EDITORIAL

Trials Within Trials—Optimizing the Delivery of RCTs

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In this issue of *JAMA*, Johansen and colleagues[1] report the results of a trial that investigated the impact of digital recruitment letter formats on recruitment to a larger clinical trial, the DANFLU-2 trial (NCT05517174) comparing high-dose vs standard-dose quadrivalent influenza vaccine in older adults. In this trial, investigators randomized invitees to the DANFLU-2 trial in a 1:1:1 ratio to receive 1 of 3 different recruitment letter layouts (single-page vs double-page vs double-page with emphasized elements) and in a 1:1:1 ratio to receive 1 of 3 different color schemes (dark red, blue, or green), resulting in a combined 3 × 3 factorial design (9 distinct layout-color combinations). The authors found significantly higher enrollment with the single-page letter (16.28% enrolled in DANFLU-2) compared with the 2 different double-page letter formats (16.02% and 15.29%), but no difference across color schemes.

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A major strength of their study is the massive sample size, randomizing 934 049 potential trial participants to receive the different letter types. Johansen and colleagues were able to achieve this because DANFLU-2 was designed as a registry-based trial, in which potential participants were identified through data extracts from the Danish Health Data Authority and digital recruitment letters were sent through the government electronic letter system. Informed consent was not required for entry into the nested recruitment letter trial because, under Danish legislation, data extracts from government registries do not require consent and the intervention is very low risk. Such waivers of informed consent are crucial for any study evaluating trial consent or recruitment strategies because requiring consent before entering such a study would preferentially select for patients who are already more likely to enter a research study.

This large sample size enabled the investigators to detect small effect sizes that may have otherwise not been identified in a smaller study. Because variation across the different recruitment forms was subtle, it is unlikely that there would have been large differences in enrollment percentages across groups. Indeed, the absolute risk differences between the 1-page letter and the 2 different double-page letters (with and without emphasized elements) were 0.25% and 0.98%, respectively. Although these differences may seem trivial at first blush, when magnified across their specific trial setting involving up to 1 million trial invitees, these figures could translate into enrollment of an additional 9800 participants if the single-page letter is adopted. However, the generalizability of these findings to other trials is less clear—a 1% difference in enrollment rate may not be that important when considering more modestly sized trials.

Therefore, more studies are needed to find strategies to improve the way researchers enroll and consent patients for clinical trials. Insufficient participant enrollment is a top reason that trials are terminated prematurely; even among trials that reach their enrollment target, approximately 80% do not do so within their prespecified period, requiring prolongation of the study or addition of more study sites.[2,3] All of this represents tremendous research waste and inefficiency by increasing operational costs. Clinical trial funding is a scarce resource, and the research community should do its best to ensure that these resources are used efficiently.

Beyond increasing absolute enrollment numbers, more studies should examine ways to ensure equitable access to clinical trials. Trial enrollment and consent processes can unintentionally exclude patients experiencing different aspects of marginalization, eg, patients from a different cultural/linguistic background or patients with different literacy, education, or socioeconomic levels.[4,5] For example, in their trial, Johansen and colleagues excluded participants who have applied for an exemption from the government electronic letter system (eg, due to lack of internet access or low level of digital literacy). Others have documented how the length, complexity, and readability of trial consent forms can similarly exclude patients from different marginalized groups from participating in clinical trials.[4,5] Reducing barriers to clinical trial participation in an equitable manner is important to ensure that clinical trials reflect the diversity of patient populations, and innovations in trial enrollment processes are required to reach that goal.

The study within a trial (SWAT) design is optimal to investigate and improve processes of how clinical trials are conducted.[6] This study by Johansen and colleagues is an example of a SWAT, a self-contained research study embedded within a larger host clinical trial, but with its own separate protocol and analysis that do not affect the overall conduct or scientific integrity of the host trial. Beyond enrollment or recruitment processes, SWATs can answer questions about any aspect of trial conduct, such as participant retention and follow-up, data collection processes, results reporting, and knowledge translation. The Trial Forge initiative has published a series of guidance papers outlining different methodological aspects unique to SWATs.[6]

The clinical trial community could look to the technology and business worlds, where SWATs have their analogous counterpart: the A/B test. In an A/B test, end users (eg, consumers) are randomized to receive different versions of user interfaces or marketing material, and an outcome metric is measured and analyzed.[7] For example, a mobile app could randomize users to 1 of 2 different button types for an

advertisement and measure the click-through rate for that button. A/B testing is often continuous and iterative and tests multiple different combinations of variables in parallel (like a factorial design), maximizing efficiency. For research to optimize aspects of clinical trials, one might think of the trial as a user interface, with the goal of SWATs to maximize the click-through rate in terms of recruitment.

Other investigators have conducted SWATs aiming to improve trial recruitment. A previous systematic review (including studies published up to February 2015) identified 68 trials of methods to increase recruitment to randomized trials.[8] These trials tested 72 different comparisons, but, of them, only 3 were supported by high-certainty evidence rated by the GRADE approach. Two of these 3 interventions were associated with significant improvements in recruitment: the use of open-label trials rather than placebo or blinded trials[9,10] and the use of telephone reminders to potential participants who do not respond to a postal invitation.[11,12] The third intervention, use of a bespoke user-testing approach to develop participant information leaflets, had little to no impact on patient recruitment. Other interventions had only low to moderate evidence and were not associated with significant improvement in recruitment. Two studies compared mailing shorter vs longer participant information leaflets with trial invitation letters. Neither study demonstrated a significant difference in recruitment across groups, as was observed in Johansen et al,[13,14] although this may have been due to the much smaller sample sizes involved in these prior studies.

It is interesting to note that in the study by Johansen et al,[1] the actual content did not vary across recruitment letter formats—instead, the content was fit into a single page for the single-page letter vs spread out across 2 pages for the double-page letter formats. Despite the same volume of information, the single-page letter resulted in a higher recruitment rate. We hypothesize that in this case, the difference is attributed to a difference in perception of the volume of information (ie, 1 page seems less intimidating than 2 pages) rather than the actual volume of information. Further research should be conducted to investigate the optimal format and content density for trial enrolment material.

To that aim, we are currently conducting a SWAT within the *Staphylococcus aureus* Network Adaptive Platform (SNAP) trial, a large international adaptive platform trial studying different management questions surrounding *S aureus* bloodstream infection.[15] As part of designing the consent material for the SNAP trial, we developed a novel layered consent strategy, whereby basic information about the trial is provided in simple bullet point, with embedded links for participants who want to access more detailed information (including supplementary video information). A qualitative study found that patients strongly supported this layered approach to information delivery and valued the agency they had in controlling the amount of information processed.[16] We are testing this novel consent intervention in a SWAT, SIMPLY-SNAP, where we are randomizing potential SNAP participants to undergo this simplified layered consent vs a conventional full-length consent form.[17] The primary outcome is trial enrollment, but we are also tracking as secondary and exploratory outcomes of participant understanding of the trial, participant satisfaction with the consent process, and measures of participant diversity in the enrolled population.

The problems surrounding clinical trial recruitment and consent are ripe for innovative solutions. Every clinical trial offers opportunities for embedded studies to rethink and refine how clinical trials are conducted. Clinical trialists, ethics boards, and regulatory bodies should support innovation in trial processes and their study, instead of relying on the same recruitment and consent methods that have been used for decades.

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Published Online: June 25, 2025. doi:10.1001/jama.2025.10107

Conflict of Interest Disclosures: None reported.

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