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Supplementary appendix 6

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Appendix 6

Section 1: Detailed methods for non-inferiority analysis

To identify the most appropriate comparator studies, we conducted a literature review of peer-reviewed research on clinical effectiveness of the medication regimens used in the SAFE study (Table 1). We identified three comparison clinical trials that studied the same combined regimen used in the SAFE study (pooled n=951)[25-27], and one comparison clinical trial that studied the same misoprostol alone regimen studied in the SAFE study (n=512)[24]. These four comparison studies served as the historical controls for the non-inferiority analysis. For the non-inferiority analysis, we calculated the difference (D) in the proportion of those with complete abortions in the SAFE sample (p_T), as compared to the pooled proportion of participants with complete abortions in historical controls (p_C), clustered by study, and assessed whether the difference was less than or equal to 5%, the pre-specified margin of interest (δ).[37-39] We then computed a one-sided 95% confidence interval for this difference in proportions ($p_C - p_T$). The one-sided upper confidence bound for the difference is given by:

$$UB = \hat{p}_C - \hat{p}_T + z_{1-\alpha}\sqrt{\frac{\hat{p}_T(1-\hat{p}_T)}{n_T} + \frac{\hat{p}_C(1-\hat{p}_C)}{n_C}}$$

where $\hat{p}_C$ and $\hat{p}_T$ are the observed proportions of success in the clinical control arm and SAFE study arm respectively; n_C and n_T are the sample sizes of the corresponding groups, and $z_{1-\alpha}$ is the $(1-\alpha)$-percentile of a standard normal distribution.[37-39] We rejected the null hypothesis of the *inferiority* of self-managed medication abortion, and accepted the alternative hypothesis of the *non-inferiority* of self-managed medication abortion compared to clinically managed medication abortion, if UB $\leq \delta$.

Section 2a. Medication sourcing among 961 participants recruited from callers to abortion accompaniment groups in Argentina and Nigeria in 2019-2020, who completed at least one follow-up.

		Mife+Miso		Misoprostol alone		Unknown	
		n	%	n	%	n	%
N in follow-up		*356*	*100*	*593*	*100*	*12*	*100*
Details of obtaining pills at one-week follow-up	**Have you gotten the pills yet?**						
	No	0	0.0	0	0.0	7	58.3
	Yes	325	91.3	592	99.8	5	41.7
	Missing at one-week	31	8.7	1	0.2	0	0.0
	How were the pills packaged? (select all that apply)						
	Loose pills	2	0.6	78	13.2	0	0.0
	Blister pack	6	1.9	514	86.8	2	40.0
	Other (primarily "envelope")	317	97.5	0	0.0	3	60.0
	Have you taken the pills yet?						
	Yes	325	91.3	592	99.8	2	16.7
	No	0	0.0	0	0.0	4	33.3
	Missing at one-week	31	8.7	1	0.2	6	50.0
	Reasons for not taking the pills						
	Decided to continue the pregnancy	0	0.0	0	0.0	3	25.0
	Decided to get an MVA	0	0.0	0	0.0	1	8.3
	Missing	0	0.0	0	0.0	8	66.7

Section 2b. Medication utilization among 951 participants recruited from abortion accompaniment groups in Argentina and Nigeria in 2019-2020, who completed at least one follow-up and reported taking pills.

		Mife+Miso		Misoprostol alone		Unknown	
		n	%	n	%	n	%
Medication Regimen							
First Dose	*Medication, 1st dose*						
	Mifepristone	356	100.0	0	0.0	0	0.0
	Misoprostol	0	0.0	593	100.0	0	0.0
	Unknown	0	0.0	0	0.0	12	100.0
	Number of pills taken, 1st dose						
	1	356	100.0	8	1.3	0	0.0
	2	0	0.0	10	1.7	1	8.3
	3	0	0.0	17	2.9	1	8.3
	4	0	0.0	558	94.1	0	0.0
	Route of Administration, 1st Dose						
	Buccal	1	0.3	0	0.0	0	0.0
	Oral	354	99.4	6	1.0	1	8.3
	Sublingual	1	0.3	583	98.5	0	0.0
	Vaginal	0	0.0	3	0.5	0	0.0
	Other	0	0.0	1	0.2	1	8.3
Second Dose	*Medication, 2nd dose*						
	Mifepristone	3	0.8	0	0.0	0	0.0
	Misoprostol	353	99.2	592	99.8	1	8.3
	Missing	0	0.0	1	0.2	11	91.7
	Number of pills taken, 2nd dose						
	1	3	0.8	6	1.0	0	0.0
	2	4	1.1	14	2.4	1	8.3
	3	0	0.0	9	1.5	1	8.3
	4	349	98.0	562	94.8	0	0.0
	Route of Administration, 2nd Dose						
	Buccal	5	1.4	0	0.0	0	0.0
	Oral	3	0.8	6	1.0	1	8.3
	Sublingual	274	77.0	584	98.5	0	0.0
	Vaginal	74	20.8	1	0.2	0	0.0
	Other	0	0.0	1	0.2	1	8.3
	Missing	0	0.0	1	0.2	10	83.3
Third Dose	*Medication, 3nd dose*						
	Mifepristone	1	0.3	0	0	0	0
	Misoprostol	22	6.2	573	96.6	1	8.3
	Missing	0	0	20	3.4	1	8.3
	Number of pills taken, 3rd dose						
	1	1	0.3	4	0.7	0	0.0
	2	22	6.2	12	2	1	8.3
	3	0	0	7	1.2	1	8.3
	4	0	0	546	92.1	0	0.0
	5	0	0	1	0.2	0	0.0
	Missing	0	0.0	23	3.9	10	83.3
	Route of Administration, 3nd Dose						
	Buccal	1	0.3	0	0	0	0.0
	Oral	1	0.3	5	0.8	1	8.3
	Sublingual	21	5.9	568	95.8	0	0.0
	Vaginal	0	0	0	0	0	0.0
	Other	0	0	0	0	1	8.3
	Missing	0	0	20	3.4	10	83.3

Section 3. Factors that influenced self-report of abortion completion at last follow-up among 951 participants recruited from abortion accompaniment groups in Argentina and Nigeria in 2019-2020, who completed at least one follow-up and reported taking pills.

Factors that influenced self-report of abortion completion at last follow-up	Any regimen (n=951)		Mifepristone + Misoprostol (n=356)		Misoprostol alone (n=593)	
	n	%	n	%	n	%
Among those who felt their abortion was complete (n=939):						
Pregnancy symptoms went away	709	75.5	235	67.5	471	79.4
I felt the pregnancy come out	616	65.6	239	68.7	377	63.6
Negative pregnancy test, home	175	18.6	0	0.0	175	29.5
I saw the gestational sac	165	17.6	164	47.1	1	0.2
Counselor told me I was no longer pregnant	137	14.6	135	38.8	2	0.3
Negative pregnancy test at facility, blood	93	9.9	3	0.9	89	15
Ultrasound	67	7.1	43	12.4	24	4.0
Doctor/nurse told me I was no longer pregnant	63	6.7	60	17.2	3	0.5
Negative pregnancy test at facility, urine	25	2.7	0	0.0	24	4.0
Return of menses	16	1.7	0	0.0	16	2.7
Amount/nature of bleeding experienced	8	0.9	0	0.0	8	1.5
Body awareness/internal sense	5	0.5	0	0.0	5	0.8
Other	2	0.2	1	0.3	1	0.2
Among those who felt their abortion was NOT complete or were unsure of completion (n=10):						
I did not feel the pregnancy come out	3	30.0	3	37.5	0	0.0
Have not had time to confirm with test or ultrasound	2	20.0	1	12.5	1	50.0
I did NOT see the gestational sac	1	10.0	1	12.5	0	0.0
Doctor/nurse told me I was STILL pregnant	1	10.0	1	12.5	0	0.0
Bleeding is ongoing	1	10.0	0	0.0	1	50.0
I was expecting to see more blood	1	10.0	1	12.5	0	0.0
Missing	2	20.0	2	25.0	0	0.0

Section 4. Healthcare seeking during or after self-managed abortion among 192 participants recruited from callers to abortion accompaniment groups in Argentina and Nigeria in 2019-2020.

	All participants		Mife+Miso		Misoprostol alone	
	n	%	n	%	n	%
Sought health care at any point in follow-up	192	20.0	120	33.7	71	12.0
Reasons for seeking healthcare (% given among those who sought HC)						
To confirm completion of abortion	157	81.8	90	75.0	66	93.0
Concern about pain	12	6.3	11	9.2	1	1.4
Concern about bleeding	12	6.3	11	9.2	1	1.4
Concern about discharge	5	2.6	3	2.5	2	2.8
Concernt about fever	5	2.6	4	3.3	1	1.4
Concern about nausea	2	1.0	2	1.7	0	0.0
Concern about diarrhea	0	0.0	0	0.0	0	0.0
For a manual vacuum aspiration (MVA)	1	0.5	1	0.8	0	0.0
For a dilation & curetage (D&C)	0	0.0	0	0.0	0	0.0
For another reason	12	6.3	9	7.5	3	4.2
Treatment received (% given among full sample)						
Ultrasound	80	8.4	63	17.7	17	2.9
Pain medications	25	2.6	21	5.9	4	0.7
Kept for observation only	23	2.4	20	5.6	3	0.5
Intravenous fluids	19	2.0	17	4.8	2	0.3
Antiobiotics	16	1.7	12	3.4	4	0.7
Manual Vacuum Aspiration (MVA)	15	1.6	12	3.4	3	0.5
Other medications (not for pain or infection)	12	1.3	10	2.8	2	0.3
Stayed overnight	12	1.3	10	2.8	2	0.3
Additional misoprostol	7	0.7	6	1.7	1	0.2
Blood transfusion	6	0.6	6	1.7	0	0.0
Dilation & curettage (D&C)	2	0.2	2	0.6	0	0.0
Not listed	8	0.8	4	1.1	4	0.7

Section 5. Details for historical control studies included in the non-inferiority analysis.

To construct the non-inferiority control cohort, we utilized published data from four historical clinical studies that evaluated either of the two medication abortion regimens studied in the SAFE study. For mifepristone and misoprostol, this was 200mg of misoprostol orally, followed 24-48 hours later by 800ug misoprostol sublingually. For misoprostol only, the regimen was three doses of 800ug of misoprostol administered sublingually every 3 hours. In this appendix, we report the citation information and Table 1 for each included historical control study, as well as a constructed table directly comparing key participant and pregnancy characteristics between historical control samples and the SAFE study samples by medication regimen.

Misoprostol-alone historical control study:

1. Von Hertzen H, Piaggio G, Huong NT, Arustamyan K, Cabezas E, Gomez M, Khomassuridze A, Shah R, Mittal S, Nair R, Erdenetungalag R. Efficacy of two intervals and two routes of administration of misoprostol for termination of early pregnancy: a randomised controlled equivalence trial. The Lancet. 2007 Jun 9;369(9577):1938-46.

Study setting: 11 obstetrics and gynaecology departments in teaching hospitals in Yerevan, Armenia; Havana, Cuba; Tbilisi, Georgia; Mumbai, New Delhi, and Trivandrum, India; Ulaanbaatar, Mongolia; and Hanoi and Ho Chi Minh City, Vietnam.

Table 1. Baseline characteristics for all participants enrolled

	Sublingual 3 h (n=517)
Demographic and physical	
Age (years)	26·7 (5·8)
Weight (kg)	53·2 (10·0)
Haemoglobin (g/L)	119·2 (11·4)
Ethnic group	
Chinese	47 (9%)
Non-Chinese Asian or black	318 (62%)
White	152 (29%)
Obstetric and gynaecological history	
Nulliparity	223 (43%)
Previous abortion	184 (36%)
Gestational age* (days)	
29–49	245 (47%)
50–56	144 (28%)
57–63	128 (25%)
Median (IQR)	50 (43–56)

Data are number (%) or mean (SD) unless otherwise indicated.
* Gestational age assessed by ultrasound

Mifepristone + Misoprostol historical control studies:

1. Tang OS, Xu J, Cheng L, Lee SW, Ho PC. Pilot study on the use of sublingual misoprostol with mifepristone in termination of first trimester pregnancy up to 9 weeks gestation. Hum Reprod. 2002;17(7):1738-40. DOI: 10.1093/humrep/17.7.1738.

Study setting: Hong Kong and Shanghai, China

Table 1. Demographic characteristics of the 100 women who underwent medical abortion with sublingual misoprostol (mean + SD)

Characteristic	
Age (years)	25.2 $\pm$ 4.9
Weight (kg)	52.0 $\pm$ 6.4
Height (cm)	161.1 $\pm$ 5.7
Gestational age (weeks)	7.87 $\pm$ 1.1
Number (%) of parous women	29 (29)
Number (%) of women with history of abortion	45 (45)

2. Tang OS, Chan CC, Ng EH, Lee SW, Ho PC. A prospective, randomized, placebo-controlled trial on the use of mifepristone with sublingual or vaginal misoprostol for medical abortions of less than 9 weeks gestation. Hum Reprod. 2003;18(11):2315-8. DOI: 10.1093/humrep/deg475.

Study setting: Hong Kong

Table 1. Demographic characteristics of the 224 women who underwent medical abortion

	Sublingual (n=112)
Age (years)*	23.5 (5.8)
Weight (kg)*	49.6 (6.5)
Height (cm)*	159.1 (4.8)
Gestational age (weeks)*	7.7 (0.9)
No. of women $\leq$ 7 weeks	29 (25.9)
No of women > 9 weeks	83 (74.1)
Number (%) of parous women	17 (15.2)
Number (%) of women with history of termination of pregnancy	35 (31.3)

* Values are mean (SD)

3. von Hertzen H, Huong NT, Piaggio G, Bayalag M, Cabezas E, Fang AH, et al. Misoprostol dose and route after mifepristone for early medical abortion: a randomised controlled noninferiority trial. BJOG. 2010;117(10):1186-96. DOI: 10.1111/j.1471-0528.2010.02636.x.

Study setting: 15 obstetrics and gynecology departments at teaching hospitals in Hong Kong and Shanghai, China; Havana (two hospitals), Cuba; Tbilisi, Georgia; Mumbai, New Delhi and Trivandrum, India; Ulaanbaatar, Mongolia; Clug Napoca, Romania; Ljubljana, Slovenia; Stockholm, Sweden; Bangkok, Thailand; and Hanoi and Ho Chi Minh City, Vietnam.

Table 1. Baseline characteristics of subjects by group

	800ug sublingual n=752
Demographic and physical	
Age (years) [mean (SD)]	26.6 (6.0)
Weight (kg) [mean (SD)]	55.3 (10.3)
Haemoglobin (g/L) [mean (SD)]	122.1 (12.0)
Ethnic group [n (%)]	
Chinese	166 (22.1)
Asian and Blacks	372 (49.5)
Caucasian	214 (28.5)
Parity [n (%)]	
Parous	410 (54.5)
Previous abortion [n (%)]	
Yes	318 (42.3)
Gestational age* (days) [n (%)]	
≤49	265 (35.2)
50–56	273 (36.3)
57–63	214 (28.5)

Comparison of SAFE cohorts and non-inferiority control cohorts on participant age and duration of pregnancy

Misoprostol-alone cohorts		
Participant age	**Mean**	**SD**
SAFE	28.7	5.8
vonHertzen 2007	26.7	5.8
Duration of pregnancy	**Median**	**IQR**
SAFE	42	37-48
vonHertzen 2007	50	43-56
Mifepristone + Misoprostol Cohorts		
Participant age	**Mean**	**SD**
SAFE	27.8	6.2
Tang 2002	25.2	4.9
Tang 2003	23.5	5.8
vonHertzen 2010	26.6	6.0
Duration of pregnancy	**Mean**	**SD**
SAFE	7.0	1.3
Tang 2002	7.8	1.1
Tang 2003	7.7	0.9
vonHertzen 2010*		**%**
<7 weeks		35.20%
8 weeks		36.30%
9 weeks		28.50%

** Mean duration of pregnancy not reported in this paper.*

Section 6. Abortion completion among 779 SAFE study participants with pregnancies <9 weeks gestation as compared to abortion completion among 1,463 historical clinical trial study participants with pregnancies <9 weeks gestation

Medication Regimen	Clinical setting vs self-managed	Study	Abortion completion	Pooled completion [95% CI]	Risk difference for complete abortion between clinically-managed vs self-managed medication abortion [95% CI]
Mifepristone + Misoprostol	Clinical	Tang 2002	94.0%	94.4% [92.3%, 95.8%]	-1.9% [-4.6%, 0.7%]
	Clinical	Tang 2003	98.2%		
	Clinical	VonHertzen 2010	93.9%		
	Self-managed	SAFE 2019-2020	96.4%	96.4% [93.4%, 98.2%]	
Misoprostol alone	Clinical	VonHertzen 2007	84.2%	84.2% [80.7%, 87.2%]	-14.8% [-18.1%, -11.6%]
	Self-managed	SAFE 2019-2020	99.0%	99.0% [97.7%, 99.7%]	