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# Effects of duration of whitening strip treatment on tooth color: A randomized, placebo-controlled clinical trial

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## ABSTRACT

**Objectives:** A randomized, double-blind, placebo-controlled clinical trial was conducted to evaluate efficacy and safety of 6% hydrogen peroxide whitening strip used twice daily over an extended, 6-week period.

**Methods:** After informed consent, 40 eligible adults were randomly assigned to 6% hydrogen peroxide whitening strips (Crest Whitestrips, The Procter & Gamble Company, USA) or placebo strips without peroxide. Treatment was twice daily for 30 min, and response was evaluated biweekly after initial (Week 2) and extended (Weeks 4 and 6) use. Tooth color was measured under standardized lighting conditions using digital image analysis, and safety was assessed from clinical examination and interview. Whitening was measured using data derived from digital images taken at baseline compared to post-treatment, with outcomes reported using the CIELAB color notation system. Analysis of variance and covariance were used to assess initial response, and repeated measures regression analysis was used to model color change during sustained use.

**Results:** Forty subjects (25–58 years old) started the study. At baseline,  $L^*$  ranged from 68.0 to 76.8,  $a^*$  ranged from 8.0 to 11.8, and  $b^*$  ranged from 16.4 to 23.1. Groups differed significantly ( $p < 0.001$ ) on all color parameters at Week 2 and thereafter, favoring the 6% hydrogen peroxide strips. Week 2 adjusted means  $\pm$  SE were  $-2.1 \pm 0.2$  for  $\Delta b^*$  and  $1.9 \pm 0.2$  for  $\Delta L^*$  for the peroxide group compared to  $-0.3 \pm 0.2$  for  $\Delta b^*$  and  $0.4 \pm 0.2$  for the placebo group. With sustained use (Weeks 2–6), the slope for the peroxide strip was estimated as  $-0.3$  for  $\Delta b^*$  and  $+0.2$  for  $\Delta L^*$  per week, with both slopes differing significantly from zero ( $p < 0.0001$ ), while slopes for the placebo strip were not significant ( $p = 0.22$ ) and nearly zero. Treatment was generally well tolerated, with adverse events confined to symptoms only.

**Conclusions:** Twice-daily use of 6% hydrogen peroxide whitening strips resulted in teeth becoming lighter and less yellow versus baseline and placebo during initial 2-week use, with no evidence of placebo response during sustained (Weeks 2–6) use.

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## 1. Introduction

At-home bleaching was formally introduced to the dental profession by Haywood and Heymann in 1989.<sup>1</sup> Early clinical

studies showed that whitening could be achieved with repeated application of 10% carbamide peroxide over a period of several days or weeks.<sup>2–4</sup> Initial concerns were raised on patient-applied bleaching treatments, including potential

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toxicity and the clinical management of adverse events.<sup>5,6</sup> Based on the early and generally favorable results, a number of comprehensive clinical trials were conducted to evaluate short-term use of carbamide peroxide bleaching agents, and post-treatment color relapse following treatment.<sup>7–11</sup> Some research targeted extended treatment with tray-delivered 10% carbamide peroxide, in part, because of the broader implications of extended use and safety outcomes.<sup>12,13</sup> Other studies evaluated whether higher concentrations of carbamide or hydrogen peroxide could be safely used to reduce treatment time.<sup>14–16</sup> Overall, this research demonstrated the safety and effectiveness of peroxide-based whitening treatment under specified conditions of use, with minor tooth sensitivity and oral irritation representing the most common adverse events of treatment.

This essentially represented the status of vital bleaching through 2000, with most professionally-supervised at-home bleaching systems using carbamide or hydrogen peroxide gel or paste applied in custom-fitted trays.<sup>17</sup> Around that time, one manufacturer introduced a novel trayless whitening approach (Crest Whitestrips, Procter & Gamble, Mason, OH, USA), in which a measured dose of hydrogen peroxide gel was applied to the anterior teeth using a flexible polyethylene strip instead of a custom or stock tray.<sup>18</sup> Subsequently, several randomized controlled trials were conducted in which 6% hydrogen peroxide strips were applied for 30 min twice daily over a 14-day period.<sup>19–22</sup> These studies, which compared 6% hydrogen peroxide strips to various negative and positive controls, demonstrated strip-based whitening after 2 weeks, with similar types of adverse events seen with the tray-based systems.

While negatively controlled and positively controlled trials provide important evidence of effectiveness and safety for vital bleaching, placebo-controlled trials allow for the direct assignment of causality.<sup>23</sup> Accordingly, this randomized, placebo-controlled, clinical study was designed to evaluate the effectiveness and tolerability of 6% hydrogen peroxide strips. As with the other trials on 6% hydrogen peroxide strips, whitening was evaluated objectively using a digital imaging system, but unlike those studies, treatment was evaluated following continuous extended use over 6 weeks to assess sustained treatment response. As such, the placebo-controlled research allowed us to assess whether sustained use of 6% hydrogen peroxide strips yielded incremental whitening after 2 weeks, and if so, whether that incremental whitening was achieved with increased side effects. In addition, by focusing on the sustained treatment phase, this design also afforded a unique opportunity to assess the appropriateness of the selected instrumental whitening method within the framework of a single clinical trial.

## 2. Materials and methods

A randomized, double-blind, placebo-controlled clinical trial was conducted to evaluate use of hydrogen peroxide whitening strips (Crest Whitestrips) over a 6-week period. The study protocol, consent and advertising were reviewed by an institutional review board (University of North Carolina, Chapel Hill, NC, USA), and before participating, all subjects

signed a consent form. There were a total of 5 visits: baseline, product distribution, and post-treatment evaluation after 2, 4 and 6 weeks, respectively. Eligibility was limited to healthy adults who desired tooth whitening. Because of the sustained, 6-week treatment, entrance was limited to individuals with starting tooth shade of A3 or darker using a 16-step value-oriented Vitapan Classical shade guide (VITA Zahnfabrik, Bad Säckingen, Germany). Candidates were excluded due to current tooth sensitivity, or esthetic restorations or orthodontics involving the anterior dentition.

After balancing for starting tooth color and age, subjects were randomly assigned to peroxide or placebo strips. Each peroxide strip contained approximately 12 mg of a 6% hydrogen peroxide gel on one side of a flexible polyethylene strip.<sup>20</sup> Placebo strips were identical, except for the absence of hydrogen peroxide. The maxillary arch was treated twice daily for 30 min. Subjects were supplied with 28 strips packaged in individual, foil over-labeled pouches, sufficient for 2 weeks treatment. In addition, subjects received a fluoride dentifrice (Crest Cavity Protection, The Procter & Gamble Company, Cincinnati, OH, USA) which was over-labeled for research use, and an extra-soft toothbrush. All test products and instructions for use were packaged in a blinded test kit with appropriate research labeling for distribution.

Test products were distributed, subsequent treatment was unsupervised, and efficacy and safety were assessed bi-weekly over 6 weeks. At each recall, continuance criteria were checked and verified. A comprehensive oral examination of the oral and peri-oral region was conducted to discern changes in oral status, and subjects were interviewed to ascertain the occurrence of symptoms, including specifically the presence or absence of tooth sensitivity and oral irritation, during the treatment period. For subjects with positive examination or interview findings, event type, onset, duration, and possible test product relationship were assessed. Assigned test strips were resupplied at each post-treatment visit, again in blinded packaging, for a total of 84 strips.

Whitening was measured instrumentally using digital image analysis. With this method, subjects were positioned in a chin rest and standard images of the anterior facial dentition were collected with a digital camera (HC-1000, Fuji Film Corp., Tokyo, Japan), zoom lens (Fujinon 4x75, Fuji Film Corp., Tokyo, Japan) and dual extraoral light sources (Dedotec USA, Ashley Falls, MA, USA).<sup>24</sup> The system used a fixed light-subject-camera geometry where the distance from the body of the camera to the front of the chin rest was 27 cm, with the lights mounted 30.5 cm from the system centerline to the bulb in forward position at a 45° angle. Each light was fitted with a 150 W, 24 V tungsten halogen bulb powered with a tunable voltage power supply. Light filters, which were a series construction of a thermal shield, a daylight conversion filter and a linear polarizer, were mounted to the lights using standard mounting brackets. Room conditions were selected to eliminate extraneous light, such that the only light was provided by the imaging system light sources, filters/polarizers, and the adjustable power supply.

Prior to daily use (and hourly thereafter), color measurement was calibrated using a 70% grey MacBeth standard (N-8, GretagMacbeth, New Windsor, NY, USA) and 22-chip custom color standard (Color Checker, GretagMacbeth, New Windsor,

**Table 1 – Baseline demographics, behavioral parameters and tooth color.**

Baseline	Peroxide strip (n = 20)	Placebo strip (n = 20)	Two-sided p-value
<i>Demographics</i>			
Age (mean, SD)	43.0 (9.04)	41.2 (11.07)	0.577
Female (N, %)	15 (75.0%)	12 (60.0%)	0.501
<i>Behavioral parameters</i>			
Yes, tobacco (N, %)	3 (15.0%)	0 (0.0%)	0.231
Yes, coffee/tea/cola (N, %)	19 (95.0%)	19 (95.0%)	0.999
<i>Tooth color (mean, SD)</i>			
Lightness ( $L^*$ )	72.7 (2.5)	72.8 (2.1)	0.908
Green-red ( $a^*$ )	9.8 (1.1)	10.1 (1.0)	0.461
Blue-yellow ( $b^*$ )	19.2 (1.7)	19.2 (1.3)	0.996

NY, USA).<sup>24</sup> For imaging, subjects were positioned in the chin rest, retractors were inserted for access, and a single digital image was collected of the anterior facial dentition by an operator who was blinded as to treatment assignment, study objectives, and timing. Captured images were processed and color corrected to standards, and saved to disk as .tif files by subject number and visit sequence. Measurement, including orientation, image capture and processing, required less than 2 min per subject image.

Discriminant analysis was used to objectively identify maxillary facial anterior teeth pixels within each image using a standard method.<sup>25</sup> The RGB color values of each pixel were extracted using image analysis software (Optimus, Media Cybernetics, Inc., Silver Spring, MD, USA). These RGB values were averaged and then converted to CIE  $L^*a^*b^*$  values using regression analysis of the RGB color values of the custom color standard against the assigned MacBeth  $L^*a^*b^*$  values under illuminant C conditions.<sup>24</sup> A single set of color values was generated for each subject, representing the average color, and group mean values for lightness ( $L^*$ ), and green-red ( $a^*$ ), and blue-yellow ( $b^*$ ) were derived for analysis.

Efficacy was determined by comparing color change at each time point to baseline using analysis of covariance with the baseline value as the covariate. Reduced yellowness ( $-\Delta b^*$ ) and increased lightness ( $+\Delta L^*$ ) were the primary and secondary outcome variables because of the correlations between these changes and first-person perception of tooth whitening.<sup>19</sup> For a given post-baseline visit, these were calculated as  $\Delta b^* = b^*_{\text{visit}} - b^*_{\text{baseline}}$  and  $\Delta L^* = L^*_{\text{visit}} - L^*_{\text{baseline}}$ . In addition,

analysis of variance (ANOVA) methods were used for the treatment comparisons of the directionless measurement  $\Delta E^*$ , where  $\Delta E^* = (\Delta L^{*2} + \Delta a^{*2} + \Delta b^{*2})^{1/2}$ . Statistical testing was 2-sided at a 5% level of significance. To assess sustained treatment response during the Week 2–6 period, a repeated measures regression analysis was used to model color change from baseline ( $\Delta b^*$ ,  $\Delta L^*$ ,  $\Delta E^*$ ) versus the number of weeks of treatment for each group. A compound symmetry covariance structure was used to model the variability and correlations between weeks separately for each group. Safety data were summarized by type and severity.

### 3. Results

Forty subjects were enrolled in the study. Age ranged from 25 to 58 years, and 27 (68%) subjects were female. Pre-treatment tooth color varied, with ranges of 68.0–76.8 for  $L^*$ , 8.0–11.8 for  $a^*$ , and 16.4–23.1 for  $b^*$ . Groups were balanced on demographic and behavioral parameters and baseline tooth color (Table 1). One subject in the peroxide group was dismissed early as a recall failure. Four other subjects (1 in the peroxide group, 3 in the placebo group) completed the study, but were excluded from the statistical analysis because of missed visits or non-compliance.

Beginning at Week 2, the first post-treatment visit, the peroxide group exhibited greater color improvement than placebo, with adjusted mean between-group differences ranging from 1.6 to 1.8 units for  $\Delta b^*$  and  $\Delta L^*$  (Table 2). These

**Table 2 – Treatment comparisons at Weeks 2, 4 and 6 ANCOVA ( $\Delta b^*$  and  $\Delta L^*$ ) and ANOVA ( $\Delta E^*$ ).**

Group	Adjusted mean (SE) and p-values					
	$\Delta b^*$		$\Delta L^*$		$\Delta E^*$	
	Mean (SE)	p-Value	Mean (SE)	p-Value	Mean (SE)	p-Value
Week 2 (N = 39)						
Peroxide strip	–2.1 (0.2)	0.0001	1.9 (0.2)	0.0001	3.1 (0.2)	0.0001
Placebo strip	–0.3 (0.2)		0.4 (0.2)		0.9 (0.2)	
Week 4 (N = 36)						
Peroxide strip	–2.6 (0.2)	0.0001	2.7 (0.2)	0.0001	4.1 (0.3)	0.0001
Placebo strip	0.1 (0.2)		0.4 (0.2)		0.8 (0.3)	
Week 6 (N = 37)						
Peroxide strip	–3.3 (0.3)	0.0001	2.7 (0.3)	0.0001	4.6 (0.3)	0.0001
Placebo strip	–0.4 (0.3)		0.2 (0.3)		1.0 (0.3)	

**Table 3 – Color change ( $\Delta b^*$ ,  $\Delta L^*$  and  $\Delta E^*$ ) per week treatment comparisons repeated measures regression analysis, Week 2–6.**

Parameter	Color change per week			Treatment comparisons	
Group	Intercept (SE)	Slope (SE)	p-Value	Slope difference	p-Value
$\Delta b^*$					
Peroxide strip	−1.5 (0.3)	−0.3 (0.0)	0.0001	−0.3 (0.1)	0.0001
Placebo strip	−0.2 (0.2)	−0.00 (0.00)	0.863		
$\Delta L^*$					
Peroxide strip	1.6 (0.3)	0.2 (0.0)	0.0001	0.2 (0.1)	0.0001
Placebo strip	0.5 (0.2)	−0.0 (0.0)	0.22		
$\Delta E^*$					
Peroxide strip	2.5 (0.4)	0.4 (0.0)	0.0001	0.4 (0.1)	0.0001
Placebo strip	0.9 (0.1)	0.0 (0.0)	0.69		

treatment differences increased at Week 4, ranging from 2.3 to 2.7 units, and by Week 6, groups differed by 2.5–2.9 units for  $\Delta b^*$  and  $\Delta L^*$ . Response was similar for the derived parameter  $\Delta E^*$ , ranging from 2.2 units at Week 2 to 3.6 units at Week 6, and groups differed significantly ( $p < 0.0001$ ) on  $\Delta b^*$ ,  $\Delta L^*$  and  $\Delta E^*$  at all time points.

With sustained use (Weeks 2–6), the linear rate (slope) for the peroxide strip was estimated as  $-0.3$  for  $\Delta b^*$  and  $+0.2$  for  $\Delta L^*$  per week (Table 3). Both slopes differed significantly from zero ( $p < 0.0001$ ). Slopes for the placebo strip were not significant for either  $\Delta b^*$  or  $\Delta L^*$  during this 4-week period.

While the slopes were greater with  $\Delta E^*$ , the profile was generally similar to that seen with  $\Delta b^*$  and  $\Delta L^*$  (Figs. 1–3). Between-group comparisons showed significant ( $p < 0.001$ ) differences in slope estimates of  $-0.3$  for  $\Delta b^*$ ,  $0.2$  for  $\Delta L^*$ , and  $0.4$  for  $\Delta E^*$  per week of sustained use. For  $\Delta b^*$ , the between time point correlation was  $0.9$  for the peroxide group compared to  $0.3$  for the placebo group. For other parameters ( $\Delta L^*$  and  $\Delta E^*$ ), correlations were higher for the peroxide strip than for the control.

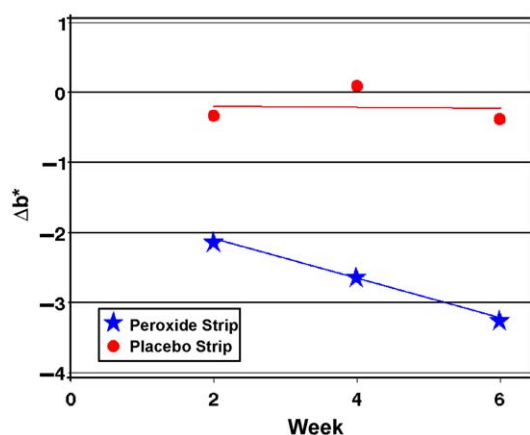
Treatment was generally well tolerated, with adverse events confined to symptoms only. Examination was unremarkable, and there were no product-related adverse events detected any of the recall visits (Table 4). A total of 14 (35%) subjects reported oral symptoms at some time during the 6-week study. No adverse events were serious, and nearly all

were classified as mild in severity. Onset date was generally earlier in the peroxide group (median onset at day 3) compared to the control (median day 18). No subject discontinued or modified treatment early due to an adverse event.

#### 4. Discussion

This randomized, placebo-controlled clinical trial evaluated twice-daily use of 6% hydrogen peroxide whitening strips over an extended, 6-week period. This represented a threefold longer total duration compared to routine treatment, and response was monitored throughout both the initial and sustained usage. In this clinical trial, whitening was evident following 2 weeks use of 6% hydrogen peroxide whitening strips, with significant ( $p < 0.01$ ) decreases in yellowness ( $\Delta b^*$ ) and increases in lightness ( $\Delta L^*$ ) for the peroxide strip group relative to baseline and the placebo control. These findings are consistent with other 14-day clinical outcomes using the same strips and methods in different studies conducted in Europe and North America.<sup>19–22</sup> Additional whitening was measured with sustained use, with groups differing significantly ( $p < 0.001$ ) for all color parameters at all post-treatment times throughout the 6-week study. Previous reports on tray-based peroxide delivery systems suggest that longer treatment regimens might be indicated to improve clinical response, and based on this new research, the tray observations are extended to include 6% hydrogen peroxide strips.<sup>17</sup>

Unlike effectiveness, which generally increased with incremental use, safety findings were not appreciably affected by treatment duration. Like the earlier tray-based bleaching studies, minor tooth sensitivity and gingival irritation were the most common adverse events in this clinical trial.<sup>5,17</sup> Even with extended use, adverse events were generally infrequent, symptomatic (i.e., not clinically visible), and mild in severity, and none of these events contributed to treatment modification or drop out. Adverse events were reported for both groups, with the median date on onset being earlier in the 6% hydrogen peroxide strip group compared to placebo. In the peroxide strip group, over 80% of all tooth sensitivity or gingival irritation started during the first 14 treatment days. After 2 weeks, the placebo group had twice as many newly reported adverse events as the experimental strip, suggesting the absence of a cumulative treatment effect on tolerability.



**Fig. 1 – Unadjusted mean change ( $\Delta b^*$ ) and sustained use (Weeks 2–6) regression by group.**

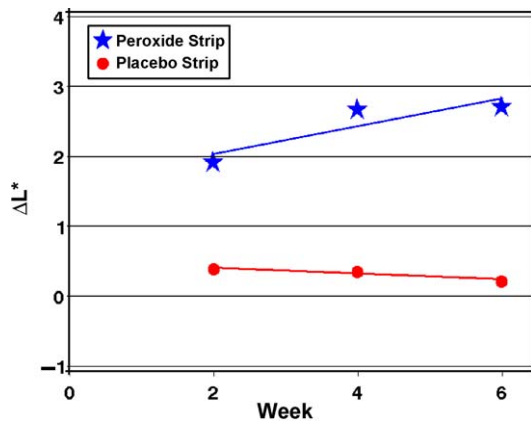


Fig. 2 – Unadjusted mean change ( $\Delta L^*$ ) and sustained use (Weeks 2–6) regression by group.

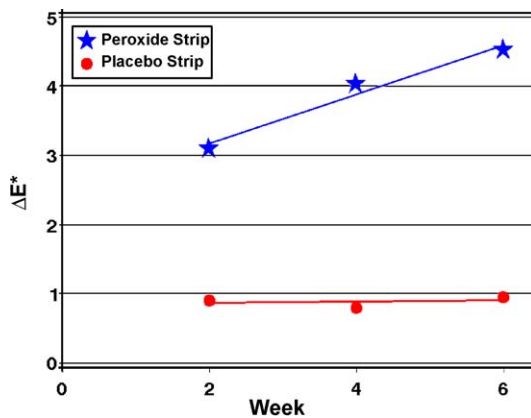


Fig. 3 – Unadjusted mean change ( $\Delta E^*$ ) and sustained use (Weeks 2–6) regression by group.

Of interest, the initial and sustained treatment periods separately provide important perspectives on the utility of digital image analysis, the instrumental method used in this placebo-controlled clinical trial. With the initial response, 2 weeks use of 6% hydrogen peroxide strips resulted in an adjusted mean  $\Delta b^*$  of  $-2.1$  and a  $\Delta L^*$  of  $1.9$ . These results are remarkably consistent with an independent, 7-study meta-analysis of 6% hydrogen peroxide strips collected over a 4-year period at a single (different) center.<sup>26</sup> Outcomes from that

meta-analysis ( $\Delta b^*$  of  $-2.3$  and a  $\Delta L^*$  of  $2.0$ ) were within 5–7% of that measured in this new trial. With sustained use, the method demonstrated significant color improvement for 6% hydrogen peroxide strips without a placebo response. The Week 2–6 slope for the peroxide strip was estimated as  $-0.3$  for  $\Delta b^*$  and  $+0.2$  for  $\Delta L^*$  per week, differing significantly from zero ( $p < 0.0001$ ), and contrasting from the placebo strip response which was not significant ( $p = 0.22$ ) and near zero ( $-0.0$  for  $\Delta b^*$  and  $+0.0$  for  $\Delta L^*$ ).

Two outcomes from the repeated measures model warrant further consideration. First, there was some evidence of a whitening response for in the placebo group relative to baseline during the initial 2-week treatment period. From the model, the estimated baseline intercept (SE) for  $\Delta L^*$  was  $0.5$  ( $0.2$ ), differing significantly ( $p < 0.01$ ) from zero, while in contrast, the estimated intercept for  $\Delta b^*$  was  $-0.2$  ( $0.2$ ), and not significantly different ( $p = 0.26$ ) from zero. Since study subjects did not receive a prophylaxis prior to treatment, we may have measured minor, superficial stain removal as  $\Delta L^*$ , and the derived  $\Delta E^*$ . Second, the repeated measures model did not show a whitening plateau despite 6 weeks daily use of 6% hydrogen peroxide strips. During the sustained treatment period, slopes for  $\Delta b^*$ ,  $\Delta L^*$  and  $\Delta E^*$  were significantly different ( $p < 0.001$ ) from zero, and more treatment yielded more whitening. One possibility for this sustained whitening was entrance criteria. Subjects in this study could have started with darker shades (A3+ at baseline) compared to other studies, so more response was theoretically possible. The other possibility was the overall short contact time typical of daytime strip treatment. While this study involved twice-daily use of whitening strips over a 6-week period, the total strip contact time (42 h) was less than might be expected with just 1 week overnight use of a professionally dispensed tray.<sup>9</sup>

From a methodological perspective, repeated measures modeling of sustained placebo use can provide useful perspective on measurement validity within a controlled clinical trial. In this new study, the placebo group  $\Delta E^*$  intercept differed significantly ( $p < 0.001$ ) from zero. While this was consistent with an initial placebo response,  $\Delta E^*$  was flat during the sustained use period, where the slope did not differ significantly ( $p = 0.69$ ) from zero. During the Week 2–6 period, there was no evidence of a placebo response, even with a derived response parameter such as  $\Delta E^*$ , which is subject to simple measurement variability and other factors.<sup>27</sup> Further research might be indicated to ascertain whether this observation extends to other vital bleaching studies or instrumental methods.

Table 4 – Treatment-related oral irritation or tooth sensitivity all subjects.

	Peroxide strip # (%)	Placebo strip # (%)	Overall # (%)
Number of subjects	20 (100.0)	20 (100.0)	40 (100.0)
Subject reported			
Oral irritation	5 (25.0)	2 (10.0)	7 (17.5)
Tooth sensitivity	7 (35.0)	2 (10.0)	9 (22.5)
Examiner observed			
Oral irritation	0 (0.0)	0 (0.0)	0 (0.0)

## 5. Conclusions

Twice-daily use of 6% hydrogen peroxide whitening strips resulted in significant improvement in tooth color relative to baseline and placebo that was sustained over 6 weeks use. While there was a clinical benefit to extended treatment, there was no evidence for any effect of treatment duration on the type, number or severity of adverse events associated with treatment. The consistent initial whitening response and sustained outcomes, coupled with a measured flat placebo response during sustained use, further establish the appro-



priateness of digital image analysis for clinical trials of tooth whitening.

### Conflict of interest statement

The authors on my paper are from University of North Carolina and Procter & Gamble. The UNC authors declare no COI.

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