Success of Masking 5% Povidone-Iodine Treatment: The Reducing Adenoviral Patient Infected Days Study

Meredith M. Whiteside, OD, FAAO,[1]* Ellen S. Shorter, OD, FAAO,[2] Mathew S. Margolis, MD,[3] Fatima Alvi, MD,[3] Julia B. Huecker, MS,[3] Tammy P. Than, OD, FAAO,[4] Mary K. Migneco, OD, FAAO,[3] Jennifer S. Harthan, OD, FAAO,[5] Christina E. Morettin, OD, FAAO,[5] Andrew T. E. Hartwick, OD, PhD, FAAO,[6] Spencer D. Johnson, OD, FAAO,[7] Chamila D. Perera, PhD,[3] and Mae O. Gordon, PhD[3]

SIGNIFICANCE: The effectiveness of masking is rarely evaluated or reported in single- or double-masked clinical trials. Knowledge of treatment assignment by participants and clinicians can bias the assessment of treatment efficacy.

PURPOSE: This study aimed to evaluate the effectiveness of masking in a double-masked trial of 5% povidone-iodine for the treatment of adenoviral conjunctivitis.

METHODS: The Reducing Adenoviral Patient Infected Days study is a double-masked, randomized trial comparing a one-time, in-office administration of 5% povidone-iodine with artificial tears for the treatment of adenoviral conjunctivitis. Masking was assessed by asking participants and masked clinicians at designated time points if they believed the treatment administered was povidone-iodine or artificial tears, or if they were unsure. Adequacy of masking was quantified using a modified Bang Blinding Index.

RESULTS: Immediately after treatment, 34% of participants who received povidone-iodine and 69% of those who received artificial tears guessed incorrectly or were unsure of their treatment (modified Bang Indices of 0.31 and –0.38, respectively). On day 4, 38% of the povidone-iodine participants and 52% of the artificial tear participants guessed incorrectly or were unsure of their treatment (modified Bang Indices of 0.24 and –0.05, respectively), indicating adequate and ideal masking. On days 1, 4, 7, 14, and 21, masked clinicians guessed incorrectly or were unsure of treatment in 53%, 50%, 40%, 39%, and 42% among povidone-iodine participants compared with 44%, 35%, 38%, 35%, and 39% among artificial tears participants, respectively. The modified Bang Indices for clinician masking in the povidone-iodine group ranged from –0.05 to 0.25 and from 0.13 to 0.29 in the artificial tears group.

CONCLUSIONS: Masking of participants and clinicians was adequate. Successful masking increases confidence that subjective measurements are not biased. We recommend quantitative assessment and reporting the effectiveness of masking in ophthalmic clinical trials.

Optom Vis Sci 2021;98:469–475. doi:10.1097/OPX.0000000000001691

Supplemental Digital Content: *Direct URL links are provided within the text.*

SDC

Author Affiliations:
[1]University of California, Berkeley, School of Optometry, Berkeley, California
[2]Illinois Eye and Ear Infirmary, University of Illinois at Chicago, Chicago, Illinois
[3]Department of Ophthalmology and Visual Sciences, Washington University, St. Louis, Missouri
[4]Department of Optometry, Carl Vinson Veterans Medical Center, Dublin, Georgia
[5]Illinois College of Optometry, Chicago, Illinois
[6]Ohio State University College of Optometry, Columbus, Ohio
[7]Northeastern State University College of Optometry, Tahlequah, Oklahoma
*mwhitesi@berkeley.edu

Randomized controlled clinical trials are regarded as the criterion standard for determining the efficacy of an intervention in health care. Critical to the success of these trials, however, is that participants and clinicians are masked and therefore have no knowledge of treatment allocation. If unmasked, participants may exhibit conscious and/or unconscious bias that influences their symptom reporting (e.g., ocular redness, tearing, and eyelid swelling) and their performance in functional assessments (e.g., visual acuity measurements and visual field testing). Participant bias may also affect compliance with dosing regimens and study withdrawal rates because of participants' beliefs regarding whether they received treatment or placebo. Unfortunately, many of these biases cannot be corrected by analytic methods.[1–3] Bias of study clinicians may also affect outcome assessments (e.g., grading of clinical signs), data collection, analytical interpretations, and even the formulations of conclusions.[3,4] Investigator and/or participant bias due to knowledge of treatment allocation can have substantial effects on efficacy reporting, resulting in treatment effects being exaggerated by 10 to 36%[5–9] and greater heterogeneity in subjective outcomes.[10] In a systematic review of 21 trials in which masked and unmasked observers assessed subjective outcomes, unmasked observers detected 26% fewer failure events on average and were more optimistic in 36% of the assessments as compared with masked observers.[4]

Despite the importance of masking in treatment trials, its effectiveness is seldom reported in individual studies,[11–13] particularly in ophthalmic literature. In a review of ophthalmic treatment trials

over a 4-year period (Appendix, available at http://links.lww.com/OPX/A487), approximately 6% (4/69) reported the effectiveness of masking. Of the four studies reporting on masking effectiveness, only two provided details regarding the methodology on how the effectiveness was quantified,[14,15] with the other two simply stating that no participants were unmasked during the study.[16,17]

Most methods to assess masking involve querying participants and/or clinicians to guess which treatment (control/placebo vs. treatment medication) was received/given during the trial. Results can be divided into three-response categories (treatment, control/placebo, or "do not know") or five-response categories in which participants who indicate they think they know which trial arm they are in also indicate whether they strongly or somewhat believe their choice is correct. These responses are traditionally analyzed using χ^2 or κ statistical testing. A disadvantage of these methods is that they ignore the "do not know" response and only compare the correct and incorrect responses. To factor in the "do not know" response, two masking indexes have been created: (1) the James Index is a modification of the κ statistic that includes the "do not know" response and assesses overall masking without distinguishing between treatment arms (treatment vs. control) and (2) the Bang Index that includes the "do not know" response and allows for the evaluation of the treatment and control arms independently.[18] In brief, the Bang Index calculates the difference between the proportions of correct and incorrect guesses by excluding "do not know" responses in the numerator but including them in the denominator. Thus, the Bang Index assumes that a "do not know" response indicates masking.[11] A more detailed description of the Bang Index statistics is described in prior literature.[2,11,18]

The aim of this study is to assess masking in a double-masked pilot study investigating the efficacy of 5% povidone-iodine for adenoviral conjunctivitis. Adenoviral conjunctivitis is a common cause of conjunctivitis that can cause significant discomfort. Although generally self-limiting, because of its contagious nature, it is not uncommon for affected individuals to be furloughed from school or work for 1 to 2 weeks. Although there currently is no Food and Drug Administration–approved treatment of adenoviral conjunctivitis, a treatment that shortens the duration of infection could have a substantial impact on an individual's quality of life and potentially limit outbreaks.[19,20] Many agents, such as corticosteroids, virustatic agents, interferon, immune suppressants, and antiseptic agents, have been tested as treatments for adenoviral conjunctivitis with minimal success.[21,22] In the current study, we systematically assessed masking because a common perception is that neither patients nor clinicians could be masked to povidone-iodine, which can cause irritation, and has a distinctive odor and amber color that distinguishes it from artificial tears, the control. The effectiveness of treatment masking (whether povidone-iodine or artificial tears were administered) was assessed in both participants and clinicians after treatment and then at follow-up visits. In adherence to the 2013 SPIRIT recommendations for clinical trials,[23] we used a standardized protocol and the Bang Index as a quantitative method for assessing masking effectiveness.

METHODS

Study Design

The Reducing Adenoviral Patient Infected Days study is a multicenter, double-masked, randomized pilot study comparing the safety and efficacy of a one-time, in-office administration of ophthalmic 5% povidone-iodine compared with artificial tears for the treatment of adenoviral conjunctivitis. Participants were 18 years or older presenting with red eye(s) onset of ≤4 days and a positive point-of-care test for adenoviral conjunctivitis. The primary measure of treatment efficacy was reduction in viral load, and secondary measures included improvement in patient-reported symptoms and clinician-graded signs. Institutional review board approval was obtained by each study site and the Coordinating Center at Washington University in St. Louis, MO. Informed consent was obtained from all participants in compliance with the ethical principles of the Declaration of Helsinki.

Study Protocol

Concealed centralized randomization was performed to minimize biased randomization. Treatment allocation was determined by the Coordinating Center and concealed in sequentially numbered sealed boxes that contained either 5% povidone-iodine or artificial tears in a 1:1 ratio. A unique sequential ID number with no reference to treatment assignment was assigned to each participant.

At the baseline/randomization visit, the unmasked clinician instilled one drop of proparacaine followed by four to five drops of either 5% ophthalmic povidone-iodine or artificial tears. Participants were instructed to close their eyes for 2 minutes and to move their eyes in all directions to distribute the treatment solution to the ocular surface, while the clinician used a gloved finger to apply gentle pressure to the closed lids. Then, a 2×2 gauze pad moistened with the assigned solution was used to dab along the eyelid margins of the closed eye. After a 2-minute exposure to the treatment, a nonpreserved buffered sterile saline solution was used to generously lavage the eye, and another gauze pad moistened with sterile saline was used to wipe the eyelid margins to remove all traces of the study medication. After instillation of the assigned solution, participants were asked to guess whether they believed they received artificial tears or povidone-iodine, or if they were unsure of which treatment they received. Post-treatment follow-up examinations were on days 1 to 2, 4 (days 3 to 5), 7 (days 6 to 10), 14 (days 11 to 17), and 21 (days 18 to 21). At the day 4 examination, participants were again asked the same question as to what treatment they believed they had received. Similarly, masked clinicians were asked which treatment they believed the participant received or if they were unsure. Initially, masked clinicians only answered this question at the day 14 examination; however, the protocol was amended 7 months into the study to assess masking at each follow-up visit. At each visit (days 1 to 2, 4, 7, 14, and 21), primary and secondary outcome measures were assessed by a masked clinician. Primary measures of viral load were determined by collecting conjunctival swab tear samples. Secondary measures included recording patient-reported symptoms, and clinical evaluation included Snellen visual acuity, lymph node palpation, and grading of clinical signs with slit-lamp biomicroscopy by the masked clinician. Strategies to decrease follow-up loss included setting appointments at the conclusion of each participant evaluation and contacting participants by telephone and e-mail. In addition, in the event that an in-person visit could not be completed, a verbal questionnaire or e-mailed questionnaire was offered.

Measuring Effectiveness of Masking

Effectiveness of masking was analyzed using participant guesses at day 0 and day 4 and guesses of masked clinicians at each follow-up visit. The Bang Index was used to compare the proportion of respondents guessing correctly to those who incorrectly

guessed the treatment assignment in each randomization group separately.[11] The Bang Index is scaled from –1 to 1, with a score of 0 indicating the optimal masking. A score of "1" indicates a complete lack of masking (i.e., all participants guessed their treatment assignment correctly), and "–1" indicates opposite guessing (i.e., all individuals incorrectly guessed their treatment assignment). A Bang Index of ±0.20 indicates a range of ideal masking.[11,18] Beyond ideal, adequacy of masking was based on a priori criteria[18] defined as the following:

–0.20 to +0.20 = "ideal"
+0.21 to +0.24 = "adequate"
+0.25 to +0.29 = "fair"
+0.30 or higher = "less than fair"

In addition, a failure to achieve masking would be deemed if the 95% confidence limit of the index did not include the null value (0).[2,11]

For this study, the Bang Index was modified by combining "unsure" responses with incorrect responses. If the concern is that participants who think they received povidone-iodine may exhibit bias and exaggerate treatment effects, we reasoned that participants who either believed they received artificial tears or did not know which treatment they received would both not exhibit these bias traits and were therefore appropriately grouped together. The rationale for pooling "unsure" with incorrect guesses among participants was applied to clinician guesses as well.

Analyses were done using SAS (V9.4) Software (Statistical Analysis Software, 2018; Cary, NC). In addition to calculating the modified Bang Index, the proportion of correct versus unsure/incorrect responses of participants and clinicians was compared at each visit for the povidone-iodine and artificial tears groups using a two-sided Fisher exact test (PROC FREQ). Changes in the proportion of correct versus unsure/incorrect responses over time within each randomization group were analyzed using generalized linear models (PROC GENMOD).

RESULTS

The CONSORT diagram (Fig. 1) indicates participant flow.

Participant Masking

Immediately after treatment, 34% (10/29) of the participants who received povidone-iodine guessed incorrectly or were unsure which treatment they received (modified Bang Index of 0.31; 95% confidence interval, 0.02 to 0.60) indicative of less than adequate masking. Among participants who received artificial tears, 69% (18/26) guessed incorrectly or were unsure of which treatment they received (modified Bang Index of –0.38; 95% confidence interval, –0.68 to +0.09), indicating that a significant number either believed that they received the povidone-iodine treatment or were unsure of the treatment (Table 1). At baseline, there was a statistically significant difference in masking between the participants who received povidone-iodine versus those who received artificial tears ($P = .01$).

On day 4, 38% (8/21) of the povidone-iodine participants guessed incorrectly or were unsure which treatment they received (modified Bang Index of 0.24; 95% confidence interval, –0.11 to +0.59), indicating adequate masking. Among participants who received artificial tears, 52% (11/21) guessed incorrectly or were unsure which treatment they received (modified Bang Index of –0.05; 95% confidence interval, –0.41 to +0.31), indicating ideal masking (Table 1). At day 4, there was no significant difference in masking between the povidone-iodine and artificial tears groups ($P = .53$). There was also no difference between the randomization groups in the proportion of participants making correct and unsure/incorrect guesses over time ($P = .27$).

Clinician Masking

There was no difference in masked clinician guesses in the proportion of correct versus unsure/incorrect guesses between randomization groups for any visit ($P > .05$). In addition, there was no difference between the randomization groups in the proportion of masked clinicians making correct and unsure/incorrect guesses over time ($P = .72$).

Fig. 2 shows the percentage of masked clinicians who guessed incorrectly or were unsure of the participant randomization group over the duration of the study. At the day 1 to 2 visit, masked clinicians guessed incorrectly or were unsure in 53% (10/19) of the participants in the povidone-iodine group (modified Bang Index of –0.05; 95% confidence interval, –0.43 to +0.32), indicating ideal masking. Masked clinicians guessed incorrectly or were unsure in 44% (7/16) of the participants in the artificial tears group (modified Bang Index of 0.13; 95% confidence interval, –0.28 to +0.53), indicating ideal masking (Table 2).

At the day 4 visit, masked clinicians guessed incorrectly or were unsure in 50% (7/14) of the participants in the povidone-iodine group (modified Bang Index of 0.0; 95% confidence interval, –0.44 to +0.44), indicating ideal masking. Masked clinicians guessed incorrectly or were unsure in 35% (6/17) of the participants in the artificial tears group (modified Bang Index of 0.29; 95% confidence interval, –0.09 to +0.68), indicating fair masking (Table 2).

On days 7, 14, and 21, masked clinicians guessed incorrectly or were unsure in 39 to 42% of the participants in the povidone-iodine group (modified Bang Indices between 0.17 and 0.25), and guessed incorrectly or were unsure between 35 and 39% in the artificial tears group (modified Bang Indices ranged between 0.23 and 0.29), indicating fair masking (Table 2).

DISCUSSION

Effectiveness of masking is especially important in ophthalmic studies where outcome measures are often qualitative and susceptible to influence from knowledge of treatment allocation. An important objective of the Reducing Adenoviral Patient Infected Days pilot study was to determine if participants and clinicians could be masked to treatment allocation, despite marked color difference and potential odor and irritation of povidone-iodine compared with artificial tears. Treatment efficacy in the Reducing Adenoviral Patient Infected Days study was assessed using subjective measures such as visual acuity, clinician grading of clinical signs, and patient-reported symptoms. Masking in the Reducing Adenoviral Patient Infected Days study was more successful than initially hypothesized and determined to be adequate overall. Measures taken to protect double masking included concealed randomization allocation, administration of topical anesthetic before instillation of artificial tears or povidone-iodine to minimize differences in ocular comfort, thorough saline lavage of the eye and adnexa to eliminate residual yellow-brown evidence of povidone-iodine,

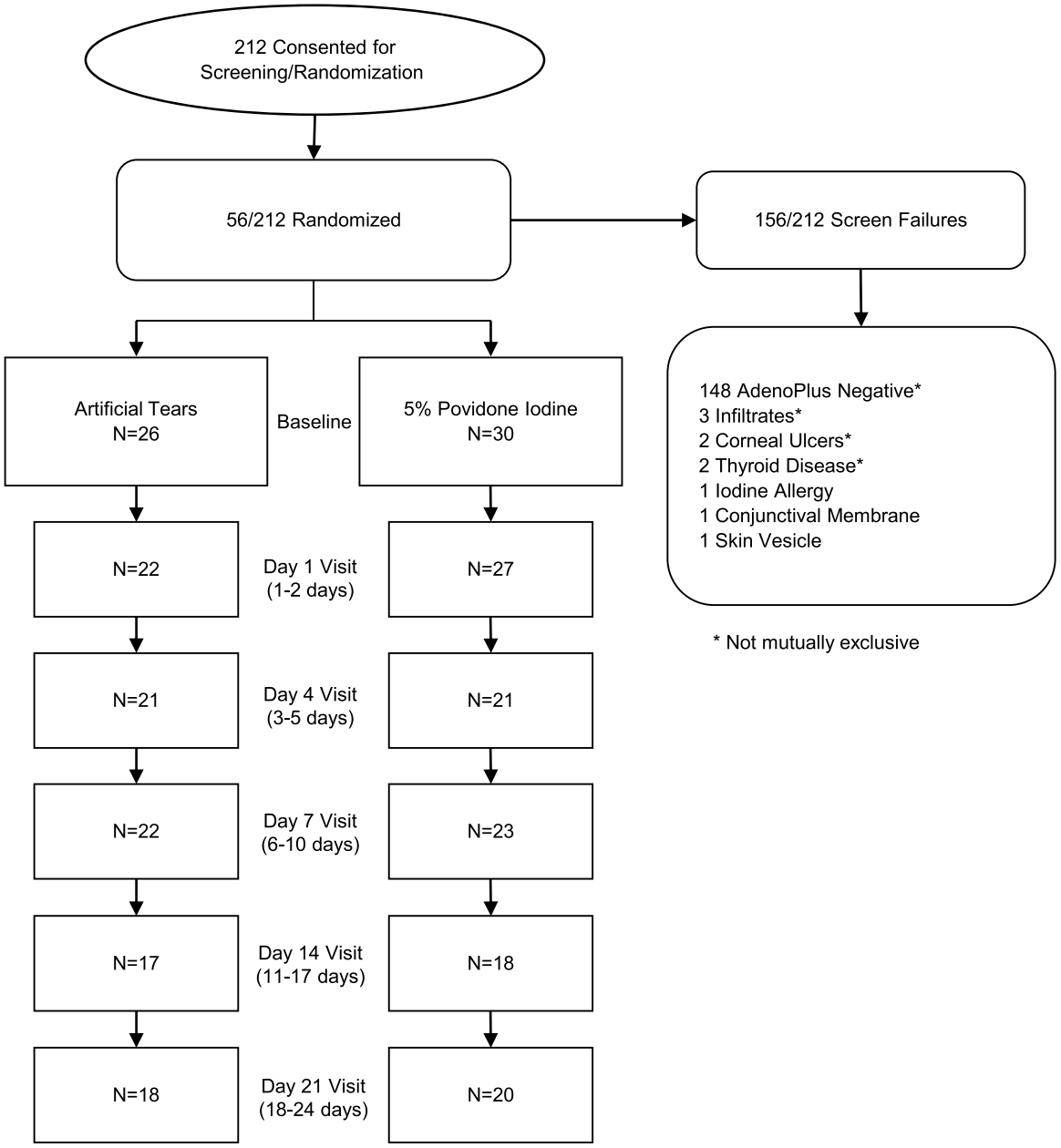

FIGURE 1. CONSORT diagram of participant flow.

and scheduling all follow-up study visits with a masked clinician without access to treatment assignments.

When masking is optimal, the number of unsure responses should be high, and the number of incorrect and correct guesses should be equal. Immediately after instillation on day 0, it is not surprising that a high proportion (66%) of participants in the povidone-iodine group guessed correctly: povidone-iodine has a markedly different appearance, and a participant's sensation with this drop may be quite different from artificial tears. Surprisingly, a high proportion (54%) of participants in the artificial tears group were unsure, or 15% guessed incorrectly. Statistical comparison of adequacy of masking of participants between the povidone-iodine and artificial tears groups on day 0 shows that masking is different between those randomized to povidone-iodine versus artificial tears ($P < .01$). The modified Bang Index for masking of the povidone-iodine group was less than fair, and many of those receiving artificial tears either were unsure or mistakenly believed that they received the treatment. However, by day 4, masking improved to adequate in the povidone-iodine group and was ideal in the artificial tears group. At this point, the proportions of masking between the two groups were not different ($P > .10$). Clinician masking for the povidone-iodine group was ideal at days 1 and 4 and remained fair or better through day 21. Clinician masking for the artificial tears group, which was ideal on day 1, decreased to fair and adequate masking throughout follow-up. Although Fig. 2 shows a difference in clinician masking between povidone-iodine and artificial tears on days 1 and 4, the differences in masking were not significant between the randomization groups (povidone-iodine and artificial tears; $P > .01$).

TABLE 1. Participant guesses of treatment assignment to 5% PVP-I or AT

Study visit	Treatment group	Correct guess, n (%)	Incorrect guess (n)	Unsure guess (n)	Incorrect + Unsure, n (%)	Modified Bang Index (95% CI)
Day 0	PVP-I (n = 29)	19 (66)	2	8	10 (34)	0.31 (0.02 to 0.60)
	AT (n = 26)	8 (31)	4	14	18 (69)	–0.38 (–0.68 to –0.09)
Day 4	PVP-I (n = 21)	13 (62)	3	5	8 (38)	0.24 (–0.11 to +0.59)
	AT (n = 21)	10 (48)	4	7	11 (52)	–0.05 (–0.41 to 0.31)

AT = artificial tears; CI = confidence interval; PVP-I = povidone-iodine.

The trend of no difference between the groups continued through days 7 to 21 ($P > .01$). Of interest, however, is that trend analysis of the povidone-iodine group in Fig. 2 shows that success of masking decreases after day 4 to levels that are closer to those for the artificial tears group. A possible explanation is that clinicians made inferences regarding treatment assignment based on serial clinical findings and/or participant comments regarding their experiences.

In the end, although masking is important, less than perfect masking does not necessarily invalidate the subjective outcomes. Unmasking can occur because of a variety of valid reasons. Unmasking does not introduce a bias if unmasking occurs because the treatment is obviously effective. Unmasking can also occur because of side effects, which does not necessarily introduce bias. Thus, while masking should be evaluated as a way to have a high-quality study design, subjective outcomes may be validated when confirmed by objectives measures. For example, in the Reducing Adenoviral Patient Infected Days study, a reduction in viral titers over time as measured by quantitative polymerase chain reaction helped to validate findings of patient-reported symptoms and clinical signs.

There are several limitations to this study. The Reducing Adenoviral Patient Infected Days study was designed as a pilot study with a small sample size. Not every participant returned for every examination. On day 4, the missed visit rates were 19% in the artificial tears group and 30% in the povidone-iodine group. The reasons for not returning were not specifically queried; however, many of these missed visits were scheduled for a weekend. Participants in the artificial tears group reported immediate reduction in discomfort after instillation of artificial tears, so it is possible they missed follow-up visits because their symptoms improved.[24] Future studies should consider assessing reasons for participant and clinician guesses of treatment allocation. Because the differences between the two treatments may have contributed to participant unmasking,

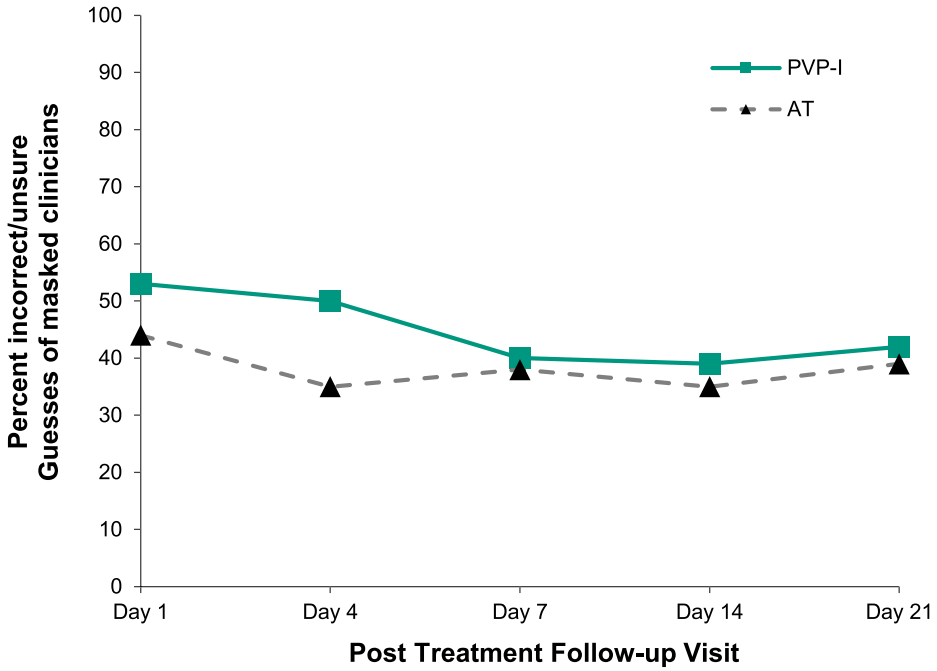

FIGURE 2. Percentage of masked clinicians who guessed incorrectly or unsure of participant randomization group. AT = participants who were administered artificial tears; PVP-I = participants who were administered povidone-iodine.

TABLE 2. Masked clinician guesses of participant treatment assignment to 5% PVP-I or AT

Study visit	Treatment group	Correct guess, n (%)	Incorrect guess (n)	Unsure guess (n)	Incorrect + Unsure, n (%)	Modified Bang Index (95% CI)
Day 1	PVP-I (n = 19)	9 (47)	3	7	10 (53)	–0.05 (–0.43 to +0.32)
	AT (n = 16)	9 (56)	2	5	7 (44)	0.13 (–0.28 to +0.53)
Day 4	PVP-I (n = 14)	7 (50)	5	2	7 (50)	0.00 (–0.44 to +0.44)
	AT (n = 17)	11 (65)	3	3	6 (35)	0.29 (–0.09 to +0.68)
Day 7	PVP-I (n = 15)	9 (60)	3	3	6 (40)	0.25 (–0.22 to +0.62)
	AT (n = 16)	10 (63)	3	3	6 (38)	0.24 (–0.15 to +0.65)
Day 14	PVP-I (n = 18)	11 (61)	1	6	7 (39)	0.22 (–0.16 to +0.60)
	AT (n = 17)	11 (65)	4	2	6 (35)	0.29 (–0.09 to +0.68)
Day 21	PVP-I (n = 12)	7 (58)	1	4	5 (42)	0.17 (–0.30 to +0.63)
	AT (n = 13)	8 (62)	3	2	5 (39)	0.23 (–0.21 to +0.67)

AT = artificial tears; CI = confidence interval; PVP-I = povidone-iodine.

future studies using formulations of povidone-iodine could consider a control that simulates the sting, smell, and discoloration of povidone-iodine.

Because it is common in clinical vision research to use subjective measures such as participant symptoms and clinical signs as outcome measures, the inclusion of masking assessments can improve the quality of clinical trials. Subjective findings that are prone to bias due to poor masking may cause researchers to draw erroneous conclusions. Using a quantitative measurement such as a modified Bang Index to evaluate participant or clinician bias can help in bolstering the validity of results. Although it is difficult to know why the inclusion of masking assessment is not routinely done in vision research, there are a few possibilities. There may be a perception that less-than-ideal masking can either weaken or even negate any outcomes/findings. If a treatment is found to be effective, the optimization and assessment of masking protocols can make the study design more complex and add expense. For example, adding additional study personnel to maintain masking and creating control medications that have similar appearance and cause similar side effects may all increase expenses and time commitments. Finally, in reviewing study design, it is not always easy to anticipate or determine the cause of unmasking because it can be multifactorial.

In summary, masking of participants in the Reducing Adenoviral Patient Infected Days study was adequate for the povidone-iodine group and ideal for the artificial tears group on day 4. Clinician masking through the study was adequate for both the povidone-iodine group and the artificial tears group. Routine inclusion of masking assessment in research can augment the validity of trial results and increase the impact on clinical practice by strengthening the conclusions. We recommend ophthalmic research studies to use a quantitative index of masking, such as the Bang Index, to improve study design and strengthen confidence in outcomes.

ARTICLE INFORMATION

Supplemental Digital Content: The Appendix is an assessment of masking in ophthalmic literature explaining the method by which a PubMed literature search was performed. In addition, details are given for the justification of using the modified Bang Blinding Index.

Appendix Table A1: Comparison of original Bang and modified Bang Blinding Index. Participant guesses of treatment assignment in the povidone-iodine group and artificial tears group at day 0 and day 4. The Appendix is available at http://links.lww.com/OPX/A487.

Submitted: June 25, 2020

Accepted: February 7, 2021

Funding/Support: Foundation for the National Institutes of Health (5 R21 EY030524 and 5 R34 EY023633), Core grants P30 EY001792 (University of Illinois), P30 EY002687 (Washington University) and an unrestricted grant from Research to Prevent Blindness.

Conflict of Interest Disclosure: None of the authors have reported a financial conflict of interest.

Study Registration Information: https://clinicaltrials.gov/ct2/show/NCT02472223.

Author Contributions and Acknowledgments: Conceptualization: ESS, TPT, MKM, ATEH, SDJ, MOG; Data Curation: JBH; Formal Analysis: MSM, JBH, TPT, MKM, ATEH, CDP, MOG; Funding Acquisition: TPT, MOG; Investigation: MMW, ESS, TPT, MKM, JSH, CEM, ATEH, MOG; Methodology: ESS, TPT, MKM, ATEH, MOG; Project Administration: TPT, MOG; Resources: MKM, MOG; Supervision: TPT, MOG; Writing – Original Draft: MMW, ESS, MSM, FA, JBH, TPT, MKM, JSH, CEM, ATEH, SDJ, MOG; Writing – Review & Editing: MMW, ESS, JBH, TPT, MKM, JSH, CEM, ATEH, SDJ, MOG.

The authors thank Heejung Bang, PhD, Tavé van Zyl, MD, and Timothy Bossie, OD, FAAO.

REFERENCES

1. Juni P, Altman DG, Egger M. Systematic Reviews in Health Care: Assessing the Quality of Controlled Clinical Trials. BMJ 2001;323:42–6.

2. Bang H, Flaherty SP, Kolahi J, et al. Blinding Assessment in Clinical Trials: A Review of Statistical Methods and a Proposal of Blinding Assessment Protocol. Clin Res Regul Aff 2010;27:42–51.

3. Schulz KF, Grimes DA. Blinding in Randomised Trials: Hiding Who Got What. Lancet 2002;359:696–700.

4. Schulz KF, Chalmers I, Hayes RJ, et al. Empirical Evidence of Bias. Dimensions of Methodological Quality Associated with Estimates of Treatment Effects in Controlled Trials. JAMA 1995;273:408–12.

5. Savovic J, Jones HE, Altman DG, et al. Influence of Reported Study Design Characteristics on Intervention Effect Estimates from Randomized, Controlled Trials. Ann Intern Med 2012;157:429–38.

6. Hróbjartsson A, Thomsen AS, Emanuelsson F, et al. Observer Bias in Randomised Clinical Trials with Binary Outcomes: Systematic Review of Trials with Both Blinded and Non-blinded Outcome Assessors. BMJ 2012;344:e1119.

7. Hróbjartsson A, Emanuelsson F, Skou Thomsen AS, et al. Bias Due to Lack of Patient Blinding in Clinical Trials. A Systematic Review of Trials Randomizing Patients to Blind and Nonblind Sub-studies. Int J Epidemiol 2014; 43:1272–83.

8. Page MJ, Higgins JP, Clayton G, et al. Empirical Evidence of Study Design Biases in Randomized Trials: Systematic Review of Meta-epidemiological Studies. PLoS One 2016;11:e0159267.

9. Wood L, Egger M, Gluud LL, et al. Empirical Evidence of Bias in Treatment Effect Estimates in Controlled Trials with Different Interventions and Outcomes: Meta-epidemiological Study. BMJ 2008;336:601–5.

10. Savovic J, Turner RM, Mawdsley D, et al. Association between Risk-of-bias Assessments and Results of Randomized Trials in Cochrane Reviews: The ROBES Meta-epidemiologic Study. Am J Epidemiol 2018;187: 1113–22.

11. Bang H, Ni L, Davis CE. Assessment of Blinding in Clinical Trials. Control Clin Trials 2004;25:143–56.

12. Moustgaard H, Clayton GL, Jones HE, et al. Impact of Blinding on Estimated Treatment Effects in Randomised Clinical Trials: Meta-epidemiological Study. BMJ 2020; l6802:368.

13. Hróbjartsson A, Pildal J, Chan AW, et al. Reporting on Blinding in Trial Protocols and Corresponding Publications Was Often Inadequate but Rarely Contradictory. J Clin Epidemiol 2009;62:967–73.

14. Sivaprasad S, Vasconcelos JC, Prevost AT, et al. Clinical Efficacy and Safety of a Light Mask for Prevention of Dark Adaptation in Treating and Preventing Progression of Early Diabetic Macular Oedema at 24 Months (CLEOPATRA): A Multicentre, Phase 3, Randomised Controlled Trial. Lancet Diabetes Endocrinol 2018;6:382–91.

15. Hoerauf H, Feltgen N, Weiss C, et al. Clinical Efficacy and Safety of Ranibizumab versus Dexamethasone for Central Retinal Vein Occlusion (COMRADE C): A European Label Study. Am J Ophthalmol 2016;169: 258–67.

16. Tauber J, Karpecki P, Latkany R, et al. Lifitegrast Ophthalmic Solution 5.0% versus Placebo for Treatment of Dry Eye Disease: Results of the Randomized Phase III OPUS-2 Study. Ophthalmology 2015; 122:2423–31.

17. Donnenfeld ED, Karpecki PM, Majmudar PA, et al. Safety of Lifitegrast Ophthalmic Solution 5.0% in Patients With Dry Eye Disease: A 1-year, Multicenter, Randomized, Placebo-controlled Study. Cornea 2016; 35:741–8.

18. Kolahi J, Bang H, Park J. Towards a Proposal for Assessment of Blinding Success in Clinical Trials: Up-to-date Review. Community Dent Oral Epidemiol 2009; 37:477–84.

19. Ohnsman CM. Exclusion of Students with Conjunctivitis from School: Policies of State Departments of Health. J Pediatr Ophthalmol Strabismus 2007;44: 101–5.

20. Centers for Disease Control and Prevention (CDC). Adenovirus-associated Epidemic Keratoconjunctivitis Outbreaks—Four States, 2008–2010. MMWR Morb Mortal Wkly Rep 2013;62:637–41.

21. Labib BA, Minhas BK, Chigbu DI. Management of Adenoviral Keratoconjunctivitis: Challenges and Solutions. Clin Ophthalmol 2020;14:837–52.

22. Yazar H, Yarbag A, Balci M, et al. The Effects of Povidone Iodine (Ph 4.2) on Patients with Adenoviral Conjunctivitis. J Pak Med Assoc 2016;66:968–70.

23. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. Ann Intern Med 2013;158:200–7.

24. Shorter E, Whiteside M, Harthan J, et al. Safety and Tolerability of a One-time, In-office Administration of 5% Povidone-iodine in the Treatment of Adenoviral Conjunctivitis: The Reducing Adenoviral Patient Infected Days (RAPID) Study. Ocul Surf 2019;17:828–32.