Addressing Reviewer Comments

0. Setup

Reading packages

```r
library(tidyverse)
```

```
## Warning: package 'tidyverse' was built under R version 3.5.2

## -- Attaching packages --------------------------------------- tidyverse 1.2.1 --

## v ggplot2 3.0.0     v purrr   0.2.5
## v tibble  1.4.2     v dplyr   0.7.6
## v tidyr   0.8.1     v stringr 1.3.1
## v readr   1.2.1     v forcats 0.3.0

## -- Conflicts ------------------------------------------ tidyverse_conflicts() --
## x dplyr::filter() masks stats::filter()
## x dplyr::lag()    masks stats::lag()
```

Creating file paths

```r
if(Sys.info()["user"]=="JVARGH7"){
  path_ic_documentation <- "C:/code/support/interstitial_cystitis/documentation"
  path_ic_data <- "C:/Cloud/OneDrive - Emory University/Papers/Interstitial Cystitis/data"
  path_ic_save <- "C:/Cloud/OneDrive - Emory University/Papers/Interstitial Cystitis/working"
}
```

```r
ic <- readRDS(paste0(path_ic_save,"/ic_submit.RDS"))
```

1. Confounding by Race?

SP: Regarding the lack of adjustment, I note that the outcome does not vary by any characteristic beyond race. I would make the argument that there is no opportunity for confounding by a table 1 characteristic other than race.

I would also do an analysis restricted to whites, eliminating the potential for confounding by race. Hopefully you will get similar results (even if statistical significance is lost). If not, you may have a genuine confounding problem.

```r
table(ic$race,ic$outcome,useNA="always")
```

```
##
##            no yes <NA>
##   1 White 137  17    0
##   2 Black  43   2    0
##   3 Other  15   5    0
##   <NA>      0   0    0
```

a. Fisher's Test for Whites

```
with(ic[ic$race=="1 White",],table(outcome,elmiron))
```

```
##        elmiron
## outcome no yes
##     no  96  41
##     yes  3  14
```

Odds Ratio:

```
(96*14)/(3*41)
```

```
## [1] 10.92683
```

OR from Fisher's Exact Test is Hypothesized Odds Ratio

```
with(ic[ic$race=="1 White",],fisher.test(outcome,elmiron))
```

```
##
##  Fisher's Exact Test for Count Data
##
## data:  outcome and elmiron
## p-value = 4.291e-05
## alternative hypothesis: true odds ratio is not equal to 1
## 95 percent confidence interval:
##   2.793577 61.435540
## sample estimates:
## odds ratio
##   10.74508
```

2. Composite Outcome?

Regarding the composite outcome, there are a couple of things to explore. First, you could similarly restrict the OR calculation to the estimable sample, ie exclude Grade 1 from the sample and show that the results go in the same direction for Grade 2-4 (I computed an OR=3.75 when I tried this out). Second, you can do a Fishers exact test with Grade 1 as one level, and group Grade 2-4 together; or then do an extension of the test where you can have more than 2 columns. Fishers exact test is neat in that it doesn't produce an OR (or a risk, or an odds) but it computes all of the 2x2 tables that could possibly be observed and provides the likelihood of that particular 2x2 table or one more extreme being observed. Basically, it circumvents the problem of computing the OR. You will definitely get a significant result here because this is an extreme distribution. Finally, as a note of caution –knowing nothing about this disease process or drug, the results are quite striking . . . could confounding by indication be an issue (where physicians are prescribing this drug to a group of patients precisely because they have this morbidity)? This can be a problem in a cross-sectional study. You may have addressed this in the text, but I only read the abstract and looked at the tables.

a. OR for Estimable Sample- Exclude Grade 1

```
with(ic[ic$cases!="1 Definite",],table(outcome,elmiron))
```

```
##        elmiron
## outcome  no yes
##     no  135  60
##     yes   4   6
```

Odds Ratio:

```
6*135/(60*4)
```

```
## [1] 3.375
```

```
with(ic[ic$cases!="1 Definite",],fisher.test(outcome,elmiron))
```

```
##
##  Fisher's Exact Test for Count Data
##
## data:  outcome and elmiron
## p-value = 0.07914
## alternative hypothesis: true odds ratio is not equal to 1
## 95 percent confidence interval:
##   0.76338 16.75991
## sample estimates:
## odds ratio
##   3.352567
```

b. OR for Alternate Grouping: Grade 1 vs 2,3,4

```
ic$outcome_2b <- with(ic, as.factor(ifelse(cases %in% c("1 Definite"),"yes","no")))
```

```
with(ic,table(outcome_2b,elmiron))
```

```
##           elmiron
## outcome_2b  no yes
##        no  139  66
##        yes   0  14
```

Fisher's Exact Test:

```
with(ic,fisher.test(outcome_2b,elmiron))
```

```
##
##  Fisher's Exact Test for Count Data
##
## data:  outcome_2b and elmiron
## p-value = 3.443e-07
## alternative hypothesis: true odds ratio is not equal to 1
## 95 percent confidence interval:
##  6.662281      Inf
## sample estimates:
## odds ratio
##        Inf
```

c. Test for Alternate Grouping: Grade 1 vs 3,4

```r
with(ic[ic$cases!="2 Possibly",],table(outcome,elmiron))
```

```
##         elmiron
## outcome  no yes
##     no  135  60
##     yes   0  14
```

```r
with(ic[ic$cases!="2 Possibly",],fisher.test(outcome,elmiron))
```

```
##
##  Fisher's Exact Test for Count Data
##
## data:  outcome and elmiron
## p-value = 2.045e-07
## alternative hypothesis: true odds ratio is not equal to 1
## 95 percent confidence interval:
##  7.091033      Inf
## sample estimates:
## odds ratio
##        Inf
```