Supplementary Table 3. Publications with reported inter-group significance of adverse events

Publication and study design	Intervention and Comparator	No. Subjects	Main AE outcome	Statistical Significance
Lang (1998)[45] Randomized parallel double blind	Delmopinol hydrochloride 2.0 mg	53	Tooth staining 20% 3 months;16% 6 months	Significant differences between placebo and delmopinol ($p< 0.01$) and placebo and CHX ($p<0.001$)
	Placebo	50	No AE	
	CHX digluconate 2.0 mg	53	Tooth staining 3 months 69%; 6 months 88%	
Yeung (1995)[94] Double-blind parallel with 2 arms	Delmopinol 2 mg/ml HCL	22	tongue numbness 12; oral mucosa desquamation 3; burning sensation 1; taste loss 1; altered taste 3; oral ulcer 2	No significant differences between groups in all AE ($p>0.05$)
	Placebo	25	oral mucosa desquamation 1; oral ulcer 4; sore gums 2	
Bascones (2005)[11] Double masked crossover with 3 phases	0.12% CHLX + 0.05% NaF	30	Tongue staining 3	Tongue staining: significant differences between the treatments ($p=0.0141$). During the treatment with CHX-CPC, the frequency of tongue staining was greater than that observed with CHX-NaF ($p=0.0078$) and CHX ($p=0.0467$)
	0.12% CHX	30	Tongue staining 5	
	CHX+0.05% CPC chloride	30	Tongue staining 12	
Brecx (1993)[56] Triple blind parallel randomized	125 ppm F from americium fluoride and 125 ppm F from stannous fluoride, 5.0% alcohol and 0.025% aspartame	9	Teeth staining as discoloration index	Placebo: less staining than active groups ($p<0.001$). CHX groups: at all time points higher staining than fluoride group ($p<0.001$) .
	0.2% CHX digluconate and 5.0% alcohol	10		
	Placebo	12		
Ciancio (1992)[83] Randomized double-blind	0.1% stannous flouride	27	Tooth staining by Lobene index	No significant differences between groups ($p>0.05$)
	Placebo	28		
Horwitz (2000)[65] Parallel double blind	Americium fluoride/ stannous fluoride AmF/SnF2	15	Tooth staining (as % of tooth with no visible staining) 3 weeks – 0.47 ±0.21 12 weeks – 0.72 ± 0.19	At 3 weeks –significant ($p=0.025$), at 6 weeks – not significant ($p>0.05$) differences between groups
	0.12% CHX	17	3 weeks – 1.12 ± 0.19 6 weeks – 0.60 ±0.13	
Kumar (2013)[63] Randomized parallel double blind with 3 arms	0.2% CHX gluconate	16	Oral itching 5 oral soreness 4	No significant difference between the three treatments for the occurrence of adverse events (Chi-squared test = 1.95; P = 0.377)
	0.03% triclosan + 0.025% sodium fluoride NaF + 12% ethyl alcohol	16	Oral itching 8 Aphthous ulcer 4	
	0.2% CHX + 0.3% triclosan + 0.3% NaF + 0.09% Zn chloride $ZnCl_2$	16	Oral itching 5 dryness 4	
Duss (2010)[48] Randomized parallel with 2 arms	0.05 CHX/herbal extract combination	23	Staining by Lobene index	At weeks 4 and 12, more staining in the control group ($p<0.05$ and $p<0.001$, respectively). A higher risk for staining in the control group (crude OR: 2.3:1, 95% CI: 1.3 to 4.4, $p<0.01$).
	0.1% CHX	22		
Charles (2004)[57] Randomized blind parallel	EO	34	Tooth staining by Lobene extrinsic tooth stain index	At 3 and 6 months, significantly more gingival region stain in the EO group ($p<0.05$) and the CHX group ($p<0.001$) compared with the control group; at both examinations, the level of stain in the CHX group was significantly greater ($p<0.001$) than that in the EO group.
	0.12% CHX	36		
	5% alcohol	38		

Cortellini (2008)[53] Cross over and 2 arms	0.2% CHX+ADS	24	Teeth staining 1st week: 2/23 in Incisal, 9/23 in approx, 2/23 in gingiva; 2nd week: 6/24 in Incisal, 15/24 in approx, 5/24 in gingiva 1st week: gingival inflammation 35%; oedema 35%; mucosal irritation 1.0%	No significant differences between the two treatments for any of other than staining variables. At week 1, CHX caused consistently less pigmentations than the control CHX in all the evaluated areas of the dental surfaces (odds ratio (OR)=0.083 $p<0.0001$ in the incisal area, OR=0.036 $p<0.0001$ in the approximal area and OR=0.065 $p<0.0001$ in the gingival area)
	0.2% CHX	24	Teeth staining 1st week: 17/24 in Incisal, 20/24 in approx, 14/24 in gingiva; 2nd week: 12/23 in Incisal, 22/23 in approx, 12/23 in gingiva 1st week: gingival inflammation 21%; oedema 42%; mucosal irritation 1.0%	
Eldridge (1998)[36] Parallel 3 arms	0.12% alcohol free CHX	10	Brown hairy tongue: 80%	The CHX groups had significantly more AE ($p<0.05$) than the EO group.
	EO	11	Brown hairy tongue: 9.10%	
	0.12% CHX	11	Brown hairy tongue: 54.50%	
Ernst (1998)[49] Parallel randomized 2 arms	0.2% CHX Gluconate	65	Teeth staining increased from 30.4% to 45.2%, mucosal irritation 1.5%, taste change 27.60%	No significant differences in teeth staining between groups.
	0.1% CHX	65	Teeth staining increased from 34.2% to 48.4%, taste change 18.40%	
Ernst (2005)[58] Parallel randomized double-blind with 3 arms	CHX	30	Teeth staining as Discoloration index	Significant differences (p=0.0056) when all three groups compared. When CHX and Hexatidine group compared, significant difference (p=0.0035) after 4 weeks, but not significant (p=0.757) after 14 days. When CHX and placebo were compared, significant differences after 14 days (p=0.015) and 4 weeks (p=0.0001). No sign differences when placebo and CHX were compared at 14 days (p=0.1464) or 4 weeks (p=0.1262)
	Hexatidine	30		
	Placebo	30		
Escribano (2010)[18] Parallel 2 arms	0.05% CHX digluconate+0.05% CPC+other ingredients	25	Tooth staining 14 Burning feeling o14	Tooth staining tendency towards statistical significance (p=0.07). The same occurred for the burning feeling of the mouth, (p=0.08). No significant differences between groups for any of the other patient-centred variables
	Placebo	22	Tooth staining 4 Burning feeling o 4	
Gürgan (2006)[67] Parallel 2 arms	0.2% CHX	40	Numerous side effects reported	All subjective side effects. significantly higher frequencies in the test group compared to the placebo, except for pain and pruritus. Significant differences in the results for the rest of the oral mucosa in the test group compared to the placebo group. Significant differences between the test and placebo groups for discolorations of tongue and tooth surfaces (χ^2 and Fisher exact tests)
	Placebo	40		
Jenkins (1993)[69] Double blinded parallel randomized	0.12% CHX+NaF	51	stain area: 49% (objective), 82% (subjective); stain intensity 1.03 (buccal), 1.06 (lingual); soreness 2	For all stain areas the differences between groups were significant (p<0.001). For stain intensity differences between groups were significant (p<0.001). Soreness and tingling not significant; for taste change, significant (p<0.05) change (Mann-Whitney test)
	Placebo	51	stain area: 4% (objective) 14% (subjective); stain intensity 0.14 (buccal), 0.42 (lingual); soreness 1	
Leyes Borrajo (2002)[70] Double blind 3 parallel groups	0.12% CHX +Alcohol	30	Tooth staining 27	Significant differences between groups found, Chi square test of independence, p<0.05
	0.12 CHX without alcohol	27	Tooth staining 30	
	Placebo	39		

Olsson (2012)[50] Randomized double-blind crossover	Alcohol based 0.1% CHX	10	Tooth staining as 1=no stain, 2=spots, 3=abundant stain. Patient assessment of change in taste and smarting by VAS score	All differences between groups were non-significant (Mann–Whitney test)
	Alcohol free 0.12% CHX	10		
Quirynen (2001)[27] Double-blind, randomised, crossover	CHX 0.12 % alcohol, CHX 0.2 % 0.05% CPC, CHX 0.12 % sodium fluoride 0.05%	16	Tooth staining (mean Quigley and Hein score) remained low	No significant differences between groups ($p>0.75$) in all cases
	CHX 0.2 % alcohol	16		
Santhosh (2010)[51] Randomized double blind crossover	0.2% CHX	24	Oral itching 25% oral soreness 29% burning 8% ulcer 20% dryness 16%	No significant differences
	CHX+NaF+ZnCl2	24	Oral itching 4% oral soreness 25% burning 4% ulcer 12.5% dryness 29%	
Santos (2004)[17] Randomized, double-blind, prospective, placebo-controlled, parallel	0.05% CHX + 0.05% CPC	17	Tooth staining	Significant difference in intensity of staining (p=0.02, Mann–Whitney test) between groups.
	Placebo	16	Tooth staining	
Solís (2011)[55] Crossover randomized double masked	CHX 0.2% with ADS	15	Teeth staining	Significant less tooth staining with the test group (p <0.01)
	CHX 0.2%	15		
Zimmer (2015)[19] Four arms parallel blind randomized	0.06% CHX+ 0.025% NaF+Alcohol	39	teeth staining 4 weeks: 17; 8 weeks: 18 tongue staining 4 weeks: 12; 8 weeks: 18	No significant differences between groups for discoloration of the tongue. For tooth staining significant more occurrences in the three rinsing groups when compared to the negative control (P < 0.001, Chi square test).
	0.06% CHX+ 0.025% NaF	39	teeth staining 4 weeks: 9; 8 weeks: 21 tongue staining 4 weeks: 11; 8 weeks: 22 gastrointestinal infection 1	
	0.06% CHX+ 0.025% NaF+0.03% CPC	37	teeth staining 4 weeks: 18; 8 weeks: 25 tongue staining 4 weeks: 16; 8 weeks: 23 gastrointestinal infection 4	
	Only brushing twice daily	40	teeth staining 4 weeks: 3; 8 weeks: 8 tongue staining 4 weeks: 8; 8 weeks: 14	
Costa (2012)[15] Parallel with 2 arms	0.07 %CPC	35	Staining by Lobene index	Significant higher levels of staining observed in the test group after 3 (p = 0.007) and 6 months (p < 0.001)
	Placebo	32		

AE: adverse events; CHX: Chlorhexidine; EO: Essential Oils; CPC: CetylPyridinium Chloride; ADS: anti discoloration system