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Supplementary appendix

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A randomised placebo-controlled trial of mifepristone and misoprostol versus misoprostol alone for the management of missed miscarriage

Supplementary appendix

Table S1. Further Details of the Participants at Baseline		
Descriptive characteristic	**Mifepristone + Misoprostol (N = 357)**	**Placebo + Misoprostol (N = 354)**
Pregnancy history		
Live birth – no. (%)		
0	63/357 (18)	70/354 (20)
1	111/357 (31)	118/354 (33)
2	45/357 (13)	39/354 (11)
≥3	25/357 (7)	23/354 (7)
Stillbirth – no. (%)		
0	238/357 (67)	246/354 (69)
1	6/357 (2)	3/354 (1)
2	0/357 (-)	1/354 (<1)
Miscarriage – no. (%)		
0	120/357 (34)	121/354 (34)
1	62/357 (17)	77/354 (22)
2	29/357 (8)	24/354 (7)
≥3	33/357 (9)	28/354 (8)
Ectopic pregnancy – no. (%)		
0	231/357 (65)	241/354 (68)
1	13/357 (4)	9/354 (3)
Molar pregnancy – no. (%)		
0	244/357 (68)	249/354 (70)
1	0/357 (-)	1/354 (<1)
Termination – no. (%)		
0	191/357 (54)	192/354 (54)
1	44/357 (12)	45/354 (13)
2	7/357 (2)	10/354 (3)
≥3	2/357 (1)	3/354 (1)
Pregnancy of unknown location – no. (%)		
0	241/357 (68)	250/354 (71)
1	3/357 (1)	0/354 (-)
Demographic data		
Progesterone levels – nmol/L		
Mean (SD)	17·0 (4·2)	22·8 (12·8)
Not measured – no. (%)	355/357 (99)	350/354 (99)
Days from date of US diagnosing missed miscarriage to randomisation - days		
Mean (SD)	1·5 (3·3)	1·9 (4·6)
Medical history		
Diabetes – no. (%)		
Yes	4/357 (1)	7/354 (2)
No	352/357 (99)	347/354 (98)
Renal disease – no. (%)		
Yes	3/357 (1)	1/354 (<1)
No	353/357 (99)	353/354 (99)
Cardiac disease – no. (%)		
Yes	1/357 (<1)	1/354 (<1)
No	355/357 (99)	353/354 (99)
Chronic hypertension – no. (%)		
Yes	2/357 (1)	1/354 (<1)
No	354/357 (99)	353/354 (99)
Thyroid disease – no. (%)		
Yes	12/357 (3)	13/354 (4)
No	344/357 (96)	341/354 (96)

Cancer – no. (%)		
Yes	2/357 (1)	0/354 (-)
No	354/357 (99)	354/354 (100)
Other – no. (%)		
Yes	46/357 (13)	44/354 (12)
No	310/357 (87)	310/354 (88)

Note: Missing data are <1% unless otherwise presented.

Table S2. Description of interventions		
Descriptive characteristic	**Mifepristone + Misoprostol (N = 357)**	**Placebo + Misoprostol (N = 354)**
Mifepristone or placebo taken – no. (%)		
Yes	354/357 (99)	350/354 (99)
No	2/357 (1)	4/354 (1)
If no, reason:		
Woman changed her mind	2/2 (100)	3/4 (75)
Sac already passed	0/2 (-)	0/4 (-)
Other[1]	0/2 (-)	1/4 (25)
Misoprostol taken – no. (%)		
Yes	321/357 (90)	334/354 (94)
No	35/357 (10)	20/354 (6)
If no, reason:		
Woman changed her mind	0/35 (-)	0/20 (-)
Woman did not attend hospital	3/35 (9%)	0/20 (-)
Sac already passed	27/35 (77%)	16/20 (80%)
Other[2]	5/35 (14%)	4/20 (20%)
If Yes, route of administration of first dose of misoprostol – no. (%)		
Per vaginal	286/321 (89)	299/334 (90)
Per os	30/321 (9)	28/334 (8)
Sublingual	5/321 (2)	7/334 (2)
Additional doses of misoprostol taken – no. (%)		
Yes	50/357 (14)	65/354 (18)
1 additional dose	40/50 (80)	51/65 (78)
2 additional doses	7/50 (14)	12/65 (18)
≥3 additional doses	3/50 (6)	2/65 (3)
Mean number of additional doses (SD)	1·3 (0·7)	1·3 (0·6)
Median number of additional doses [IQR]	1 [1 - 1]	1 [1 - 1]
No	271/357 (76)	269/354 (76)
First dose not taken	35/357 (10)	20/354 (6)
If Yes, route of administration of first additional dose – no. (%)		
Per vaginal	36/50 (72)	46/65 (71)
Per os	7/50 (14)	11/65 (17)
Sublingual	7/50 (14)	8/65 (12)
If Yes, dose of first additional dose (mcg)		
Mean (SD, N)	656·0 (185·3, 50)	692·3 (169·8, 65)
Median [IQR]	800 [400 – 800]	800 [600 – 800]
If Yes, days since mifepristone/placebo of first additional dose – no. (%)		
Mean (SD,N)	6.7 (6.6, 50)	6.2 (6.8, 64)
Median [IQR]	4 [3 - 7]	4 [4 - 7]

[1] Participant wanted to take the trial treatment on a different day, but was not able to come back to the hospital to collect it, and declined having the treatment delivered to her address.

[2] (Mifepristone + Misoprostol) (1) Participant changed her mind and opted for surgical management; (2) Participant went for surgery due to heavy bleeding; (3) Participant experienced very heavy bleeding and abdominal cramps so she contacted the early pregnancy unit for advice and was told NOT to take the misoprostol tablets, as likely sac already passed; (4) Participant started to bleed heavily at 08:00am. Reviewed by doctor and consultant. Clinical advice was that there was no need for misoprostol and scan would be of no consequence today. Patient returned for day 7 scan as per protocol for study; (5) Participant attended A&E with heavy blood loss and pain, opted for surgical intervention. Requested no further medical management. (Placebo + Misoprostol) (1) Participant called early pregnancy unit on 07/03/2018 to say she has been having heavy bleeding and passing clots. Misoprostol cancelled, participant attended for her scan; (2) Participant was admitted on the 23/03/2018 due to heavy and uncontrollable bleeding. Went to surgery straight as she almost collapsed; (3) Participant experience heavy vaginal bleeding 24 hours after taking mifepristone/placebo and required

surgical management of miscarriage therefore misoprostol not given; (4) Participant stated she has passed the fetus at home this morning.

Note: Missing data are <3% unless otherwise presented.

Table S3. Adherence		
Outcome	**Mifepristone + Misoprostol (N=357)**	**Placebo + Misoprostol (N=354)**
Number adherent with treatment regimen[1]	337/357 (94)	341/354 (96)
Number non-adherent	20/357 (6)	13/354 (4)

[1] Defined as taking the allocated mifepristone or placebo on day 0 and subsequently misoprostol on day 2 unless the gestational sac has been passed before the scheduled time for misoprostol; in the latter case, the patient will be deemed to be adherent to the trial medication as long as the allocated mifepristone or placebo is taken on day 0.

Table S4. Primary Outcome Sensitivity Analysis - Excluding women requiring primary outcome information provided by Blinded Endpoint Review Committee (BERC)

Outcome	Mifepristone + Misoprostol (N = 357)	Placebo + Misoprostol (N = 354)	Estimate[1] (95% CI)	P-value
Primary outcome				
Failure to pass the gestational sac spontaneously within 7 days after randomisation – no. (%)	59/329 (18)	81/333 (24)	0·75 (0·55-1·02)	0·06
Assessed by BERC and excluded from this analysis	19	15		
Missing	9	6		

[1] Value <1 favours Mifepristone plus Misoprostol combination group. The risk ratio was adjusted for minimisation variables: maternal age, body mass index, previous parity, gestational age and amount of bleeding. The clustering effect of randomising centres was accounted for by using robust standard errors at centre level.

Table S5. Adverse side effects and Serious Adverse Events				
Outcome	**Mifepristone + Misoprostol (N=357)**	**Placebo + Misoprostol (N=354)**	**Estimate[1] (95% CI)**	**P-value**
Adverse side effects[2,3]	26/357 (7)	24/354 (7)	1·08 (0·64-1·84)	0·76
Requirement for a blood transfusion[2]	11/352 (3)	5/351 (1)	2·19 (0·75-6·39)[5]	0·15
Serious adverse events[2,4]	5/357 (1)	2/354 (1)	2·48 (0·47-13·07)[5]	0·28
Death	0/357 (-)	0/354 (-)	-	-

[1] Value <1 favours Mifepristone plus Misoprostol combination group. The risk ratio was adjusted for minimisation variables: maternal age, body mass index, previous parity, gestational age and amount of bleeding. The clustering effect of randomising centres was accounted for by using robust standard errors at centre level.

[2] Collected up to discharge.

[3] Total number of women experiencing at least one adverse side effect.

[4] Total number of women experiencing at least one serious adverse event.

[5] Unadjusted model used due to non-convergence.

Note: Missing data are <3% unless otherwise presented.