Item	Details
Section 1: Reviewer and study information	
Reviewer name	Sam Barton and Vicky Wakefield
Study ID (Author name, year)	Akhavan 2014
Study details (journal, year, volume, page range)	J Obstet Gynaecol Res Vol 40, 2110–2113
Language of publication	English
Type of report (full paper/only abstract/conference abstract)	Full paper
Section 2: study information	
Location and number of sites	Imam Khomeini, Hospital, Tehran, Iran. Not specifically stated but study seems to be located at one site.
Trial sponsor	Study funded by Vice Chancellor of Research of Tehran University of Medical Sciences
Conflicts of interest	Paper states “The authors do not have any financial relationships with any companies”.
Patient enrolment (how patients were enrolled, and date to date of enrolment)	Patients from Imam Khomeini Hospital, Tehran, Iran meeting the inclusion criteria were enrolled. No further details on enrolment or the enrolment dates were reported.
Trial design (e.g., RCT, cross-over RCT)	RCT Six-arm RCT. Three arms evaluate treatments of interest in combination with zinc sulphate, which is not of interest to this review. Data for these three arms have not been extracted.
Trial duration (including any period of follow-up)	Imiquimod 5% given for 8 weeks. Podophyllin 20% given for 8 weeks. After that, people were visited monthly to the 8th month (i.e., 6 months of follow up)..
Line of therapy (first, recurrent, persistent)	Unclear from reporting in paper.
Inclusion criteria	Women aged 20–50 years, isolated vulvar lesion, normal Pap smear and colposcopy, and no immune or systemic disease at the time of admission.
Exclusion criteria	Recalcitrant lesions, unwillingness of the patient to continue treatment or not showing up for the follow-up examinations
All outcomes reported in paper	Response to treatment: paper states that response to treatment was assessed at 3 weeks after the initiation of treatment but data for response to treatment are not reported. Unclear whether this outcome is actually assessing wart clearance (presume so?) Duration of response – not further defined in paper. Have taken duration of response to be time between complete clearance of the wart and relapse, which is not an outcome of interest to our review. Unclear how response has been assessed.

	Relapse at 3 and 6 months after treatment.			
Subgroups evaluated	Not reported			
Stratification	Not reported			
Baseline measurement of disease	Not reported			
Treatment	**Imiquimod 5%**	**Cryotherapy**	**Podophyllin 20%**	
Randomised, N	42	42	42	
Withdrawals (please specify reasons for withdrawal, including treatment discontinuation, and loss to follow-up; use different rows for different reasons), n (%)	5 2 patients with recalcitrant lesions or unwillingness 3 patients did not return for examination	6 1 patient with recalcitrant lesions or unwillingness 5 patients did not return for examination	4 2 patients with recalcitrant lesions or unwillingness 2 patients did not return for examination	
Treatment regimen (duration of treatment, delivery, dose, formulation, and concomitant medications)	Imiquimod 5% administered as a topical cream three times a week for a total duration of 8 weeks. Further details not available.	Cryotherapy. No information on timing of cryotherapy or number of treatments.	Patients in the podophyllin group received 20% topical solution administered once a week for 8 weeks	
Duration/number of administered treatment (i.e., mean length of or number of administrations of treatment, with SD/SE if given. If no mean presented, median values with ranges)	Not reported			
Baseline patient characteristics	**Imiquimod 5%**	**Cryotherapy**	**Podophyllin 20%**	**p value**
Mean age, (with SD/SE if given), years (range)	Baseline characteristics not reported by group. It is stated that “All groups were the same in terms of baseline characteristics, including age, parity and number of marriages”.			
Duration of disease	Study included women only.			
Site of AGW, n (%)				

Type of AGW (e.g., non-keratinised, keratinised), n (%)		
Mean number of AGWs, with SD/SE if given		
Mean area of AGW (mm^2)		
Sex (M/F), n (%)		
Any previous treatment, n (%)		
Ethnicity, n (%)		
Section 3: Outcomes		
Outcome	**Definition**	
AGW clearance at completion of treatment	Response to treatment is referred to but data for this assessment are not reported. Paper states that response to treatment was assessed at 3 weeks after the initiation of treatment but data for response to treatment are not reported. Unclear whether this outcome is actually assessing wart clearance	
AGW clearance at other time points		
Recurrence of AGW	Relapse at 3 and 6 months after treatment. No information on how many women achieved complete clearance after treatment: paper states that therapeutic benefit seen in 3–4 weeks after treatment initiation. Presume all women achieved clearance of their wart? Difficult to interpret results without knowledge of proportion of women in each group achieving complete clearance.	
Time to complete clearance	Mean time to response (weeks)	
Volume of wart clearance (e.g., proportion of patients with 50% clearance)	Not reported	
Relief of symptoms during treatment	Not reported	
Appearance of new warts during treatment	Not reported	
Quality of life (trial scale used)	Not reported	
Adverse events (please specify)	Not reported	

Malignancy	Not reported								
Section 4: Data extraction form									
Outcome	**Timeframe**	**Imiquimod 5%**		**Cryotherapy**		**Podophyllin 20%**		**Estimate of effect**	**CI and p value**
Dichotomous outcomes									
		n	N	n	N	n	N	No estimates of effect or p values for comparisons of interest to our review.	
Recurrence of AGW	3 months	0	42	1	42	2	42		
Recurrence of AGW	6 months	10	42	11	42	9	42		

Section 5: Clinical trial quality			
Outcome	**Risk of bias**	**Risk assessment[a]**	**Comments**
Recurrence of AGW	Random sequence generation	?	Limited details reported. Paper states that women were "block randomised" but details on size of blocks or how sequence was generated are not available
	Allocation concealment	?	Details not available on methods implemented to conceal allocation
	Selective reporting	?	Protocol not available and unclear what outcomes were prespecified, and what data were captured during the study.
	'Other Bias'	?	Insufficient information to assess other risks of bias.
	Blinding (participants & personnel)	?	Level of masking not discussed in the full publication. Given the differences in the type of treatment across groups (solution versus cream versus cryotherapy), it would be difficult to mask participants and treating physicians to treatment allocated but this is not likely to affect assessment of recurrence of AGW.
	Blinding of outcomes assessment	?	It is stated that "The physician examining the patients was not aware of the group allocation of the patients". However, it is unclear whether the physician would be able to discern which treatment a person had received based on scarring or other marks on the skin.
	Incomplete outcome data	?	Not all people randomised were included in the analysis. Unclear why people who did not show up for the follow-up examinations were excluded from the

			study. The researchers seem to have done a complete-case analysis. However, level of drop out was low.
Overall rating of bias		?	

Section 6: Additional comments		
Additional comments		
Further information that could be requested from authors	***Methodological information***	
	Method of randomisation	×
	Level of masking (if masked, who was masked)	×
	Method for allocation concealment	×
	Method for maintaining masking during the trial	×
	Baseline characteristics	
	Mean and median age of people in each group (with accompanying measure of variation)	×
	Breakdown by site of AGW in each group	×
	Mean number and area of AGW at baseline in each group	×
	Proportion of people with (i) single, (ii) few (2–5), or (iii) multiple (≥6) AGWs at baseline in each group	×
	Breakdown of type of AGW (non-keratinised vs keratinised) in each group	×
	Immune status (immunosuppressed vs not immunosuppressed) in each group	×
	Any previous treatment	×
	Ethnicity	×
	Trial conduct	
	Was there a trial sponsor?	
	Did any of the authors have a conflict of interest?	
	When was complete clearance was recorded?	×
	Number of people lost to follow-up in each group	
	Number of people who withdrew from each group, and reasons for withdrawal	
	Is the reported analysis based on an intention-to-treat population?	
	Any concomitant medications received in each group?	×
	Did both groups receive the same care except for allocated treatment?	×
	Results	
	Complete clearance in each group based on subgroups of:	×
	site of AGW	×
	number of AGW at baseline (subgroups of few [2–5] and multiple [≥6])	×
	type of AGW (non-keratinised vs keratinised)	×
	immune status (immunosuppressed vs not immunosuppressed)	×
	Miscellaneous	

[a] Key for risk assessment: ✓ = low risk of bias; ? = unclear risk of bias; and x = high risk of bias.

Abbreviations used in table: AGW, anogenital wart; CI, confidence interval; n, number of patients with the outcome; N, number of patients assessed; QoL, quality of life; RCT, randomised controlled trial; SD, standard deviation; SE, standard error.

Item	Details
Section 1: Reviewer and study information	
Reviewer name	Vicky Wakefield and Sam Barton
Study ID (Author name, year)	Braga 2017
Study details (journal, year, volume, page range)	Acta Cir. Bras. 2017;32(6):482-490
Language of publication	English
Type of report (full paper/only abstract/conference abstract)	Full
Section 2: study information	
Location and number of sites	Authors were affiliated with Universidade Federal de São Paulo, Brazil. Reported that "Research performed at Postgraduate Program in Interdisciplinary Surgical Science, Escola Paulista de Medicina, Universidade Federal de São Paulo (UNIFESP), Brazil." With patient enrolment at 1 site: the public centre for specialized consultations in the municipality of Contagem, Minas Gerais.
Trial sponsor	None reported
Conflicts of interest	Stated that there are no conflicts of interest, financial or otherwise
Patient enrolment (how patients were enrolled, and date to date of enrolment)	January 2013 to April 2014. People were those attending the coloproctology service for sexually transmitted diseases at the public center for specialized consultations of the municipality of Contagem, Minas Gerais
Trial design (e.g., RCT, cross-over RCT)	RCT, but people act as their own control. The anal and perianal region of the same individual was divided into two semicircles, following the model proposed by Billingham. Each treatment method was applied to one semicircle, chosen by simple randomization. Thirty-seven people were included in the study
Trial duration (including any period of follow-up)	Treatment was performed until all lesions were cleared. During the postoperative period, people were evaluated by means of fortnightly proctological examinations during the first month and then monthly examinations until the sixth month of follow-up.
Line of therapy (first, recurrent, persistent)	Unclear (10 people had received some form of previous treatment)

Inclusion criteria	People over the age of 18 years with anal condyloma or perianal condyloma, or both, over the whole circumference of the anal or perianal region. **It is noted that lesions caused by HPV were confirmed in 32 individuals (86.5%), while the histology of the remaining five was unspecific.**	
Exclusion criteria	People who presented either unilateral condylomatous lesions or lesions that were too large for treatment at an outpatient service or who did not agree were not included	
All outcomes reported in paper	Relapse: NB – Argon plasma and electrofulguration were performed until the lesions disappeared, from a macroscopic point of view.	
Subgroups evaluated	Various Age (≤30 years vs >30 years) Gender (male vs female) Initiated sexual life (≤20 years vs >20 years) Number of partners (<2 vs 2 to 5 vs ≥6) Anal coitus (yes vs no) Anal manipulation (yes vs no) Smoking (yes vs no) Location of AGW (anal vs perianal vs perianal and anal vs other) Previous treatment (yes vs no) Oncotic cytology (NIL vs LSIL vs HSIL) Genotype (high risk vs low risk vs others) Seropositive versus seronegative people	
Stratification	None	
Baseline measurement of disease	The condylomatous lesions were diagnosed by means of proctological examinations. These examinations consisted of static and dynamic inspection, rectal touching, anoscopy and high-resolution anoscopy using 3% acetic acid. All the patients underwent specimen collection for histology, oncotic cytology and polymerase chain reaction (PCR) evaluations.	
Treatment	**Argon plasma**	**Electrofulguration**
Randomised, N	37 (one half of anal region) Argon plasma was applied on the right side of 22 people and on the left side of 15	37 (one half of anal region) Electrofulguration was applied on the right side of 15 patients and on the left side of the other 22.
Withdrawals n (%)	Not reported. Reported that 46 patients were eligible. However, only 37 participated in the entire study. Unclear whether nine people dropped out pre- or post- randomisation.	
Treatment regimen	Treatment was carried out respecting the epithelial planes, with the objectives of improving results and minimizing complications, as described by Reid. If residual lesions were diagnosed, new applications were performed, respecting the type of treatment previously performed on the given semicircle. Treatment was performed until all lesions cleared, from a macroscopic point of view.	

Duration/number of administered treatment		A total of 119 operations were performed among the 37 people. The areas treated with fulguration underwent up to three therapeutic sessions, while areas treated with argon required up to four sessions (no statistically significant difference in number of sessions). More areas responded to a single session of argon plasma treatment (21 vs 18).		
Baseline patient characteristics		**Argon plasma**	**Electrofulguration**	**p value**
Age, years	≤30	17		
	>30	20		
Duration of disease		Not reported		
Site of AGW, n (%)	Anal	8		
	Perianal	3		
	Anal and perianal	21		
	Other	5		
Type of AGW, n (%)		It was reported that the histological results revealed that 32 (86.5%) of patients had condylomata acuminata and 5 (13.5%) of patients had unspecified lesions.		
Mean number of AGWs, with SD/SE if given		Not reported		
Mean area of AGW (mm^2)		Not reported		
Sex (M/F), n (%)	Male	34		
	Female	3		
Any previous treatment, n (%)	Yes	10		
	No	27		
Ethnicity, n (%)		Not reported		
Section 3: Outcomes				
Outcome		**Definition**		
AGW clearance at completion of treatment		No set time frame and treatment was repeated until all lesions cleared.		

AGW clearance at other time points	Not reported
Recurrence of AGW	Relapse of AGW.
Time to complete clearance	Not reported
Volume of wart clearance (e.g., proportion of patients with 50% clearance)	Not reported
Relief of symptoms during treatment	Not reported
Appearance of new warts during treatment	Not reported
Quality of life (trial scale used)	Not reported
Adverse events (please specify)	Not reported
Malignancy	Not reported

Section 4: Data extraction form

Outcome (delete outcomes not reported)	**Timeframe**	**Argon plasma**		**Electrofulguration**		**Estimate of effect**	**CI and p value**
Dichotomous outcomes							
		n	N	n	N		
Recurrence of AGW	6 months after treatment	16	37	19	37		p = 0.478
Recurrence of AGW Seropositive people	6 months after treatment	8	14	11	14		
Recurrence of AGW Seronegative people	6 months after treatment	8	23	8	23		
Recurrence of AGW Age ≤30 years	6 months after treatment	9	17	9	17		
Recurrence of AGW Age >30 years	6 months after treatment	7	20	10	20		

Recurrence of AGW Men	6 months after treatment	13	34	17	34		
Recurrence of AGW Women	6 months after treatment	3	3	2	3		
Recurrence of AGW Anal	6 months after treatment	2	8	3	8		
Recurrence of AGW Perianal	6 months after treatment	2	3	2	3		
Recurrence of AGW Anal and perianal	6 months after treatment	8	21	11	21		
Recurrence of AGW Other	6 months after treatment	4	5	3	5		
Recurrence of AGW Previous treatment	6 months after treatment	6	10	7	10		
Recurrence of AGW No previous treatment	6 months after treatment	10	27	12	27		

Section 5: Clinical trial quality

Outcome	**Risk of bias**	**Risk assessment[a]**	**Comments**
	Random sequence generation	?	Randomisation method described as simple, additional information on methods not available
	Allocation concealment	?	No details reported
	Selective reporting	?	Protocol not available. Study seems to have been designed to assess recurrence as people were treated until complete clearance.
	'Other Bias'	?	Insufficient information to assess potential sources of other bias
Recurrence of AGW	Blinding (participants & personnel)	?	Information on level of masking not available. Likely to be able to mask participants to treatment received as they receive both treatments.

	Blinding of outcomes assessment	?	Information on level of masking not available. Unclear whether blinded assessor was involved
	Incomplete outcome data	?	Analysis is based on 37 (out of 46) people who completed the full study. Reasons for withdrawal and loss to follow up are not reported.
Overall rating of bias		?	Insufficient information available in the full publication to determine risk of bias associated with study

Section 6: Additional comments		
Additional comments	**It is noted that lesions caused by HPV were confirmed in 32 individuals (86.5%), while the histology of the remaining five was unspecific.** Eradication of condylomatous lesions among all the patients was reached after 120 days of treatment. HIV-positive status was reported in 14 (37.8%) patients.	
Further information that could be requested from authors	***Methodological information***	
	Method of randomisation	✓
	Level of masking (if masked, who was masked)	✓
	Method for allocation concealment	✓
	Method for maintaining masking during the trial	✓
	Baseline characteristics	
	Mean and median age of people in each group (with accompanying measure of variation)	✓
	Breakdown by site of AGW in each group	
	Mean number and area of AGW at baseline in each group	✓
	Proportion of people with (i) single, (ii) few (2–5), or (iii) multiple (≥6) AGWs at baseline in each group	✓
	Breakdown of type of AGW (non-keratinised vs keratinised) in each group	✓
	Immune status (immunosuppressed vs not immunosuppressed) in each group	
	Any previous treatment	
	Ethnicity	✓
	Trial conduct	
	Was there a trial sponsor?	
	Did any of the authors have a conflict of interest?	
	When was complete clearance was recorded?	
	Number of people lost to follow-up in each group	
	Number of people who withdrew from each group, and reasons for withdrawal	✓
	Is the reported analysis based on an intention-to-treat population?	
	Any concomitant medications received in each group?	✓

	Did both groups receive the same care except for allocated treatment?	✓
	Results	
	Complete clearance in each group based on subgroups of:	
	site of AGW	
	number of AGW at baseline (subgroups of few [2–5] and multiple [≥6])	
	type of AGW (non-keratinised vs keratinised)	
	immune status (immunosuppressed vs not immunosuppressed)	
	Miscellaneous	

[a] Key for risk assessment: ✓ = low risk of bias; ? = unclear risk of bias; and x = high risk of bias.

Abbreviations used in table: AGW, anogenital wart; CI, confidence interval; n, number of patients with the outcome; N, number of patients assessed; QoL, quality of life; RCT, randomised controlled trial; SD, standard deviation; SE, standard error.

Item	Details
Section 1: Reviewer and study information	
Reviewer name	Vicky Wakefield and Sam Barton
Study ID (Author name, year)	Stockfleth 2008
Study details (journal, year, volume, page range)	Br J Dermatol 158, 1329–1338
Language of publication	English
Type of report (full paper/only abstract/conference abstract)	Full report
Section 2: study information	
Location and number of sites	46 dermatological, gynaecological and urological centres throughout Europe and South Africa, including university hospitals, hospitals and clinical practices.
Trial sponsor	MediGene AG. Quintiles GmbH acted as the conducting CRO
Conflicts of interest	A.M., H.T. and C.T. are employees of the sponsor, MediGene AG, Munich, Germany, and hold MediGene AG stocks E.S. is a consultant for MediGene AG. E.S., H.B., R.O. and F.G. have a contractual involvement as study investigators.
Patient enrolment (how patients were enrolled, and date to date of enrolment)	Patient enrolment started on 30 September 2002 and ended on 20 May 2003. The last patient completed the study on 2 December 2003. Information on recruitment not available.

Trial design (e.g., RCT, cross-over RCT)	RCT Patients were randomly assigned to Polyphenon E 15% ointment, Polyphenon E 10% ointment or vehicle in a 2 : 2 : 1 allocation ratio
Trial duration (including any period of follow-up)	Maximum duration of treatment of 16 weeks, or until complete clearance of all warts (baseline and newly appearing during treatment), whichever came first. During the treatment period, wart measurements and local tolerability parameters, AEs, concomitant medication and drug compliance were checked every other week. At the last (end of treatment) visit, screening and baseline examinations were repeated. For complete responders, a 12-week treatment-free follow-up phase directly followed to assess wart recurrence, with visits after 4 and 12 weeks to assess recurrence rate.
Line of therapy (first, recurrent, persistent)	Exact line of therapy for this round of AGW unclear. All people enrolled had had a previous episode of AGWs. It is stated “The majority of patients (462; 91.8%) had one episode, 19 (3.8%) patients had two, and 22 (4.4%) patients had three or more previous episodes”.
Inclusion criteria	• Women and men, 18 years of age or older, with two to 30 clinically diagnosed EGWs with a total wart area of 12–600 mm^2 were eligible. • Locations of warts were glans penis, penile shaft, scrotum and foreskin for men, vulva for women, and the inguinal, perineal and perianal skin areas for both genders. • Female patients and partners of male patients with childbearing potential had negative pregnancy tests and were to use effective contraception during the treatment period.
Exclusion criteria	Patients were not enrolled if they: • had a current episode of herpes genitalis or any other current and⁄or recurrent genital or uncontrolled infection, including known human immunodeficiency virus infection; • had participated in an investigational trial; • had treatment of anogenital warts or had systemic intake of virostatics or immunosuppressive medication within 30 days prior to enrolment; • had organ allograft; • had skin conditions that may interfere with the study drug; • had internal (vaginal or rectal) warts that required treatment; • were lactating.
All outcomes reported in paper	Primary endpoint: complete clearance of all warts (new and baseline) within the 16-week treatment period. Other outcomes assessed: • Complete clearance of baseline warts; • Total wart number; • Total wart area; • Partial clearance (of at least 50%; unclear whether clearance based on number of warts or wart area); • Recurrence; • Development of new warts (during follow-up not treatment); • Time to complete clearance;

	• Adverse events; • Local signs and symptoms.		
Subgroups evaluated	Not reported		
Stratification	Gender (male/female)		
Baseline measurement of disease	It is stated that warts were measured during screening and baseline visits: additional detail is not available		
Treatment	**Polyphenon E 15% ointment**	**Polyphenon E 10% ointment**	**Placebo**
Randomised, N	201	199	103
Withdrawals (please specify reasons for withdrawal, including treatment discontinuation, and loss to follow-up; use different rows for different reasons), n (%)	40 withdrawals 16 (8.0%) people withdrew consent 6 (3.0%) non-compliant with study procedures 6 (3.0%) terminated because of an adverse event Other reasons for withdrawal not reported	29 withdrawals 10 (5.0%) people withdrew consent 7 (3.5%) non-compliant with study procedures 1 (0.5%) terminated because of an adverse event Other reasons for withdrawal not reported	23 withdrawals 9 (8.7%) people withdrew consent 2 (1.9%) non-compliant with study procedures 1 (1.0%) terminated because of an adverse event Other reasons for withdrawal not reported
Treatment regimen (duration of treatment, delivery, dose, formulation, and concomitant medications)	Patients were instructed to apply the allocated ointment three times daily, each application about 8 h apart to all EGWs for 16 weeks or until complete clearance of all warts (whichever occurred first). If treatment of local skin reactions was needed, paracetamol could be given orally. No additional topical treatment was allowed.		
Duration/number of administered treatment (i.e., mean length of or number of administrations of treatment, with SD/SE if given. If no mean presented, median values with ranges)	Mean duration of treatment: 92.9 days Treatment reductions per visit: maximum of 6.1% Treatment interruptions per visit: maximum of 10.3%	Mean duration of treatment: 98.7 days Treatment reductions per visit: maximum of 5.4% Treatment interruptions per visit: maximum of 5.9%	Mean duration of treatment: 95.8 days Treatment reductions per visit: maximum of 5.0% Treatment interruptions per visit: maximum of 4.8%

Baseline patient characteristics	**Polyphenon E 15% ointment**	**Polyphenon E 10% ointment**	**Placebo**	**p value**
Mean age, (with SD/SE if given), years (range)	30.8 (SD 11.1) (17–69)	30.6 (SD 10.8) (16–98)	30.4 (SD 10.9) (18–60)	0.9070

Duration of disease	Not reported			
Site of AGW, n (%)	The most affected areas were located at the penis shaft (65.0%) and the glans penis (24.2%) in men, and the vulva (84.1%) and perianal area (21.7%) in women. AGW sites not reported by treatment group			
Type of AGW (e.g., non-keratinised, keratinised), n (%)	Not reported			
Mean number of AGWs (SD)	8.2 ± 6.3	8.3 ± 5.8	7.2 ± 4.6	P = 0.5147 and 0.1804 for Polyphenon E 15% and 10%, respectively, versus placebo
Median number of AGWs	6.0	6.0	6.0	
Mean area of AGW (mm^2)	94.2 ± 116.5	99.5 ± 117.1	75.6 ± 79.2	P = 0.9152 and 0.3882 for Polyphenon E 15% and 10%, respectively, versus placebo
Median area of AGW (mm^2)	50.5	51.0	51.5	
Sex (M/F), n (%)	Men: 105 (52.2) Women: 96 (47.8)	Men: 110 (55.3) Women: 89 (44.7)	Men: 62 (60.2) Women: 41 (39.8)	0.4174
Any previous treatment, n (%)	Although all patients had at least one previous episode of EGWs, only 180 (35.8%) patients, similarly in all three treatment groups, had received treatment for previous episodes			
Ethnicity, n (%)				
African	6 (3.0)	6 (3.0)	4 (3.9)	0.9709
Asian	1 (0.5)	1 (0.5)	1 (1.0)	
Caucasian	191 (95.0)	189 (95.0)	97 (94.2)	
Hispanic	1 (0.5)	0 (0)	0 (0)	
Other	2 (1.0)	3 (1.5)	1 (1.0)	
Section 3: Outcomes				
Outcome	**Definition**			
AGW clearance at completion of treatment	Complete clearance of all warts (new and baseline) within the 16-week treatment period. Also reports complete clearance of baseline warts alone within the 16-week treatment period.			
AGW clearance at other time points	Not reported			
Recurrence of AGW	Recurrence in those achieving complete clearance (evaluated over 12 weeks)			

Time to complete clearance	Median time to complete clearance of all warts
Volume of wart clearance (proportion of people with at least 50% clearance)	Partial clearance of AGWs of at least 50%, unclear whether clearance is based on number of warts or on wart area.
Relief of symptoms during treatment	Not reported
Appearance of new warts during treatment	Not reported
Quality of life (trial scale used)	Not reported
Adverse events (please specify)	Local skin signs and symptoms
Malignancy	Not reported

Section 4: Data extraction form

Outcome (delete outcomes not reported)	**Timefram e**	**Polyphenon E 15% ointment**		**Polyphenon E 10% ointment**		**Placebo**		**Estimate of effect**	**CI and p value**
Dichotomous outcomes									
		n	N	n	N	n	N		
AGW clearance at completion of treatment (all warts)	16 weeks	102	194	99	195	38	102	LOCF analysis Taken reported p values to be for comparison of active treatment versus vehicle. 15% ointment versus vehicle: p = 0.0143 10% ointment versus vehicle: p = 0.0280	
AGW complete clearance of baseline warts	16 weeks	106	194	102	195	40	102	LOCF analysis 15% ointment versus placebo: p = 0.0143 10% ointment versus placebo: p = 0.0376	
Recurrence of AGW	12 week follow-up	6	102	4	99	1	38		
Volume of wart clearance (proportion of people with at least	16 weeks	77.3%		78.0%		52.9%		P < 0.001 for both 15% and 10% ointment versus placebo	

50% clearance of AGWs)								
Adverse events								
Local skin reactions (signs and symptoms)	16 weeks	169	196	159	195	63	103	Denominator calculated by reviewer based on percentages reported by author (authors state safety population based on 502 people, but numbers indicate analysis based on 494 people)
Local skin signs	16 weeks	152	201	153	198	47	103	Denominator calculated by reviewer based on percentages reported by author
Severe	16 weeks	25	201	8	198	2	103	
	The most frequently observed local skin signs were erythema, oedema and erosion							
Adverse events other than local reactions	16 weeks	44 (70 events)	201	47 (84 events)	198	22 (26 events)	103	P = 0.89 between the 15% and 10% ointment groups
Mild	16 weeks	28	201	24	198	17	103	
Moderate	16 weeks	17	201	30	198	6	103	
Severe	16 weeks	7	201	2	198	1	103	
The most frequently reported AEs, headaches (19 patients; 3.8%), respiratory tract infections (eight patients; 1.6%) and influenza (seven patients, 1.4%), were evenly distributed in the three treatment groups and were not related to the study medication								
Continuous outcomes								
		Mean	SD/SE	N	Mean	SD/SE	N	
Median time to complete clearance		16.3 (2.0 to 18.9 weeks)		16.4 (4.0 to 18.1 weeks)		16.7		15% ointment versus vehicle: p = 0.0595 10% ointment versus vehicle: p = not reported

Section 5: Clinical trial quality			
Outcome	**Risk of bias**	**Risk assessment[a]**	**Comments**
	Random sequence generation	?	Although randomization sequence was generated by Almedica HPS AG (Reinach⁄Basel, Switzerland) details on methods to generate sequence are unavailable. Throughout the study, the randomization list was not available at the study centres or to the project teams.

	Allocation concealment	?	No information available on methods implemented to conceal allocation. Randomisation carried out by an external company, and likely that the company also responsible for allocation (centralised), but this not stated. It is stated that "Centres were provided with medication kits that had a pre-assigned patient number, with each patient allocated the lowest available number". Also, "Patient randomization and initial dispensing of study medication were done at baseline followed by treatment initiation". Unclear how this allocation system works with random sequence generation.
	Selective reporting	x	Many results only partially and unclear why patients missing from some analyses or the total number in some of the analyses.
	'Other Bias'	?	Insufficient information to assess
AGW clearance at completion of treatment and at other time points	Blinding (participants & personnel)	?	Study described as double blind but no information available on who is masked and how masking has been maintained
	Blinding of outcomes assessment	?	Unclear whether outcome assessor is masked to treatment
	Incomplete outcome data	x	Not true ITT analysis but includes most people randomised. Number lost to follow-up is unclear. Total number of people withdrawing is high (~20%). Number of people withdrawing, together with reasons for withdrawal, is balanced across the groups. Designated high risk of bias because of high withdrawal rate.
Recurrence of AGW	Blinding (participants & personnel)	?	Study described as double blind but no information available on who is masked and how masking has been maintained
	Blinding of outcomes assessment	?	Unclear whether outcome assessor is masked to treatment
	Incomplete outcome data	x	Not true ITT analysis but includes most people randomised. Number lost to follow-up is unclear. Number of people withdrawing is high (~20%). Number of

			people withdrawing, together with reasons for withdrawal, is balanced across the groups. Designated high risk of bias because of high withdrawal rate.
Time to complete clearance	Blinding (participants & personnel)	?	Study described as double blind but no information available on who is masked and how masking has been maintained
	Blinding of outcomes assessment	?	Unclear whether outcome assessor is masked to treatment
	Incomplete outcome data	x	Not true ITT analysis but includes most people randomised. Number lost to follow-up is unclear. Number of people withdrawing is high (~20%). Number of people withdrawing, together with reasons for withdrawal, is balanced across the groups. Designated high risk of bias because of high withdrawal rate.
Volume of wart clearance (proportion of patients with at least 50% clearance)	Blinding (participants & personnel)	?	Study described as double blind but no information available on who is masked and how masking has been maintained
	Blinding of outcomes assessment	?	Unclear whether outcome assessor is masked to treatment
	Incomplete outcome data	x	Unclear how many people are included in the analysis: results presented as percentage with no absolute event rate.
Adverse events	Blinding (participants & personnel)	?	Study described as double blind but no information available on who is masked and how masking has been maintained
	Blinding of outcomes assessment	?	Unclear whether outcome assessor is masked to treatment
	Incomplete outcome data	x	Safety population includes most people randomised (excludes one person). Number lost to follow-up is unclear. Number of people withdrawing is high (~20%). Number of people withdrawing, together with reasons for withdrawal, is balanced across the groups. Designated high risk of bias because of high withdrawal rate.
Overall rating of bias		x	Designated as overall high risk of bias due to some concerns around level of withdrawal.
Section 6: Additional comments			

Additional comments		
Further information that could be requested from authors	***Methodological information***	
	Method of randomisation	×
	Level of masking (if masked, who was masked)	×
	Method for allocation concealment	×
	Method for maintaining masking during the trial	×
	Baseline characteristics	
	Mean and median age of people in each group (with accompanying measure of variation)	
	Breakdown by site of AGW in each group	
	Mean number and area of AGW at baseline in each group	
	Proportion of people with (i) single, (ii) few (2–5), or (iii) multiple (≥6) AGWs at baseline in each group	×
	Breakdown of type of AGW (non-keratinised vs keratinised) in each group	×
	Immune status (immunosuppressed vs not immunosuppressed) in each group	
	Any previous treatment	
	Ethnicity	
	Trial conduct	
	Was there a trial sponsor?	
	Did any of the authors have a conflict of interest?	×
	When was complete clearance was recorded?	
	Number of people lost to follow-up in each group	×
	Number of people who withdrew from each group, and reasons for withdrawal	
	Is the reported analysis based on an intention-to-treat population?	
	Any concomitant medications received in each group?	
	Did both groups receive the same care except for allocated treatment?	×
	Results	
	Complete clearance in each group based on subgroups of:	
	site of AGW	×
	number of AGW at baseline (subgroups of few [2–5] and multiple [≥6])	×
	type of AGW (non-keratinised vs keratinised)	×
	immune status (immunosuppressed vs not immunosuppressed)	
	Miscellaneous	
	Please clarify if partial clearance is based on wart count or wart area.	

[a] Key for risk assessment: ✔ = low risk of bias; **?** = unclear risk of bias; and **×** = high risk of bias.

Abbreviations used in table: AGW, anogenital wart; CI, confidence interval; n, number of patients with the outcome; N, number of patients assessed; QoL, quality of life; RCT, randomised controlled trial; SD, standard deviation; SE, standard error.

Item	Details
Section 1: Reviewer and study information	
Reviewer name	Sam Barton and Natalie Masento
Study ID (Author name, year)	Tatti 2008
Study details (journal, year, volume, page range)	Obstet Gynecol 111, 1371–1379
Language of publication	English
Type of report (full paper/only abstract/conference abstract)	Full report
Section 2: study information	
Location and number of sites	50 dermatology, gynecology, and urology services of participating hospitals and practices in the United States, Latin America, and Romania
Trial sponsor	MediGene AG
Conflicts of interest	Dr Tatti has served as a clinical study investigator (contracted research) for MediGene AG (Munich, Germany). Dr Swinehart was one of the study investigators, and for this purpose he has a contract with MediGene AG. Dr Thielert, Professor Tawfik, and Dr Mescheder are employees of MediGene AG, and they receive a salary from and own stock in the company. Dr Beutner is a study investigator, consultant, congress speaker, and holds membership on the advisory committee for MediGene AG. He is a consultant and shareholder in Epitome Pharmaceuticals (Halifax, Nova Scotia).
Patient enrolment (how patients were enrolled, and date to date of enrolment)	It is stated that the trial was conducted between July 2003 and August 2004. Unclear whether the dates relate to enrolment alone or to date of completion of the study. Patients were recruited from participating centres.
Trial design (e.g., RCT, cross-over RCT)	RCT Patients were randomly assigned to sinecatechins 15% ointment, sinecatechins 10% ointment or vehicle in a 2 : 2 : 1 allocation ratio
Trial duration (including any period of follow-up)	Maximum duration of treatment of 16 weeks, or until complete clearance of all warts (baseline and newly appearing during treatment), whichever came first. For complete responders, a 12-week treatment-free follow-up phase directly followed to assess wart recurrence, with visits after 4 and 12 weeks to assess recurrence rate.
Line of therapy (first, recurrent, persistent)	Exact line of therapy for this round of AGW mixed. Most people (414/502 [82.5%]) enrolled had not had a previous episode of AGWs. It is stated “59 (11.8%) patients previously had one

	episode, 20 (4.0%) patients had two episodes, and nine (1.8%) patients had three or more episodes".		
Inclusion criteria	• Women and men, 18 years of age or older, with two to 30 clinically diagnosed external or perianal EGWs with a total wart area of 12–600 mm^2 were eligible. • Female patients with childbearing potential had negative pregnancy tests. Also, male patients and female partners of male patients with child bearing potential had to use effective contraception during the treatment period.		
Exclusion criteria	Patients were not enrolled if they: • had a current episode of herpes genitalis acute or chronic infection with hepatitis B or C virus, human immunodeficiency virus, any other current or recurrent genital or uncontrolled infection; • were former or current participants in an investigational trial; • had treatment of external anogenital warts or had systemic intake of virostatics (with the exception of systemic acyclovir and analogues) or immunosuppressive medication within 30 days prior to enrolment; • had organ allograft; • had skin conditions that may interfere with the study drug; • had internal (vaginal or rectal) warts that required treatment; • were breast-feeding.		
All outcomes reported in paper	Primary endpoint: complete clearance of all warts (new and baseline) within the 16-week treatment period. Other outcomes assessed: • Complete clearance of baseline warts; • Partial clearance (of at least 50%, and less than 50%, based on wart area); • Recurrence; • Development of new warts (during follow-up not treatment);		
Subgroups evaluated	Men versus women		
Stratification	Not reported		
Baseline measurement of disease	It is stated that warts were measured during screening and baseline visits. Locations of baseline and new warts as well as recurrent warts were recorded and distinguishably labeled on a dermagram. Photographs served to document wart clearance or progression.		
Treatment	**Sinecatechin 15% ointment**	**Sinecatechin 10% ointment**	**Placebo**
Randomised, N	196	202	104
Withdrawals (please specify reasons for withdrawal, including treatment discontinuation, and loss to follow-up; use different rows for	37 withdrawals 16 (8.2%) people withdrew consent 7 (3.6%) lack of efficacy/treatment failure	40 withdrawals 20 (9.9%) people withdrew consent 4 (2.0%) lack of efficacy/treatment failure	21 withdrawals 4 (3.8%) people withdrew consent 6 (5.8%) lack of efficacy/treatment failure

different reasons), n (%)	1 (0.2%) terminated because of an adverse event Other reasons for withdrawal not reported	0 (0%) terminated because of an adverse event Other reasons for withdrawal not reported	0 (0%) terminated because of an adverse event Other reasons for withdrawal not reported
Treatment regimen (duration of treatment, delivery, dose, formulation, and concomitant medications)	Presented in 15g aluminium tube – 1 tube for every 2 weeks of treatment. Trial staff supervised the initial application. Patients were instructed to apply the allocated ointment to all external warts three times daily, each application about 8 h apart until warts completely healed or for a maximum of 16 weeks. Control visits scheduled every 2 weeks. Concomitant medications allowed and recorded including oral paracetamol or acetaminophen prescribed for local skin reactions.		
Duration/number of administered treatment (i.e., mean length of or number of administrations of treatment, with SD/SE if given. If no mean presented, median values with ranges)	Not reported		

Baseline patient characteristics	**Sinecatechin 15% ointment**	**Sinecatechin 10% ointment**	**Placebo**	**p value**
Mean age, (with SD/SE if given), years (range)	31.2 (SD 12.26)	31.3 (SD 11.53)	32.5 (SD 12.95)	0.630
Duration of disease: mean time between start of current episode and start of treatment, weeks	44	55	48	
Site of AGW, n (%)	Baseline warts were mainly located on the vulva (207 [41.2%] female patients) and the penis shaft (185 [36.9%] male patients), followed by the perianal area (91 [18.1%] patients), perineal area (77 [15.3%] patients), and glans penis (59 [11.8%] male patients).			
Type of AGW (e.g., non-keratinised, keratinised), n (%)	Not reported			
Median number of AGWs	Not reported			

Median area of AGW (mm^2)	Not reported			
Sex (M/F), n (%)	Men: 100 (51.0) Women: 96 (49.0)	Men: 102 (50.5) Women: 100 (49.5)	Men: 56 (53.8) Women: 48 (46.2)	0.857
Any previous treatment, n (%)	Not reported			
Ethnicity, n (%)				
African	5 (2.6)	3 (1.5)	2 (1.9)	0.662
Asian	0 (0)	1 (0.5)	0 (0)	
White	57 (29.1)	67 (33.2)	29 (27.9)	
Hispanic	134 (68.4)	131 (64.9)	72 (69.2)	
Other	0 (0)	0 (0)	1 (1.0)	

Section 3: Outcomes	
Outcome	**Definition**
AGW clearance at completion of treatment	Complete clearance of all warts (new and baseline) within the 16-week treatment period. Also reports complete clearance of baseline warts alone within the 16-week treatment period.
AGW clearance at other time points	Not reported
Recurrence of AGW	Recurrence in those achieving complete clearance (evaluated over 12 weeks)
Time to complete clearance	Not reported
Volume of wart clearance (proportion of people with at least 50% clearance)	Partial clearance of AGWs of at least 50% and also less than 50% Wart clearance was determined as the percentage reduction of the wart area (ie, maximal wart length perpendicular to maximal wart width) at the final evaluation relative to the area when the wart was first detected.
Relief of symptoms during treatment	Not reported
Appearance of new warts during treatment	Not reported
Quality of life (trial scale used)	Not reported
Adverse events (please specify)	Local skin signs and symptoms
Malignancy	Not reported

Section 4: Data extraction form						
Outcome (delete outcomes not reported)	**Timeframe**	**Sinecatechin 15% ointment**	**Sinecatechin 10% ointment**	**Placebo**	**Estimate of effect**	**CI and p value**

Dichotomous outcomes									
		n	N	n	N	n	N		
AGW clearance at completion of treatment	16 weeks	111	194	111	197	35	104	15% ointment versus vehicle: OR 2.64 (1.61 to 4.33) 10% ointment versus vehicle: OR 2.55 (1.55 to 4.17)	LOCF analysis 15% ointment versus vehicle: p <0.001 10% ointment versus vehicle: p <0.001
AGW clearance of baseline warts	16 weeks	114	194	120	197	35	104	15% ointment versus vehicle: OR 2.81 (1.71 to 4.62) 10% ointment versus vehicle: OR 3.07 (1.87 to 5.05)	LOCF analysis 15% ointment versus vehicle: p <0.001 10% ointment versus vehicle: p <0.001
Recurrence of AGW	12 week follow-up	7	111	11	111	3	35		
Volume of wart clearance (proportion of people with at least 50% clearance of AGWs, but not complete)	16 weeks	41	194	34	196	18	103	P < 0.001 for both 15% and 10% ointment versus placebo, when complete responders included	
Volume of wart clearance (proportion of people with less than 50% clearance of AGWs)	16 weeks	32	194	32	196	31	103		

Adverse events									
Local skin reactions (signs and symptoms)	16 weeks	171	196	172	202	75	104		
Itching (severe)	16 weeks	28	196	30	202	2	104		
	Most local reactions were of mild to moderate intensity, with less severe reactions. The predominant severe local skin reaction was itching in all three treatment groups								
Adverse events other than local reactions	16 weeks	15	196	15	202	N/R	104		
The most frequently reported types of adverse events related to study medication were infections and infestations in 15 (3.0%) patients and blood and lymphatic system disorders in 10 (2.0%) patients. All other types of adverse event affected less than 2% of patients. Severe related adverse events were documented for 5 (2.6%) and 2 (1.0%) patients treated with sinecatechins ointment 15% and 10%, respectively, including lymphadenitis, skin ulcer, vulvitis, and vulvovaginitis. Vulvitis was the only case of primary reason for discontinuation due to an adverse event (except for pregnancies).									

Section 5: Clinical trial quality			
Outcome	**Risk of bias**	**Risk assessment[a]**	**Comments**
	Random sequence generation	✓	Randomization sequence generated by a random number generator using the method of permuted blocks (block size = 5).
	Allocation concealment	?	No information available on methods implemented to conceal allocation. The randomization list was never available to investigators or the project team. And it is stated that “Participating centers were provided with blinded medication kits that had a preassigned patient number, with each patient allocated to the lowest available number”. Also, patient randomization and initial dispensing of study medication were done at baseline followed by treatment initiation. Unclear how this allocation system works with random sequence generation.
	Selective reporting	✓	Outcomes referred to in methods are reported in text.
	‘Other Bias’	?	Insufficient information to assess
AGW clearance at completion of treatment	Blinding (participants & personnel)	?	Study described as double blind but no information available on who is masked. It is stated that “Vehicle was of identical

			color and consistency as sinecatechins ointments to ensure blinding". The 15%, 10%, or vehicle ointments were presented in 15-g aluminium tubes (one tube for 2 weeks of treatment) prepared by Haupt Pharma, Berlin, Germany.
	Blinding of outcomes assessment	?	Unclear whether outcome assessor is masked to treatment
	Incomplete outcome data	x	Not true ITT analysis but includes most people randomised. Number lost to follow-up is unclear. Total number of people withdrawing is high (~20%). Number of people withdrawing, together with reasons for withdrawal, is balanced across the groups. Designated high risk of bias because of high withdrawal rate.
Recurrence of AGW	Blinding (participants & personnel)	?	Study described as double blind but no information available on who is masked. It is stated that "Vehicle was of identical color and consistency as sinecatechins ointments to ensure blinding". The 15%, 10%, or vehicle ointments were presented in 15-g aluminium tubes (one tube for 2 weeks of treatment) prepared by Haupt Pharma, Berlin, Germany.
	Blinding of outcomes assessment	?	Unclear whether outcome assessor is masked to treatment.
	Incomplete outcome data	x	Not true ITT analysis but includes most people randomised. Number lost to follow-up is unclear. Number of people withdrawing is high (~20%). Number of people withdrawing, together with reasons for withdrawal, is balanced across the groups. Designated high risk of bias because of high withdrawal rate.
Volume of wart clearance (proportion of patients with at least 50% or less than 50% clearance)	Blinding (participants & personnel)	?	Study described as double blind but no information available on who is masked. It is stated that "Vehicle was of identical color and consistency as sinecatechins ointments to ensure blinding". The 15%, 10%, or vehicle ointments were presented in 15-g aluminium tubes (one

			tube for 2 weeks of treatment) prepared by Haupt Pharma, Berlin, Germany.
	Blinding of outcomes assessment	?	Unclear whether outcome assessor is masked to treatment
	Incomplete outcome data	x	Unclear how many people are included in the analysis: results presented as percentage with no absolute event rate.
Adverse events	Blinding (participants & personnel)	?	Study described as double blind but no information available on who is masked and how masking has been maintained
	Blinding of outcomes assessment	?	Unclear whether outcome assessor is masked to treatment
	Incomplete outcome data	x	Safety population includes most people randomised (excludes one person). Number lost to follow-up is unclear. Number of people withdrawing is high (~20%). Number of people withdrawing, together with reasons for withdrawal, is balanced across the groups. Designated high risk of bias because of high withdrawal rate.
Overall rating of bias		x	Designated as overall high risk of bias due to some concerns around level of withdrawal.

Section 6: Additional comments		
Additional comments		
Further information that could be requested from authors	***Methodological information***	
	Method of randomisation	×
	Level of masking (if masked, who was masked)	×
	Method for allocation concealment	×
	Method for maintaining masking during the trial	×
	Baseline characteristics	
	Mean and median age of people in each group (with accompanying measure of variation)	
	Breakdown by site of AGW in each group	
	Mean number and area of AGW at baseline in each group	
	Proportion of people with (i) single, (ii) few (2–5), or (iii) multiple (≥6) AGWs at baseline in each group	×
	Breakdown of type of AGW (non-keratinised vs keratinised) in each group	×
	Immune status (immunosuppressed vs not immunosuppressed) in each group	
	Any previous treatment	

	Ethnicity	
	Trial conduct	
	Was there a trial sponsor?	
	Did any of the authors have a conflict of interest?	×
	When was complete clearance was recorded?	
	Number of people lost to follow-up in each group	×
	Number of people who withdrew from each group, and reasons for withdrawal	
	Is the reported analysis based on an intention-to-treat population?	
	Any concomitant medications received in each group?	
	Did both groups receive the same care except for allocated treatment?	×
	Results	
	Complete clearance in each group based on subgroups of:	
	site of AGW	×
	number of AGW at baseline (subgroups of few [2–5] and multiple [≥6])	×
	type of AGW (non-keratinised vs keratinised)	×
	immune status (immunosuppressed vs not immunosuppressed)	
	Miscellaneous	
	Please clarify if partial clearance is based on wart count or wart area.	

[a] Key for risk assessment: ✓ = low risk of bias; **?** = unclear risk of bias; and **x** = high risk of bias.

Abbreviations used in table: AGW, anogenital wart; CI, confidence interval; n, number of patients with the outcome; N, number of patients assessed; QoL, quality of life; RCT, randomised controlled trial; SD, standard deviation; SE, standard error.