Supplemental Online Content

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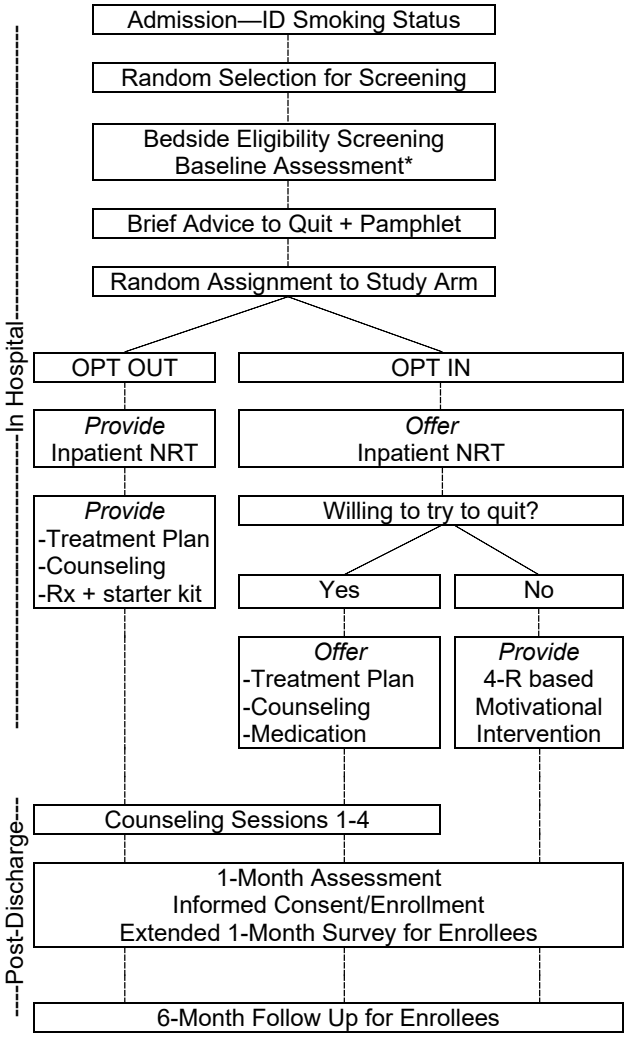
This supplemental material has been provided by the authors to give readers additional information about their work.

eFigures and Tables

eFigure. Study organization



eTable 1. Fidelity ratings for baseline inpatient session by treatment group

	Pre-randomization neutrality in baseline survey administration				Post-randomization [b] adherence to intervention protocol/style		
	# sessions rated	mean [a]	(sd)		# sessions rated	mean [a]	(sd)
All Arms Combined	412	4.9	0.31		426	4.8	0.49
Opt In Not Willing	67	4.9	0.34		70	4.8	0.51
Opt In Willing	108	4.9	0.40		114	4.7	0.62
Opt Out	237	5.0	0.25		242	4.9	0.39

[a] Scales range from 1-5, with higher numbers indicating greater neutrality/style adherence.
[b] Adherence to Opt-in/Opt-out style and protocol per randomized treatment arm.
Note. Fidelity was assessed not on a random sample but on a sample designed to rate each counselor on each intervention style (opt-out, opt-in willing to quit; opt-in not willing to quit) on a regular basis. On a 5-point scale (1=low neutrality, 5 =completely neutral) we evaluated the degree to which counselors remained neutral (not engaging in conversation that could encourage patients to accept or decline treatment) during baseline assessment, prior to randomization. On a 5-point scale (1=low fidelity, 5 = high fidelity) we also evaluated the overall degree to which counselors used the correct language and treatment approach to which each patient had been randomly assigned (opt out vs opt in willing/not willing). Using a 3-point scale (yes/no/patient refused), we also assessed whether each component of care was offered/provided in the correct manner (opt out vs opt in willing/not willing) (eTable 2).

eTable 2. Fidelity to treatment components by treatment group

	Opt In Not Willing		Opt In Willing		Opt Out		All Arms Total	
	n = 70		n = 114		n = 242		n = 426	
	No.	%	No.	%	No.	%	No.	%
Arranged Inpatient Medication								
Fidelity demonstrated	70	100.0	112	98.2	235	97.1	417	97.9
Yes, arranged medications	9	12.9	33	28.9	188	77.7	230	54.0
Pt. refused or did not want medications	61	87.1	79	69.3	47	19.4	187	43.9
Provided Brief Advice to Quit								
Fidelity demonstrated, provided advice	65	92.9	113	99.1	235	97.1	413	96.9
Provided Educational Materials								
Fidelity demonstrated	69	98.6	104	91.2	237	97.9	410	96.2
Yes, provided brochure or booklet	67	95.7	104	91.2	234	96.7	405	95.1
Pt. refused materials	2	2.9	0	0.0	3	1.2	5	1.2
Arranged Outpatient Medication								
Fidelity demonstrated			109	95.6	236	97.5	345	96.9
Yes, arranged medications			57	50.0	211	87.2	268	75.3
Pt. refused or did not want medications			52	45.6	25	10.3	77	21.6
Completed Tx Plan								
Fidelity demonstrated			112	98.2	236	97.5	348	97.8
Yes, completed treatment plan			40	35.1	231	95.5	271	76.1
Pt. refused treatment plan			72	63.2	5	2.1	77	21.6
Provided Starter Pack Instructions								
Fidelity demonstrated			101	88.6	202	83.5	303	85.1
Yes, provided instructions			50	43.9	173	71.5	223	62.6
NA, Pt. did not receive starter pack			51	44.7	29	12.0	80	22.5
Arranged Follow-up Counseling								
Fidelity demonstrated			113	99.1	232	95.9	345	96.9
Yes, arranged counseling			67	58.8	231	95.5	298	83.7
Pt. refused follow-up counseling			46	40.4	1	0.4	47	13.2
Overall Fidelity for All Components	204	97.1	764	95.7	1613	95.2	2581	95.5

Note. Fidelity was assessed not on a random sample but on a sample designed to rate each counselor on each intervention style (opt-out, opt-in willing to quit; opt-in not willing to quit) on a regular basis. Using a 3-point scale (yes/no/patient refused), we assessed whether each component of care was offered/provided in the correct manner (opt out vs opt in willing/not willing).

eTable 3. Probabilities that the opt-out group achieved better psychological outcomes than the opt-in group

	Posterior mean[a] (95% Bayesian credible interval)		Bayesian posterior probability (That Opt out is better than Opt In)
	Opt In N=270	Opt Out N=469	
Working alliance with provider[b]	3.20 (3.12, 3.29)	3.37 (3.32, 3.42)	1.00
Implied recommendation/endorsement[c]	3.17 (3.09, 3.25)	3.34 (3.29, 3.39)	1.00
I had a lot of control over whether I tried to quit smoking [d] n (% yes)	86.64% (82.07, 90.63)	88.41% (85.19, 91.28)	0.75
I didn't feel forced to try to quit smoking [d] n (% yes)	80.98% (75.88, 85.65)	76.81% (72.66, 80.65)	0.10

[a]All models are Binomial (flat priors) or Normal (flat priors) with posterior means and 95% highest density intervals unless noted. At least 10000 burn-in and 40000 Markov chain draws were performed.
[b]Working Alliance Inventory for Tobacco (WAIT-3).[29] Mean of 3 items each with possible range, 1-4, Strongly Agree – Strongly Disagree: My tobacco counselor and I agreed on clear tobacco treatment goals for me; My tobacco counselor and I agreed on the method I would use to achieve my tobacco treatment goals; I felt that my tobacco counselor appreciated me.
[c]Mean of 3 items each with possible range, 1-4, Strongly Agree – Strongly Disagree: My tobacco counselor believed that I want to quit smoking; My tobacco counselor was confident that I would be able to quit smoking; My tobacco counselor believed that medication and counseling would help me quit smoking.
[d]Adapted from the MacArthur Admission Experience Survey.[26]

eMethods. Changing the Default Bayesian analysis and statistical approach

Unique features of the trial included the posttest only delayed-consent randomized control group design[1], and Bayesian adaptive trial design.[2] The posttest-only design controls for all of the threats to internal validity that a pretest-posttest design controls for. In addition, it avoids testing effects by minimizing repeated measurement—especially prior to the intervention. This will enable us to see the true effects of changing the default on initial treatment choices. The Bayesian adaptive design study determined our sample size and how patients were allocated to groups.[2] Bayesian designs are becoming widely used in PCORI pragmatic clinical trials, because they are efficient and ethical—they can get answers to research questions early, and they allocate more patients to the better-performing treatment arm.[3] The study also evaluated the impact of psychological mediators on treatment participation and smoking cessation, in order to gain insight into why and how changing the default did—or did not—work.

Clinical Trial Timeline and Procedures

The trial employs a posttest-only randomized study design among 1,000 inpatients with consent for extended data collection at month 1 and follow-up at month 6. It was implemented over 4 ½ years.

Population-based inclusion in the trial via random selection for eligibility screening. UKanQuit had access via the EHR to a real-time, comprehensive list of all smokers in the hospital—the *tobacco use list*. For the purposes of the study, research staff randomly selected patients from the tobacco use list for the trial, and provided selected patients' names to UKanQuit staff for baseline assessment, randomization, and intervention. Random selection of potential participants served 2 purposes. First, it enabled the trial to test the change of default among a population-based sample of all hospitalized smokers, to enhance generalizability of the findings. Second, it ensured that smokers *not* seeking tobacco treatment were included in the trial, which enhanced our ability to detect the effect of changing the default among smokers who have not requested, and who are not "ready", for treatment. Patients who requested or who had orders for tobacco treatment were included in the trial only if they were randomly selected. We randomly selected potential participants because we did not have the staffing to include all smokers in the hospital into the trial. In order to randomly select smokers into the trial, on a daily basis research staff pasted all smokers in the hospital into an excel file, used a function to randomly order patients, and used a random number table to select patients from the list into a subset of patients to be screened for eligibility.

Eligibility and intake assessment. UKanQuit hospital staff visited all randomly selected smokers. For all study patients, staff assessed and addressed patient comfort, provided brief advice to quit, and provided an 8-page quit smoking pamphlet to all OPT OUT patients and to OPT IN patients who state they were willing to quit smoking. A 2-page brochure was provided to all OPT IN patients who stated they were not willing to quit smoking. UKanQuit staff then assessed eligibility and collect intake data. UKanQuit staff recorded eligibility for the study on their clinic service tablet computer, along with standard service administrative data, which included demographics, smoking characteristics including willingness to quit, and contact information for 1-month follow up. These administrative data constituted baseline data for the clinical trial.

Random allocation to study groups. A function was programmed into the tablet intake form for UKanQuit staff to press that randomized eligible smokers to either OPT OUT or OPT IN. UKanQuit staff assisted smokers to quit in accordance with the treatment they were randomized.

Project Measures

Among participants who provided consent, we conducted additional surveys—beyond UKanQuit service data intake—at months 1 and 6. Data resided in the UKanQuit service database managed by Niaman Nazir.

Consent and retention. During their inpatient treatment, all patients randomized to the trial were notified that an evaluator would call them at 1 month following discharge to administer a brief survey about the tobacco treatment the patient received in the hospital (with no mention of randomization or participation in a clinical trial). Also during inpatient treatment patients were asked to provide their Social Security Number (SSN) to permit the evaluator to provide $25 reimbursement for the survey. Hence, patients were expecting the survey and most had provided a SSN and been given an "empty" gift card to facilitate reimbursement for the brief survey at 1-month post discharge.

The 1-month consent form followed several steps (see Supplement 5): 1) collect a short set of data (Part A) from all participants as part of routine UKanQuit evaluation – Part A included collecting current smoking status; 2) inform all patients that $25 would be loaded onto their "empty" gift card for participating in the brief survey; 3) debrief the patient on the randomized trial without disclosing what arm the patient was assigned to; 3) notify the patient there would be additional assessments and reimbursement if they consented to participate in the trial; 4) collect consent and administer a lengthier survey (Part B) to consenters; 5) Ask consenters who had self-reported they quit (in Part A - prior to knowing they were in a trial) to provide biochemical verification of cessation. To avoid encouragement to falsify sample, the consent form directed the research staff to explain that the saliva sample was needed to "determine the amount of nicotine and organic compounds left in the system of people who have quit smoking."

Tobacco abstinence. Outcome measures were adapted from the Society for Research on Nicotine and Tobacco's Workgroup on Abstinence Measures and Workgroup on Biochemical Verification.[4] Only smokers who self-reported abstinence completed verification. Our primary endpoint was 7-day, self-reported and verified cigarette abstinence at 1 month after randomization. In accordance with common analytic procedures for tobacco treatment trials, patients who did not consent to follow up, and those who consented but who were not reached or not verified, were counted as smokers.

*Verification of abstinence***.** We used either mailed salivary cotinine, anabasine or in-person expired air carbon monoxide (CO) testing to confirm smoking status. Saliva samples were stored in a -20^{o} freezer until laboratory analysis. Participants who reported 7-day point prevalence abstinence, and who were not taking nicotine replacement, were asked to provide a salivary cotinine sample. Cotinine was the measure of choice because of its sensitivity and specificity.[4] We used a cut-point of $\leq$10 ng/ml to differentiate smokers from nonsmokers.[5] Prior to the COVID-19 pandemic participants reported abstinence but who were still using nicotine replacement, or those who refused salivary cotinine, were verified via CO. Those with $\leq$10 ppm were considered abstinent. During the COVID-19 pandemic carbon monoxide testing was discontinued. During the COVID-19 pandemic we used mailed salivary anabasine testing to verify abstinence among participants who reported not having smoked in the past 7 days, but who reported use of nicotine replacement, electronic cigarettes or other tobacco products. The cut-point for anabasine was <1 ng/ml to differentiate smokers from nonsmokers.[6,7]

Secondary outcomes, mediators, and moderators. Counseling time was collected throughout the trial and was summarized as 'total counseling time' for analyses. We assessed the type, the dose, and the number of days medication was used via the method of Williams et al.[8] This was summarized as 'any use of medication post-discharge' and 'number of days of medication use' for analyses. Default-related variables were derived from the literature on choice theory and

included smokers' perceptions of provider attitudes toward tobacco treatment, smokers perceptions of the degree to which their provider recommended tobacco treatment, perceptions of being coerced into treatment and the quality of therapeutic alliance between themselves and their providers.[9-13]

Intervention costs. We prospectively tracked variable intervention costs. Costs included inpatient counselor services, postdischarge counselor time, and initial pharmacotherapy dispensed at baseline. During the 1-month follow-up call, we asked participants to recall their use of pharmacotherapy after the initial supply. Personnel time was valued at Bureau of Labor Statistics (www.bls.gov) wages plus benefits for an appropriately trained health promotion professional. Pharmacotherapy cost was based upon retail prices estimated from on-line pharmacy websites, e.g., www.drugstore.com during the study. Intervention costs were tracked as they are incurred. We excluded research costs. Given that all costs are short-term (<6 months), we did not discount either costs or benefits.

Fidelity monitoring. Fidelity to components was assessed by in-person fidelity assessment checks during hospital consults and by analysis of digitally recorded inpatient counseling sessions. To assess the quality of the intervention and control conditions, we assessed the degree to which UKanQuit staff accurately: 1) identified eligible/ineligible participants; 2) provided brief advice and the study pamphlet; 4) randomized patients and performed the appropriate intervention for OPT OUT and OPT IN; 5) addressed post-discharge medications; and 6) provided information regarding the post discharge counseling to patients as randomized. Digital recording was only conducted on patients who provided written consent for the audio recording of the counseling session.

Data Management

Survey and EMR data were directly entered via tablet into REDCap. Data manager Mr. Nazir conducted data cleaning, conversion into proper format for data analysis, and recoding using standard operating procedures. All data were imported into SAS for study analyses. Cleaning and management routines (e.g. conversion of birth dates to ages, logical checks for continuous variables, compliance with skip patterns, missing data codes) were be conducted using SAS.

Data Analysis: Overview of Hypotheses and Analyses

The overall study design was a posttest only design with random assignment to groups. We conducted process, outcome, mediation, and cost analyses. Prior to initiating outcome analyses of quantitative data, we compared baseline data across groups to evaluate whether random allocation achieved equivalent groups. Bayesian analysis (see *Statistical Model*, below) will answer our main outcome. When conducting the final analysis we excluded participants who refused consent and patients who died or who were incarcerated.

Data Analysis: Bayesian Study Design, Outcome Analyses, and Cost Effectiveness

We performed a prospective randomized comparative effectiveness *Bayesian adaptive design study*.[14] This approach is a highly efficient and ethical strategy for comparative effectiveness clinical trials design, because it allocates more patients to effective treatments and can answer the research question earlier than conventional designs.[15] In Bayesian adaptive designs, one primary endpoint is used to drive the adaptive randomization. This endpoint is compared across study groups periodically, and more patients are randomized to the stronger arm, until a predetermined probability that one arm has "maximum utility" is reached, which signals the end of the comparative trial. Our endpoint was the percentage of patients who quit smoking at 1-month (4 weeks) post-study randomization. We performed our first planned interim analyses when we randomized 400 patients. The arm that appeared to be performing the best had more participants allocated to it in the subsequent randomization period. A new adaptive randomization structure

was updated every 13 weeks, using up-to-date 1-month outcome data, until we randomized all 1,000 participants.

Virtual participant response. In accordance with guidelines for adaptive design power analyses[14], we assumed several virtual (or "pretend") responses to determine the power, sample size and time (duration) needed for our study. We created several scenarios for quit rates using three assumptions. One virtual response was the 'expected' quit rates, another was 'small but unlikely' quit rates, and the third was 'no differences' in quit rates.

Accrual (enrollment) patterns. Accrual patterns refer to how rapidly we enroll patients in the trial. These are important to Bayesian adaptive designs for determining the length of the trial. Based on accrual patterns for EQUIP and other hospital studies conducted by Drs. Richter and Ellerbeck, we assumed that the accrual patterns would follow a Poisson distribution with an average of 6.7 patients per week.

Virtual response patterns for quit rate endpoint			
	OPT IN	OPT OUT	
		Efficacy	
No differences	15.7%	15.7%	Both have equal quit rates
Small but unlikely	15.7%	20.0%	Opt-Out is moderately better
Expected	15.7%	25.2%	Opt-Out is better at expected differences

Statistical model. For this study the primary endpoint was modeled $S_{Qj}|n_j \sim \text{Bino}(n_j, \theta^Q_j)$ quitting. In addition, we provided "uninformative" priors, $\text{logit}(\theta^Q_j) \sim N(0,100^2)$. Using the endpoint data and the prior probabilities, we then used Markov Chain Monte Carlo computations to obtain the Bayesian posterior distributions for the endpoint (i.e., quitting.) We proposed to stop randomizing into the comparative trial if the probability of a study arm having best utility was greater than 0.9925 at both 1-month AND 6-months. The arm (or drug) having the maximum quit rate was $M_T=\max(\theta^Q_1, \theta^Q_2)$. The stopping rule was mathematically $P(\theta^Q_1 > \theta^Q_2) > .9925$ or $P(\theta^Q_1 < \theta^Q_2) > .9925$), this had to take place both at 1-month and 6-month endpoints. If a best arm was not identified after 500 patients randomized, this procedure and accrual would continue until a best arm was identified or we randomized all 1000 patients. If we were to reach our stopping rule before 1,000 patients randomized, we would continue to recruit patients, but we would stop randomization and recruit the remaining patients into the more effective study arm. We proposed to do so because this was the first trial to experimentally test the impact of changing a treatment default. We believed it was important to maximize our cases to enable us to conduct mediation analyses to determine the mechanisms that underlie the impact of treatment defaults.

Adaptive Randomization: allocation. After the best utility probability was evaluated the next round of patients who were randomized using a formula, which is $V^*_j=\text{sqrt}(P(\theta^Q_j > \theta^Q_{j'})\text{Var}(\theta^Q_j)/(n_j+1))$ and θ^Q_j and $\theta^Q_{j'}$ are the utility parameter (i.e. smoking quitting rate parameter) of the two arms at 1-month only, that took advantage of the information gained from our analyses up to that point. The newly enrolled patient allocated to the j^{th} arm was proportional to $V^*_j=\text{sqrt}(P(\theta^Q_j > \theta^Q_{j'})\text{Var}(\theta^Q_i)/(n_{jT}+1))$. This type of allocation tends to have more desirable properties then simply using $\Pr(M_{jT}= \theta^Q_1)$. In other words, using this approach allowed us to assign more patients to the most promising arm, and fewer patients to the least. We confirmed this finding with a subsequent analysis and evaluation (>.99), at 1-month OR 6-month endpoints, after all data from patients were obtained, as some were actively in the study when the early success criterion was identified.

Power, sample size, and trial duration. We performed three sets of trial simulations based on the various combinations of quit rates endpoints for both 1-month and 6-months (Table 5). Each set involved many trial simulations that identified power (the probability of success) in two scenarios—one for early success (i.e., being able to stop randomization early) and one for late success (i.e.,

upon randomizing all 1000 patients). While two of these combinations are very unlikely to occur, we included all scenarios. First, under the 'expected' quit rates at 1-month and 'expected' at 6-months, we estimated (identified) that 75% of the simulated trials had early success, 24% late success, and only 1% had incomplete results. Thus this scenario had 99% power. The average sample size of this trial scenario was 789 patients with more than half (546) in the better OPT-OUT arm. The average length of these simulated trials was 145 weeks. Second**,** if there is 'expected' quit rates at 1-month and 'small but unlikely' quit rates at 6-months, we estimated (identified) that 23% of the simulated trials had early success, 68% had late success, and 9% had incomplete results. This trial scenario had 91% power and the sample size of this trial scenario was on average 947 with more than half (696) in the better OPT-OUT arm. The average length of this trial scenario was 167 weeks. Third, we examined the scenario that serves as our null hypothesis (no differences) at both 1-month and 6-months. In this scenario there are no differences in quit rates among the arms. The extent to which this scenario is "successful" actually reflects our Type I error rate. For this scenario, we estimated (identified) that 0% of the simulated trials had early success, 5% late success. Thus this trial scenario produced an appropriate expected Type I error (α=.05,). The sample size of this scenario on average was 1000 patients, with half (500) in the OPT OUT arm. The average length of the trials under this scenario was 175 weeks— approximately 3 years of recruitment. Hence, our sample size of 1,000, in 3 years of recruitment, provided ample time and patients to identify project outcomes under all 3 scenarios.

Cost analyses for Hypothesis 3. We conducted a cost-effectiveness analysis to explicitly document the relative costs and benefits of OPT OUT versus OPT IN. Dr. Nazir and Dr. Shireman managed the cost effectiveness analysis. Our cost analytic framework generally followed the guidelines adopted by the Centers for Disease Control (CDC) in accordance with the consensus Panel on Cost-Effectiveness in Health and Medicine.[16] The cost-effectiveness analysis was set up as an incremental cost-effectiveness ratio (ICER). We anticipated that OPT OUT would be more costly and more effective than OPT IN. Incremental cost-effectiveness analysis identifies the marginal benefit of switching from one intervention to the other and is the ratio of the difference in costs divided by the difference in effectiveness between the two treatment options. The outcome assessed was be biochemically verified 7-day point prevalence abstinence at 1 month. The ICER indicated the added cost per additional quitter OPT OUT versus OPT IN, a metric that will allow comparisons to other smoking cessation economic studies. In designing these analyses, we considered using a societal perspective, as recommended by current national guidelines.[18] The societal perspective, however, requires quality-adjusted life years (QALYs) as the denominator. Since this is a short-term study, we decided against attempting to estimate changes in QALYs, and focused instead on cost per quit. Confidence intervals for costs and quit rates were estimated using Bootstrapping using samples of 1,000.

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