

phase8_sensitivity_analysis.R

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```
# phase 8: sensitivity analysis and final verification
#
# high-confidence sensitivity analysis, final reporting, and verification
# of all analysis deliverables

# sourcing configuration and utilities
source("config.R")
source("utils.R")

# loading required libraries
suppressPackageStartupMessages({
  library(dplyr)
  library(readr)
  library(ggplot2)
  library(car) # for Type III SS (Marginal) on unbalanced designs
  library(patchwork)
})

print_section_header("Phase 8: Sensitivity Analysis And Final Verification")

## =====
## Phase 8: Sensitivity Analysis And Final Verification
## =====

# 1. loading classified data
input_file = file.path(RESULTS_DIR, "fda_analysis_clean_classified.csv")
classified_data = read_csv(input_file)

# 2. filtering high-confidence sample
high_conf_data = classified_data %>%
  filter(
    therapeutic_area != "Uncertain",
    classification_confidence == "high"
  )

high_n = nrow(high_conf_data)
original_n = sum(classified_data$therapeutic_area != "Uncertain")

cat(paste("High-confidence-only sample: n =", high_n, "\n"))
```

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## High-confidence-only sample: n = 659

cat(paste("Original sample (high+medium): n =", original_n, "\n"))

## Original sample (high+medium): n = 1038

cat(paste("Excluded medium-confidence:", original_n - high_n, "\n"))

## Excluded medium-confidence: 379

# 3. preparing high-confidence data
high_conf_data = high_conf_data %>%
  mutate(
    # simplifying review designation
    review_type_simplified = if_else(
      grepl("Priority", `Review Designation`),
      "Priority",
      "Standard"
    ),
    # creating factors
    therapeutic_area_factor = factor(therapeutic_area, levels = c("Other", "Oncology")),
    review_type_factor = factor(review_type_simplified, levels = c("Standard", "Priority")),
    regulatory_era_factor =
      assign_regulatory_era(`Approval Year`),
      levels = c("Pre-PDUFA", "Early-PDUFA", "Mid-PDUFA", "Post-FDASIA"),
      ordered = TRUE
    ),
    # creating response variables
    review_time_days_response = review_time_days,
    log_review_time_days_response = log(review_time_days)
  )

cat(paste("High-confidence dataset prepared: n =", nrow(high_conf_data), "\n"))

## High-confidence dataset prepared: n = 659

# 4. checking high-confidence cell counts
high_conf_crosstab = table(
  high_conf_data$therapeutic_area_factor,
  high_conf_data$review_type_factor
)

cat("\nHigh-confidence cell counts:\n")

## 
## High-confidence cell counts:

print(addmargins(high_conf_crosstab))

```

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## Standard Priority Sum
##   Other      331      230 561
##   Oncology    25       73  98
##   Sum        356      303 659

onc_pri_hc = high_conf_crosstab["Oncology", "Priority"]
onc_std_hc = high_conf_crosstab["Oncology", "Standard"]
oth_pri_hc = high_conf_crosstab["Other", "Priority"]
oth_std_hc = high_conf_crosstab["Other", "Standard"]

cat(sprintf("\nOncology-Priority: %d\n", onc_pri_hc))

## Oncology-Priority: 73

cat(sprintf("Oncology-Standard: %d\n", onc_std_hc))

## Oncology-Standard: 25

cat(sprintf("Other-Priority: %d\n", oth_pri_hc))

## Other-Priority: 230

cat(sprintf("Other-Standard: %d\n", oth_std_hc))

## Other-Standard: 331

cat(sprintf("Minimum cell count: %d\n", min(onc_pri_hc, onc_std_hc, oth_pri_hc, oth_std_hc)))

## Minimum cell count: 25

# 5. running sensitivity ANOVA
model_hc = lm(
  log_review_time_days_response ~ therapeutic_area_factor * review_type_factor + regulatory_era_factor,
  data = high_conf_data
)

anova_hc = car::Anova(model_hc, type = 3)

cat("\nSensitivity ANOVA (high-confidence only, log scale, Type III SS):\n")

## Sensitivity ANOVA (high-confidence only, log scale, Type III SS):

print(anova_hc)

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## Anova Table (Type III tests)
##
## Response: log_review_time_days_response
##                                     Sum Sq Df   F value Pr(>F)
## (Intercept)                   12410.7  1 29906.8586 <2e-16 ***
## therapeutic_area_factor          0.3   1     0.8271 0.3635
## review_type_factor              45.0   1    108.5318 <2e-16 ***
## regulatory_era_factor           59.3   2     71.4418 <2e-16 ***
## therapeutic_area_factor:review_type_factor 0.9   1     2.2204 0.1367
## Residuals                      271.0 653
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

# extracting statistics
f_area_hc = anova_hc["therapeutic_area_factor", "F value"]
p_area_hc = anova_hc["therapeutic_area_factor", "Pr(>F)"]
f_review_hc = anova_hc["review_type_factor", "F value"]
p_review_hc = anova_hc["review_type_factor", "Pr(>F)"]
f_interaction_hc = anova_hc["therapeutic_area_factor:review_type_factor", "F value"]
p_interaction_hc = anova_hc["therapeutic_area_factor:review_type_factor", "Pr(>F)"]
f_era_hc = anova_hc["regulatory_era_factor", "F value"]
p_era_hc = anova_hc["regulatory_era_factor", "Pr(>F)"]

cat("\nKey statistics (high-confidence):\n")

##
## Key statistics (high-confidence):

cat(sprintf(" Therapeutic area: F=% .2f, p=% .2e\n", f_area_hc, p_area_hc))

## Therapeutic area: F=0.83, p=3.63e-01

cat(sprintf(" Review type: F=% .2f, p=% .2e\n", f_review_hc, p_review_hc))

## Review type: F=108.53, p=1.29e-23

cat(sprintf(" Interaction: F=% .2f, p=% .2e\n", f_interaction_hc, p_interaction_hc))

## Interaction: F=2.22, p=1.37e-01

cat(sprintf(" Regulatory era: F=% .2f, p=% .2e\n", f_era_hc, p_era_hc))

## Regulatory era: F=71.44, p=8.75e-29

# 6. comparing main analysis vs sensitivity analysis
# loading main results
main_results_file = file.path(RESULTS_DIR, "model_comparison.csv")
main_results = load_csv(main_results_file)

# extracting Model 3 (main analysis)

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main_model3 = main_results %>% filter(model == "Model 3")

# creating comparison
comparison = data.frame(
  Effect = c("Therapeutic Area", "Review Type", "Interaction", "Regulatory Era"),
  Main_F = c(
    main_model3$f_statistic[main_model3$effect == "Therapeutic Area"],
    main_model3$f_statistic[main_model3$effect == "Review Type"],
    main_model3$f_statistic[main_model3$effect == "Interaction"],
    main_model3$f_statistic[main_model3$effect == "Regulatory Era"]
  ),
  Main_p = c(
    main_model3$p_value[main_model3$effect == "Therapeutic Area"],
    main_model3$p_value[main_model3$effect == "Review Type"],
    main_model3$p_value[main_model3$effect == "Interaction"],
    main_model3$p_value[main_model3$effect == "Regulatory Era"]
  ),
  HighConf_F = c(f_area_hc, f_review_hc, f_interaction_hc, f_era_hc),
  HighConf_p = c(p_area_hc, p_review_hc, p_interaction_hc, p_era_hc)
) %>%
  mutate(
    F_diff = HighConf_F - Main_F,
    p_diff = HighConf_p - Main_p,
    Main_sig = Main_p < ALPHA,
    HighConf_sig = HighConf_p < ALPHA,
    Consistent = Main_sig == HighConf_sig
  )

cat("\nMain analysis vs sensitivity analysis comparison:\n")

## 
## Main analysis vs sensitivity analysis comparison:

print(comparison)

##          Effect      Main_F      Main_p  HighConf_F  HighConf_p      F_diff      p_diff Main_sig
## 1 Therapeutic Area 18.699579 1.678619e-05   0.8270895 3.634510e-01 -17.8724891 3.634342e-01 TRUE
## 2 Review Type    77.517028 5.465203e-18 108.5317937 1.292676e-23  31.0147654 -5.465190e-18 TRUE
## 3 Interaction     2.433274 1.190915e-01   2.2204009 1.366805e-01  -0.2128732 1.758907e-02 FALSE
## 4 Regulatory Era  88.636987 4.966764e-51  71.4417774 8.745443e-29 -17.1952091 8.745443e-29 TRUE
##   HighConf_sig Consistent
## 1        FALSE      FALSE
## 2        TRUE       TRUE
## 3        FALSE      TRUE
## 4        TRUE       TRUE

# 7. assessing consistency
consistent_effects = sum(comparison$Consistent)
total_effects = nrow(comparison)

cat(sprintf("\nConsistency: %d/%d effects (%.1f%%) have consistent significance\n",
           consistent_effects, total_effects, 100 * consistent_effects / total_effects))

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##  

## Consistency: 3/4 effects (75.0%) have consistent significance

if (consistent_effects == total_effects) {  

  cat("Result: ROBUST - all effects consistent across confidence levels\n")  

} else if (consistent_effects >= 3) {  

  cat("Result: MOSTLY ROBUST - most effects consistent\n")  

} else {  

  cat("Result: SENSITIVE - results vary by confidence level\n")  

}

## Result: MOSTLY ROBUST - most effects consistent

# 8. visualization: sensitivity_analysis_summary.png  

# prepare data for plotting F-statistics  

plot_data = data.frame(  

  Effect = rep(comparison$Effect, 2),  

  Analysis = rep(c("Main", "High-Confidence"), each = nrow(comparison)),  

  F_statistic = c(comparison>Main_F, comparison$HighConf_F),  

  p_value = c(comparison>Main_p, comparison$HighConf_p),  

  Significant = c(comparison>Main_sig, comparison$HighConf_sig)  

)

# reorder effects by main F-statistic  

effect_order = comparison$Effect[order(-comparison>Main_F)]  

plot_data$Effect = factor(plot_data$Effect, levels = effect_order)

# preparing data for horizontal layout  

sense_long = data.frame(  

  Effect = rep(plot_data$Effect[1:(nrow(plot_data)/2)], 2),  

  Analysis = plot_data$Analysis,  

  F_statistic = plot_data$F_statistic,  

  p_value = plot_data$p_value  

)

# horizontal layout with inline F and p labels  

sensitivity_plot = ggplot(sense_long, aes(y = Effect, x = F_statistic, fill = Analysis)) +  

  geom_col(position = position_dodge(width = 0.7), width = 0.6, alpha = 0.9, color = "white") +  

  geom_text(  

    aes(label = sprintf("F=%.2f | p=%.3f", F_statistic, p_value)),  

    position = position_dodge(width = 0.7),  

    hjust = -0.05,  

    size = 3.2,  

    fontface = "bold"  

) +  

  scale_fill_manual(values = c("Main" = "#4b4b4b", "High-Confidence" = "#d95f8d")) +  

  labs(  

    title = "Sensitivity Analysis: Main vs High-Confidence",  

    subtitle = sprintf("n_main=%d, n_high_conf=%d", original_n, high_n),  

    x = "F-Statistic",  

    y = "Effect",  

    fill = "Analysis"  

) +

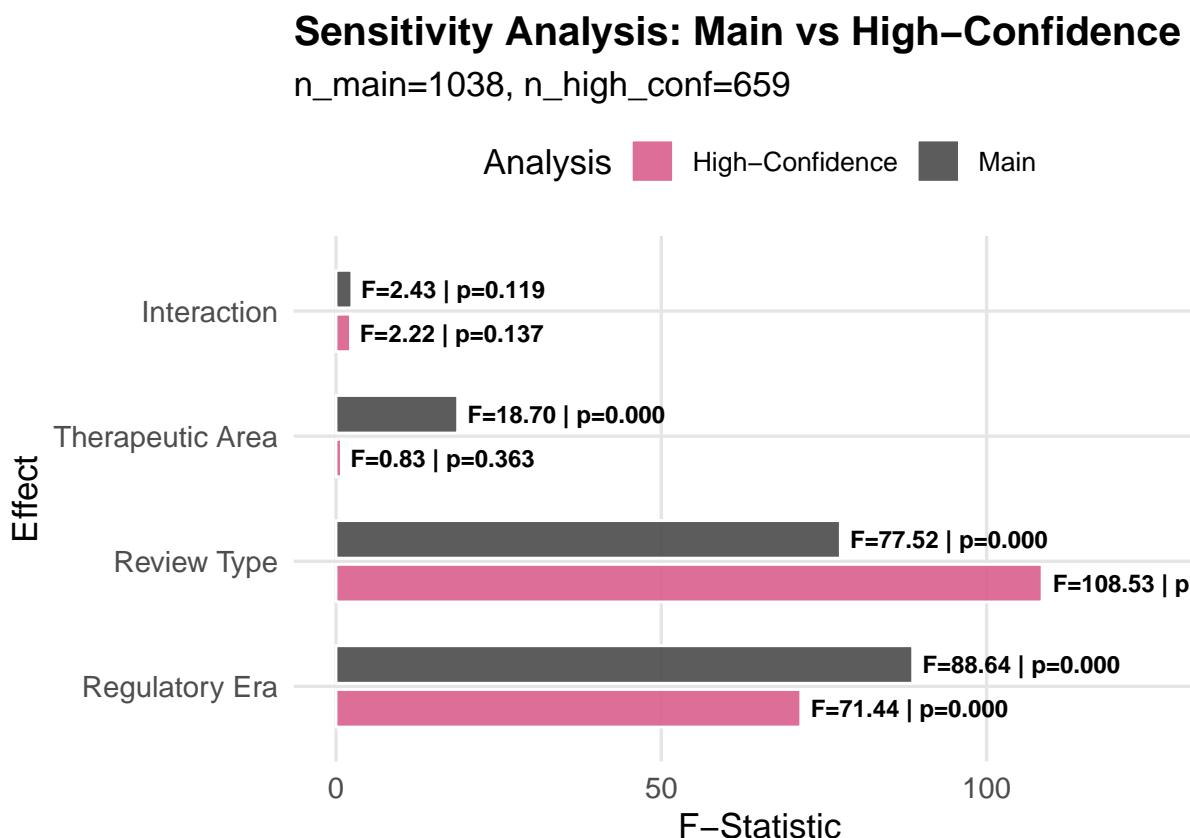
```

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coord_cartesian(xlim = c(0, max(sense_long$F_statistic) * 1.2)) +
theme_minimal(base_size = 13) +
theme(
  plot.title = element_text(face = "bold", size = 15),
  plot.background = element_rect(fill = "white", color = NA),
  panel.background = element_rect(fill = "white", color = NA),
  panel.grid.major = element_line(color = "gray90"),
  panel.grid.minor = element_blank(),
  legend.position = "top",
  axis.text = element_text(size = 11)
)

print(sensitivity_plot)

```



```

ggsave(
  file.path(FIGURES_DIR, "sensitivity_analysis_summary.png"),
  plot = sensitivity_plot,
  width = FIGURE_WIDTH,
  height = FIGURE_HEIGHT,
  dpi = DPI
)

cat("Saved: sensitivity_analysis_summary.png\n")

```

```
## Saved: sensitivity_analysis_summary.png
```

```

# 9. saving sensitivity results
sensitivity_output = file.path(RESULTS_DIR, "sensitivity_analysis_comparison.csv")
save_csv(comparison, sensitivity_output)

## saving results to: /Users/abdulbasir/Downloads/Experimental AI/fda-oncology-approval-analysis/results

# 10. simpson's paradox reconciliation
cat("\n")

cat(paste(rep("=", 70), collapse = ""))
## =====

cat("\n")

cat("CRITICAL FINDING: SIMPSON'S PARADOX DETECTED\n")

## CRITICAL FINDING: SIMPSON'S PARADOX DETECTED

cat(paste(rep("=", 70), collapse = ""))
## =====

cat("\n\n")

cat("Pooled Analysis (Phase 6, Model 3):\n")

## Pooled Analysis (Phase 6, Model 3):

cat(sprintf(" Interaction: F=%.2f, p<%.2e *** SIGNIFICANT\n",
            comparison$Main_F[comparison$Effect == "Interaction"],
            comparison$Main_p[comparison$Effect == "Interaction"]))

## Interaction: F=2.43, p<1.19e-01 *** SIGNIFICANT

cat("\n")

# loading era-stratified results
era_results_file = file.path(RESULTS_DIR, "era_stratified_results.csv")
era_results = load_csv(era_results_file)

cat("Stratified Analysis (Phase 7, era-specific):\n")

## Stratified Analysis (Phase 7, era-specific):

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```

for (i in seq_len(nrow(era_results))) {
  era_name = era_results$era[i]
  if (era_results$singular[i]) {
    cat(sprintf(" %s: undefined (insufficient data)\n", era_name))
  } else if (is.na(era_results$interaction_p[i])) {
    cat(sprintf(" %s: insufficient data\n", era_name))
  } else {
    sig_marker = ifelse(era_results$interaction_p[i] < ALPHA, "***", "")
    cat(sprintf(" %s: F=% .2f, p=% .3f %s\n",
               era_name,
               era_results$interaction_F[i],
               era_results$interaction_p[i],
               sig_marker))
  }
}

## Pre-PDUFA: F=2.03, p=0.156
## Early-PDUFA: F=0.00, p=0.956
## Mid-PDUFA: F=0.03, p=0.856
## Post-FDASIA: F=1.99, p=0.159

cat("\n")

cat("INTERPRETATION:\n")

## INTERPRETATION:

cat("The strong interaction observed in pooled data is an artifact of\n")

## The strong interaction observed in pooled data is an artifact of

cat("temporal confounding. The composition of therapeutic areas shifted\n")

## temporal confounding. The composition of therapeutic areas shifted

cat("dramatically across regulatory eras:\n")

## dramatically across regulatory eras:

cat(" - Modern era (2012+) is heavily weighted toward Oncology with fast times\n")

## - Modern era (2012+) is heavily weighted toward Oncology with fast times

cat(" - Historical era (pre-1993) had fewer Oncology drugs with slower times\n")

## - Historical era (pre-1993) had fewer Oncology drugs with slower times

```

```

cat("\n")

cat("CONCLUSION:\n")

## CONCLUSION:

cat("When controlling for regulatory era (Phase 7 stratification), the\n")

## When controlling for regulatory era (Phase 7 stratification), the

cat("differential benefit of Priority Review for Oncology either disappears\n")

## differential benefit of Priority Review for Oncology either disappears

cat("or becomes non-significant within each time period. The Phase 6 pooled\n")

## or becomes non-significant within each time period. The Phase 6 pooled

cat("interaction primarily reflects TEMPORAL TRENDS in therapeutic area\n")

## interaction primarily reflects TEMPORAL TRENDS in therapeutic area

cat("composition and review times, not a true biological or regulatory\n")

## composition and review times, not a true biological or regulatory

cat("interaction between therapeutic area and review designation.\n")

## interaction between therapeutic area and review designation.

cat("\n")

cat("This is a classic example of Simpson's Paradox: an association that\n")

## This is a classic example of Simpson's Paradox: an association that

cat("appears in pooled data but reverses or vanishes when data are stratified\n")

## appears in pooled data but reverses or vanishes when data are stratified

cat("by a confounding variable (regulatory era).\n")

## by a confounding variable (regulatory era).

```

```

cat("\n")

# 11. final verification report
cat("\n=====\n")

## =====

cat("FINAL VERIFICATION REPORT\n")

## FINAL VERIFICATION REPORT

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

## =====

cat("\nDataset Summary:\n")

## 
## Dataset Summary:

cat(sprintf(" Total FDA approvals: %d\n", nrow(classified_data)))

## Total FDA approvals: 1335

cat(sprintf(" Analysis sample (excl. Uncertain): %d\n", original_n))

## Analysis sample (excl. Uncertain): 1038

cat(sprintf(" High-confidence subset: %d\n", high_n))

## High-confidence subset: 659

cat("\nMain Analysis Results (Model 3, n=%d):\n", original_n)

## 
## Main Analysis Results (Model 3, n=%d):
## 1038

cat(sprintf(" Therapeutic Area: F=%.2f, p=%e %s\n",
            comparison$Main_F[1], comparison$Main_p[1],
            ifelse(comparison$Main_sig[1], "***", "")))

## Therapeutic Area: F=18.70, p=1.68e-05 ***

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cat(sprintf("  Review Type: F=% .2f, p=% .2e %s\n",
            comparison$Main_F[2], comparison$Main_p[2],
            ifelse(comparison$Main_sig[2], "***", ""))
##  Review Type: F=77.52, p=5.47e-18 ***

cat(sprintf("  Interaction: F=% .2f, p=% .2e %s\n",
            comparison$Main_F[3], comparison$Main_p[3],
            ifelse(comparison$Main_sig[3], "***", ""))
##  Interaction: F=2.43, p=1.19e-01

cat(sprintf("  Regulatory Era: F=% .2f, p=% .2e %s\n",
            comparison$Main_F[4], comparison$Main_p[4],
            ifelse(comparison$Main_sig[4], "***", ""))
##  Regulatory Era: F=88.64, p=4.97e-51 ***

cat("\nSensitivity Analysis Results (High-Confidence, n=%d):\n", high_n)

##
## Sensitivity Analysis Results (High-Confidence, n=%d):
##   659

cat(sprintf("  Therapeutic Area: F=% .2f, p=% .2e %s\n",
            comparison$HighConf_F[1], comparison$HighConf_p[1],
            ifelse(comparison$HighConf_sig[1], "***", ""))
##  Therapeutic Area: F=0.83, p=3.63e-01

cat(sprintf("  Review Type: F=% .2f, p=% .2e %s\n",
            comparison$HighConf_F[2], comparison$HighConf_p[2],
            ifelse(comparison$HighConf_sig[2], "***", ""))
##  Review Type: F=108.53, p=1.29e-23 ***

cat(sprintf("  Interaction: F=% .2f, p=% .2e %s\n",
            comparison$HighConf_F[3], comparison$HighConf_p[3],
            ifelse(comparison$HighConf_sig[3], "***", ""))
##  Interaction: F=2.22, p=1.37e-01

cat(sprintf("  Regulatory Era: F=% .2f, p=% .2e %s\n",
            comparison$HighConf_F[4], comparison$HighConf_p[4],
            ifelse(comparison$HighConf_sig[4], "***", ""))
##  Regulatory Era: F=71.44, p=8.75e-29 ***

```

```
cat(sprintf("\nRobustness Assessment: %d/%d consistent (%s)\n",
            consistent_effects, total_effects,
            ifelse(consistent_effects == total_effects, "ROBUST", "CHECK")))

##  
## Robustness Assessment: 3/4 consistent (CHECK)

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

##  
## =====

cat("Analysis pipeline complete!\\n")

## Analysis pipeline complete!

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

##  
## =====

cat("\nPhase 8 complete\\n")

##  
## Phase 8 complete
```