RESEARCH LETTER

Randomized Experiment of Recruitment Letter Design to Maximize Clinical Trial Enrollment

Most new medical therapies only offer small to moderate benefits above high-level standard care and require increasingly large trials to demonstrate efficacy in light of generally declining incidence rates of major clinical outcomes.[1,2] Cost-effective strategies to improve trial recruitment are therefore urgently needed. Prior investigations have yielded mixed results, and those assessing the effects of modifying written recruitment material have often been limited by small sample sizes and high risk of bias.[3,4] Therefore, within the context of the DANFLU-2 (A Pragmatic Randomized Trial to Evaluate the Effectiveness of High-Dose Quadrivalent Influenza Vaccine vs Standard-Dose Quadrivalent Influenza Vaccine in Older Adults) trial, a randomized experiment was conducted to investigate whether varying digital recruitment letter layout and color scheme would impact trial enrollment.

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Supplemental content

Methods | DANFLU-2 (NCT05517174) is an ongoing pragmatic randomized trial of high-dose inactivated influenza vaccine vs standard-dose inactivated influenza vaccine in adults 65 years or older in Denmark,[5] conducted under approval from the Medical Research Ethics Committees in Denmark and the Danish Medicines Agency (EU CT number: 2022-500657-17-00). During the recruitment period of the trial's second influenza season (2023-2024), as a study within a trial, we conducted a randomized experiment of digital recruitment letter strategies in which we varied layout and color scheme in a 3 × 3 factorial design. Invitees were randomized in a 1:1:1 ratio to receive 1 of 3 layout variants (single-page letter, 2-page letter, or enhanced 2-page letter with additional colored text boxes emphasizing certain elements) and also in a 1:1:1 ratio to receive 1 of 3 color schemes (dark red, blue, or green) (**Figure 1**). Danish citizens who opted for physical letters instead of email were excluded. Text content was identical across all letters. All letters included a colored box with a link to the sign-up website. English translations of the letters can be found in the eMethods in Supplement 1. The recruitment letters were delivered through the Danish governmental electronic mailbox system. The primary end point of this analysis was enrollment into DANFLU-2. Two-sided *P* values <.05 were considered statistically significant. This report follows the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Results | A total of 934 049 Danish citizens ≥65 years were identified and randomized to receive different letter types. The mean (SD) age of participants was 74.4 (6.4) years and 484 589 (51.9%) were female. Letters were successfully delivered to 99.95% of those randomized. DANFLU-2 enrolled a total of 160 451 participants during the 2023-2024 season. Enrollment was significantly more likely among participants who received the single-page letter compared with the 2-page letter (16.28% vs 16.02%; difference, 0.25 [95% CI, 0.07-0.44] percentage points; *P* = .007) and the enhanced 2-page letter (16.28% vs 15.29%; difference, 0.98 [95% CI, 0.80-1.16] percentage points; *P* < .001) (**Figure 2**). The 2-page letter was more effective than the enhanced 2-page letter. No differences were observed across color schemes. No interactions were observed between letter layout and color scheme (all *P* values for interaction >.75). Compared with the enhanced 2-page letter, the effect estimates observed with both the 1-page letter and the standard 2-page letter were significantly greater among males compared with females as well as among younger compared with older individuals (Figure 2).

Discussion | As the largest individually randomized influenza vaccine trial ever conducted, DANFLU-2 offered a unique opportunity to test the effects of different invitation letter design features on trial enrollment on a very large scale. The results of the current study suggest a preference for shorter-form messaging with differences of approximately 1 percentage point in absolute terms and approximately 6% in relative terms. Consequently, compared with the least effective letter (the enhanced 2-page letter), sending the most effective letter (the 1-page letter) to 1 000 000 potential participants would result in an additional approximately 9800 trial participants, thereby increasing the probability of reaching the planned sample size and securing sufficient statistical power. The potential heterogeneity observed according to age and sex suggests potential additional benefit from further tailored strategies. Although the results may not be directly generalizable to trials with other designs or conducted in different settings, these findings do underline the importance of carefully considering design and style of participant-facing material in clinical trials, including recruitment letters, particularly in decentralized pragmatic trials where broadly distributed, low-touch recruitment strategies are often necessary.

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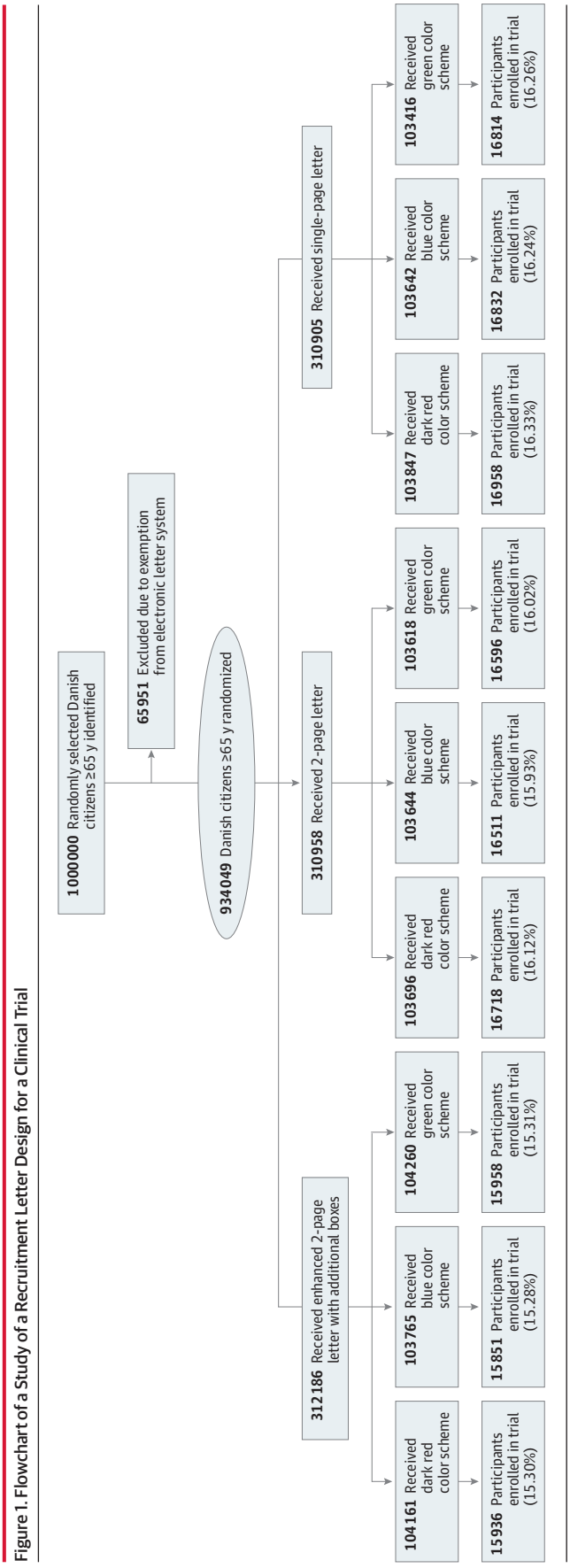

Figure 1. Flowchart of a Study of a Recruitment Letter Design for a Clinical Trial

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Author Contributions: Drs Johansen and Biering-Sørensen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Conflict of Interest Disclosures: Dr Mafham reported receiving grants and study drugs from Novo Nordisk outside the submitted work. Dr Harris reported receiving personal fees from and may hold shares in Sanofi as an employee during the conduct of the study. Dr Solomon reported receiving grants from Alexion, Alnylam, Applied Therapeutics, AstraZeneca, Bellerophon, Bayer, BMS, Boston Scientific, Cytokinetics, Edgewise, Eidos/BridgeBio, Gossamer, GSK, Ionis, Lilly, National Institutes of Health/National Heart, Lung, and Blood Institute, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Tenaya, Theracos, and US2.AI and receiving personal fees from Abbott, Action, Akros, Alexion, Alnylam, Amgen, Arena, AstraZeneca, Bayer, BMS, Cardior, Cardurion, Corvia, Cytokinetics, GSK, Intellia, Lilly, Novartis, Roche, Theracos, Quantum Genomics, Tenaya, Sanofi Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, and Valo outside the submitted work. Dr Biering-Sørensen reported receiving grants from Sanofi during the conduct of the study and personal fees from Sanofi Pasteur, GSK, Novo Nordisk, IQVIA, Parexel, Amgen, CSL Seqirus, Bayer, Novartis, GE Healthcare, and AstraZeneca and grants from Sanofi Pasteur, Pfizer, AstraZeneca, Boston Scientific, GE Healthcare, Novartis, Novo Nordisk, and Bayer outside the submitted work. No other disclosures were reported.

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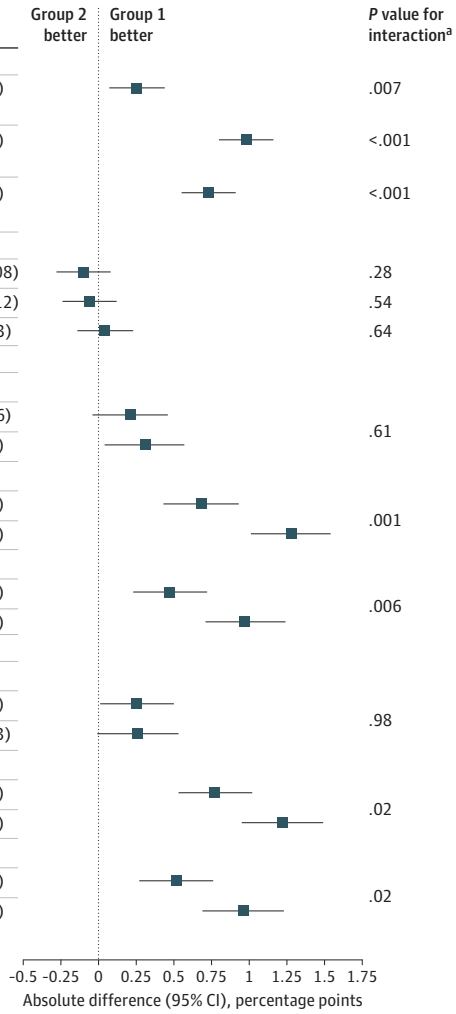
Data Sharing Statement: See Supplement 2.

Figure 2. Effects of Recruitment Letter Layout and Color Scheme on Trial Enrollment

	No. of participants/total No. (%)		Absolute difference (95% CI), percentage points	P value for interaction[a]
	Group 1	Group 2		
Letter type				
1-Page (group 1) vs standard 2-page (group 2)	50 604/310 905 (16.28)	49 826/310 958 (16.02)	0.25 (0.07 to 0.44)	.007
1-Page (1) vs enhanced 2-page (2)	50 604/310 905 (16.28)	47 745/312 186 (15.29)	0.98 (0.80 to 1.16)	<.001
Standard 2-page (1) vs enhanced 2-page (2)	49 826/310 958 (16.02)	47 745/312 186 (15.29)	0.73 (0.55 to 0.91)	<.001
Color scheme				
Blue (1) vs red (2)	49 194/311 051 (15.82)	49 612/311 704 (15.92)	-0.10 (-0.28 to 0.08)	.28
Green (1) vs red (2)	49 369/311 294 (15.86)	49 612/311 704 (15.92)	-0.06 (-0.24 to 0.12)	.54
Green (1) vs blue (2)	49 369/311 294 (15.86)	49 194/311 051 (15.82)	0.04 (-0.14 to 0.23)	.64
According to age, y (subgroup analysis)				
1-Page (1) vs standard 2-page (2)				
≥73.7	22 933/155 389 (14.76)	22 538/154 911 (14.55)	0.21 (-0.04 to 0.46)	.61
<73.6	27 671/155 516 (17.79)	27 288/156 047 (17.49)	0.31 (0.04 to 0.57)	
1-Page (1) vs enhanced 2-page (2)				
≥73.7	22 933/155 389 (14.76)	22 001/156 292 (14.08)	0.68 (0.43 to 0.93)	.001
<73.6	27 671/155 516 (17.79)	25 744/155 894 (16.51)	1.28 (1.01 to 1.54)	
Standard 2-page (1) vs enhanced 2-page (2)				
≥73.7	22 538/154 911 (14.55)	22 001/156 292 (14.08)	0.47 (0.23 to 0.72)	.006
<73.6	27 288/156 047 (17.49)	25 744/155 894 (16.51)	0.97 (0.71 to 1.24)	
According to sex (subgroup analysis)				
1-Page (1) vs standard 2-page (2)				
Female	24 341/161 654 (15.06)	23 864/161 208 (14.80)	0.25 (0.01 to 0.50)	.98
Male	26 263/149 251 (17.60)	25 962/149 750 (17.34)	0.26 (-0.01 to 0.53)	
1-Page (1) vs enhanced 2-page (2)				
Female	24 341/161 654 (15.06)	23 104/161 727 (14.29)	0.77 (0.53 to 1.02)	.02
Male	26 263/149 251 (17.60)	24 641/150 459 (16.38)	1.22 (0.95 to 1.49)	
Standard 2-page (1) vs enhanced 2-page (2)				
Female	23 864/161 208 (14.80)	23 104/161 727 (14.29)	0.52 (0.27 to 0.76)	.02
Male	25 962/149 750 (17.34)	24 641/150 459 (16.38)	0.96 (0.69 to 1.23)	



Comparisons were analyzed using the intention-to-treat principle. No adjustments were made for multiple comparisons. The median age of the study population was 73.7 years.

[a]The *P* values for letter type and color scheme are *P* values for effect and were derived from χ^2 tests. Interaction *P* values were calculated on the absolute scale using binomial regression with interaction terms.

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Sex-Based Differences in Pediatric Mental Health Hospitalizations at US Acute Care Hospitals

Approximately 1 in 5 US children have a mental health diagnosis. Nationally representative data analyzed by our group have shown that pediatric mental health hospitalizations at acute care hospitals increased 25.8% between 2009 and 2019.[1] After this study period, the COVID-19 pandemic resulted in unprecedented social changes and worsening mental health symptoms, especially among adolescent girls.[2] However, postpandemic, few studies have examined sex-based differences in pediatric mental health hospitalizations, which may indicate differential mental health needs unmet by community-based care.

Supplemental content

This study extended the prior 2009-2019 analysis by evaluating how the number of pediatric mental health and suicide/self-harm–related hospitalizations changed in 2022 and characterizing sex-based differences over time.

Methods | This cross-sectional study analyzed the 2009-2022 Kids' Inpatient Database (KID), released every 3 years by the