

STAT 565
Methods in Biostatistics

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TOPICS

- **Human/Animal Health Studies**
 - Randomized Clinical Trials
 - Observational Studies
- **Time to event analysis**
- **Analysis of repeated measures**
- **Dealing with Missing Data**
- **Meta Analysis**

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Survival Analysis

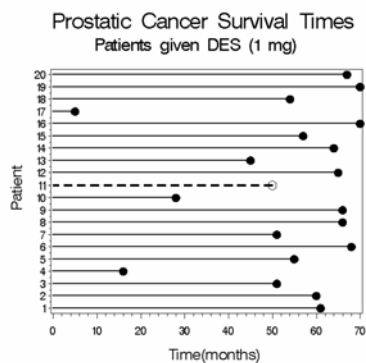
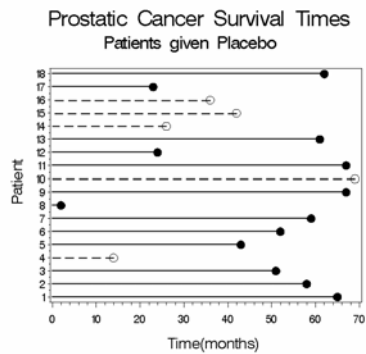
- **Basic concepts**
- **Kaplan-Meier Estimation**
- **Using Covariate Information**
 - Proportional hazards models
 - Accelerated Failure Times
 - Model assessment
- **Correlated Failure Times**

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Example 1.1: Prostatic cancer

- **Compare two treatments**
 - placebo
 - 1.0 mg of diethylstilbestrol (DES)
- **Survival times**
 - start-point: when patient is randomized to a treatment
 - end-point: death from prostatic cancer
 - right censoring:
 - * death from other causes
 - * lost to follow up
 - * end of study period

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- Other prognostic factors
 - age of the patient
 - serum hemoglobin level
 - size of tumor
 - Gleason index (tumor stage and grade)

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Example 1.2: Schizophrenia

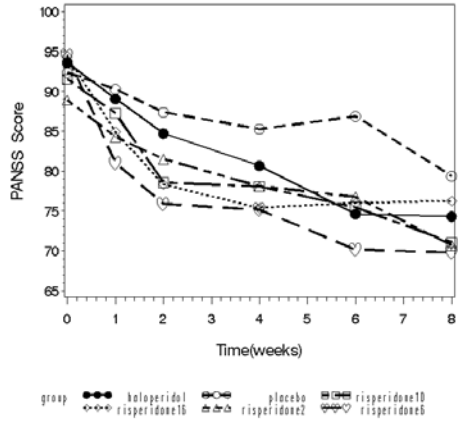
- 523 patients
 - age between 18 and 65
 - good general health
 - initial PANSS between 60 and 120
- Drug therapies
 - placebo
 - Standard therapy: haloperidol (20 mg)
 - Novel compound: risperidone (2, 6, 10, or 16 mg)

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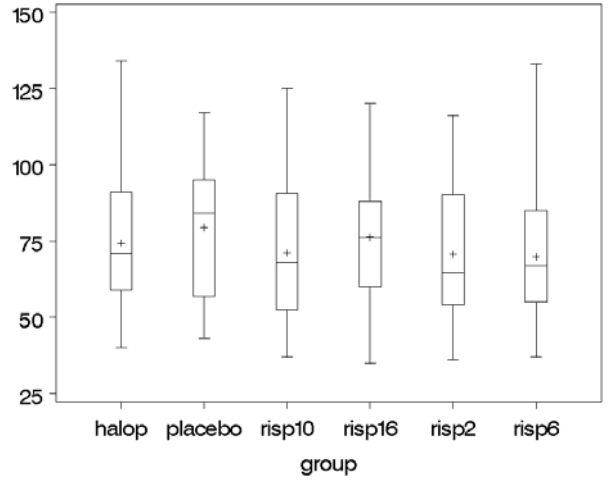
- Response: score on the Positive and Negative Symptom Scale (PANSS)
 - measured at -1, 0, 1, 2, 4, 6, 8 weeks
 - Clinical improvement: reduction of 20 in PANSS
- Objective: Compare time trends in mean PANSS scores for the six treatments.

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PANSS Rating Scale



PANSS Scores at 8 weeks



Missing Data

Percentage of dropouts by treatment group

	p	h	r2	r6	r10	r16	Total
Dropouts	69	59	59	40	45	39	270
Total	88	87	87	86	87	88	523

Missing Data

Reasons for Dropout

Abnormal lab results	4
Adverse experience	26
Inadequate response	183
Inter-current illness	3
Lost to follow-up	3
Other reason	7
Uncooperative	25
Withdrew consent	19

Course Information

Instructor: Kenneth J. Koehler
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Course Notes:

As they become available copies will be made available as PDF files on the course web page:

[http://www.public.iastate.edu/
~kkoehler/stat565/stat565.html](http://www.public.iastate.edu/~kkoehler/stat565/stat565.html)

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Textbooks:

Collett, David, *Modelling Survival Data in Medical Studies*, 2nd edition, Chapman & Hall/CRC, 2003. ISBN 1-58488-325-1

Diggle, Peter J., Heagerty, Patrick, Liang, Kung-Yee, Zeger, Scott L., *Analysis of Longitudinal Data*, 2nd edition, Oxford University Press, 2002. ISBN 0-19-852484-6

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Computation:

SAS and R code for examples covered in the lectures will be posted on the course web page. You should have a calculator that you can bring to exams.

Grades:

Assignments (15%)
Midterm Exam (25%)
Project(25%)
Final Exam (35%)

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Reading Assignments

<u>Topic</u>	<u>Readings</u>
1. Observational Studies, randomized clinical trials	Notes
2. Survival Analysis: survival and hazard functions	Collett: Chapter 1
3. Nonparametric methods	Collett: Chapters 2, 12
4. Parametric models	Collett: Chapter 5
5. Cox regression model	Collett: Chapters 3, 4
6. Time dependent covariates	Collett: Chapter 8
7. Longitudinal studies	Diggle: Chapters 1-3
8. Mixed linear models	Diggle: Chapters 4,5
9. Methods for count data	Diggle: parts of chapters 7-9
10. Handling missing data	Diggle: Chapter 12
11. Meta analysis	Notes

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Books on Clinical Trials and Observational Studies

1. Friedman, L. W., Furberg, C. D., and DeMets, D. L. (1998) *Fundamentals of Clinical Trials, 3rd edition*, Springer-Verlag, New York. ISBN 0-387-98586-7
2. Chow, Shein-Chung, Shao Jun, and Wang, Hansheng (2003) *Sample Size Calculations in Clinical Research* CRC Press, Taylor & Francis Group, Boca Raton, ISBN: 0-8247-0970-5
3. Rosenbaum, Paul, R. (2002) *Observational Studies, 2nd edition*, New York, Springer-Verlag

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Books on Survival Analysis

1. Kalbfleisch, J. D. and Prentice, R. L. (2002) *The Statistical Analysis of Failure Time Data, 2nd edition*, Wiley, Hoboken, New Jersey, ISBN 0-471-36357-X
2. Klein, J. P. and Moeschberger, M. L. (2003) *Survival Analysis: Techniques for Censored and Truncated Data, 2nd ed.* Springer-Verlag, New York. ISBN 0-387-95399-X
3. Therneau, T. M., and Grambsch, P. M. (2000) *Modeling Survival Data: Extending the Cox model*, Springer-Verlag, New York.
4. Fleming, T. R. and Harrington, D. P. (1991) *Counting Processes and Survival Analysis*, Wiley, New York. ISBN 0-471-52218-X

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Books on Analysis of Longitudinal Studies

1. Fitmaurice, G. M., Laird, N. M., and Ware, J. M. (2004) *Applied Longitudinal Analysis*, Wiley Hoboken, New Jersey. ISBN 0-471-21487-6
2. Davidian, Marie, (2005) *Applied Longitudinal Data Analysis* Springer-Verlag, New York. ISBN: 0-387-40337-X
3. Molenberghs, Geert and Verbeke, Geert (2005) *Models for Discrete Longitudinal Data*, Springer-Verlag, New York. ISBN: 0-387-25144-8
4. Pinheiro, J. C. and Bates, D. M. (2000) *Mixed-effects Models in S and S-PLUS* Springer-Verlag, New York.

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Books on R

1. Dalgaard, Peter, (2002) *Introductory Statistics with R*, Springer-Verlag, New York. Corrected 3rd printing, 2004, ISBN: 0-387-95475-9
2. Venables, W. N. and Ripley, B. D. (2002) *Modern Applied Statistics with S, 4th edition*, Springer-Verlag, New York. ISBN: 0-387-95457-0
3. Venables, W. N. and Ripley, B. D. (2004) *S Programming, Corrected 3rd printing*, Springer-Verlag, New York. ISBN: 0-387-98966-8
4. Krause, Andreas and Olson, Melvin (2005) *The Basics of S-PLUS 4th ed.*, Springer-Verlag, New York. ISBN: 0-387-26109-5

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Information on SAS

Manuals: (Available in Snedecor 115)

1. **SAS/STAT User's Guide, Version 8, Volume 1, Cary, NC: SAS Institute Inc. 1999**
2. **SAS/STAT User's Guide, Version 8, Volume 2, Cary, NC: SAS Institute Inc. 1999**
3. **SAS/STAT User's Guide, Version 8, Volume 3, Cary, NC: SAS Institute Inc. 1999**

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SAS Books

1. *SAS Survival Analysis Techniques for Medical Research, 2nd Edition*
SAS Institute, Cary, N.C. (\$ 39.95)
2. *Survival Analysis Using the SAS System: A Practical Guide,*
SAS Institute, Cary, N.C. (\$ 41.95)
3. *Longitudinal Data and SAS: A Programmer's Guide,*
SAS Institute, Cary, N.C. (\$ 29.85)

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Websites

1. **SAS:**
www.sas.com
2. **Venables & Ripley libraries:**
www.stats.ox.ac.uk/pub/MASS3/sites.html
3. **R libraries:**
www.r-project.org
<http://rh-mirror.linux.iastate.edu/CRAN/>
4. **Splus/Insightful Corporation**
www.insightful.com
cm.bell-labs.com/stat/NLME
5. **Data sets in Collett's book:**
www.crcpress.com/e_products/downloads/
6. **Data sets in Diggle, et al.:**
faculty.washington.edu/heagerty/

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