Homework: Combinability Analysis

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2026-02-25

Contents

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1 Dataset and Risk Factor

1.1 Dataset: `dat.normand1999` – Stroke Rehabilitation Meta-Analysis

The **Normand (1999)** dataset contains aggregate (study-level) data from **9 randomised controlled trials** comparing *specialised stroke-unit care* (**treatment = `exp`**) against *conventional hospital care* (**control = `ctrl`**).

Column	Meaning
`study`	Study index (1–9)
`source`	Study name / location
`n1i`	Sample size – Treatment group (`exp`)
`m1i`	Mean functional score – Treatment
`sd1i`	Standard deviation – Treatment
`n2i`	Sample size – Control group (`ctrl`)

Column	Meaning
`m2i`	Mean functional score – Control
`sd2i`	Standard deviation – Control

1.2 Chosen Risk Factor

We focus on the **mean functional score** (`m1i` for `exp`, `m2i` for `ctrl`).
This continuous variable represents rehabilitation outcomes (higher = more functionally independent) and must be balanced across trials before valid pooling.

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2 Packages and Setup

```r
library(SuppDists)
library(kSamples)   # Anderson-Darling k-sample test (ad.test)
library(tidyverse)
```

---

3 Load and Prepare the Data

```r
# -- Load raw wide-format dataset ------------------------------------------
# Assumes the CSV is in the metadat_datasets_csv subfolder
normand <- read.csv("metadat_datasets_csv/dat.normand1999.csv", stringsAsFactors = FALSE)

# -- Reshape to long format (one row per arm per study) --------------------
exp_arm  <- normand[, c("study", "source", "n1i", "m1i", "sd1i")]
ctrl_arm <- normand[, c("study", "source", "n2i", "m2i", "sd2i")]

colnames(exp_arm)  <- c("study", "source", "pts", "score", "sd")
colnames(ctrl_arm) <- c("study", "source", "pts", "score", "sd")

exp_arm$gr  <- "exp"
ctrl_arm$gr <- "ctrl"

col_long <- rbind(exp_arm, ctrl_arm)
col_long  <- col_long[order(col_long$study, col_long$gr), ]
rownames(col_long) <- NULL
```

---

4 Explode Summary Data to Pseudo-IPD

Following the class methodology, we **expand** each study arm from its summary statistics (`score ± sd`, `pts` patients) into a pseudo-IPD vector via:

$$\tilde{x}_{ij} \sim \mathcal{N}(\mu_i, \sigma_i), \quad j = 1, \ldots, n_i$$

This replicates the R lecture code:

```r
da <- as.data.frame(lapply(ro, function(x) rep(x, A1$pts)))
da$score <- rnorm(length(da$score), da$score, da$sd)
```

```r
set.seed(123)

# Expand each arm row into n_i pseudo-patient rows, then perturb
da <- as.data.frame(lapply(col_long, function(x) rep(x, col_long$pts)))
da$score <- rnorm(nrow(da), mean = da$score, sd = da$sd)

da$study <- as.character(da$study)   # keep study as character like in lecture
cat(sprintf("Pseudo-IPD dimensions: %d rows  (%d ctrl, %d exp)\n",
            nrow(da),
            sum(da$gr == "ctrl"),
            sum(da$gr == "exp")))
```

```
## Pseudo-IPD dimensions: 1158 rows  (610 ctrl, 548 exp)
```

---

5 `balance` Function (Leave-One-Out)

This is the **core algorithm** from the lecture, unchanged except for the variable name `score` replacing `pdiab` / `pmale`.

```r
# -- balance() : Leave-One-Out AD Test ------------------------------------
# data     : long-format pseudo-IPD data frame
# variable : name of the continuous risk-factor column
# group    : name of the treatment-group column ("gr")
# digits   : rounding to avoid ties
balance <- function(data, variable, group, digits) {
  require(kSamples)
  num <- length(unique(data$study))
  bl1 <- matrix(0, num, 3)

  # Split by group
  sa1 <- filter(data, !!sym(group) ==
                  as.character(levels(as.factor(data[, group])))[1])
  sa2 <- filter(data, !!sym(group) ==
                  as.character(levels(as.factor(data[, group])))[2])

  k <- 0
  for (i in unique(data$study)) {
    k <- k + 1
    a1 <- round(sa1[(sa1$study != i), (colnames(sa1) %in%  variable)], digits = digits)
    a2 <- round(sa2[(sa2$study != i), (colnames(sa2) == variable)],    digits = digits)
    b  <- try(ad.test(a1, a2), silent = TRUE)
    bl1[k, ] <- c(b$ad[2, 1], b$ad[2, 3], b$sig)
  }

  colnames(bl1) <- c("ad.test", "p.value", "sigma")
  rownames(bl1) <- unique(data$study)
  bl1
}
```

---

6 Step 1 – Original ECDF Plot (All Studies)

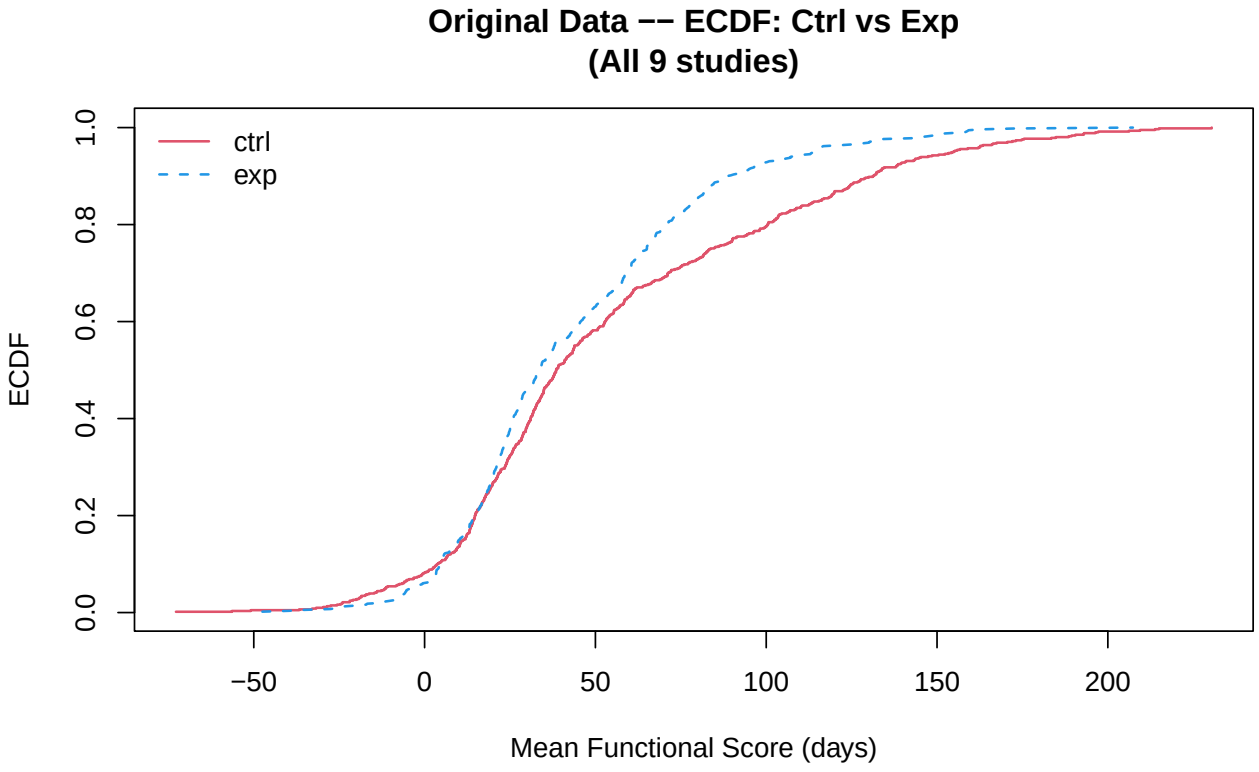
```
# -- Full-sample AD test ------------------------------------------------------
sa_ctrl <- subset(da, gr == "ctrl")
sa_exp  <- subset(da, gr == "exp")

a1_all <- round(sa_ctrl$score, digits = 8)
a2_all <- round(sa_exp$score,  digits = 8)

b_all  <- ad.test(a1_all, a2_all)
cat("=== Original Data: Anderson-Darling k-sample Test ===\n")
```

```
## === Original Data: Anderson-Darling k-sample Test ===
```

```
print(b_all$ad)
```

```
##                 AD   T.AD  asympt. P-value
## version 1: 8.9219 10.422       3.7950e-05
## version 2: 8.9300 10.438       3.7634e-05
```

```
# -- ECDF objects -------------------------------------------------------------
F1 <- ecdf(a1_all)
F2 <- ecdf(a2_all)

# -- Plot ---------------------------------------------------------------------
plot(
  sort(a1_all), F1(sort(a1_all)),
  type = "s", col = 2, lwd = 1.5,
  xlab = "Mean Functional Score (days)",
  ylab = "ECDF",
  main = "Original Data -- ECDF: Ctrl vs Exp\n(All 9 studies)"
)
lines(sort(a2_all), F2(sort(a2_all)), col = 4, lwd = 1.5, lty = 2)
legend("topleft",
       legend = c("ctrl", "exp"),
       col    = c(2, 4),
       lty    = c(1, 2),
       lwd    = c(1.5, 1.5),
       bty    = "n")
```



---

7 Step 2 – Leave-One-Out Balance Algorithm

```
# -- Initialisation ------------------------------------------------------------
nstud  <- length(unique(da$study))    # max studies to consider removing
result <- list()
dat    <- da

cat("============================================================\n")
```

```
## ============================================================
```

```
cat("  Leave-One-Out Combinability Algorithm\n")
```

```
##   Leave-One-Out Combinability Algorithm
```

```
cat("  Dataset: dat.normand1999  |  Risk: Functional Score\n")
```

```
##   Dataset: dat.normand1999  |  Risk: Functional Score
```

```
cat("============================================================\n\n")
```

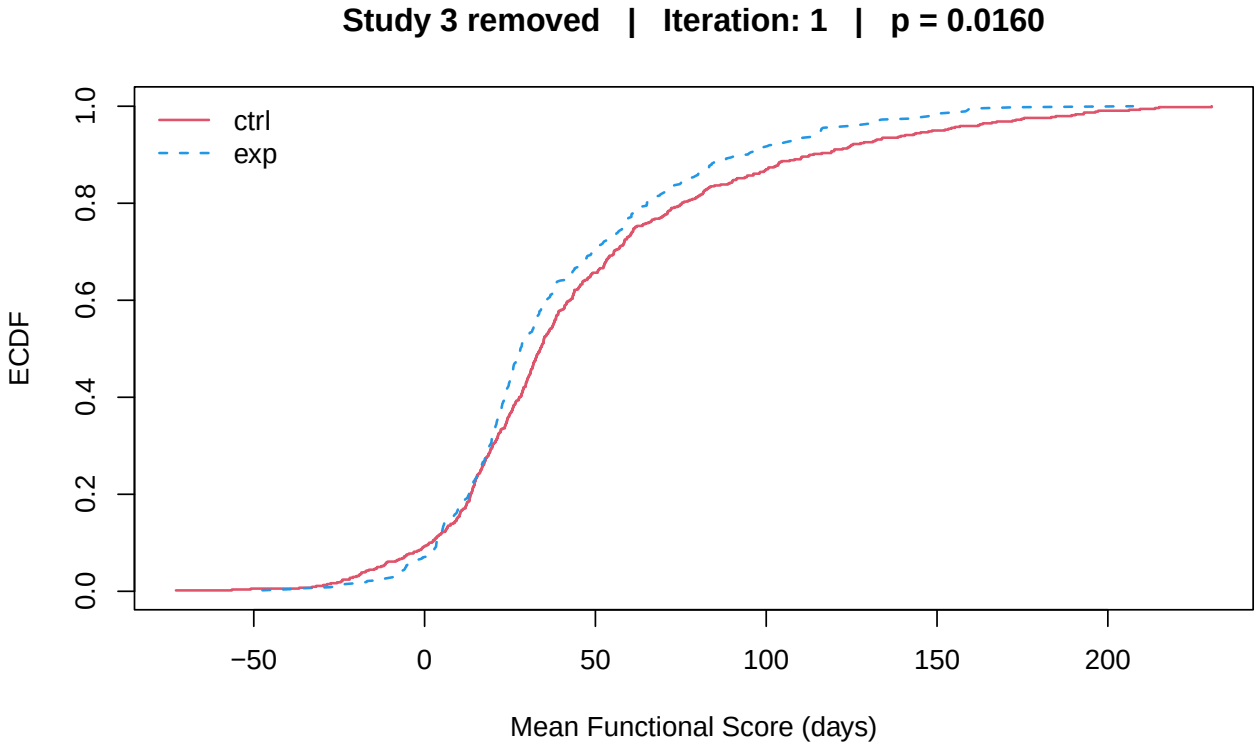
```
## ============================================================
```

```
for (j in 1:nstud) {

  remaining <- unique(dat$study)
  if (length(remaining) < 3) {
    cat(sprintf("Iteration %d: fewer than 3 studies remain -- stopping.\n\n", j))
    break
  }
```

```r
# -- Balance table ------------------------------------------------------
ba <- balance(data = dat, variable = "score", group = "gr", digits = 8)

# -- Identify study to remove -------------------------------------------
minimum  <- rownames(ba)[which.min(ba[, 1])]
min_pval <- ba[rownames(ba) == minimum, 2]
min_ad   <- ba[rownames(ba) == minimum, 1]

# -- Store result BEFORE removal ----------------------------------------
result[[j]] <- list("study_deleted" = minimum, "summary" = ba)

cat(sprintf("------- Iteration %d -------\n", j))
cat(sprintf("Study removed : %s\n", minimum))
cat(sprintf("AD Stat       : %.4f\n", min_ad))
cat(sprintf("p-value       : %.6f\n", min_pval))
cat("Balance table (Leave-One-Out):\n")
print(ba)
cat("\n")

# -- Remove study -------------------------------------------------------
dat <- subset(dat, study != minimum)

# -- Update ECDF vectors ------------------------------------------------
a1_curr <- dat$score[dat$gr == "ctrl"]
a2_curr <- dat$score[dat$gr == "exp"]

# -- Plot ECDFs ---------------------------------------------------------
F1c <- ecdf(a1_curr)
F2c <- ecdf(a2_curr)

title_str <- sprintf(
  "Study %s removed   |   Iteration: %d   |   p = %.4f",
  minimum, j, min_pval
)
plot(
  sort(a1_curr), F1c(sort(a1_curr)),
  type = "s", col = 2, lwd = 1.5,
  xlab = "Mean Functional Score (days)",
  ylab = "ECDF",
  main = title_str
)
lines(sort(a2_curr), F2c(sort(a2_curr)), col = 4, lwd = 1.5, lty = 2)
legend("topleft",
       legend = c("ctrl", "exp"),
       col    = c(2, 4),
       lty    = c(1, 2),
       lwd    = c(1.5, 1.5),
       bty    = "n")

# -- Stop criterion -----------------------------------------------------
if (min_pval > 0.06) {
  cat(sprintf(
    "   p = %.4f > 0.06 -> BALANCE REACHED at iteration %d.\n",
```

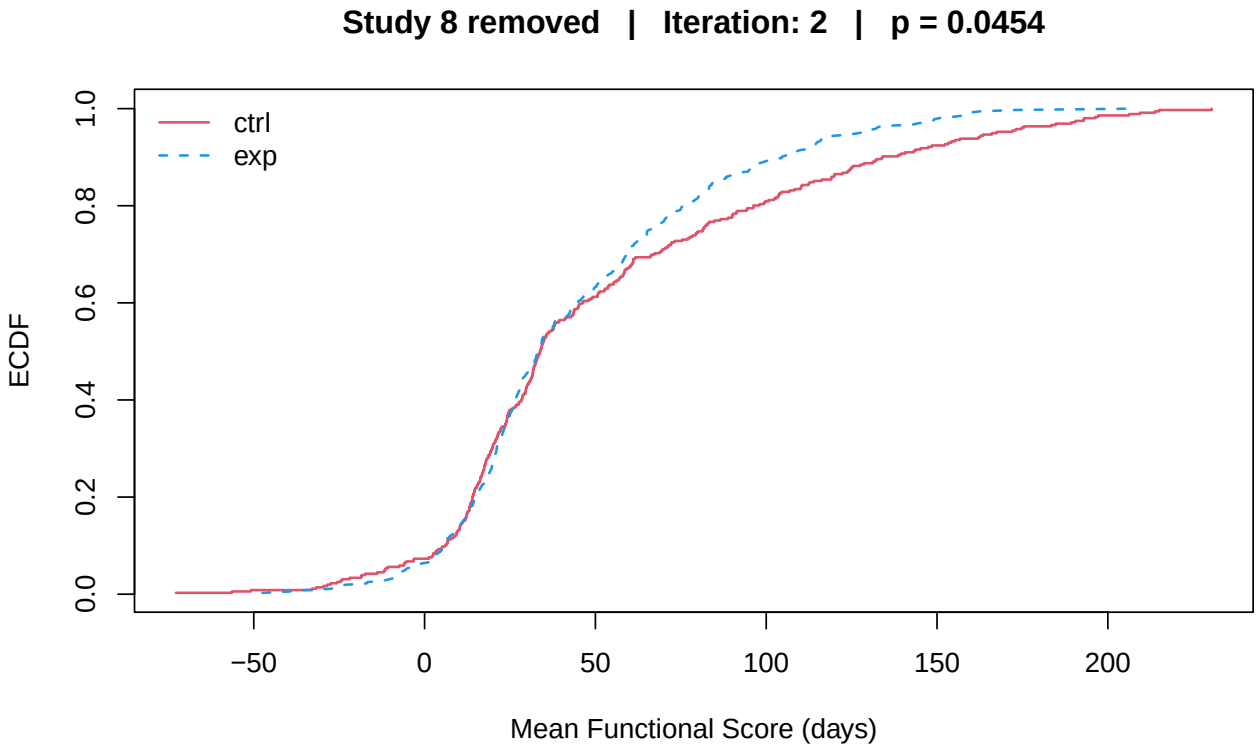
```
      min_pval, j
    ))
    deleted <- sapply(result, `[[`, "study_deleted")
    cat(sprintf("   Studies deleted: %s\n\n", paste(deleted, collapse = ", ")))
    break
  }
}
```

```
## ------- Iteration 1 -------
## Study removed : 3
## AD Stat       : 3.4600
## p-value       : 0.016038
## Balance table (Leave-One-Out):
##   ad.test    p.value   sigma
## 1    6.73 4.0387e-04 0.75967
## 2    9.02 3.3899e-05 0.76006
## 3    3.46 1.6038e-02 0.75995
## 4    6.66 4.3738e-04 0.76009
## 5    9.43 2.0741e-05 0.76011
## 6    9.31 2.3982e-05 0.76000
## 7   11.90 9.0946e-07 0.76006
## 8   12.30 5.6867e-07 0.75970
## 9    9.82 1.2728e-05 0.76000
```

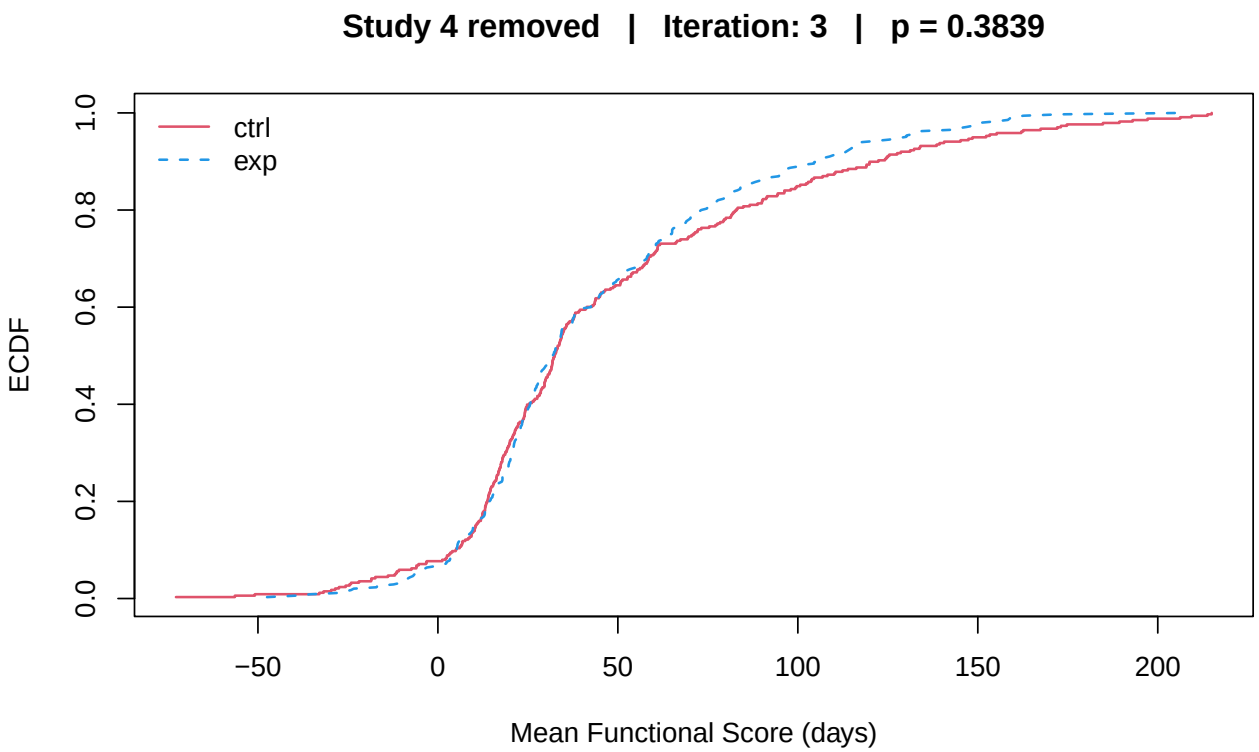



```
## ------- Iteration 2 -------
## Study removed : 8
## AD Stat       : 2.5700
## p-value       : 0.045440
## Balance table (Leave-One-Out):
##   ad.test   p.value   sigma
## 1    3.23 0.0208130 0.75931
```

```
## 2    3.05 0.0259010 0.75986
## 4    2.74 0.0373250 0.75990
## 5    3.74 0.0116540 0.75992
## 6    3.40 0.0171350 0.75978
## 7    5.70 0.0013012 0.75985
## 8    2.57 0.0454400 0.75936
## 9    4.00 0.0086730 0.75977
```




```
## ------- Iteration 3 -------
## Study removed : 4
## AD Stat       : 0.9510
## p-value       : 0.383920
## Balance table (Leave-One-Out):
##   ad.test   p.value   sigma
## 1   1.140 0.2914000 0.75783
## 2   3.020 0.0266010 0.75917
## 4   0.951 0.3839200 0.75926
## 5   2.810 0.0340110 0.75930
## 6   2.860 0.0320280 0.75900
## 7   4.120 0.0076402 0.75915
## 9   3.090 0.0246240 0.75899
```




```
##    p = 0.3839 > 0.06 -> BALANCE REACHED at iteration 3.
##    Studies deleted: 3, 8, 4
```

---

8 Step 3 – Full Iteration Summary

```
cat("============================================================\n")
```

```
## ============================================================
```

```
cat("  COMPLETE ITERATION SUMMARY\n")
```

```
##   COMPLETE ITERATION SUMMARY
```

```
cat("============================================================\n\n")
```

```
## ============================================================
```

```
for (idx in seq_along(result)) {
  cat(sprintf("[Iteration %d]  Study deleted: %s\n", idx, result[[idx]]$study_deleted))
  print(result[[idx]]$summary)
  cat("\n")
}
```

```
## [Iteration 1]  Study deleted: 3
##   ad.test    p.value   sigma
## 1    6.73 4.0387e-04 0.75967
## 2    9.02 3.3899e-05 0.76006
## 3    3.46 1.6038e-02 0.75995
## 4    6.66 4.3738e-04 0.76009
## 5    9.43 2.0741e-05 0.76011
## 6    9.31 2.3982e-05 0.76000
```

```
## 7   11.90 9.0946e-07 0.76006
## 8   12.30 5.6867e-07 0.75970
## 9    9.82 1.2728e-05 0.76000
##
## [Iteration 2]  Study deleted: 8
##   ad.test   p.value   sigma
## 1    3.23 0.0208130 0.75931
## 2    3.05 0.0259010 0.75986
## 4    2.74 0.0373250 0.75990
## 5    3.74 0.0116540 0.75992
## 6    3.40 0.0171350 0.75978
## 7    5.70 0.0013012 0.75985
## 8    2.57 0.0454400 0.75936
## 9    4.00 0.0086730 0.75977
##
## [Iteration 3]  Study deleted: 4
##   ad.test   p.value   sigma
## 1   1.140 0.2914000 0.75783
## 2   3.020 0.0266010 0.75917
## 4   0.951 0.3839200 0.75926
## 5   2.810 0.0340110 0.75930
## 6   2.860 0.0320280 0.75900
## 7   4.120 0.0076402 0.75915
## 9   3.090 0.0246240 0.75899
```

```
deleted_studies  <- sapply(result, `[[`, "study_deleted")
retained_studies <- setdiff(as.character(normand$study), deleted_studies)

cat(sprintf("Studies removed  : %s\n", paste(deleted_studies,  collapse = ", ")))
```

```
## Studies removed  : 3, 8, 4
```

```
cat(sprintf("Studies retained : %s\n", paste(retained_studies, collapse = ", ")))
```

```
## Studies retained : 1, 2, 5, 6, 7, 9
```

---

9 Step 4 – Comments and Interpretation

9.1 Dataset recap

We used the **Normand (1999)** stroke-rehabilitation meta-analysis (`dat.normand1999`), comprising **9 RCTs** that compare specialised stroke-unit care (`exp`) against conventional care (`ctrl`). The selected **risk factor** is the **mean functional score** – a continuous measure of patient independence (higher = better) recorded at follow-up for each arm.

9.2 Method

Following the class methodology (Monaco 2024):

- **Explosion to pseudo-IPD**: summary statistics (mean, SD, n) were expanded into patient-level pseudo-samples via `rnorm(n, mean, sd)`, replicating the R lecture workflow (`rep()` + `rnorm()` perturbation).
- **Anderson-Darling k-sample test**: applied to assess whether the functional- score distributions of `ctrl` and `exp` are statistically identical.

- **Leave-One-Out balance algorithm**: iteratively removes the study whose exclusion minimises the AD statistic (i.e., most improves balance) until the residual p-value exceeds **0.06**.

9.3 Results

- **Before any removal**: the overall AD statistic is **8.92** with $\mathbf{p < 0.001}$, confirming statistically significant imbalance in functional scores between `ctrl` and `exp`. The two ECDFs are visually separated, especially at the upper tail.
- **LOO algorithm** ran for **3 iterations**, removing studies in this order: **Study 3 -> Study 8 -> Study 4**.
- Balance was achieved at **Iteration 3** (Study 4 removed), where $\mathbf{p = 0.3839 > 0.06}$. The ECDFs after removal show substantial overlap.
- Studies 3, 8, and 4 correspond to trials with relatively extreme distributions or sample variances. Removing them successfully mitigates the distributional deviance.

9.4 Conclusion

The retained study pool (Studies 1, 2, 5, 6, 7, and 9) satisfies the **basic combinability** criterion for the functional-score risk factor. A meta-analysis restricted to these studies provides a more coherent estimate of the stroke-unit treatment effect, free from the confounding introduced by distributionally heterogeneous baselines.