Example 2

PRO responder analysis

Paolo Eusebi, Sonja Hartnack

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PRO

- A patient-reported outcome (PRO) measure, one type of clinical endpoint, is any report on the status of a patient's health condition that comes directly from the patient.

PRO responder analysis

- Quantitative PRO measures ideally are analyzed on their original scale.
- Responder analyses are used to aid the interpretation of those primary analyses.
- Responder analysis is based on the determination of a threshold for meaningful improvement or deterioration.
- Between-group differences in responder proportions or percentages may be understood more intuitively than a difference in mean scores from rating scales.

Example

- Data from a randomized, double-blind, placebo-controlled, fexible-dose, sildenafl citrate (Viagra) trial in which men were randomized to receive sildenafl or placebo for 12 weeks
- Responder analyses performed on the six-item erectile function domain of the International Index of Erectile Function (IIEF; range: 1–30, higher scores are better), a PRO measure.
- The table below shows the unadjusted data of response by treatment where a responder is classifed as having had a normal erectile function, defined as a score on the erectile function domain above 25 (26 to 30) after 12 weeks of treatment.

Response	Sildenafil	Placebo
Yes	54	16
No	58	99

Example

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- The unadjusted proportion who responded with sildenafil was 0.48 (54/112), while the unadjusted proportion who responded with placebo was 0.14 (16/115).
- The estimated response ratio (RR) is 3.47 (95% CI=2.15 to 5.71).

Miscassification bias

- A validation study of the responder threshold found that the cutoff of 25 has a sensitivity of 0.97 and a specificity of 0.88.
- The table below shows the corresponding bias-corrected data of response by treatment according to well-known formulas. (Cappelleri and Chambers 2021)

Response	Sildenafil	Placebo
Yes	47.7	2.6
No	64.3	112.4

- The adjusted proportion who responded with sildenafil was 0.43 (47.7/112), while the adjusted proportion who responded with placebo was 0.02 (2.6/115).
- The estimated RR is 18.84.

Miscassification again!

- The estimated adjusted response ratio of 18.84 was much higher than the estimated unadjusted response ratio of 3.47.
- Cappelleri and Chambers assume that responder status is measured with an imperfect tool, but that the sensitivity and specificity of the tool are precise, and that they contribute to the adjusted table without margins of uncertainty.
- In reality, the original study provided uncertainty estimates for sensitivity (95% CI=0.95 to 0.98) and specificity (95% CI=0.80 to 0.93).

Prior calibration

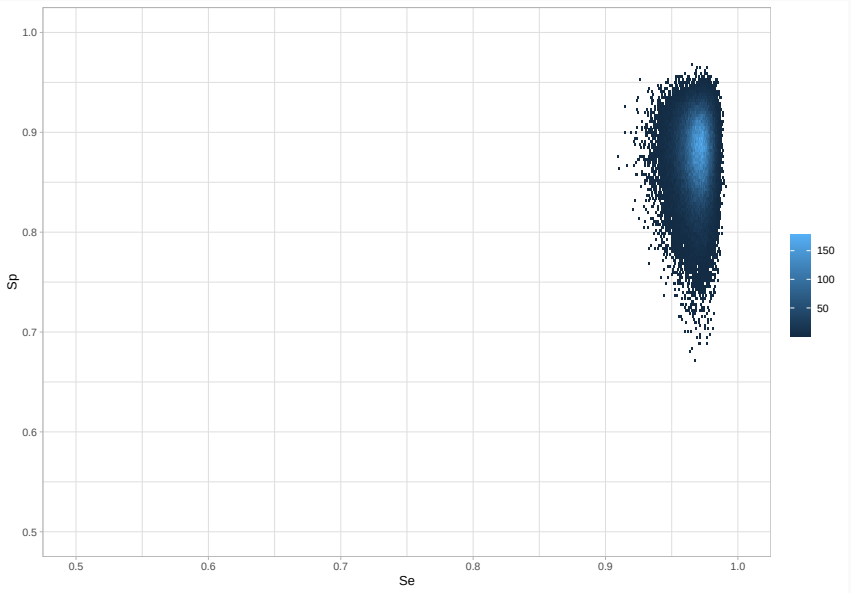
A convenient way to include measure of uncertainty is to use a Bayesian framework of inference.

```
logit_Se_mu <- logit(0.97)
logit_Se_sd <- 0.27
logit_Se_tau0 <- 1/(logit_Se_sd^2)
theta_Se <- rnorm(100000, mean=logit_Se_mu, sd=logit_Se_sd)
Se <- exp(theta_Se)/(1+exp(theta_Se))
round(quantile(Se, c(0.025, 0.5, 0.975)), 2)
##  2.5%   50% 97.5%
##  0.95  0.97  0.98
logit_Sp_mu <- logit(0.88)
logit_Sp_sd <- 0.31
logit_Sp_tau0 <- 1/(logit_Sp_sd^2)
theta_Sp <- rnorm(100000, mean=logit_Sp_mu, sd=logit_Sp_sd)
Sp <- exp(theta_Sp)/(1+exp(theta_Sp))
round(quantile(Sp, c(0.025, 0.5, 0.975)), 2)
##  2.5%   50% 97.5%
##  0.80  0.88  0.93
```

Prior calibration

```
r = -0.1
y <- rmvnorm(
  n = 10000,
  mean = c(logit_Se_mu, logit_Sp_mu),
  sigma = matrix(
    c(logit_Se_sd, -r,
      -r,          logit_Sp_sd),
    nrow = 2,
    byrow = T
  )
)
```

Prior calibration



Model

```
bm_nondif <- " model {
for (i in 1:m) {
# likelihood
                y[i,1] ~ dbin(prob[i], N[i])
                prob[i] <- pi[i]*Se + (1-pi[i])*(1-Sp)
}
A <- N[1] * pi[1]; C <- N[1] * (1-pi[1])
B <- N[2] * pi[2]; D <- N[2] * (1-pi[2])
# priors for prevalence parameters
                pi[1] ~ dbeta(1,1)
                pi[2] ~ dbeta(1,1)
# priors for sens and spec
logit_Se ~ dnorm(logit_Se_mu, logit_Se_tau0)
Se <- exp(logit_Se)/(1+exp(logit_Se))
logit_Sp ~ dnorm(logit_Sp_mu, logit_Sp_tau0)
Sp <- exp(logit_Sp)/(1+exp(logit_Sp))
RR = pi[1]/pi[2]
#data# m, N, y, logit_Se_mu, logit_Sp_mu, logit_Se_tau0, logit_Sp_tau0
#inits#
#monitor# Se, Sp, pi, RR, A, C, B, D
}"
```

Results: bias-adjusted

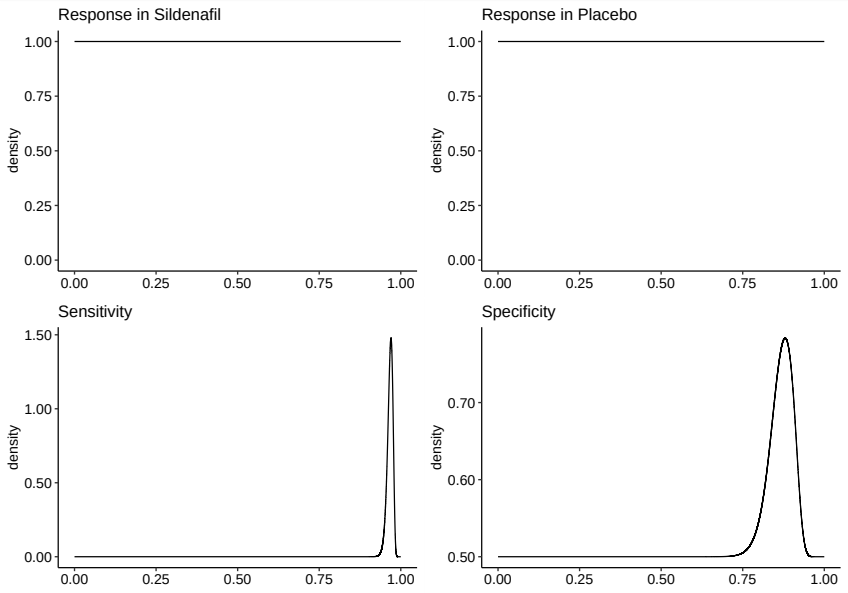
```
## Loading required namespace: rjags
```

	Lower95	Median	Upper95	Mean	SD	Mode	MCerr	MC%ofSD	SSeff	AC.10	psrf
Se	0.952	0.970	0.984	0.969	0.008	NA	0.000	0.6	29967	-0.003	1
Sp	0.839	0.889	0.936	0.888	0.025	NA	0.000	0.6	24397	-0.004	1
pi[1]	0.321	0.431	0.543	0.432	0.057	NA	0.000	0.6	28336	-0.004	1
pi[2]	0.000	0.047	0.118	0.052	0.035	NA	0.000	0.7	22008	-0.003	1
RR	1.819	9.316	82.096	42.262	549.715	NA	3.246	0.6	28675	0.000	1
A	35.926	48.325	60.857	48.378	6.424	NA	0.038	0.6	28336	-0.004	1
C	51.143	63.675	76.074	63.622	6.424	NA	0.038	0.6	28336	-0.004	1
B	0.001	5.349	13.551	5.954	4.065	NA	0.027	0.7	22008	-0.003	1
D	101.449	109.651	114.999	109.046	4.065	NA	0.027	0.7	22008	-0.003	1

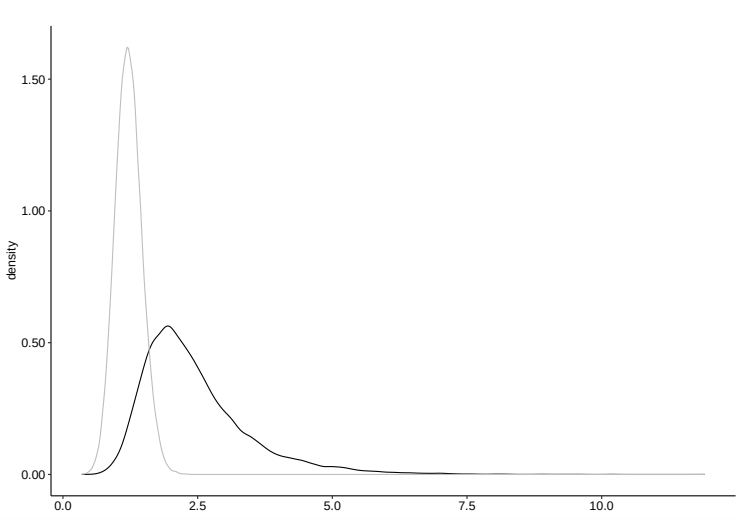
Results: unadjusted

	Lower95	Median	Upper95	Mean	SD	Mode	MCerr	MC%ofSD	SSeff	AC.10	psrf
pi[1]	0.393	0.482	0.574	0.482	0.046	NA	0.000	0.6	30000	0.003	1
pi[2]	0.086	0.144	0.210	0.145	0.032	NA	0.000	0.6	31894	-0.004	1
RR	1.956	3.356	5.290	3.491	0.904	NA	0.005	0.6	29907	-0.001	1
A	43.982	54.010	64.272	54.009	5.191	NA	0.030	0.6	30000	0.003	1
C	47.728	57.990	68.018	57.991	5.191	NA	0.030	0.6	30000	0.003	1
B	9.858	16.517	24.197	16.730	3.720	NA	0.021	0.6	31894	-0.004	1
D	90.803	98.483	105.142	98.270	3.720	NA	0.021	0.6	31894	-0.004	1

Plots


Response in Sildenafil
density
1.00
0.75
0.50
0.25
0.00
0.00
0.25
0.50
0.75
1.00
Response in Placebo
density
1.00
0.75
0.50
0.25
0.00
0.00
0.25
0.50
0.75
1.00
Sensitivity
density
1.50
1.00
0.50
0.00
0.00
0.25
0.50
0.75
1.00
Specificity
density
0.70
0.60
0.50
0.00
0.25
0.50
0.75
1.00

Posterior: bias-adjusted (black) vs. unadjusted (grey)



References

Cappelleri, Joseph C., and Richard Chambers. 2021. "Addressing Bias in Responder Analysis of Patient-Reported Outcomes." *Therapeutic Innovation & Regulatory Science* 55 (5): 989–1000. https://doi.org/10.1007/s43441-021-00298-5.