



Mixed Models & Measured Outcomes R Tips from the Clinical Trenches

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Agenda

- Clinical example: longitudinal endpoint + site effects
- `lm()`, `glm()`, `lme4::lmer()` patterns that scale
- broom + purrr automation (incl. safe pipelines)
- Flextable + rmarkdown for submission-ready outputs



Clinical Use Case We'll Mimic

- Multicenter trial: subjects nested in sites
- Repeated outcomes across visits (baseline, Week 4/8/12)
- Binary responder at Week 12 (e.g., UAS7 responder)
- Need: consistent outputs for tables + traceability

Demo Data (Longitudinal + Site Effects)

```
set.seed(42)
library(dplyr); library(tidyr)

n_site <- 12; n_per <- 60
site_tbl <- tibble(
  site=factor(paste0("S",1:n_site)),
  site_b0=rnorm(n_site,0,2)
)

df <- tidyr::crossing(site=site_tbl$site, id_in=1:n_per) %>%
  left_join(site_tbl, by="site") %>%
  mutate(usubjid=paste0(site,"-",id_in),
         age=round(rnorm(n(),40,12)),
         trt=factor(sample(c("PBO","TRT"), n(), TRUE)),
         x=rnorm(n()))
```

	site	site_b0
1	S1	2.7419169
2	S2	-1.1293963
3	S3	0.7262568
4	S4	1.2657252
5	S5	0.8085366

	site	id_in	site_b0	usubjid	age	trt	x
1	S1	1	2.7419169	S1-1	23	TRT	-0.56818585
2	S1	2	2.7419169	S1-2	37	PBO	-1.05845067
3	S1	3	2.7419169	S1-3	38	TRT	0.25931354
4	S1	4	2.7419169	S1-4	48	PBO	0.37313450
5	S1	5	2.7419169	S1-5	37	TRT	1.26466677

Demo Data (Longitudinal + Site Effects)

```
visits <- tibble(visit=factor(c("BL","W4","W8","W12"),  
                             levels=c("BL","W4","W8","W12")))
```

```
ad <- df %>% crossing(visits) %>%  
  mutate(week = recode(visit, BL=0L, W4=4L, W8=8L, W12=12L),  
         mu = 10 + 0.8*x + 0.04*age + 0.6*(trt=="TRT") +  
           0.15*week + site_b0,  
         outcome = mu + rnorm(n(),0,2.5))
```

	visit
1	BL
2	W4
3	W8
4	W12

	site	id_in	site_b0	usubjid	age	trt	x	visit	week	mu	outcome
1	S1	1	2.741917	S1-1	23	TRT	-0.5681858	BL	0	13.80737	16.556981
2	S1	1	2.741917	S1-1	23	TRT	-0.5681858	W4	4	14.40737	19.123630
3	S1	1	2.741917	S1-1	23	TRT	-0.5681858	W8	8	15.00737	17.035502
4	S1	1	2.741917	S1-1	23	TRT	-0.5681858	W12	12	15.60737	19.152978
5	S1	2	2.741917	S1-2	37	PBO	-1.0584507	BL	0	13.37516	14.473081

Realism: Missingness + Tidy Cleaning

```
set.seed(99)
ad$outcome[sample(nrow(ad), size=0.06*nrow(ad))] <- NA
```

```
ad_clean <- ad %>%
  filter(!is.na(outcome)) %>%
  group_by(usubjid) %>%
  mutate(base = outcome[visit=="BL"][1],
         chg = outcome - base,
         responder = as.integer(chg <= -5)) %>%
  ungroup() %>%
  mutate(x_c = scale(x, center=TRUE, scale=FALSE))
```

	site	id_in	site_b0	usubjid	age	trt	x	visit	week	mu	outcome	base	chg	responder	x_c[, 1]
1	S1	1	2.741917	S1-1	23	TRT	-0.5681858	BL	0	13.80737	16.55698	16.55698	0.00000000	0	-0.5843522
2	S1	1	2.741917	S1-1	23	TRT	-0.5681858	W4	4	14.40737	19.12363	16.55698	2.56664952	0	-0.5843522
3	S1	1	2.741917	S1-1	23	TRT	-0.5681858	W8	8	15.00737	17.03550	16.55698	0.47852119	0	-0.5843522
4	S1	1	2.741917	S1-1	23	TRT	-0.5681858	W12	12	15.60737	19.15298	16.55698	2.59599696	0	-0.5843522
5	S1	2	2.741917	S1-2	37	PBO	-1.0584507	BL	0	13.37516	14.47308	14.47308	0.00000000	0	-1.0746171

lm(): Quick Baseline Model (Cross-Section)

```
lm_w12 <- ad_clean %>%  
  filter(visit=="W12") %>%  
  lm(chg ~ trt + x_c + age, data = .)  
  
summary(lm_w12)
```

```
Residuals:  
      Min       1Q   Median       3Q      Max   
-10.2215  -2.2757  -0.0333   2.3896  12.3806   
  
Coefficients:  
              Estimate Std. Error t value Pr(>|t|)      
(Intercept)   1.34687    0.49647   2.713  0.00685 **   
trtTRT         0.34665    0.27634   1.254  0.21014      
x_c           -0.02705    0.13779  -0.196  0.84440      
age            0.01252    0.01168   1.071  0.28441      
---  
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1  
  
Residual standard error: 3.484 on 639 degrees of freedom  
(33 observations deleted due to missingness)  
Multiple R-squared:  0.004268, Adjusted R-squared:  -0.0004072  
F-statistic: 0.9129 on 3 and 639 DF, p-value: 0.4343
```

glm(): Binary Responder (Week 12)

```
ad_w12 <- ad_clean %>% filter(visit=="W12") %>%
  mutate(responder = as.integer(chg <= -5))
# example threshold
```

```
glm_resp <- glm(responder ~ trt + x_c + age,
  data=ad_w12, family=binomial)
```

```
summary(glm_resp)
exp(coef(glm_resp)) # odds ratios
```

```
Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept) -3.29022    0.91115  -3.611 0.000305 ***
trtTRT      -0.05026    0.52556  -0.096 0.923819
x_c          0.10606    0.26119   0.406 0.684704
age         -0.01102    0.02218  -0.497 0.619266
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 142.39  on 642  degrees of freedom
Residual deviance: 141.96  on 639  degrees of freedom
(33 observations deleted due to missingness)
AIC: 149.96

Number of Fisher Scoring iterations: 6
```

```
> exp(coef(glm_resp)) # odds ratios
(Intercept)      trtTRT          x_c          age
0.03724577  0.95098528  1.11188426  0.98904099
```

lme4::lmer(): Mixed Model for Repeated Measures

```
library(lme4)
```

```
Imm <- lmer(chg ~ trt*visit + x_c + age + (1|site) +  
            (1|usubjid),  
            data = ad_clean)  
summary(Imm)
```

```
Correlation of Fixed Effects:
```

	(Intr)	trtTRT	vistW4	vistW8	vstW12	x_c	age	tTRT:W4	tTRT:W8
trtTRT	-0.345								
visitW4	-0.285	0.389							
visitW8	-0.285	0.388	0.477						
visitW12	-0.286	0.389	0.478	0.477					
x_c	-0.002	-0.065	-0.002	-0.005	0.001				
age	-0.863	0.006	0.004	0.005	0.005	0.031			
trtTRT:vsW4	0.197	-0.569	-0.687	-0.328	-0.329	0.001	-0.003		
trtTRT:vsW8	0.197	-0.569	-0.329	-0.689	-0.329	0.004	-0.003	0.480	
trtTRT:vW12	0.196	-0.570	-0.329	-0.328	-0.688	0.000	-0.003	0.481	0.481

```
Linear mixed model fit by REML ['lmerMod']
Formula: chg ~ trt * visit + x_c + age + (1 | site) + (1 | usubjid)
Data: ad_clean

REML criterion at convergence: 12916.1

Scaled residuals:
    Min       1Q   Median       3Q      Max
-3.4976 -0.5610 -0.0003  0.5696  3.7396

Random effects:
 Groups   Name                Variance Std.Dev.
usubjid   (Intercept)    2.97576   1.7250
site      (Intercept)    0.01245   0.1116
Residual                    6.25496   2.5010
Number of obs: 2610, groups:  usubjid, 685; site, 12

Fixed effects:
              Estimate Std. Error t value
(Intercept)  -0.310927   0.322363  -0.965
trtTRT         0.025302   0.233239   0.108
visitW4        0.614279   0.189719   3.238
visitW8        1.447225   0.190432   7.600
visitW12       1.843919   0.189719   9.719
x_c           -0.121348   0.083032  -1.461
age            0.007537   0.007035   1.071
trtTRT:visitW4  0.288822   0.276081   1.046
trtTRT:visitW8 -0.051507   0.276279  -0.186
trtTRT:visitW12 0.354832   0.275933   1.286
```

Clinical Interpretation Pattern

- Fixed effects → treatment effect (often at each visit)
- Random effects → correlation (site/subject heterogeneity)
- What you report: LS means / contrasts at key visits
- What reviewers want: traceable, consistent tables

Broom: Make Output Tidy (and Joinable)

```
library(broom);
library(broom.mixed)

tidy_lm <- tidy(lm_w12, conf.int=TRUE)
tidy_glm <- tidy(glm_resp, conf.int=TRUE,
  exponentiate=TRUE)
tidy_lmm <- broom.mixed::tidy(lmm, effects="fixed",
  conf.int=TRUE)
bind_rows(
  tidy_lm %>% mutate(model="lm"),
  tidy_glm %>% mutate(model="glm"),
  tidy_lmm %>% mutate(model="lmer")
) %>% select(model, term, estimate, conf.low, conf.high)
%>% head(12)
```

```
# A tibble: 12 x 5
  model term      estimate conf.low conf.high
  <chr> <chr>      <dbl>   <dbl>   <dbl>
1 lm    (Intercept)  1.35    0.372    2.32
2 lm    trtTRT      0.347  -0.196    0.889
3 lm    x_c        -0.0271 -0.298    0.244
4 lm    age         0.0125 -0.0104    0.0355
5 glm    (Intercept)  0.0372  0.00557   0.200
6 glm    trtTRT      0.951    0.329    2.69
7 glm    x_c         1.11    0.664    1.85
8 glm    age         0.989    0.947    1.03
9 lmer   (Intercept) -0.311  -0.943    0.321
10 lmer   trtTRT      0.0253 -0.432    0.482
11 lmer   visitW4     0.614    0.242    0.986
12 lmer   visitW8     1.45    1.07    1.82
```

Automation Depth: One Function, Many Endpoints

```
fit_models <- function(dat){  
  list(  
    lm = lm(chg ~ trt + x_c + age, data=filter(dat, visit=="W12")),  
    glm = glm(responder ~ trt + x_c + age,  
              data=filter(dat, visit=="W12"), family=binomial),  
    lmm = lmer(chg ~ trt*visit + x_c + age + (1|site) + (1|usubjid),  
              data=dat)  
  )  
}  
  
res <- fit_models(ad_clean)  
purrr::imap_dfr(res, ~ tidy(.x, conf.int=TRUE), .id="model") %>% head(10)
```

Automation Depth: One Function, Many Endpoints (cont.)

A tibble: 10 × 10

	model	term	estimate	std.error	statistic	p.value	conf.low	conf.high	effect	group
	<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>	<dbl>	<dbl>	<chr>	<chr>
1	lm	(Intercept)	1.35	0.496	2.71	0.00685	0.372	2.32	NA	NA
2	lm	trtTRT	0.347	0.276	1.25	0.210	-0.196	0.889	NA	NA
3	lm	x_c	-0.0271	0.138	-0.196	0.844	-0.298	0.244	NA	NA
4	lm	age	0.0125	0.0117	1.07	0.284	-0.0104	0.0355	NA	NA
5	glm	(Intercept)	-3.29	0.911	-3.61	0.000305	-5.19	-1.61	NA	NA
6	glm	trtTRT	-0.0503	0.526	-0.0956	0.924	-1.11	0.990	NA	NA
7	glm	x_c	0.106	0.261	0.406	0.685	-0.410	0.616	NA	NA
8	glm	age	-0.0110	0.0222	-0.497	0.619	-0.0547	0.0324	NA	NA
9	lmm	(Intercept)	-0.311	0.322	-0.965	NA	-0.943	0.321	fixed	NA
10	lmm	trtTRT	0.0253	0.233	0.108	NA	-0.432	0.482	fixed	NA



Safe Pipelines: Don't Let One Failure Kill the Run

```
safe_fit <- purrr::possibly(fit_models, otherwise=NULL)
```

```
out <- safe_fit(ad_clean)
```

```
safe_tidy <- purrr::possibly(~ tidy(.x, conf.int=TRUE),  
otherwise=tibble())
```

```
purrr::imap_dfr(out, safe_tidy, .id="model") %>%  
  count(model)
```

```
# A tibble: 3 x 2  
  model      n  
  <chr> <int>  
1 glm         4  
2 lm          4  
3 lmm        13
```

Publication-Ready Tables with flextable

```
library(flextable)
```

```
tbl <- tidy_lm %>%  
  transmute(  
    Term = term,  
    Estimate = round(estimate, 3),  
    `95% CI` = paste0("(", round(conf.low,3), ", ", "  
      round(conf.high,3), ")"),  
    `P-value` = signif(p.value, 3)  
  )  
ft <- flextable(tbl) %>% autofit()
```

Table 1.1: Modeling Report

Term	Estimate	95% CI	P-value
(Intercept)	1.347	(0.372, 2.322)	0.00685
trtTRT	0.347	(-0.196, 0.889)	0.21000
x_c	-0.027	(-0.298, 0.244)	0.84400
age	0.013	(-0.01, 0.035)	0.28400

-95% confidence interval is derived using Greenwood's formula.



— — —

output: html_document

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```
ft      # flextable object prints in report
```

///

Key Takeaways + Practical Checklist

- Use `lmer()` when correlation is real (sites/subjects/visits)
- Standardize outputs with `broom` / `broom.mixed`
- Automate with `purrr` + safe defaults (possibly/safely)
- Generate tables & reports reproducibly (`flextable` + `rmarkdown`)

Thank You !!!