

Delfini Group™, LLC



Evidence- & Value-based Solutions For Health Care

Clinical Improvement Consults, Content, Seminars, Training & Tools

Recalculating Intention-to-Treat Analyses

Rescuing the Baby While Throwing out the Bathwater



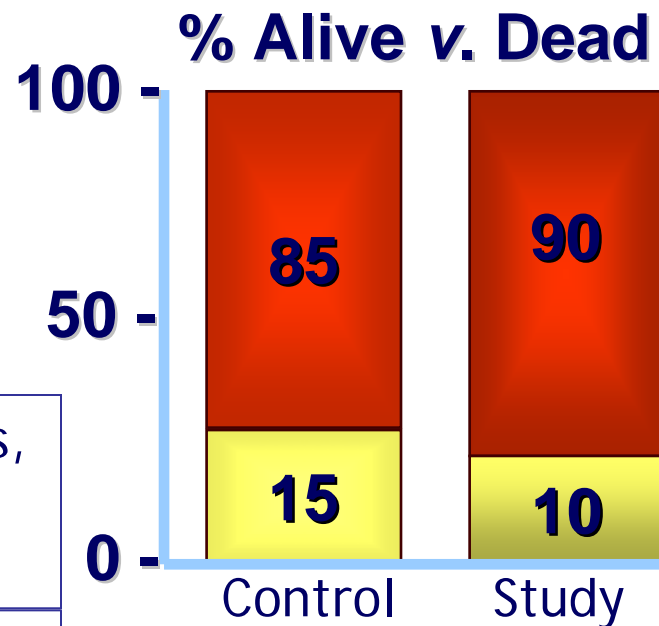
Or how to salvage an otherwise useful study from a host of missing or poorly assigned values...



Problem & the Solution

- Missing values are too high and the author did not do an ITT analysis and/or you do not agree with the imputation method the author used to assign missing values
- A solution is to verify the “reported” statistical significance of selected outcomes

These numbers are the basis for the 2x2 table, from whence many statistics come...



A 2 x 2 Table for calculating p-values, confidence intervals, diagnostic test measure functions, etc. ↓

	Alive	Dead
Control Group	85	15
Study Group	90	10



See Weblinks on www.delfini.org for calculators...

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Analyze a 2x2 contingency table

Enter your data

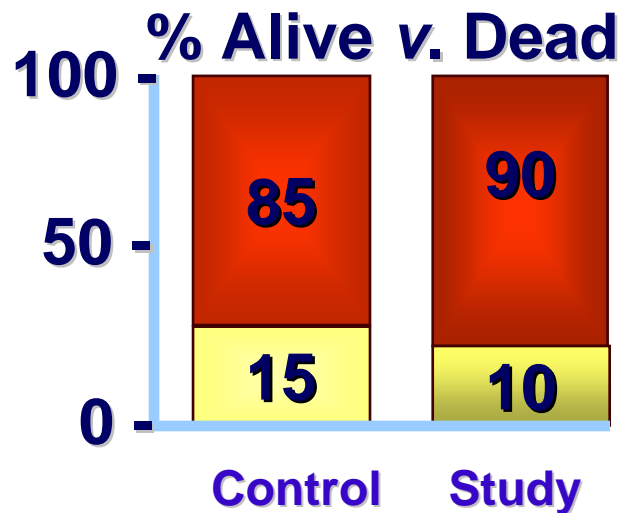
Enter the number of subjects actually observed. Don't enter proportions, percentages or means.

[Learn how to create a contingency table.](#)

	Outcome 1	Outcome 2
Group 1	<input type="text"/>	<input type="text"/>
Group 2	<input type="text"/>	<input type="text"/>

Create a 2x2 Table

From this →



To this ↓

	Alive	Dead
Control Group	<input type="text" value="85"/>	<input type="text" value="15"/>
Study Group	<input type="text" value="90"/>	<input type="text" value="10"/>

Imputation Methods We Favor

- Sensitivity analyses test the strength of the data
- Look for a conservative approach that does not favor the intervention studied
- Extreme-case analysis puts the intervention through the toughest test as it tests a worst-case scenario
 - Missing in intervention group are counted as “treatment failures”
 - Missing in comparison group are counted as “treatment successes”
- Application of control event rate is a conservative choice
- Baseline-carried forward may be a conservative choice
- Mixed effects models

Case Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Treatment with Prednisolone or Acyclovir in Bell's Palsy

Frank M. Sullivan, Ph.D., Iain R.C. Swan, M.D., Peter T. Donnan, Ph.D.,
Jillian M. Morrison, Ph.D., Blair H. Smith, M.D., Brian McKinstry, M.D.,
Richard J. Davenport, D.M., Luke D. Vale, Ph.D., Janet E. Clarkson, Ph.D.,
Victoria Hammersley, B.Sc., Sima Hayavi, Ph.D., Anne McAteer, M.Sc.,
Ken Stewart, M.D., and Fergus Daly, Ph.D.

N Engl J Med 2007;357:1598-607. PMID: 17942873



Study Aims

- The Health Technology Assessment Program of the National Institute for Health Research commissioned an independent academic group to determine whether prednisolone or acyclovir used early in the course of Bell's palsy improves the chances of recovery.

Sullivan 07—PMID: 17942873

- Aim: RCT to determine whether prednisolone or acyclovir used early in the course of Bell's palsy improves the chances of recovery
- Intervention: Patients were randomly assigned to receive 10 days of treatment with prednisolone, acyclovir, both agents or placebo
- Primary outcome measure: House-Brackmann grading system for facial-nerve function—a widely used clinical system for grading recovery from facial-nerve paralysis caused by damage to lower motor neurons
- Duration: 9 months

Study Conclusion

- In patients with Bell's palsy, early treatment with prednisolone significantly improves the chances of complete recovery at 3 and 9 months. There is no evidence of a benefit of acyclovir given alone or an additional benefit of acyclovir in combination with prednisolone.
- But is this benefit from prednisolone true?

Sullivan 07—PMID: 17942873

- Missing Data:
 - Prednisolone + acyclovir $10/134=7.5\%$
 - Prednisolone-only $11/138=7.9\%$
 - Acyclovir + placebo $15/138=10.9\%$
 - Placebo group $19/141=13.5\%$
 - Total loss = $55 / 551 = 10\%$

ITT Exercise: Prednisolone

Study Arms	Prednisolone + Acyclovir	Prednisolone + Placebo	Acyclovir + Placebo	Placebo + Placebo
Randomized	134	138	138	141
Sought active Rx	2	2	1	3
Lost to f/u	8	9	14	16

Treatment Success: Grade 1 on House-Brackmann scale at 9 months

- Prednisolone = 237/251 analyzed of 272 randomized
- No Prednisolone = 200/245 analyzed of 279 randomized

Green = Tx Failures; Pink = Tx Success!

Study Arms	Prednisolone+ Acyclovir	Prednisolone + Placebo	Acyclovir + Placebo	Placebo + Placebo
Randomized	134	138	138	141
Sought active Rx	2 ☹️	2 ☹️	1 ☹️	3 ☹️
Lost to f/u	8 ☹️	9 ☹️	14 😊	16 😊

Treatment Success: Grade 1 on House-Brackmann scale at 9 months

- Prednisolone = 237/272 randomized
- No Prednisolone = 200 + 30/279 randomized

When we do an extreme case ITT analysis ...



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Number needed to treat (NNT)

How effective is a clinical treatment? Because many people find it hard to think about small fractions, these kind of data are better understood when converted to the Number Needed to Treat or NNT. Enter the number of patients in each group who had the "good" or "bad" outcome, and this calculator will convert to NNT and explain the results.

Enter the actual number of patients in each group. Don't enter fractions, percentages, or rates per 1000 or some other value.

	Good Outcome	Bad Outcome
control	<input type="text" value="230"/>	<input type="text" value="49"/>
experimental	<input type="text" value="237"/>	<input type="text" value="35"/>

Desired confidence level:

Eh voila!!! Prednisolone Fails Toughest Test

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Number needed to treat

Your data

	Good Outcome	Bad Outcome
control	230	49
experimental	237	35

Calculated results

17.56 percent of control subjects had the adverse outcome.

12.87 percent of experimental subjects had the adverse outcome.

The difference, the absolute risk reduction, is 4.70 percent.

The 95% confidence interval for this difference ranges from -1.29% to 10.68% .

The NNT (Number Needed to Treat) is 22 . This means that about one in every 22 patients will benefit from the treatment.

Because the 95% confidence interval for the absolute risk reduction extends from a negative number (treatment may harm) to a positive number (treatment may benefit), it is tricky to compute a 95% CI for the NNT. Here is the best way to express the 95% confidence interval (DG Altman, British Medical Journal, 317:1309-1312, 1998):

You can't say with 95% certainty whether experimental is harmful, has no effect, or is helpful compared to control. You can say with 95% certainty that one of these statements is true:

- The experimental treatment is helpful (compared to control), and the number needed to help is greater than 9.4
- The experimental treatment is harmful (compared to control), and the number needed to harm is greater than 77.8

Actually, no big surprise...but what to do now?

Application of Control Event Rate

Documentation	Pred	No Pred	% No Pred Improved Outcomes of Completers				
Randomized	272	279					
Grade 1 on HB at 9 mos (count as improved)	237	200	82%	← Control Event Rate			
Completed	251	245					
Not Completed	21	34					
Sought Active Tx (count as failure)	4	4					
Pool for Reanalysis	17	30					
Application of Control Event Rate	14	24		→ Patients reanalyzed as better			
Reanalyze as Failed	3	6		→ Patients reanalyzed as failed			
Total Randomized	272	279					
Total Reanalyzed as Successes	251	224					
Total Reanalyzed as Failed	21	55					

Application of Control Event Rate to All Not Completing Study and Not Seeking Active Tx



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Number needed to treat (NNT)

How effective is a clinical treatment? Because many people find it hard to think about small fractions, these kind of data are better understood when converted to the Number Needed to Treat or NNT. Enter the number of patients in each group who had the "good" or "bad" outcome, and this calculator will convert to NNT and explain the results.

Enter the actual number of patients in each group. Don't enter fractions, percentages, or rates per 1000 or some other value.

	Good Outcome	Bad Outcome
control	<input type="text" value="224"/>	<input type="text" value="55"/>
experimental	<input type="text" value="251"/>	<input type="text" value="21"/>

Desired confidence level:

It works!!!



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Number needed to treat

Your data

	Good Outcome	Bad Outcome
control	224	55
experimental	251	21

Calculated results

19.71 percent of control subjects had the adverse outcome.

7.72 percent of experimental subjects had the adverse outcome.

The difference, the absolute risk reduction, is 11.99 percent.

The 95% confidence interval for this difference ranges from 6.35% to 17.64% .

The NNT (Number Needed to Treat) is 9 . This means that about one in every 9 patients will benefit from the treatment.

The 95% confidence interval for the NNT ranges from 5.7 to 15.8



It even works with applying Control Event Rate only to controls...



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Number needed to treat (NNT)

How effective is a clinical treatment? Because many people find it hard to think about small fractions, these kind of data are better understood when converted to the Number Needed to Treat or NNT. Enter the number of patients in each group who had the "good" or "bad" outcome, and this calculator will convert to NNT and explain the results.

Enter the actual number of patients in each group. Don't enter fractions, percentages, or rates per 1000 or some other value.

	Good Outcome	Bad Outcome
control	<input type="text" value="224"/>	<input type="text" value="55"/>
experimental	<input type="text" value="237"/>	<input type="text" value="35"/>

Desired confidence level:

We are happy!!!



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4. [View results](#)

Number needed to treat

Your data

	Good Outcome	Bad Outcome
control	224	55
experimental	237	35

Calculated results

19.71 percent of control subjects had the adverse outcome.

12.87 percent of experimental subjects had the adverse outcome.

The difference, the absolute risk reduction, is 6.85 percent.

The 95% confidence interval for this difference ranges from 0.71% to 12.98% .

The NNT (Number Needed to Treat) is 15 . This means that about one in every 15 patients will benefit from the treatment.

The 95% confidence interval for the NNT ranges from 7.7 to 140.5



ITT Re-analysis

- Re-analysis using a conservative approach can help us conclude efficacy in an otherwise valid study
- Estimate of effect is unknown

Delfini Excel Tool Available

Study Reference	Sullivan Bells Palsy NEJM October 2007										
Reviewer & Date	Strite/Stuart - 01/16/08										
Endpoint for Calculations	Grade 1 on House-Brackmann scale at 9 months										
Study Period	9 mos										
Imputation Method/Assumptions	81.6% of missing patients in all groups assigned to recovery based on percent recovered in No Pred Group										
Enter: "Improved" or "Harmed"	improved			Imputation Method Information							
	Study	Control		Applied	81.6%	missing recovered - both groups					
Enter agents	Prednisolone	No Pred									
# of people improved OR use % below	237	200	If using "# people," ensure % section in rows 16,17 & 18 is clear. These cells override % cells.								
% of people improved			If using "% people," ensure # of people in row above is clear. Otherwise # of people overrides.								
If %, type in choice of denominator			Type randomized, completers or other (option to specify if you choose other).								
If "other," enter denominator to be applied			Complete only if denominator chosen is "other." Enter numbers you want used to calculate.								
Variables	Prednisolone	No Pred	Total	Prednisolone	No Pred	Total					
Number randomized	272	279	551	49.4%	50.6%	100.0%	Number randomized				
Author reports as completers	251	245	496	45.6%	44.5%	90.0%	Author reports as completers				
From above, rounded calculation for improved	237	200	437	43.0%	36.3%	79.3%	From above, rounded calculation for improved				
Not completed study	21	34	55	3.8%	6.2%	10.0%	Not completed study				
Discontinued due to treatment failure	4	4	8	0.7%	0.7%	1.5%	Discontinued due to treatment failure				
Remainder not completing study	17	30	47	3.1%	5.4%	8.5%	Remainder not completing study				
From remainder, you assign outcomes as improved	14	24	38	2.5%	4.4%	7.0%	From remainder, you assign outcomes as improved				
Total to be counted as improved	251	224	475	45.5%	40.7%	86.3%	Total to be counted as improved				
Total to be counted as not improved	21	55	76	3.8%	9.9%	13.7%	Total to be counted as not improved				
Total Subjects	272	279	551	49.4%	50.6%	100.0%	Total Subjects				
Recomputed Two-by-two Table							If not statistically significant, NNT/NNH is misleading.				
	Not Improved	Improved	Total	Not Improved	Improved	Total	ARR/ARI	NNT/NNH	Study Period	Enter p-value	
Prednisolone Subjects	21	251	272	7.8%	92.2%	100.0%	Prednisolone Subjects				
No Pred	55	224	279	19.5%	80.5%	100.0%	11.8%	8	9 mos	0.0487	
Total	76	475	551				RRR =	60.2%		Fisher's Exact	



Non-inferiority & Equivalence Trials

- Conservative approaches should not be used as that will push toward non-inferiority or equivalence