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Recruitment for Longitudinal, Randomised Pregnancy Trials Initiated Preconception: Lessons from the Effects of Aspirin in Gestation and Reproduction Trial

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Abstract

Background: Recruitment into large, preconception randomised clinical trials (RCT) is challenging. We describe clinic and community-based preconception recruitment strategies for the Effects of Aspirin in Gestation and Reproduction (EAGeR) trial and highlight approaches that were and were not successful. This longitudinal RCT was conducted at four major sites in the US. Eligible women had one to two prior pregnancy losses and were actively trying to become pregnant.

Methods: Provider/clinic and community-based outreach strategies were utilised, and the recruitment rate and costs of methods were assessed.

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Ethics approval

The institutional review board at each participating center (University of Utah, Intermountain Healthcare, the State University of New York at Buffalo, The Commonwealth Medical College, and the University of Colorado) approved the study, and participants provided written informed consent. A data safety and monitoring board provided oversight.

Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site:

Results: A screening questionnaire was completed by 5485 women; 42.4% (n = 2323) screened were initially eligible, of whom 50.7% (n = 1228) were randomised. Provider/clinic-based recruitment yielded the highest number eligible of those screened (30.1%) and also the most randomised participants overall (40.3%). The next highest yield came from direct mail and brochures/flyers at 13.1% and 12.5% of women randomised, respectively. However, direct mailings cost \$720 per participant randomised. Other than word of mouth, provider/clinic-based recruitment was the most cost effective method, costing an average of \$60 per randomised participant. Web-based recruitment yielded 4.7% of participants at a cost of \$278 per randomised participant.

Conclusions: Provider and clinic-based recruitment was the most effective and cost-efficient method of recruitment in a preconception intervention study of reproduction among women.

Keywords

research subject recruitment; preconception; low-dose aspirin; pregnancy

Preconception recruitment of women is critical for studies of fecundity or trials examining obstetric and perinatal outcomes of preconception-initiated interventions. Yet, unlike studies which recruit already pregnant women who readily present for routine prenatal care at predictable time windows,^{1–3} reaching women during the preconception time period remains challenging, as a large proportion of pregnancies are not specially planned and thus would not be recruited for such studies,⁴ not all couples attempting to conceive become pregnant, and couples often don't let their pregnancy intentions be known. Indeed, information regarding efficient and cost-effective strategies for preconception recruitment is needed to aid research efforts.⁵ The purpose of this analysis was to evaluate the time and cost-effectiveness of multiple recruitment strategies utilised in the Effects of Aspirin in Gestation and Reproduction (EAGeR) trial.

Methods

Study design and target population

The EAGeR Trial was a multi-site, double blind, randomised, placebo controlled trial designed to study the effect of low-dose aspirin (LDA) on live birth (2007–11).^{6,7} The trial aimed to enroll approximately 1600 healthy women, aged 18–40, with one or two previous pregnancy losses, no diagnosis or history of infertility, and who were trying to become pregnant. The protocol required multiple biospecimen (e.g. blood, urine) collections and study visits throughout preconception and pregnancy. Clinical sites for recruitment included The University of Utah, (49 months), The Commonwealth Medical College in Scranton, Pennsylvania (34 months), the State University of New York (25 months), and the University of Colorado (20 months).

Recruitment methods

All recruitment methods were approved by local Institutional Review Boards. Provider/clinic-based recruitment involved posting brochures/flyers in clinic and waiting rooms and patient restrooms of hospitals and clinics, private practices, and community health centres

throughout the catchment areas and supplying materials for providers and clinic staff to present to potential participants. Locations included hospital departments (emergency, obstetric, postpartum, same-day surgery, and ultrasound) and community clinical sites (obstetrics and gynecology, paediatrics, family medicine). Study staff visited locations up to twice monthly to meet with clinic staff, answer questions, and replenish supplies. Letters with study information were sent from providers to patients of these clinics who had a previous loss or met the age criteria (direct mailings).

Community outreach methods were also employed. No-cost methods included interviews with local newspapers, magazines, radio stations, and television outlets; informational emails to hospital and university staff distribution lists; social media (i.e. Facebook); link-outs to study web site from University and medical college web sites; utilisation of community common areas for study advertisements (e.g. stores, churches, etc.); and word of mouth. Paid methods included maintenance of the study web site; newspaper, magazine, radio, and web advertisements; and hosting booths at expos and fairs.

Utilisation of methods varied by site employing a 'do what works best' model appropriate to local culture and resources (Table S1). A pre-screening questionnaire was implemented in-person or by telephone at the time of initial contact which collected initial eligibility criteria and the source of recruitment. Recruitment costs were determined by spending reports.

Results

Women ($n = 5485$) completed the initial screening questionnaire. Of the 2323 (42.4%) women who were potentially eligible based on the initial screen, 1577 (67.9%) consented and attended the baseline screening visit, and 1397 were confirmed as eligible. Sixty (4.3%) eligible women discontinued the enrollment process, and 109 (7.8%) women were identified as pregnant at the baseline visit or became pregnant before randomisation, resulting in a total of 1228 women participating. Body mass index (BMI), race, education, and income of participants did not differ significantly by recruitment method (Table 1). Though age and marital status of participants were shown to significantly vary by type of recruitment method, differences between methods were small.

The highest yield of participants recruited was from provider/clinics, accounting for 30.0% of women prescreened and 40.3% of women randomised (Table 2). Provider/clinic recruitment was also the lowest cost (\$60/participant) and \$29 668 in total, representing 12% of total recruitment supply expenditure. However, study staff costs were over \$3000 per month at sites utilising providers/clinics as leading recruitment methods, and varied from \$2000 to \$6556 per month overall. Direct mailings resulted in the second largest proportion of women randomised with 161 (13.1%) women. However, given the cost and total numbers of mailings sent, mailings constituted the highest average cost at \$720 per participant enrolled/ randomised. Indeed, the greatest supply cost of \$115 872 was spent on direct mailings that included mailings from health care providers and purchased community mailings. Of note, \$113 457 (98%) of this total occurred in one site, primarily for community mailings. Direct mail resulted in 44 participants at this site and 117 participants from all other sites combined. A similar proportion of women ($n = 154$, 12.5%) learned of

the study through brochures/flyers displayed at community sites. Other methods each accounted for <6% of randomised women. Word of mouth, which was entirely no cost, accounted for 7.4% of women randomised. In total, \$243 447 was spent on recruitment supply costs, while \$481 119 supported recruitment-related study staff time (Table S2).

Comment

Recruitment of women prior to conception for participation in a fertility and pregnancy-related trial was feasible on a large scale, and was most efficient and cost-effective utilising a foundation of provider and clinic-based recruitment methods. Clinic-based recruitment was particularly efficient in identifying women who were likely to be randomised to the study. Over 40% of women randomised in the EAGeR trial were identified through provider/clinic-based recruitment, with an approximate cost of \$60 in supplies per participant. In contrast, web-based and mass media methods resulted in the fewest randomised participants and with higher cost. Nonetheless, other methods should be considered to complement clinic/provider-based recruitment strategies, as the combination of multiple other methods incrementally contributed the remaining 60% of participants.

Other studies or trials aiming to recruit women or couples preconception have utilised entirely web-based recruitment and data collection methods resulting in low costs (\$160 total cost per participant in SmartGravid Study⁸) for longitudinal, large-scale observational studies.^{8,9} Similarly, important studies of pregnancy loss have accomplished preconception recruitment for data collection which did not require study visits in a clinic, utilising both provider and community-based methods.^{10,11} A small ($n = 30$) feasibility study of preconception recruitment and retention for a traditional longitudinal gynecologic study involving multiple clinical exams utilising only nonprovider-based methods (e.g. paid advertisements) reported poor study retention over time, however.¹² Furthermore, television, radio and newspaper ads, and Internet-based ads proved relatively expensive in the current study and were less efficient recruitment strategies compared with clinic/provider-based approaches. However, it is not known whether these broad-reach approaches increased familiarity and/or acceptability of local women to the study, and subsequently augmented recruitment within the provider/clinic category.

The Longitudinal Investigation of Fertility and the Environment study used a community-based recruitment strategy utilising marketing databases of fishing and hunting license registries in 16 counties in Texas and Michigan. Over 500 couples were enrolled with high compliance with the study protocol, but cost data were unavailable.⁵ Another study recruited a proportion of study participants preconception ($n = 103$ of 800 total), utilising both clinic and community-based approaches. The authors noted that while 83% of participants recruited preconception resulted from community-based strategies, recruitment from public clinics allowed for greater enrollment of minorities and women of lower income.¹³ It may be that indirect, Internet, and community-based methods are most effective and cost-efficient for studies that utilise indirect and web-based participant contact strictly for observational data collection, but recruitment to trials requiring a clinical intervention, specimen collections, and exams in clinic is more successfully accomplished with the support of health care providers and in the clinics themselves.

It is worth noting that in order to recruit and, importantly, *retain* participants, significant study personnel dedication was needed to ensure success. Thus, sufficient study staff support was crucial in addition to the direct costs of study recruitment described here. Also, regional and cultural differences could account for varying success with the different recruitment strategies. Indeed, investigators must be cognizant of racial, ethnic, and cultural differences that may influence research participation by working closely with the local infrastructure.¹⁴

To our knowledge, this is one of the largest longitudinal trials and studies of pregnancy and its outcomes with preconception study enrollment. The cohort had above-average income and education and was predominantly white,¹³ potentially limiting generalisability, though four distinct geographic regions were utilised. It is not possible to assess unmeasured factors specific to each site which may impact the success of different recruitment methods at individual sites, but site-based recruiting strategies have been proven effective in other studies.^{2,3} Strategies and associated costs were prospectively and meticulously tracked throughout stages of initial patient contact, eligibility, enrollment, and randomisation. Also, a large variety of methods were employed and compared.

Fertile women planning to become pregnant may be successfully recruited into a longitudinal trial lasting through conception, pregnancy, delivery, and postpartum through multiple methods of recruitment. However, provider/clinic-based approaches proved most time and cost-effective in the current trial, which was augmented by an established infrastructure of research support. These findings confirm the feasibility of successfully conducting a preconception-initiated trial involving a clinical intervention lasting through the end of pregnancy, despite considerable demands of the protocol and strict eligibility criteria.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Demographic characteristics of randomised participants by recruitment method: EAGeR Trial

	Provider/ Clinics		Posters/Flyers		Direct mail		Web/Email		TV/Radio/ Newspaper		Other		Word of mouth		Source missing		Total		P
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age	28.4	4.7	28.6	5.1	29.8	4.9	30.5	4.8	29.2	5.3	28.0	4.9	27.7	4.5	28.9	4.3	28.7	4.8	0.001
BMI	25.8	6.3	27.4	7.6	26.1	6.6	26.3	7.9	27.0	6.0	27.4	7.0	26.9	5.7	26.2	6.4	26.4	6.6	0.26
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Education	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
> High School	426	87.7	130	86.1	137	86.2	50	87.7	43	79.6	56	78.9	76	85.4	123	84.3	1041	86.2	0.35
High School Graduate	52	10.7	20	13.2	20	12.6	4	7.0	9	16.7	11	15.5	11	12.4	15	14.0	142	11.8	
<High School Graduate	8	1.6	1	0.7	2	1.3	3	5.3	2	3.7	4	5.6	2	2.2	3	2.0	25	2.1	
<hr/>																			
Race																			
Not white	22	4.5	10	6.6	11	6.9	5	8.8	3	5.6	4	5.6	3	3.4	7	6.0	65	5.4	0.62
White	465	95.7	141	93.4	148	93.1	52	91.2	51	94.4	67	94.4	86	96.6	134	94.3	1144	94.7	
<hr/>																			
Marital Status																			
Living with Partner	28	5.8	7	4.6	10	6.3	5	8.8	7	13.0	3	4.2	5	5.6	6	5.0	71	5.9	0.003
Married	455	93.6	138	91.4	141	88.7	48	84.2	43	79.6	68	95.8	82	92.1	133	94.3	1108	91.7	
Other	4	0.8	6	4.0	8	5.0	4	7.0	4	7.4	0	0.0	2	2.2	2	1.0	30	2.5	
<hr/>																			
Annual Income																			
<\$19 999	42	8.6	13	8.6	9	5.7	4	7.0	3	5.6	8	11.3	6	6.7	9	7.0	94	7.8	0.075
\$20 000-\$39 999	104	21.4	47	31.1	34	21.4	8	14.0	18	33.3	31	43.7	29	32.6	34	23.1	305	25.2	
\$40 000-\$74 999	76	15.6	14	9.3	29	18.2	11	19.3	9	16.7	7	9.9	9	10.1	22	16.1	177	14.7	
\$75 000-\$99 999	60	12.3	14	9.3	21	13.2	12	21.1	6	11.1	4	5.6	11	12.4	20	12.1	148	12.3	
\$100 000	205	42.2	63	41.7	66	41.5	22	38.6	17	31.5	21	29.6	34	38.2	56	42.2	484	40.1	

Differences across recruitment strategies were determined by analysis of variance for continuous variables or chi square test for categorical variables.

Table 2.

Recruitment supply costs: EAGeR Trial

Recruitment method	Initial screening questionnaire <i>n</i> (% of total)	Randomised <i>n</i> (% of total)	No. pre-screened per each randomised	Total cost	Cost per randomised
Provider/clinics ^a	1643 (30.0)	495 (40.3)	3.3	\$29 668	\$60
Community brochures/flyers ^b	890 (16.2)	154 (12.5)	5.8	\$39 370	\$256
Direct mail	751 (13.7)	161 (13.1)	4.7	\$115 872	\$720
Web/Email	496 (9.0)	58 (4.7)	8.6	\$16 150	\$278
TV/Radio/Newspaper	455 (8.3)	55 (4.5)	8.3	\$35 959	\$583
Other ^c	373 (6.8)	72 (5.9)	5.2	\$6428	\$89
Word of mouth	346 (6.3)	91 (7.4)	3.8	\$0.00	\$0.00
Source missing	531 (9.7)	142 (11.6)	3.7	-	-
Total	5485	1228	4.5	\$243 447	\$198

^aProvider/Clinic recruitment costs include brochures and flyers posted in clinics, which were estimated to comprise 40% of total brochure/flyer costs.^bCommunity brochures/flyers those posted in community settings outside of the clinics.^cOther recruitment method most often included participant 'not remembering' where she heard of the study.