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Adherence in a pragmatic randomized controlled trial on prophylactic iron supplementation during pregnancy in Maputo, Mozambique

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Abstract

Objective: Assessing the level of adherence and its determinants is important in appraising the overall effectiveness of trials. The present study aimed to evaluate the extent of adherence and its determinants in a pragmatic randomized controlled trial of Fe prophylaxis during pregnancy in Maputo, Mozambique.

Design: A pragmatic randomized controlled trial.

Setting: Two health centres (1º de Maio and Machava) in Maputo, Mozambique.

Subjects: Pregnant women (≥12 weeks' gestation, ≥18 years old, non-high-risk pregnancy; *n* 4326) attending prenatal care consultations at two health centres were randomized to receive routine Fe (*n* 2184; 60 mg ferrous sulfate plus 400 μg folic acid daily throughout pregnancy) or selective Fe (*n* 2142; screening and treatment for anaemia and daily intake of 1 mg folic acid).

Results: The level of adherence was 79 % for having two or more visits, 53 % for adequate prenatal care and 67 % for complete intake of Fe/folic acid tablets during the trial. The correlation between the adherence measures ranged between 0·151 and 0·739. Adherence did not differ by trial arm, but there were centre differences in adequate prenatal visits and intake of tablets. Older women (>20 years) and those with a history of abortion were more likely to achieve greater adherence, whereas an increased number of previous births decreased the likelihood of adherence. HIV positivity decreased the likelihood of adherence in one trial centre and increased it in the other.

Conclusions: The variation in adherence by trial centre, women's characteristics and outcome measures suggests that adherence in trials fully depends on participants' behaviour and can be increased by paying attention to contextual factors.

Keywords
Adherence
Iron prophylaxis
Pregnancy
HIV
Pragmatic trial
Mozambique

Adherence in trials is important because it can serve both as an indicator of the success of the intervention and as a predictor of study outcomes[1–3]. Adherence is generally defined as the extent to which a patient follows advice regarding health, such as taking medication, modifying risky habits and keeping scheduled medical appointments[1,3]. Extensive research has been undertaken to study the level of adherence and its impact on health outcomes in trials of various health interventions. In developing country settings, most studies on trial adherence have focused on antiretroviral therapy for HIV[4–6].

There are however limited data on the extent of adherence in trials of interventions other than HIV therapy in developing countries. In these settings, health-care systems are inadequate, with several structural difficulties that impede health programme implementation and accessibility[7,8]. Consequently, achieving adequate follow-up of study participants and ensuring their optimal adherence to medications and the trial protocol are challenging.

Fe-deficiency anaemia remains common in many developing countries[9–11]. While prophylactic Fe supplementation has been shown to ameliorate Fe-deficiency anaemia in these settings[12], its effect on the mother and child has so far yielded mixed findings[5,13]. There is evidence that Fe may increase the incidence of infections[13–15], and this heightens the concern about routine Fe supplementation in malaria-endemic and HIV-prone developing countries. We set out to evaluate the effects of prophylactic Fe

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supplementation during pregnancy on maternal and child health in Maputo, Mozambique, a malaria-endemic and HIV-prevalent setting[13,16]. Specifically, we carried out a pragmatic randomized controlled trial comparing routine Fe prophylaxis (i.e. routine Fe supplementation from the first prenatal visit until delivery) *v.* selective Fe prophylaxis (i.e. screening for anaemia and Fe supplementation only to those found to be anaemic) during pregnancy[13,16]. Pragmatic trials are useful for comparing and informing choices between different treatment policies and are more suitable to study effects in normal clinical practice. In these types of trial design, placebo and blinding are not customary[17–19]. The trial provided us with an opportunity to learn more about adherence in this setting.

An objective of the trial was to evaluate whether the two Fe administration policies are feasible in an ordinary health-care setting. Evaluating the level of adherence to trials of Fe supplementation and assessing potential determinants of adherence may constitute a key step in ascertaining the effectiveness of prophylactic Fe supplementation[20]. Several studies in real life have shown that maternal educational status, age, socio-economic status, forgetfulness, perceived side-effects of medications, medication delivery mechanisms, nutritional status and risky behaviours such as smoking and alcohol intake were some of the main determinants of adherence to Fe or other multivitamin supplementation, particularly in developing country settings[20–23]. The aim of the present paper was to examine the extent of participants' adherence to the trial and to assess the factors that may influence adherence.

Methods

Study design and participants

The details of the PROFEG Trial have been described elsewhere[13,16]. The trial was designed as a pragmatic randomized trial comparing two Fe administration policies on maternal and child health in two health centres (1° de Maio and Machava) in Maputo: routine Fe (Fe prophylaxis from the first to the last prenatal visit) *v.* selective Fe (screening and treatment for anaemia). Women who were not at high obstetric risk and those aged 18 years and older were included in the study. Altogether, 2184 women were randomized to the routine Fe group and 2142 women to the selective Fe group. The routine Fe group received 30 tablets (supply of one month) of 60 mg elemental Fe as ferrous sulfate plus 400 μg folic acid per day, while those in the selective Fe group received 30 tablets of 1 mg folic acid per day, calculated to last to the next visit; the recommended frequency of visits was once per month.

At each visit, the women were instructed and encouraged to take the Fe/folic acid tablets they were given. The Hb of women in the selective Fe group was measured at each visit using a rapid Hb measure, HemoCue® Hb 201+ (Hemocue AB, Ängelholm, Sweden). If their Hb level was below the cut-off of <9 g/l, they received a monthly double dose of Fe (60 mg + 60 mg) for the treatment of anaemia. The tablets were given in a plastic bag with the drug's name and dose on it.

Ethical approval for the study was obtained from the Mozambique Ministry of Health Ethics Committee and a positive statement was obtained from the National Institute for Health and Welfare, Helsinki, Finland. The trial is registered at ClinicalTrials.gov, number NCT00488579 (June 2007). The first women were randomized to the trial proper between April 2007 and March 2008. The pilot was carried out between November 2006 and March 2008. The 3-month lag was due to technical difficulties in completing the trial registration.

Data collections for the study were done using standard study data forms involving three methods: (i) study nurses abstracted data from mothers' maternity cards; (ii) study nurses asked women additional questions at the time of the prenatal visits; and (iii) researchers later collected birth data from hospital birth records. Only data during pregnancy are used in the current paper. The study women were identified by the colour of the identification card stapled to their maternity card.

Adherence

Three measures of adherence were used: (i) acceptable number of prenatal visits; (ii) adequate prenatal visits index; and (iii) adequacy of intake of Fe/folic acid tablets during the trial. Women having two or more visits (including the recruitment visit) were categorized as having an acceptable number of visits. An adequate prenatal visits index was calculated by using the Adequacy of Prenatal Care Utilization (APNCU) index[24]. The APNCU index takes into account the gestational age at the initiation of care, the number of expected prenatal care visits and the number of observed visits. Here we categorized the adequate prenatal visits index into two: inadequate care (i.e. started prenatal visits after the 5th month or ≤50 % of expected visits made) *v.* adequate care (i.e. started prenatal visits before or at the 5th month and >50 % of expected visits made). The information on prenatal visits was obtained from the nurses' confirmation of a visit recorded on mothers' maternity cards.

Adequate adherence with regard to intake of Fe/folic acid tablets was defined as the intake of tablets reported at every visit attended by the woman. The woman was asked the following questions at each visit: 'Did you take the tablets during the past week?', with response options of 'regularly', 'sometimes yes and sometimes no' and 'no'. Women answering 'regularly' at each visit attended were defined as compliant. Women taking the Fe tablets were not differentiated from those taking the folic acid tablets in this question.

Statistical analysis

Women who were at 34 weeks' gestation or more at the recruitment visit (*n* 134) were excluded from all analyses,

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as most can be expected to have given birth before they could return for the next follow-up visit. Descriptive analysis was done using Pearson's χ^2 or Fisher's exact test. The bivariate correlations between the adherence measures were analysed using Pearson's correlations.

We applied logistic regression to study the determinants of adherence. The covariates studied were maternal age, previous births, history of abortion (induced or spontaneous), history of stillbirth and HIV status at enrolment. Each of the covariates was independently studied in a bivariate analysis in relation to each outcome. To examine the most important determinants of adherence, we applied stepwise logistic regression by including together all the variables that achieved a P value of ≤0·20 in the bivariate association with each of the adherence measures. All the variables that remained at the last stage of the stepwise model were simultaneously adjusted. The estimates for the determinants of adherence are presented as odds ratios accompanied by their 95 % confidence intervals. Statistical significance was taken as $P < 0{\cdot}05$. The STATA 11 statistical software package was used for the analyses.

Results

Of the 4326 women recruited to the trial, 2184 were randomly allocated to the routine Fe group and 2142 to the selective Fe group. After exclusion of the 134 women who were at 34 weeks' gestation or more at enrolment, 2126 and 2066 women were in the routine and selective Fe groups, respectively. In each study centre, the distribution of the background characteristics was comparable between the two groups (Table 1). Women in the Machava study centre were significantly older, more likely to have HIV infection at enrolment, had more previous births and were more likely to have a stillbirth than women in the 1° de Maio centre (data not shown).

Table 2 compares the adherence measures between the routine and selective Fe groups in each study centre. Most women (at least 92 % of all women) had two or more prenatal visits during the trial period and about half had adequate prenatal care. Most women took the Fe/folic acid tablets regularly at each follow-up visit, but 67 % of all women had regular intake of tablets throughout all visits. Each adherence measure was equally distributed between the trial groups in each centre. The number of prenatal visits was not statistically significantly different between the centres, but women attending the Machava study centre were more likely to have an adequate prenatal visits index than those from the 1° de Maio study centre. Women attending the 1° de Maio study centre were more likely to take the tablets than women who attended the Machava study centre.

The overall correlation coefficient between the number of visits and regular intake of tablets was low (0·151), while between an adequate prenatal visits index and regular intake of tablets, it was 0·203 (Table 3). The correlation between number of visits and adequacy of prenatal care seemed to measure the same thing, with a correlation coefficient of 0·739 (Table 3).

Table 4 shows the results of the bivariate analysis between each studied covariate and having two or more visits during the trial, for the two study centres combined and stratified by centre. Combining study centres, women ≥30 years old were more likely to have two or more prenatal visits compared with women aged ≤20 years. These results were similar in the two study centres when taken separately. Combining the study centres, women having had one previous birth were less likely to have two or more visits when compared with women who had no previous birth. These results were similar in the 1° de Maio centre but differed in the Machava centre, so that having two or more previous births increased the likelihood of having two or more visits. HIV positivity at recruitment was associated with less likelihood of having two or more visits. Having a previous abortion (induced or spontaneous) was positively associated with having two or more prenatal visits. Previous history of stillbirth was not statistically significantly associated with having two or more visits. The stepwise regression model examined the important determinants of having two or more visits while adjusting for the covariates. According to the model, increasing maternal age and having previous abortions increased the likelihood of having two or more visits, while having one or more previous births and HIV positivity decreased the likelihood (Table 4).

Table 5 shows the results of the associations between the covariates and the adequate prenatal visits index, for the two study centres combined and stratified by centre. In the Machava centre separately and in the study centres combined, women ≥30 years old were more likely to have an adequate prenatal visits index compared with women aged ≤20 years. When combining the study centres, women having had one previous birth were less likely to have an adequate prenatal visits index compared with women who had no previous birth. These results were similar in both study centres. HIV positivity at recruitment was associated with less likelihood of having an adequate prenatal visits index in both centres combined and each centre separately. Having had a previous abortion (induced or spontaneous) was positively associated with having adequate prenatal visits in the two centres combined and in the Machava centre but not the 1° de Maio centre separately. Previous history of stillbirth was not statistically significantly associated with the adequate prenatal visits index. In the stepwise regression model and after adjustments, increasing maternal age and having previous abortions increased the likelihood of an adequate prenatal visits index, while having one or more previous births and HIV positivity decreased the likelihood (Table 5).

Table 6 shows the results of the associations between each studied covariate and regular intake of tablets during

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Table 1 Characteristics of women by trial arm and study centre in the PROFEG Trial, a pragmatic randomized controlled trial of iron prophylaxis during pregnancy in Maputo, Mozambique

			1° de Maio					Machava				
	All (*n* 4192)		Selective (*n* 1318)		Routine (*n* 1350)			Selective (*n* 748)		Routine (*n* 776)		
Characteristic	*n*	%	*n*	%	*n*	%	*P* value*	*n*	%	*n*	%	*P* value*
Maternal age (years)							0·342					0·141
≤20	1140	27·2	366	27·8	415	30·7		179	23·9	180	23·2	
21–25	1555	37·1	526	39·9	490	36·3		267	35·7	272	35·1	
26–29	734	17·5	209	15·9	219	16·2		154	20·6	152	19·6	
≥30	730	17·4	204	15·4	214	15·9		141	18·9	171	22·0	
No information	33	0·8	13	1·0	12	0·9		7	0·9	1	0·1	
Previous births							0·38					0·578
0	1328	31·7	428	32·5	475	35·2		202	27·0	223	28·7	
1	1326	31·6	432	32·8	436	32·3		237	31·7	221	28·5	
≥2	1526	36·4	454	34·4	437	32·4		306	40·9	329	42·4	
No information	12	0·3	4	0·3	2	0·1		3	0·4	3	0·4	
HIV infection							0·321					0·612
No	3350	79·9	1060	80·4	1106	81·9		577	77·1	607	78·2	
Yes	842	20·1	258	19·6	244	18·1		171	22·9	169	21·8	
Previous abortion†							0·368					0·927
No	3643	86·9	1163	88·2	1172	86·8		644	86·1	664	85·6	
Yes	537	12·8	151	11·5	176	13·0		101	13·5	109	14·0	
No information	12	0·3	4	0·3	2	0·2		3	0·4	3	0·4	
Previous stillbirth							0·542					0·532
No	3864	92·2	1244	94·4	1262	93·5		661	88·4	699	90·1	
Yes	312	7·5	71	5·4	86	6·4		82	11·0	73	9·4	
No information	14	0·3	3	0·2	2	0·1		5	0·6	4	0·5	

*P value from Fisher's exact test (for cells with ≤5 observations) or χ^2 test of the difference in background characteristics between the routine and selective Fe groups in each study centre.
†Includes induced and spontaneous abortions.

Table 2 Adherence to the trial by trial arm and study centre* in the PROFEG Trial, a pragmatic randomized controlled trial of iron prophylaxis during pregnancy in Maputo, Mozambique

	1° de Maio							Machava				
	All		Selective		Routine			Selective		Routine		
Covariates	*n*	%	*n*	%	*n*	%	*P* value†	*n*	%	*n*	%	*P* value†
Number of visits‡							0·959					0·458
< 2 visits	875	20·9	284	21·6	292	21·6		141	18·9	158	20·4	
≥ 2 visits	3317	79·1	1034	78·4	1058	78·4		607	81·1	618	79·6	
Adequate prenatal visits index							0·457					0·158
Inadequate	1854	44·2	640	48·6	623	46·2		290	38·8	301	38·8	
Adequate	2234	53·3	635	48·2	682	50·5		454	60·7	463	59·7	
No information	104	2·5	43	3·2	45	3·3		4	0·5	12	1·5	
Reported regular intake of tablets at each visit												
2nd visit (*n* 2949)	2724	92·4	883	94·1	912	94·5	0·726	461	89·2	468	88·5	0·720
3rd visit (*n* 2146)	1993	92·9	588	95·2	652	96·3	0·301	374	88·6	379	88·3	0·898
4th visit (*n* 1414)	1317	93·1	381	95·7	402	97·6	0·144	266	89·9	268	87·0	0·274
5th visit (*n* 765)	708	92·6	201	97·1	199	97·1	0·986	164	88·7	144	85·7	0·409
Regular intake of tablets in all ≥ 2 visits							0·631					0·206
No§	1365	32·6	386	29·3	384	28·4		280	37·4	315	40·6	
Yes	2827	67·4	932	70·7	966	71·6		468	62·6	461	59·4	

P values for the differences between the study centres: number of visits (P = 0·131); adequate prenatal visits index (P < 0·001); intake of tablets (P < 0·001).
*Women (*n* 134) who were ≥34 weeks' gestation were excluded.
†*P* value from Fisher's exact test (for cells with expected frequency ≤ 5) or χ^2 test of difference in compliance between the routine and selective Fe groups in each study centre.
‡Including recruitment visit.
§Includes those who missed regular intake at least once.

the trial for the two study centres combined and stratified by centre. Women ≥30 years old were more likely to have had a regular intake of tablets compared with women aged ≤20 years in both centres combined and in the Machava centre separately. Combining the study centres, women having one previous birth were less likely to have had a regular intake of tablets compared with women who had had no previous birth, but having two or more

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Table 3 Bivariate Pearson correlations between the adherence measures in the PROFEG Trial, a pragmatic randomized controlled trial of iron prophylaxis during pregnancy in Maputo, Mozambique

	Number of visits	Adequate prenatal visits index	Regular intake of tablets in all ≥ 2 visits
Number of visits			
Correlation coefficient	1·000		
P value	–		
Adequate prenatal visits index			
Correlation coefficient	0·739	1·000	0·203
P value	< 0·001	–	< 0·001
Regular intake of tablets in all ≥ 2 visits			
Correlation coefficient	0·151	0·203	1·000
P value	< 0·001	< 0·001	–

Table 4 Determinants of two or more visits during the trial by study centre in the PROFEG Trial, a pragmatic randomized controlled trial of iron prophylaxis during pregnancy in Maputo, Mozambique

	≥ 2 prenatal visits											
	Unadjusted						Adjusted*,†					
	All		1° de Maio		Machava		All		1° de Maio		Machava	
Determinant	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
Maternal age (years)												
≤ 20	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.
21–25	1·06	0·89, 1·28	1·00	0·80, 1·25	1·21	0·89, 1·66	1·27	1·04, 1·56	1·26	0·99, 1·61	1·23	0·90, 1·70
26–29	1·12	0·89, 1·40	1·01	0·76, 1·34	1·34	0·93, 1·93	1·46	1·12, 1·92	1·50	1·07, 2·09	1·39	0·95, 2·01
≥ 30	1·92	1·49, 2·47	1·37	1·01, 1·85	3·58	2·26, 5·68	2·45	1·79, 3·35	2·05	1·40, 2·99	3·54	2·23, 5·64
P value	< 0·001		0·171		< 0·001		< 0·001		0·003		< 0·001	
Previous births												
0	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.		
1	0·70	0·58, 0·84	0·64	0·51, 0·81	0·82	0·60, 1·12	0·64	0·53, 0·78	0·60	0·47, 0·76		
≥ 2	0·99	0·82, 1·20	0·79	0·63, 1·00	1·47	1·07, 2·02	0·68	0·53, 0·86	0·57	0·42, 0·77		
P value	< 0·001		0·001		0·001		< 0·001		< 0·001			
HIV infection												
No	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.
Yes	0·72	0·60, 0·85	0·69	0·55, 0·86	0·75	0·56, 1·01	0·69	0·57, 0·82	0·67	0·53, 0·84	0·71	0·52, 0·96
P value	< 0·001		0·001		0·057		< 0·001		0·001		0·025	
Previous abortion												
No	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.			1·00	Ref.
Yes	1·56	1·22, 2·01	1·35	1·00, 1·83	2·05	1·32, 3·21	1·41	1·10, 1·82			1·85	1·18, 2·91
P value	< 0·001		0·051		0·002		0·008				0·007	
Previous stillbirth												
No	1·00	Ref.	1·00	Ref.	1·00	Ref.						
Yes	1·17	0·87, 1·57	1·18	0·78, 1·77	1·12	0·73, 1·73						
P value	0·298		0·436		0·596							

Ref., referent category.
*The determinants that achieved $P \leq 0{\cdot}20$ in the unadjusted model were studied together in a stepwise regression model.
†Only estimates of the variables that remained in the last stage of the stepwise model are presented here after simultaneous adjustment.

previous births increased the likelihood of having had a regular intake of tablets in the Machava centre but not in 1° de Maio centre separately. HIV positivity at recruitment was associated with less likelihood of having had a regular intake of tablets in the 1° de Maio centre but increased the likelihood in the Machava centre. Having a previous abortion (induced or spontaneous) was positively associated with having a regular intake of tablets only in the 1° de Maio study centre. Previous history of stillbirth was not statistically significantly associated with a regular intake of tablets. In the stepwise regression model and after adjustment for the covariates, increasing maternal age increased the likelihood of having had a regular intake of tablets in both centres combined and in the Machava centre separately. Having one or more previous births decreased the likelihood of having had a regular intake of tablets only in the two centres combined. HIV positivity decreased the likelihood of having had a regular intake of tablets in the 1° de Maio centre while it increased the likelihood in the Machava centre. Finally, having a previous abortion increased the likelihood of having had a regular intake of tablets only in the 1° de Maio centre (Table 6).

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Table 5 Determinants of adequate prenatal visits index by study centre in the PROFEG Trial, a pragmatic randomized controlled trial of iron prophylaxis during pregnancy in Maputo, Mozambique

	Adequate prenatal visits index											
	Unadjusted						Adjusted*,†					
	All		1° de Maio		Machava		All		1° de Maio		Machava	
Determinant	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
Maternal age (years)												
≤20	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.			1·00	Ref.
21–25	1·18	1·01, 1·38	1·12	0·93, 1·36	1·27	0·97, 1·67	1·50	1·26, 1·78			1·55	1·14, 2·10
26–29	1·00	0·83, 1·20	0·91	0·72, 1·10	1·08	0·79, 1·46	1·50	1·19, 1·88			1·47	1·01, 2·15
≥30	1·48	1·22, 1·79	1·14	0·90, 1·46	2·05	1·48, 2·84	2·35	1·83, 3·01			2·83	1·86, 4·30
P value		<0·001		0·220		<0·001		<0·001				<0·001
Previous births												
0	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.
1	0·70	0·60, 0·81	0·66	0·54, 0·80	0·76	0·58, 1·00	0·61	0·52, 0·72	0·67	0·55, 0·81	0·65	0·48, 0·87
≥2	0·76	0·66, 0·89	0·63	0·52, 0·76	0·96	0·74, 1·23	0·52	0·43, 0·64	0·63	0·52, 0·77	0·61	0·43, 0·86
P value		<0·001		<0·001		0·089		<0·001		<0·001	0·005	
HIV infection												
No	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.
Yes	0·79	0·68, 0·92	0·79	0·65, 0·97	0·75	0·58, 0·95	0·77	0·66, 0·90	0·83	0·68, 1·01	0·72	0·56, 0·93
P value		0·003		0·021		0·019		0·001		0·057		0·011
Previous abortion												
No	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.			1·00	Ref.
Yes	1·35	1·12, 1·63	1·18	0·93, 1·49	1·66	1·21, 2·28	1·21	1·00, 1·47			1·52	1·10, 2·10
P value		0·002		0·178		0·002		0·050				0·012
Previous stillbirth												
No	1·00	Ref.	1·00	Ref.	1·00	Ref.						
Yes	1·18	0·93, 1·50	1·14	0·83, 1·59	1·09	0·78, 1·54						
P value		0·167		0·451		0·616						

Ref., referent category.
*The determinants that achieved P ≤ 0·20 in the unadjusted model were studied together in a stepwise regression model.
†Only estimates of the variables that remained in the last stage of the stepwise model are presented here after simultaneous adjustment.

Discussion

Adherence in the present study was measured by the number of prenatal visits, an adequate prenatal visits index and the complete intake of Fe/folic acid tablets. The level of adherence depended on the measure used to define it: 79 % of women had at least two visits during the trial; 67 % had had a regular intake of Fe/folic acid tablets in all visits; and only about half had an adequate prenatal visits index. Adherence did not differ by trial arm, but varied unsystematically by study centre. Older women (>20 years) and those with a history of abortion were more likely to achieve greater adherence, whereas an increasing number of previous births decreased the likelihood of adherence. HIV positivity either decreased or increased the likelihood of adherence, depending on the trial centre.

We found only two previous trials that examined adherence and its determinants in Fe prophylaxis during pregnancy in developing country settings. Kulkarni *et al.*[20] measured adherence by the percentage of total eligible dose of Fe/folic acid consumed during pregnancy through the postpartum and found that only 49 % of women who participated in an Fe prophylactic trial in Nepal achieved high adherence (defined as being in the upper median of adherence). The level of adherence in that study was lower than the level observed in our study (67 %) with regard to complete intake of Fe/folic acid tablets. One of the key determinants of adherence in that particular study was maternal age, which is comparable to our results, showing that older maternal age could influence greater adherence to the trial protocol.

In a trial in the Philippines, Lutsey *et al.*[21] defined adherence as the timeliness of the first prenatal visit, visits per month and pill count, and found that only 40 % of women achieved the expected adherence in terms of pill count, which was also lower than the adherence achieved in our study using any of the indicators for adherence. In the Filipino study, married women were more likely to have greater adherence, while having more children was associated with lower adherence[21]. We did not study the influence of marital status on adherence, but the observed lower likelihood of adherence with an increasing number of children is comparable to our study.

Adherence did not differ by trial arm in our study. But the level of adherence with regard to adequacy of prenatal care and intake of tablets varied between the two study centres.

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Table 6 Determinants of regular intake of tablets during visits by study centre in the PROFEG Trial, a pragmatic randomized controlled trial of iron prophylaxis during pregnancy in Maputo, Mozambique

	Regular intake of tablets during visits											
	Unadjusted						Adjusted*,†					
	All		1° de Maio		Machava		All		1° de Maio		Machava	
Determinant	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
Maternal age (years)												
≤20	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.			1·00	Ref.
21–25	1·15	0·98, 1·35	1·04	0·85, 1·28	1·44	1·10, 1·89	1·26	1·05, 1·50			1·38	1·05, 1·81
26–29	1·04	0·86, 1·26	0·98	0·76, 1·27	1·33	0·98, 1·81	1·18	0·94, 1·49			1·28	0·94, 1·75
≥30	1·55	1·26, 1·90	1·28	0·98, 1·67	2·38	1·72, 3·29	1·77	1·37, 2·29			2·32	1·68, 3·21
P value		< 0·001		0·284		< 0·001		< 0·001				< 0·001
Previous births												
0	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.				
1	0·85	0·72, 1·00	0·82	0·67, 1·00	0·94	0·72, 1·23	0·78	0·66, 0·93				
≥2	1·04	0·89, 1·22	0·96	0·78, 1·18	1·30	1·01, 1·68	0·81	0·66, 0·99				
P value		0·033		0·119		0·022		0·017				
HIV infection												
No	1·00	Ref.	1·00	Ref.	1·00	Ref.			1·00	Ref.	1·00	Ref.
Yes	0·96	0·81, 1·12	0·74	0·60, 0·91	1·45	1·12, 1·87			0·74	0·60, 0·91	1·39	1·07, 1·80
P value		0·574		0·004		0·004				0·005		0·013
Previous abortion												
No	1·00	Ref.	1·00	Ref.	1·00	Ref.			1·00	Ref.		
Yes	1·21	0·99, 1·47	1·34	1·03, 1·76	1·10	0·81, 1·48			1·34	1·03, 1·76		
P value		0·063		0·032		0·553				0·032		
Previous stillbirth												
No	1·00	Ref.	1·00	Ref.	1·00	Ref.						
Yes	1·15	0·89, 1·48	1·16	0·80, 1·67	1·30	0·92, 1·85						
P value		0·283		0·431		0·142						

Ref., referent category.
*The determinants that achieved $P \leq 0{\cdot}20$ in the unadjusted model were studied together in a stepwise regression model.
†Only estimates of the variables that remained in the last stage of the stepwise model are presented here after simultaneous adjustment.

The variation by centre suggests that from the practical point of view, adherence can be influenced. While the determinants of adherence were in general similar between the study centres, the decreased likelihood of complete intake of Fe/folic acid tablets in 1° de Maio and increased likelihood in Machava as a result of HIV positivity could highlight some differences in the health-care systems between the two centres with regard to handling of HIV cases or the way instructions or programmes regarding HIV testing are given. From our experience, 1° de Maio was usually busier than Machava with regard to maternal health programmes undertaken and women seemed better followed up for their HIV in 1° de Maio than in Machava.

As a critical measure for assessing the success of a trial[1–3], the failure of participants to adhere to instructions in a trial protocol would undermine the possibility of evaluating the overall effectiveness of a trial[1–3]. The level of adherence in a trial could also be a predictor of the outcomes in a trial[20]. Consequently, measuring and monitoring adherence in a trial and evaluating its potential determinants are important. Some of the indicators used to assess adherence in trials include following instructions regarding a medication regimen, behaviours regarding instructions on risky habit modification and keeping scheduled medical appointments[1,3].

Clearly, each of the indicators used to assess adherence may be measuring different aspects of adherence, thus they may be providing distinctive information on the success of different aspects of a trial. Lutsey *et al.* observed correlation coefficients between 0·548 and 0·683 between the adherence indicators they studied (timeliness of first prenatal visit, visits per month and pill count)[21]. In the current study, we measured adherence using three indicators: number of visits during the trial; adequacy of prenatal care; and complete intake of Fe/folic acid tablets during the trial. The correlation coefficients between these indicators ranged from 0·151 to 0·739, which suggests that each indicator may be measuring a different aspect of adherence to the trial. Accordingly, studies should endeavour to evaluate adherence using different measures in order to gain a more comprehensive perspective on how the participants in a trial adhere to the different aspects of the trial protocol.

Conclusion

In the current pragmatic trial on Fe prophylaxis during pregnancy, women's adherence to the trial protocols with regard to number of prenatal visits and intake of Fe/folic acid tablets was above the 50th percentile. Key determinants

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of adherence were maternal age, number of previous births, HIV status and a history of abortion; consequently they should be taken into account in trials evaluating the effectiveness of prophylactic Fe supplementation during pregnancy in developing country settings. The observed centre differences in the level of adherence and its determinants may indicate that each trial centre should be carefully studied to understand the characteristics that may undermine or promote women's adherence to the trial protocol.

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