,value_label=ynf,order_label=yno,id=subjid,gee_binomial=0,gee_multinomial=0,reverse=0,chi=0,fish
er=0);
%stat_char(input=temp_other,output=tab_5_4,unit=eye,variable=meothersev,min=1,max=3,cohort=treat,ref=Placebo,questi
onlabel=Severity,tab_order=5.4,value_label=absevf,order_label=absevo,id=subjid,gee_binomial=0,gee_multinomial=0,revers
e=0,chi=0,fisher=0);

data tab_5;
        set tab_5(in=a) tab_5_1(in=b) tab_5_2(in=c) tab_5_3(in=d) tab_5_4(in=e);
        if a and index(answerlabel,'Yes')>0 then answerlabel='  Presence (%)';
        if b and index(answerlabel,'Yes')>0 then answerlabel='  Lateral';
        if c then answerlabel='    Central';
        if d then answerlabel='    Medial';
        if b or e then answerlabel='  '||answerlabel;
run;
proc datasets;
delete tab_5_1 tab_5_2 tab_5_3 tab_5_4;
quit;

/*combine the result*/
data data.tbl5_result;
length answerlabel cohort_0 cohort_1 diffs pval $200.;
set tab_:;
if tab_order in (1,3,4,8) and pvalue^=. then pval=strip(put(pvalue,pval.))||'#';
else if tab_order in (2,5) and pvalue^=. then pval=strip(put(pvalue,pval.))||'**';
else if tab_order in (6,7,9,10,11,13) and pvalue^=. then pval=strip(put(pvalue,pval.))||'~{unicode 2020}';
else pval=strip(put(pvalue,pval.));
```

```
run;
proc sort data=data.tbl5_result; by tab_order answer_order; run;

/*generate table*/
options nodate nonumber;
ods rtf file = "&TLF_path";
ods escapechar='~';
ods rtf text="~S={just=l font_size=10pt font_weight= bold} &TLF_title";
proc report data=data.tbl5_result nowd spanrows split='|' missing style(column)={background=white fontsize=9pt}

style(header)={background=white fontsize=9pt fontweight=medium};
        columns tab_order answer_order answerlabel cohort_0 cohort_1 diffs pval;
        define tab_order  / ' ' order order=internal noprint;
        define answer_order  / ' ' order order=internal noprint;
        define answerlabel / 'Safety Outcomes in study eyes' left style(column)={cellwidth=1.8in asis=ON}
style(header)={just=l};
        define cohort_0 / "Placebo" center style(column)={cellwidth=1.4in};
        define cohort_1 / "FLuorometholone" center style(column)={cellwidth=1.4in};
        define diffs / 'Difference (95% CI)' center group style(column)={cellwidth=1.4in};
        define pval / 'P-value' center group style(column)={cellwidth=1.4in};
run ;
ods rtf text="~S={just=l font_size=9pt} *IOP elevation is defined as IOP increase of 10 mmHg or more from baseline, or IOP 30
mmHg or above.";
ods rtf text="~S={just=l font_size=9pt} #derived from generalized regression models adjusting for surgeon that account for
inter-eye correlation";
ods rtf text="~S={just=l font_size=9pt} **derived from generalized regression models that account for inter-eye correlation
without adjusting for surgeon due to the small number of events";
```

```
ods rtf text="~S={just=l font_size=9pt} ~{unicode 2020}derived from chi square tests or Fisher’s exact test (well count in a cell is less than 5)";
ods rtf text="~S={just=l font_size=9pt} ~{unicode A7}Calculated as the sum of the levels (1 to 4) for each of 5 eye pain impact questions, with index value ranging from 5 to 20.";
ods rtf close;

libname in clear;
libname fm clear;
```