A Non-inferiority Test for Independent Dichotomous Variables Using a Shrinkage Proportion Estimator

Félix Almendra-Arao

UPIITA del Instituto Politécnico Nacional, México

36th Annual Conference of the International Society for Clinical Biostatistics
August 23 - 27, 2015, Utrecht, The Netherlands
Content

1 Introduction
   - Non-inferiority Tests
   - The Framework

2 A known test and the new proposal

3 Comparison of the Tests
   - Comparison of Test Sizes
   - Power Comparison

4 Example

5 Conclusions
1 Introduction
   - Non-inferiority Tests
   - The Framework

2 A known test and the new proposal

3 Comparison of the Tests
   - Comparison of Test Sizes
   - Power Comparison

4 Example

5 Conclusions
Introduction
- Non-inferiority Tests
- The Framework

A known test and the new proposal

Comparison of the Tests
- Comparison of Test Sizes
- Power Comparison

Example

Conclusions
1 Introduction
   • Non-inferiority Tests
   • The Framework

2 A known test and the new proposal

3 Comparison of the Tests
   • Comparison of Test Sizes
   • Power Comparison

4 Example

5 Conclusions
1 Introduction
   - Non-inferiority Tests
   - The Framework

2 A known test and the new proposal

3 Comparison of the Tests
   - Comparison of Test Sizes
   - Power Comparison

4 Example

5 Conclusions
Introduction

A known test and the new proposal

Comparison of the Tests

Example

Conclusions

Non-inferiority Tests

The Framework

1 Introduction
   • Non-inferiority Tests
     • The Framework

2 A known test and the new proposal

3 Comparison of the Tests
   • Comparison of Test Sizes
     • Power Comparison

4 Example

5 Conclusions
Many situations require the comparison of two groups that have been subjected to different treatments.

To compare two treatments in clinical trials: *non-inferiority (NI) tests* is an outstanding method.

**NI tests**: statistical procedures used to verify whether there exists sample evidence that a new treatment *is not substantially less effective* than a standard treatment whose efficacy is established.
Non-inferiority Tests

For the difference between two independent proportions several NI tests are known.

The test defined in Miettinen and Nurminen (1985) and Farrington and Manning (1990) has good behavior.

In this work it is proposed a different test that has similar behavior as above but with the main advantage that is more simple to use in practice.
1 Introduction
   • Non-inferiority Tests
   • The Framework

2 A known test and the new proposal

3 Comparison of the Tests
   • Comparison of Test Sizes
   • Power Comparison

4 Example

5 Conclusions

Félix Almendra-Arao
A Non-inferiority Test for Independent Dichotomous Variables
The Framework

Consider a scenario in which two treatments, a new treatment and a control or standard treatment, are to be compared via a dichotomous end point in a randomised study.

<table>
<thead>
<tr>
<th>treatment</th>
<th>units</th>
<th># of positive response</th>
</tr>
</thead>
<tbody>
<tr>
<td>standard (1)</td>
<td>$n_1$</td>
<td>$X_1$</td>
</tr>
<tr>
<td>new (2)</td>
<td>$n_2$</td>
<td>$X_2$</td>
</tr>
</tbody>
</table>

$X_i \sim Bin(n_i, p_i)$. $p_i$: probability of success for the treatment $i$.

general situation: $H_0 : p_2 \leq g(p_1)$ vs $H_1 : p_2 > g(p_1)$
difference proportions: $H_0 : p_2 \leq p_1 - d_0$ vs $H_1 : p_2 > p_1 - d_0$
A known test and the new proposal

Miettinen, Nurminen 1985; Farrington, Manning(1990)

\[ T_B(X_1, X_2) = \frac{\hat{p}_1 - \hat{p}_2 - d_0}{\sqrt{\frac{\hat{p}_1(1-\hat{p}_1)}{n_1} + \frac{\hat{p}_2(1-\hat{p}_2)}{n_2}}} \]

\( \hat{p}_i \): MLE of \( p_i \)
\( \check{p}_i \): MLE of \( p_i \) restricted under the null hypothesis

The new proposal

\[ T_A(X_1, X_2) = \frac{\hat{p}_1 - \hat{p}_2 - d_0}{\sqrt{\frac{\hat{p}_1(1-\hat{p}_1)}{n_1} + \frac{\hat{p}_2(1-\hat{p}_2)}{n_2}}} \]

\( \phi(n) = \left\lfloor \frac{n}{25} \right\rfloor + 1, \check{p}_i = \frac{X_i + \phi(n_i)}{n_i + 2\phi(n_i)} \)
Introduction
- Non-inferiority Tests
- The Framework

A known test and the new proposal

Comparison of the Tests
- Comparison of Test Sizes
- Power Comparison

Example

Conclusions
Sample sizes vs test sizes for $\alpha = 0.05$, $d_0 = 0.10$. 

Félix Almendra-Arao  
A Non-inferiority Test for Independent Dichotomous Variables
Content

1. Introduction
   - Non-inferiority Tests
   - The Framework

2. A known test and the new proposal

3. Comparison of the Tests
   - Comparison of Test Sizes
   - Power Comparison

4. Example

5. Conclusions
Power functions for $n_1 = n_2 = 60$, $\alpha = 0.05$, $d_0 = 0.10$. 
Bernard et al. (2002), reported the result of a NI trial to compare oral pristinamycin with the standard regimen of penicillin for the treatment of erysipelas in adults.

**The clinical trial**

<table>
<thead>
<tr>
<th>treatment</th>
<th>patients</th>
<th>success response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Standard.</em> Penicillin (1)</td>
<td>102</td>
<td>68 /102</td>
</tr>
<tr>
<td><em>New.</em> Oral pristinamycin (2)</td>
<td>102</td>
<td>83 /102</td>
</tr>
</tbody>
</table>

**Statistical analysis.** $d_0 = 0.10$, $\alpha = 0.05$

<table>
<thead>
<tr>
<th>Test</th>
<th>Critical Constant</th>
<th>$T(68,83)$</th>
<th>Test Size</th>
<th>Reject $H_0$?</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_A$</td>
<td>-1.70889</td>
<td>-3.96845</td>
<td>0.04883 $\alpha$ = 0.9843$\alpha$</td>
<td>Yes</td>
</tr>
<tr>
<td>$T_B$</td>
<td>-1.71727</td>
<td>-3.98089</td>
<td>0.04883 $\alpha$ = 0.9843$\alpha$</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Conclusions

- A new NI test for two proportions was constructed ($T_A$).
- As $T_B$ behaves well, we compare $T_A$ with $T_B$.
- For all analyzed configurations:
  - *Test sizes behavior.* $T_B$ is slightly better than $T_A$.
  - *Power.* Approximately equal power functions.
- $T_A$ is much simpler to calculate than $T_B$.
- By compromising between the practicality of use of and the performance of the test, $T_A$ can be a viable alternative to $T_B$. 
Further Reading

F. Almendra Arao.  

P. Bernard, O., Chosidow, and L.Vaillant.  
*Oral pristinamycin versus standard penicillin regimen to treat erysipelas in adults: Randomised, non-inferiority, open trial.*  
O. Miettinen and M. Nurminen.  
*Comparative analysis of two rates.*  

C. Farrington and G. Manning.  
*Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk.*  