Blinding Indexes - Generalized and Unified Framework - a SAS® Macro

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ABSTRACT

There is a SAS® macro (Wu & Zhu, 2022) that can calculate James' and Bang's blinding indexes (BIs). However, its capabilities are somewhat limited to the most common, simplistic scenarios. This paper extends this macro to be more flexible and comprehensive to accommodate different data types and functions/options available in the assessment of the effectiveness of blinding in clinical trials.

INTRODUCTION

After a clinical trial is completed, understanding how well blinding was retained may be useful because 'successful blinding' can be a fundamental, and potentially testable assumption when the goal is to estimate an unbiased treatment effect. The first step in the quantitative evaluation of blinding is a direct question to participants to guess – strictly speaking, provide their 'perception' – to which group they were assigned. Other individuals with relevant roles in the trial (i.e., outcome assessors, staff, clinicians) can also be asked to 'guess' treatment assignment of participants. Ideally, in a well-conducted clinical trial with a good design and ideal operation, when participants are randomly assigned to treatment and placebo groups (generally 2 or possibly more than 2 arms), the guessing would likely be correct 50% of the time. The second step involves summarizing (counting) the responses as shown in Tables 1 and 2. Finally, the third and last step involves the computation and interpretation of blinding indexes. For example, the degree of deviation from the 50% of correct guessing in each group (i.e., 'random guess') and the extent participants in both arms believe they received active intervention (i.e., 'wishful thinking') (Freed et al., 2021).

Currently, blinding indexes are considered as the reference standard measure to analyze blinding related data (Howick et al., 2020), and computing modules are available in Microsoft® Excel®, R, SAS®, and Stata® (Chen, 2008; Kim, 2014, 2016; Kim et al., 2021; Schwartz & Mercaldo, 2022; Wu & Zhu, 2022). However, the capabilities of these modules are somewhat limited to simplistic scenarios with different functions available in different software; e.g., for two treatment arms and three possible responses; no option for re-asking the subject who answered 'Don't know' (e.g., ancillary or validation purpose); no option for user-defined weights; and/or no selection of the direction of confidence intervals (CI). This paper reviews the background and context and provides a new macro for these two common indexes for blinding assessment for comprehensive data/settings in a unified framework.

BLINDING INDEX METHODS

The two most common structures for the response data regarding blinding in clinical trials are presented in Table 1 and Table 2.

Guess	Treatment assignment		Total
	Treatment	Placebo	
Treatment	n_{11}	n_{12}	$n_{1.}$
Placebo	n_{21}	n_{22}	$n_{2.}$
Don't know	n_{31}	n_{32}	$n_{3.}$
Total	$n_{.1}$	$n_{.2}$	N

i = 1 (treatment), 2 (placebo), 3 (don't know), and j = 1 (treatment), 2 (placebo). N = total participants.

Table 1. Treatment Assignment and Guess, 3x2 Format

Guess	Treatment assignment		Total
	Treatment	Placebo	
Treatment – strongly believe	n_{11}	n_{12}	$n_{1.}$
Treatment – somewhat believe	n_{21}	n_{22}	$n_{2.}$

Placebo – somewhat believe	n_{31}	n_{32}	$n_{3.}$
Placebo – strongly believe	n_{41}	n_{42}	$n_{4.}$
Don't know	n_{51}	n_{52}	$n_{5.}$
Total	$n_{.1}$	$n_{.2}$	N

i = 1, 2 (treatment), 3,4 (placebo), 5 (don't know), and j = 1 (treatment), 2 (placebo). N = total participants.

Table 2. Treatment Assignment and Guess, 5x2 Format

James' Blinding Index

The James' Blinding Index (James et al., 1996), which can be seen as an extension of the traditional *kappa* coefficient of agreement, provides a single value that represents the level of blinding in a clinical trial and is defined as:

$$BI = \frac{1+P_{DK}+(1-P_{DK})*K_D}{2},$$

where P_{DK} is the proportion of 'Don't know' responses, $K_D = (P_{Do} - P_{De})/P_{De}$ with $P_{Do} = \sum_{i=1}^{k}\sum_{j=1}^{k} w_{ij}P_{ij}/(1-P_{DK})$ and $P_{De} = \sum_{i=1}^{k}\sum_{j=1}^{k} w_{ij}P_{i.}(P_{.j} - P_{3j})/(1-P_{DK})^2$ where $P_{DK} \neq 1, P_{ij} = \frac{n_{ij}}{N}$, and w_{ij} are weights for the particular responses and *k* is the number of assignments. For $k = 2$, the following weights were proposed: for correct guess, w_{ij} = 0; for incorrect guess, $w_{ij} = 0.5$; and for 'Don't know' response, $w_{ij} = 1$, where these weights served as 'defaults' values in our macro. The James' Blinding Index may take a value from 0 (when all guesses are correct, which is a least ideal scenario) to 1 (when all guesses are 'Don't know', which can be a most ideal scenario). For random guessing, the James' BI will take a value of 0.5. Usually, the index is reported with a two-sided CI.

Bang's Blinding Index

The Bang's Blinding index (Bang et al., 2004) operates in an intuitive paradigm of unblinding beyond chance and can be estimated for each treatment assignment separately as:

$$BI_i = \left(2\frac{n_{ii}}{n_{1i}+n_{2i}} - 1\right) * \left(\frac{n_{1i}+n_{2i}}{n_{1i}+n_{2i}+n_{3i}}\right),$$

where, say, $i = 1$ for active treatment or intervention arm and $i = 2$ for placebo or control treatment arm. The Bang's Blinding Index may take a value from -1, when all guesses are incorrect to 1, when all guesses are correct. For random guessing, the Bang's BI will take a value of ≈ 0, and for wishful (or pessimistic) thinking, the summed $BIs = BI_1 + BI_2$ will take a value of ≈ 0. Usually, the index is reported with a one- or two-sided CI. An *ad-hoc* cut-off of 0.2 (or more liberal 0.3) has been used in the literature (Bang et al., 2010).

MACRO PARAMETERS

The %BI macro has one required and four optional parameters.

%macro BI(

X = /* a matrix with counts (dimension may vary) – required */,

ANCILLARY = /* an ancillary matrix (2x2) to compute Bang's Index – optional */,

JAMES_WEIGHTS = /* user-defined $w_{3\times2}$ or $w_{4\times3}$ weights for James' Blinding Index – optional.

Default: $w_{3\times2} = \begin{bmatrix} 0 & 0.75 \\ 0.75 & 0 \\ 1 & 1 \end{bmatrix}$, $w_{4\times3} = \begin{bmatrix} 0 & 0.5 & 0.75 \\ 0.5 & 0 & 0.75 \\ 0.75 & 0.75 & 0 \\ 1 & 1 & 1 \end{bmatrix}$ */,

BANG_WEIGHTS = /* user-defined $w_{5\times1}$ or $w_{6\times1}$ weights for Bang's Blinding Index – optional.

Default: $w_{3\times1} = \begin{bmatrix} 1 \\ -1 \\ 0 \end{bmatrix}$, $w_{5\times1} = \begin{bmatrix} 1 \\ 0.5 \\ -0.5 \\ -1 \\ 0 \end{bmatrix}$, $w_{6\times1} = \begin{bmatrix} 1 \\ 0.5 \\ -0.5 \\ -1 \\ 0.25 \\ -0.25 \end{bmatrix}$ */,

DIRECTION = /* specifies two-sided ('twosided' is default) or one-sided ('lower' or 'upper') 95% confidence limits– optional */

);

The format of X parameter should match the content and structure of a table for data of blinding assessment. X parameter can be a 3x2, 4x3, or 5x2 matrix as defined below.

Guess	**Treatment assignment**		→	**Matrix with counts**	**User-defined weights**	
	Treatment	**Placebo**		(See Example 1)	**James' BI**	**Bang's BI**
Treatment	n_{11}	n_{12}		X = (n_{11} n_{12}, n_{21} n_{22}, n_{31} n_{32})	(w_{11} w_{12}, w_{21} w_{22}, w_{31} w_{32})	(w_{11}, w_{21}, w_{31})
Placebo	n_{21}	n_{22}				
Don't Know	n_{31}	n_{32}				

Table 3. Input data for blinding assessment, 3x2 format. Output: James' and Bang's BIs.

Guess	**Treatment assignment**			→	**Matrix with counts**	**User-defined weights**
	Treatment, Dose 1	**Treatment, Dose 2**	**Placebo**		(See Example 2)	**James' BI**
Treatment, Dose 1	n_{11}	n_{12}	n_{13}		X = (n_{11} n_{12} n_{13}, n_{21} n_{22} n_{23}, n_{31} n_{32} n_{33}, n_{41} n_{42} n_{43})	(w_{11} w_{12} w_{13}, w_{21} w_{22} w_{23}, w_{31} w_{32} w_{33}, w_{41} w_{42} w_{43})
Treatment, Dose 2	n_{21}	n_{22}	n_{23}			
Placebo	n_{31}	n_{32}	n_{33}			
Don't know	n_{41}	n_{42}	n_{43}			

Table 4. Input data for blinding assessment, 4x3 format. Output: James' BI.

Guess	**Treatment assignment**		→	**Matrix with counts**	**User-defined weights**	
	Treatment	**Placebo**		(See Example 3)	**James' BI**	**Bang's BI**
Strongly Believe Treatment	n_{11}	n_{12}		X = (n_{11} n_{12}, n_{21} n_{22}, n_{31} n_{32}, n_{41} n_{42}, n_{51} n_{52})	(w_{11} w_{12}, w_{21} w_{22}, w_{31} w_{32}, w_{41} w_{42}, w_{51} w_{52})	(w_{11}, w_{21}, w_{31}, w_{41}, w_{51})
Somewhat Believe Treatment	n_{21}	n_{22}				
Somewhat Believe Placebo	n_{31}	n_{32}				
Strongly Believe Placebo	n_{41}	n_{42}				
Don't know	n_{51}	n_{52}				

* a 5x2 matrix will be transformed (the first row will be combined with the second row and the third row will be combined with the fourth row) into a 3x2 matrix as in Table 3.

Table 5. Input data for blinding assessment, 5x2 format. Output: James'* and Bang's BIs.

The format of optional ANCILLARY parameter (available for Bang's BI) should match the content and structure of a table for data obtained by re-asking the subjects who responded 'Don't know' in Table 5. ANCILLARY parameter/input, if specified, should be a 2x2 matrix as defined below.

Guess	**Treatment assignment**		→	**Matrix with counts**	**User-defined weights**
	Treatment	**Placebo**		(See Example 4)	**Bang's BI**
Treatment	n_{11}	n_{12}		ANCILLARY = (n_{11} n_{12}, n_{21} n_{22})	(a_{11}, a_{21})
Placebo	n_{21}	n_{22}			

Table 6. Input for data obtained by re-asking the subjects who answered Don't Know in Table 5.

JAMES_WEIGHTS and BANG_WEIGHTS are optional parameters and might be useful for sensitivity analyses (Bang et al., 2010). The structure of user-defined weights should follow the matrix structure as specified in Tables 3-5. If ANCILLARY parameter is specified, then BANG_WEIGHTS parameter is a result of vertical concatenation of Bang's BI weights from Table 5 (first four rows) and two rows from Table 6 – see Example 5. The sum of Bang's BI weights within the assignment arm must be zero, otherwise, an error message will be produced and execution will be stopped.

BEFORE RUNNING THE %BI MACRO

The macro can be considered as SAS/IML® software – its core is written in SAS/IML language and uses PROC IML computational procedure. To create a user-friendly output, SAS PROC TEMPLATE procedure was used. In order to make this macro work, you need to verify that SAS/IML component is licensed at your site. PROC SETINIT procedure can be used to identify SAS components installed:

```
proc setinit;
run;
```

EXAMPLES

The majority of the examples below are drawn from the original papers by James et al. and Bang et al., and we advise reading those papers (along with recent usages and guidance in the literature) concurrently with practicing these examples in order to put everything into perspective and learn how to interpret the results. Tables 3 and 5 present the most common designs for blinding assessment and can be reviewed in Examples 1 and 2. For blinding assessments with more complex designs, please review Examples 3-5.

Of note, some trialists do not allow the 'Don't know' option in the blinding questionnaire. In this case, our macro still works assuming that there was 0 'Don't Know', which could be a strong assumption in some cases.

The macro function *%str()* is used to pass an entire statement (a matrix with counts) into the macro.

Example 1. Based on Table V from James' 1996 paper

```
%BI(%str({145 34, 71 59, 76 38}));
```

James' Blinding Index (BI): ranges from 0 to 1

Guess	Treatment Assignment	
	Treatment	Placebo
Treatment	145	34
Placebo	71	59
Don't know	76	38

James' BI: Weights and Definitions			
	Correct Guess	Wrong Guess	Don't know
Weight	0	0.75	1

James' BI, two-sided Confidence Interval (CI)				
Type	BI Estimate	Std Err	Lower 95% CL	Upper 95% CL
Overall	0.534	0.024	0.487	0.581

Bang's Blinding Index (BI): ranges from -1 to 1 - each treatment arm assessed separately

Guess	Treatment Assignment, 3x2		Weights
	Treatment	Placebo	
Treatment	145	34	1

Placebo	71	59	-1
Don't know	76	38	0

Bang's BI, two-sided Confidence Interval (CI)				
Arm	**BI Estimate**	**Std Err**	**Lower 95% CL**	**Upper 95% CL**
Treatment, 3x2	0.253	0.048	0.159	0.348
Placebo, 3x2	0.191	0.072	0.050	0.331

Output 1. Output from Example 1

Example 2. Based on Table 6 from Bang's 2004 paper:

```
%BI(%str({38 11, 44 16, 21 21, 4 8, 170 83}));
```

James' Blinding Index (BI): ranges from 0 to 1

Guess	Treatment Assignment	
	Treatment	**Placebo**
Treatment	82	27
Placebo	25	29
Don't know	170	83

James' BI: Weights and Definitions			
	Correct Guess	**Wrong Guess**	**Don't know**
Weight	0	0.75	1

James' BI, two-sided Confidence Interval (CI)				
Type	**BI Estimate**	**Std Err**	**Lower 95% CL**	**Upper 95% CL**
Overall	0.748	0.022	0.705	0.791

Bang's Blinding Index (BI): ranges from -1 to 1 - each treatment arm assessed separately

Guess	Treatment Assignment, 3x2		Weights
	Treatment	**Placebo**	
Treatment	82	27	1
Placebo	25	29	-1
Don't know	170	83	0

No ancillary table

Guess	Treatment Assignment, 5x2		Weights
	Treatment	**Placebo**	
Strongly Believe Treatment	38	11	1
Somewhat Believe Treatment	44	16	0.5
Somewhat Believe Placebo	21	21	-0.5
Strongly Believe Placebo	4	8	-1
Don't know	170	83	0

Bang's BI, two-sided Confidence Interval (CI)				
Arm	**BI Estimate**	**Std Err**	**Lower 95% CL**	**Upper 95% CL**
Treatment, 3x2	0.206	0.035	0.137	0.275
Placebo, 3x2	0.014	0.054	-0.091	0.120
Treatment, 5x2	0.164	0.026	0.114	0.215
Placebo, 5x2	-0.004	0.035	-0.071	0.064

Output 2. Output from Example 2

Example 3. Based on Table III from James' 1996 paper:

```
%BI(%str({41 27 22, 66 72 36, 30 24 64, 44 51 52}));
```

James' Blinding Index (BI): ranges from 0 to 1

Guess	Treatment Assignment		
	Treatment, Dose 1	**Treatment, Dose 2**	**Placebo**
Treatment, Dose 1	41	27	22
Treatment, Dose 2	66	72	36
Placebo	30	24	64
Don't know	44	51	52

James' BI: Weights and Definitions				
	Correct Guess	**Correct Treatment, Wrong Dose**	**Wrong Treatment**	**Don't know**
Weight	0	0.5	0.75	1

James' BI, two-sided Confidence Interval (CI)				
Type	**BI Estimate**	**Std Err**	**Lower 95% CL**	**Upper 95% CL**
Overall	0.556	0.018	0.520	0.592

ERROR: X has wrong structure to estimate Bang's BI

Output 3. Output from Example 3

Example 4. Based on Table 8 from Bang's 2004 paper:

```
%BI(X = %str({38 11, 44 16, 21 21, 4 8, 170 83}),
ANCILLARY = %str({79 36, 86 45}));
```

James' Blinding Index (BI): ranges from 0 to 1

Guess	Treatment Assignment	
	Treatment	**Placebo**
Treatment	82	27
Placebo	25	29
Don't know	170	83

James' BI: Weights and Definitions			
	Correct Guess	**Wrong Guess**	**Don't know**
Weight	0	0.75	1

James' BI, two-sided Confidence Interval (CI)				
Type	**BI Estimate**	**Std Err**	**Lower 95% CL**	**Upper 95% CL**
Overall	0.748	0.022	0.705	0.791

Bang's Blinding Index (BI): ranges from -1 to 1 - each treatment arm assessed separately

Guess	Treatment Assignment, 3x2		Weights
	Treatment	**Placebo**	
Treatment	82	27	1
Placebo	25	29	-1
Don't know	170	83	0

Guess	Treatment Assignment, 5x2		Weights
	Treatment	**Placebo**	
Strongly Believe Treatment	38	11	1
Somewhat Believe Treatment	44	16	0.5
Somewhat Believe Placebo	21	21	-0.5
Strongly Believe Placebo	4	8	-1
Second Guess: Treatment	79	36	0.25
Second Guess: Placebo	86	45	-0.25

Bang's BI, two-sided Confidence Interval (CI)				
Arm	**BI Estimate**	**Std Err**	**Lower 95% CL**	**Upper 95% CL**
Treatment, 3x2	0.206	0.035	0.137	0.275
Placebo, 3x2	0.014	0.054	-0.091	0.120
Treatment, 5x2	0.158	0.027	0.106	0.210
Placebo, 5x2	0.013	0.036	-0.058	0.083

Output 4. Output from Example 4

Example 5. User specified weights and direction:

```
%BI(X = %str({38 11, 44 16, 21 21, 4 8, 170 83}),
ANCILLARY = %str({79 36, 86 45}),
JAMES_WEIGHTS = %str({0 0.5, 0.5 0, 1 1}),
BANG_WEIGHTS = %str({1, 0.4, -0.4, -1, 0.2, -0.2}),
DIRECTION = 'lower');
```

James' Blinding Index (BI): ranges from 0 to 1

Guess	Treatment Assignment	
	Treatment	**Placebo**
Treatment	82	27
Placebo	25	29
Don't know	170	83

James' BI: Weights and Definitions			
	Correct Guess	Wrong Guess	Don't know
Weight	0	0.5	1

James' BI, one-sided Confidence Interval (CI)				
Type	BI Estimate	Std Err	Lower 95% CL	Upper 95% CL
Overall	0.748	0.022	0.000	0.784

Bang's Blinding Index (BI): ranges from -1 to 1 - each treatment arm assessed separately

Guess	Treatment Assignment, 3x2		Weights
	Treatment	Placebo	
Treatment	82	27	1
Placebo	25	29	-1
Don't know	170	83	0

Guess	Treatment Assignment, 5x2		Weights
	Treatment	Placebo	
Strongly Believe Treatment	38	11	1
Somewhat Believe Treatment	44	16	0.4
Somewhat Believe Placebo	21	21	-0.4
Strongly Believe Placebo	4	8	-1
Second Guess: Treatment	79	36	0.2
Second Guess: Placebo	86	45	-0.2

Bang's BI, one-sided Confidence Interval (CI)				
Arm	BI Estimate	Std Err	Lower 95% CL	Upper 95% CL
Treatment, 3x2	0.206	0.035	-1.000	0.264
Placebo, 3x2	0.014	0.054	-1.000	0.103
Treatment, 5x2	0.151	0.025	-1.000	0.192
Placebo, 5x2	0.006	0.034	-1.000	0.061

Output 5. Output from Example 5

CONCLUSION

We developed a thorough tool to evaluate the quality of blinding achieved in randomized controlled trials. It will assist researchers in better understanding their data, provide more options for users, and alert researchers to notable signs/warnings of potential problems or shortcomings in the quality of blinding achieved. It should be noted that ‘true’ definitive blinding success cannot ever be known; thus, the guess status (correct, incorrect or no guess) is used as a proxy measure, and nine blinding scenarios may be accompanied to qualitatively elucidate different underlying scenarios (Bang et al., 2010; Freed et al., 2021). A global blinding index has also been proposed for multi-centers and multi-studies (Landsman et al., 2019).

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RECOMMENDED READING

- *SAS/IML® User's Guide*
- *PROC TEMPLATE Made Easy. A Guide for SAS® Users*

HOW TO GET THE MACRO

https://github.com/BlindIndex/SAS-Blinding-Index/blob/edd6b9ffebb378bda0596f12bd407146447d3425/James%20Bang%20BIs.sas

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