

## ORIGINAL ARTICLE

# Unblinded and Blinded N-of-1 Trials Versus Usual Care: A Randomized Controlled Trial to Increase Statin Uptake in Primary Care

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**BACKGROUND:** The aim was to assess whether an intervention incorporating a practicable open-label n-of-1 trial would lead to greater uptake of statin than usual care and comparable uptake to a closed-label gold-standard n-of-1 trial.

**METHODS:** We enrolled patients who had stopped or declined statins into a 3-arm trial (usual care, unblinded, and blinded n-of-1 intervention arms). Physicians advised participants randomized to usual care to take statin therapy to prevent cardiovascular disease. In both intervention arms, physicians delivered a theoretically informed intervention endorsing the value of experimenting with medication in n-of-1 trials to assess whether it caused side-effects. In these trials, participants alternated between 4 weeks of medication and no medication (unblinded arm) or randomly sorted active and placebo (blinded arm) and recorded symptoms and symptom attributions for 6 months. Thereafter, physicians discussed participants' symptom reports during active/inactive treatment periods and asked participants to resume statins if appropriate.

**RESULTS:** Seventy-three were randomized to the intervention arms and 20 to the control group. Fifty-six of 73 (77%) attempted the n-of-1 experiment; 28/36 (78%) in the unblinded arm; and 28/37 (76%) in the blinded arm. Forty-three of 56 (77%) completed the 6-month experiment and received feedback from the physician; 20/28 (71%) in the unblinded arm and 23/28 (82%) in the blinded arm. Thirty-three of 76 (45%) people restarted statins in the n-of-1 arms compared with 4/20 (20%) in the control arm, difference 24% (95% CI, 5%–43%;  $P=0.041$ ). There was no evidence this differed between blinded and unblinded arms, difference 2% (95% CI, –20% to 24%;  $P=0.86$ ). Adverse events occurred at a similar rate on and off statin.

**CONCLUSIONS:** In patients refusing or intolerant of statin, supporting experimentation with n-of-1 trials increases medication uptake compared with usual care. Alternating on-off medication in unblinded n-of-1 experiments appears as effective as a blinded experiment.

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## See Editorial by Howard and Rajasundaram

Statins reduce cardiovascular disease (CVD) risk and all-cause mortality.<sup>1</sup> Severe adverse reactions are extremely rare,<sup>2</sup> and randomized controlled trials indicate that statins are well tolerated in most users.<sup>3</sup> Nonrandomized, nonblinded, observational studies suggest statins are related to muscle pain (in the absence

of myopathy)<sup>4</sup>; and these findings are widely reported in public media.<sup>5</sup>

Nonuse of statins appears common. Data from a UK database of 11.4 million patients' records reported that the prevalence of statin use in people with a cardiovascular risk of 10% to 19% in the next 10 years was

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### WHAT IS KNOWN

- Clinical trials and blinded challenge studies show that statins are well tolerated, even in people with statin intolerance.
- Despite this, nonuse of statins is more common than use in people in whom clinical guidelines suggest statins are indicated, mostly due to fear or experience of apparent side-effects.

### WHAT THE STUDY ADDS

- Physicians delivered a behavioral intervention to encourage patients with statin intolerance or who had declined statins to use n-of-1 experiments to test their beliefs, leading to worthwhile increase in resumption of statins compared with usual care.
- Switching between use and nonuse in and recording whether symptoms occurred in the n-of-1 experiment was as effective as placebo-controlled n-of-1 experiments in supporting uptake.

### Nonstandard Abbreviations and Acronyms

<b>CVD</b>	cardiovascular disease
<b>HDL</b>	high-density lipoprotein
<b>LDL</b>	low-density lipoprotein

21% and for those with a risk score  $\geq 20\%$  it was 49%. UK guidelines recommend use above 10% risk and a third of the UK population aged 25 to 83 years without CVD have a CVD risk  $\geq 10\%$  (Frances Crowe, PhD and Tom Marshall PhD, 2021). A US registry study reported 26.5% of those eligible for statin were not taking them.<sup>6</sup>

The reasons for nonuse could relate to doctors not offering or patients not accepting statins or both. A UK study invited people without CVD but with a cardiovascular risk score  $\geq 10\%$  to a consultation to discuss statins. Only 24% attended this consultation and only 45% of attendees started statins, meaning only 11% of people offered statins agreed to start them.<sup>7</sup> A US survey of people not using statins but where this was indicated by guidelines reported that only 10% declined statins, while 59% reported never having been offered statins.<sup>6</sup> This study reported that 31% of nonusers were people who stopped statins. A UK study reported that more than half of patients starting statins in routine practice discontinued within the first year,<sup>8</sup> primarily because of intolerable adverse effects (such as muscle pain).<sup>9</sup> Discontinuation increases after periods of increased media coverage highlighting apparent adverse effects.<sup>5</sup> The US survey reported that fear of or experience of side-effects was the prime reason patients declined or stopped statins.<sup>6</sup> This accords with a systematic review of qualitative studies, which found that statin use could be explained by

the interaction of beliefs about trust in preventive efficacy and doubts over the mechanism of action combined with fears about adverse effects, including side-effects, but also relating to perceptions of dependence, and notions of the sick role.<sup>10</sup> This accords with a theory of medication adherence, which proposes that people take medication when beliefs about the necessity to do so outweigh their concerns about it, and the practicalities of adherence related to the routine of medication taking; the Perceptions and Practicalities model.<sup>11</sup>

How could widespread beliefs that statins commonly cause adverse effects have arisen despite trial evidence to the contrary? Statin intolerance could arise because patients misattribute adverse events from unrelated causes to the medication. The commonest presumed side-effects are musculoskeletal symptoms,<sup>4</sup> which are common among the age group prescribed statins. People could misattribute these musculoskeletal symptoms to statins. Once concerns are well known, patients starting statins who are aware of the potential adverse effects could anticipate experiencing them leading to their occurrence: nocebo effects.<sup>12</sup> This latter explanation is supported by data from a trial that found that transition from placebo-controlled to open-label statin use appeared to increase adverse effects.<sup>13</sup> Physicians do not have a diagnostic tool to inform patients whether symptoms experienced while taking statins are caused by them.

N-of-1 trials examine adverse effects in individual patients can help patients make decisions about treatment benefits versus harms.<sup>14</sup> In randomized n-of-1 trials, participants receive an active intervention or placebo in randomly ordered pairs. Patients are assessed on medication and on placebo to examine whether adverse effects are a result of the treatment or an alternative cause. A proof of concept trial showed that n-of-1 trials alternating statin and placebo with patients with presumed statin intolerance led to 5 of 8 patients resuming statins.<sup>15</sup>

Blinded n-of-1 trials equalize nocebo effects between arms and thus do not show whether adverse events attributed to medication by patients are caused by expectation or by misattribution. Unblinded n-of-1 trials are susceptible to nocebo effects, but by systematically recording the occurrence of symptoms when using and not using a statin, they may reveal that the patient's symptoms attributed to statin are occurring independently and were being misattributed. In addition, unblinded n-of-1 trials are the only practical option in everyday clinical practice. Given statins are effective, safe, and tolerable but commonly declined or discontinued by patients who would benefit, we developed a behavioral intervention to increase uptake and tested it in a trial. The intervention addressed both necessity beliefs and common concerns and comprised both explanation of the benefits with mechanistic information and reassurance that

side-effects were uncommon. However, the intervention aimed to allow patients to test these concerns through self-experimentation using n-of-1 trials. Our prime interest was to assess whether the behavioral intervention incorporating the practicable open-label n-of-1 trial would lead to greater uptake of statin than usual care and comparable uptake to a closed-label gold-standard n-of-1 trial. We tested this among people who had either declined or stopped statins, as necessity beliefs and concerns about side-effects are common reasons for non-use of clinically indicated statins and for both groups the main issues relate to concern about side-effects.

## METHODS

### Trial Design

This was an individually randomized groups three-arm, controlled trial of a primary-care physician delivered behavioral intervention to increase statin adherence randomizing 2:2:1 to a behavioral intervention comprising discussion with a physician and unblinded n-of-1 trial, the same discussion but with blinded n-of-1 trial, and usual care. Given our aim was to achieve uptake in a group who had previously shown that they did not want to use statins, we adopted a particular approach to recruitment and consent. We invited patients in whom statins were clinically indicated by UK guidelines and had declined to start or started and deliberately stopped statins. We asked patients to consent to discuss their cardiovascular risk with the general practitioner and ways to reduce it and to consent to the follow-up procedures. We did not mention statins at all during these discussions, and the large majority did not ask about whether this trial concerned statins. Consequently, patients' decisions to enroll in the study were unrelated willingness to experiment with statins. This consent procedure and the protocol was approved by the North of Scotland Research Ethics Committee (REF: 19/NS/0014), prospectively registered on the ISRCTN (11142694), and published.<sup>16</sup> The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Participants

Primary care physicians searched electronic health records for patients with prior statin intolerance or who had previously declined statins and in whom statins were indicated. Physicians excluded from invitation patients where their previous intolerance was severe enough that recommencing statins may comprise a significant health risk or the physician recommended the patient should not recommence statins (Appendix I). Physicians wrote to their patients and those interested to join the study contacted the research team.

### Interventions

There were 2 arms where participants received a behavioral intervention to increase the use of statins. In the behavioral intervention, the physician elicited participants' concerns about statins and sought to address these by positively endorsing the cardiovascular benefits of statins, explaining their mechanism of action to create trust, and the prevalence

of adverse events in clinical trials versus routine practice. Information was supplemented with a booklet for participants to take home (Appendix II). The physician encouraged participants to test whether their concerns about adverse effects were valid by experimenting with atorvastatin (20 mg) for periods of 4 weeks on followed by 4 weeks off, doing so 3×, totaling 6 months. Participants recorded all adverse events that occurred on each day of the last week of each 4-week period and whether they attributed the event to statin using an electronic link emailed or texted to them.

In the behavioral intervention including the unblinded n-of-1 trial, participants started with no statin for 4 weeks followed by statin and alternated like this for 24 weeks. In the behavioral intervention incorporating the blinded n-of-1 trial, which we deemed a positive control, participants were given capsules in 4-week blocks that included either an encapsulated atorvastatin tablet or filler only. To ensure that the 8-week safety check on hepatic transaminase was meaningful, we ensured the sequence was no statin followed by statin for the first two blocks and thereafter was randomized by the pharmacy. Neither physician nor patient were aware of the sequence. Participants were invited for a blood test to examine hepatic transaminase and lipids just before an 8-week follow-up appointment where physicians reviewed the effect on lipid profile with the patient and encouraged continuing the experiment, troubleshooting if needed.

The data on adverse events and attribution were collated in a report (Appendix III) displaying counts of symptoms occurring during the statin compared with the nonuse/placebo periods and whether participants attributed the symptom/s to the statin. It also presented change in LDL (low-density lipoprotein) and HDL (high-density lipoprotein) cholesterol from baseline to 8 weeks. Physicians were trained to discuss this report and, in consultation, elicit participants' conclusions about the data at a 6-month appointment. If patients were reassured that statins did not cause side-effects, physicians offered to prescribe statins long-term.

For the comparator, participants continued usual primary care but physicians asked participants to attend at 6 months, where the physician was asked to give their usual invitation to commence a statin.

### Outcomes

The primary outcomes at the study level were (1) the proportion of invited patients enrolled into the trial, (2) the proportion of enrolled patients randomized to the combined n-of-1 arms who accept the physician offer and attempt the n-of-1 experiment after the first visit, and (3) that the proportion of participants in the combined n-of-1 arms who report restarting statins full time at 6-month follow-up.

The secondary outcomes were (1) the proportion of participants who report restarting statins full time in the unblinded arm compared with the proportion in the blinded arm, (2) the difference in self-reported symptoms in the unblinded arm compared with the blinded arm (3) the proportion of times participants attributed symptoms to statins in the unblinded experiment compared with the blinded experiment (4) the difference in mean pain severity and pain interference scores during active and inactive treatment periods in the unblinded arm compared with the blinded arm,<sup>17</sup> and (5) the difference in mean beliefs about medication scores before and after

the n-of-1 experiments and the difference in these changes between the unblinded and blinded arm. Occurrence of symptoms, and if they occurred, their attribution, and pain scores (outcomes 2–4) were measured using a questionnaire administered daily on the last week of each 4-week treatment period. Medication beliefs were collected by the Beliefs about Medication General Questionnaire at baseline and 6-month follow-up.<sup>11</sup> This assessed participants' attitudes to the overuse of medications (4-items) and beliefs about the harmfulness of medications (4-items) on 5-point scales. Higher scores indicate stronger beliefs about the corresponding concepts of each 4-item subscale.

The physician-delivered first intervention was audio-recorded to assess fidelity.

## Sample Size

We estimated that 90 participants, 18 in the control arm, and 36 in each of the 2 n-of-1 arms, would provide a  $\pm 0.25$  margin of error on a 95% CI for the difference in proportions of participants restarting statins between the control arm and the combined n-of-1 arms. This sample size estimation assumed the proportion restarting statins in the n-of-1 arms was 0.50. This sample size would give 95% CIs of  $\pm 0.11$  on the proportion agreeing to start the n-of-1 experimentation assuming half did so across the n-of-1 arms. We judged that the trial itself would be unfeasible if the proportion enrolling of all those invited were  $< 0.04$ , but we assumed that it would be about 0.1. With 90 in the trial, that would give 95% CIs of  $\pm 0.02$ . We considered that these were acceptably precise estimates.

## Randomization

Participants were randomized 2:2:1 (unblinded n-of-1 experiment: blinded n-of-1 experiment: usual care) using random permuted blocks of 5 and 10. An independent researcher generated the randomization sequence using online software (www.randomization.com), stratified by general practice. The allocations were transferred to sequentially numbered sealed opaque envelopes to ensure allocation concealment. It was not possible to blind participants, physicians, and researchers after treatment allocation.

## Statistical Analyses

The primary outcome proportions were analyzed stratified by practice to derive a common difference in proportion using conditional maximum likelihood estimation in OpenEpi.com. These analyses were intention to treat, meaning everyone randomized to an arm was considered in the denominator even if they withdrew consent or did not receive the behavioral intervention.

For participants allocated to the intervention arms, we calculated the days with symptoms as a proportion of all days that daily reports were completed and days these were attributed to statins as a proportion of all days that attributions were made when using and not using statins in the blinded and unblinded n-of-1 experiment arms and simply tabulated these. We also present the mean number of days and SD participants experienced symptoms on and off statins by arm. We summarized the adverse events and coded these using MedDRA.<sup>18</sup>

We calculated the mean pain severity score and interference score for each day pain responses were recorded and

used mixed linear regression models within each arm to compare pain severity and interference when on and off statins within arms and with person set as a random effect. We calculated the difference between arms in mean pain score and interference with an analogous mixed model including a term for arm, statin use/nonuse, and their interaction. The models were fit in Stata 14.2 using the mixed command.

We calculated means and SDs for the Beliefs about Medication General Questionnaire at baseline and follow-up and mean change and its SD between baseline and follow-up. We used *t* tests in SPSS v22 to calculate differences in mean change in score between the 2 intervention arms combined and the control group, and separately between the blinded and unblinded arms.

Intervention fidelity was assessed by the presence of pre-specified criteria: explaining cholesterol, CVD risk and the physiological effect of statins, discussing the safety and tolerability of statins, describing the benefits of experimenting with medication to understand symptoms, and the blood test review.

## Patient and Public Involvement

We recruited 5 patient and public involvement panel members who had started medication for a long-term condition (or to prevent future disease that had caused intolerable adverse effects), who informed intervention design, methods, and the supporting booklet.

## RESULTS

### Fidelity

A sample of intervention consultations showed good physician fidelity, but fidelity was lower for discussing safety issues and adverse effects (Table S1).

### Participant Flow

Between 1 June 2019 and 6 September 2019, 3 general practices joined the study and invited 707 patients to participate, 119 (19%) responded to the invitation, and 93 (13%) were eligible and enrolled. Practices contributed 14, 34, and 45 participants. Thirty-six were randomly allocated to the unblinded arm, 37 to the blinded arm, and 20 to usual care. Follow-up was completed on May 8, 2020.

At baseline, nearly a fifth had established CVD and statins were indicated in the remainder for primary prevention; half the participants had hypertension. Participants were in their 70s on average, 9 in 10 were White British, and were above average socioeconomic status (Table 1).

Two participants in the unblinded arm and one in the blinded arm withdrew from the study before the behavioral intervention. Physicians wrongly deemed that 2 participants in the unblinded and 3 in the blinded arm had not declined statins previously and so the physicians did not invite them to receive the behavioral intervention. Two participants in the unblinded arm did not

**Table 1. Baseline Characteristics**

	Unblinded n-of-1 trial (n=36)	Blinded n-of-1 trial (n=37)	Usual care (n=20)	All (n=93)
Male, n (%)	16 (44)	16 (43)	8 (40)	40 (43)
Age in years, mean (SD)	73.8 (9.9)	73.5 (7.2)	74.9 (5.4)	73.9 (8.0)
Ethnicity, n (%)				
White British	35 (97)	33 (89)	19 (95)	87 (94)
Other	1 (3)	4 (11)	1 (5)	6 (6)
Employment status, n (%)				
Unemployed	0 (0)	2 (5)	0 (0)	2 (2)
Retired	29 (81)	25 (68)	18 (90)	72 (77)
Employed full time	2 (6)	4 (11)	2 (10)	8 (7)
Employed part time	3 (8)	6 (16)	0 (0)	9 (10)
Carer	1 (3)	0 (0)	(0)	1 (1)
Education level, n (%)				
None	3 (8)	4 (11)	1 (5)	8 (9)
GCSE/equivalent	8 (22)	9 (24)	5 (25)	22 (24)
A-levels/equivalent	2 (6)	8 (22)	4 (20)	14 (15)
University undergraduate	19 (53)	10 (27)	8 (40)	37 (40)
University postgraduate	4 (11)	6 (16)	2 (10)	12 (13)
IMD decile, mean (SD)*	8.1 (1.5)	7.7 (2.0)	8.1 (2.0)	7.9 (1.8)
Baseline lipids, mean (SD)†				
HDL, mmol/L	1.5 (0.4)	1.4 (0.3)	...	1.5 (0.4)
LDL, mmol/L	4.0 (1.0)	3.7 (0.9)	...	3.8 (0.9)
Comorbidities, n (%)				
Hypertension	19 (53)	17 (46)	9 (45)	45 (48)
CV Disease	7 (19)	8 (21)	2 (10)	17 (18)
Diabetes	3 (8)	1 (3)	0 (0)	4 (4)
Beliefs about medication score, mean (SD)	22.1 (4.1)	21.2 (4.3)	22.6 (4.4)	21.8 (4.2)

CV indicates cardiovascular; GCSE, general certificate of secondary education; HDL, high-density lipoprotein; IMD, index of multiple deprivation; and LDL, low-density lipoprotein.

\*IMD of the area in which the participant lived, GCSE taken at age 16 years, and A-levels are qualifications taken at 18 years.

†Baseline lipids not measured in usual care group.

attend the physician's appointment. Therefore, 30/36 (83%) participants allocated to receive the behavioral intervention in the unblinded arm and 33/37 (89%) in the blinded arm actually received it. Two participants withdrew immediately after discussion with the physician (Figure). Four other participants, 2 in the unblinded and 2 in the blinded arm withdrew during the n-of-1 experimental phase, meaning 86/93 (92%) were followed-up at 6 months.

## Primary Outcomes

Of the 73 participants randomized to the behavioral intervention arms, 56 (77%) attempted the n-of-1 experiment, which was 56/63 (89%) of those who attended the physician appointment and offered the opportunity to experiment; 28/36 (78%) of everyone randomized to the unblinded arm and 28/37 (76%) in the blinded arm. Of those who started the n-of-1 experiments, 43/56 (77%) completed the 6-month

experiment and received a feedback report from the physician; 20/28 (71%) in the unblinded arm and 23/28 (82%) in the blinded arm.

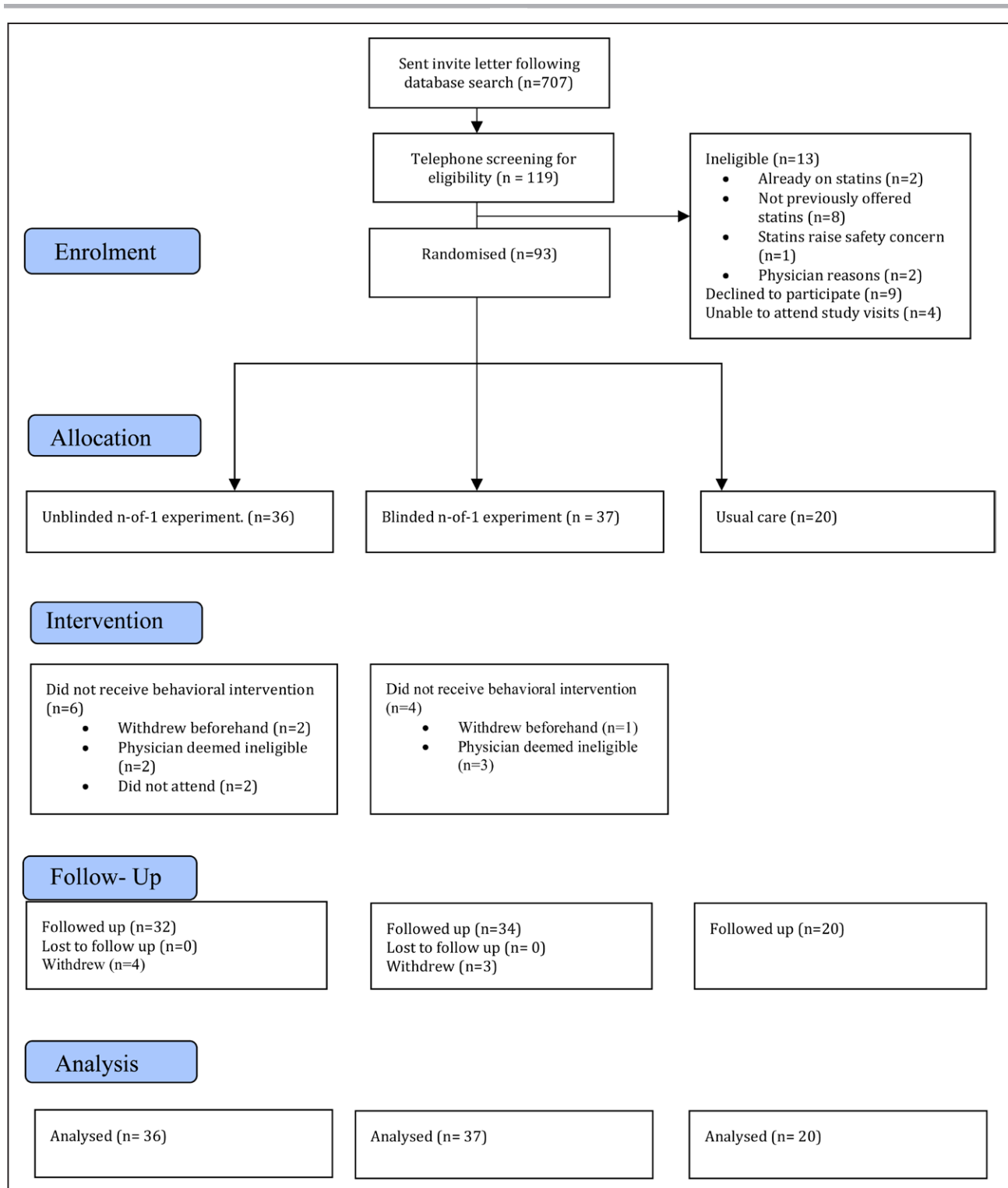
Thirty-three of 73 (45%) people restarted statins in the behavioral intervention arms compared with 4/20 (20%) in the control arm, difference 24% (95% CI, 5%–43%;  $P=0.041$ ). Of those attending the physician appointment, the corresponding figures were 52% in the intervention arms compared with 20% in the control arm, difference 31% (95% CI, 10%–51%;  $P=0.014$ ).

## Secondary Outcomes

### Proportion of Participants Restarting Statin in Blinded Versus Unblinded Arm

Of the 36 randomized to the behavioral intervention with unblinded n-of-1 experimentation, 16 (44%) restarted statins compared with 17/37 (46%) who received the blinded n-of-1, difference 2% (95% CI, –20% to 24%;  $P=0.86$ ).





**Figure. CONSORT flow diagram.**

### Self-Reported Symptoms and Attribution to Statin

Ten of 20 (50%) of participants who completed daily reports in the unblinded arm and 14/25 (56%) of participants in the blinded arm reported no symptoms in any daily report. In total, participants reported having physical symptoms on one-fifth of the days, with minimal differences between days taking or not taking statin (Table 2),

or between unblinded and blinded behavioral intervention arms. Participants reported having symptoms on 3 or 4 days in total on and off statins in both blinded and unblinded arms (Table 3). In the unblinded arm, people's attribution of symptoms differed when using statins compared with not using them. On statins, participants attributed nearly half the symptoms that occurred to the statin.

**Table 2. Total Number of Days on Which Participants Reported Occurrence of Symptoms On and Off Statins**

	Unblinded arm (n=36)		Blinded arm (n=37)	
	Statin	No statin	Statin	No statin
Experienced symptoms	20.4% of 323 days	22.3% of 340 days	20.9% of 402 days	22.4% of 388
Participants reporting	20	20	25	25
Participants could report on symptoms up to 21 days while on statins and 21 days off statins.				

When not on statins, participants attributed only a fifth of symptoms to them. In the blinded arm, participants attributed symptoms to statins on a third of occasions when on and not on statins. In addition, in the unblinded arm, participants were more certain of their attributions than in the blinded arm (Table 4). The symptoms that occurred were diverse (Table S2).

### Pain Scores

Mean pain and interference scores were very low (0.3 out of 10), and there was no meaningful difference in pain scores between unblinded and blinded arms (Appendix VI).

### Beliefs About Medications

Concerns about medication did not change over time, nor was there evidence of differences between groups (Appendix VI).

## DISCUSSION

### Summary

Three quarters of patients with prior statin intolerance or who had refused statins were prepared to commence n-of-1 experiments when their physician explained the rationale. Most completed the experiments and nearly half resumed or commenced statins compared with a fifth in the usual care group. This may be because adverse effects including pain were equally common when on compared with off statins. Participants randomized to the unblinded arm, where they simply alternated between taking and not taking statins, had similar experiences and outcomes to participants allocated to the blinded (placebo-controlled) arm.

### Strengths and Limitations

Before intervention development, we surveyed 211 physicians for feedback on our intervention plan and met with patients who had previously stopped medication due to side effects for help developing the intervention. The

intervention was developed using the principles of the person-based approach.<sup>19</sup> We used a behavioral analysis drawing on 2 frameworks to improve agreement to experiment.<sup>20,21</sup> This appears to have resulted in high fidelity from physicians and engagement by patients.

The trial had limitations. One in 8 patients invited by letter participated. While low, this slightly higher proportion than observed in similar trials inviting participants by letter for chronic disease management.<sup>22–24</sup> Recruiting to any trial of treatment for prevalent disease by letter appears to lead to between 5% and 20% of patients invited participating in the trial. This low proportion may be a function of method of invitation by letter to participate in research, rather than solely reflecting motivation to address their disease. However, here we aimed to and appeared to succeed in ensuring we recruited a population who were unaware that this was a trial concerned with statin use. The low proportion responding, however, raises the question on whether this population were typical of the general population in primary care who have concerns about statins. A larger trial is required to test the effectiveness of the intervention across a more diverse population. With ethical approval, we described the trial aims in general terms to participants, concealing that the intervention concerned statins. This ensured that we tested the intervention as it would be delivered in clinical practice, where there would be no prior consent to discussing statins with a physician. Some participants asked and were told that the intervention concerned statins, which is why some participants did not attend their physician for the initial appointment, an effect that may not happen in routine clinical practice. The intervention comprised information designed to reassure about statin tolerability and mechanism of action, and it is possible that training physicians to give this element of the intervention alone could have been enough without the experimentation. It is also worth noting that this was not an intervention to address statin intolerance alone and as such the population invited comprised people who had never tried statins. Physicians were not blinded to patient treatment allocation but were trained to deliver

**Table 3. Mean (SD) Number of Days Participants Reported Symptoms On and Off Statins**

	Unblinded (n=36)			Blinded (n=37)		
	Statin	No statin	Difference	Statin	No statin	Difference
Mean (SD) days symptoms occurred	3.3 (5.7)	3.8 (6.0)	−0.5 (3.2)	3.4 (5.4)	3.5 (5.8)	−0.1 (4.7)
Mean (SD) of symptom-free days	12.9 (7.5)	13.3 (6.5)	−0.4 (4.4)	12.7 (7.6)	12.0 (7.7)	0.7 (3.7)

**Table 4.** Attribution of Symptoms to Statins on Days When Symptoms Occurred

Attributed to statins?	Unblinded arm		Blinded arm		Total
	No statin	Statin	No statin	Statin	
Strongly agree	6 (8.5%)	14 (21.2%)	0 (0%)	0 (0%)	20 (6.5%)
Agree	9 (12.7%)	16 (24.2%)	27 (31.0%)	28 (33.7%)	80 (26.1%)
Neither	14 (19.7%)	8 (12.1%)	43 (49.4%)	44 (53.0%)	109 (35.5%)
Disagree	6 (8.5%)	10 (15.2%)	17 (19.5%)	6 (7.2%)	39 (12.7%)
Strongly disagree	36 (50.7%)	18 (27.3%)	0 (0%)	5 (6.0%)	59 (19.2%)

the blinded and unblinded intervention comparably, but the lack of blinding may have influenced outcomes. Our mechanism to feedback the results of the n-of-1 experiment required people external to the patient and physician to process the data and provide a report for physicians. Full-scale implementation of this approach in routine care would require automation of assessment of symptoms and creation of feedback reports. The intervention addressed beliefs, that may be specific to the United Kingdom, and the system of primary care may limit generalizability to other health systems. Participation in the study appeared to influence medication use in the control group, reducing the apparent benefit of the intervention. Of the 4 participants resuming medication in the usual care arm, one was prompted to attend their physician to discuss statins by the consent discussion, while one was the partner of an intervention arm participant where his experience convinced her to resume statins. The estimates of intervention effect were imprecise, and, in particular, the absence of differences between unblinded and blinded arms lacked power. Finally, statin resumption was assessed immediately after the end of the experiment and long-term follow-up would be beneficial.

Comparison With Other Studies

Researchers at McMaster University pioneered n-of-1 experimentation for patients and showed considerable success, clarifying treatment decisions in 50 of 57 cases.<sup>25</sup> A proof-of-concept study with 8 participants with statin intolerance showed that undertaking a blinded n-of-1 experiment led to 5 resuming statins, similar to the rate observed in our study.<sup>15</sup> Later n-of-1 trials have shown less promise. Several randomized trials have randomized participants to either experiment with their medication in n-of-1 trials or usual care.<sup>26–28</sup> Such trials have reported that n-of-1 experimentation entailed extra efforts and costs for physicians and patients and yielded no worthwhile benefits for patients or the health care system. However, the common factor in all 3 of these unsuccessful n-of-1 trials is that the interventions patients experimented with offer modest benefits overall (theophyllines and analgesics for chronic pain).<sup>29,30</sup> This may make differences between active and placebo conditions in these n-of-1 experiments too small to detect. In contrast, in the case of statins, there is a

large gap between the public perception of the tolerability of statins and the scientific evidence. As such, n-of-1 experimentation may yield large effects. Other interventions to increase statin uptake have intervened through complex behavioral economic interventions and have modest effects (no effect or 5% compared with 25% in our intervention).<sup>31,32</sup> Since our study was planned, 3 studies using n-of-1 methods have reported. All 3 aimed to assess whether statins cause symptoms in people with clinically diagnosed statin intolerance and, therefore, all used placebo-controlled n-of-1 designs. Kristiansen et al<sup>33</sup> randomized people using statins for secondary prevention to blinded atorvastatin and placebo. They found that most people had similar symptoms on placebo as on atorvastatin, with 28% having more symptoms on statin, and 17% more on placebo. An experimental study reported that around 90% of the total number of symptoms experienced on statin were also experienced on placebo.<sup>34</sup> The third enrolled people with myalgia in response to statins. In blinded n-of-1 trials, the mean difference in myalgia score between active and placebo on a 0 to 10 visual analogue scale was  $-0.11$  ( $-0.36$  to  $0.14$ ).<sup>35</sup> A common feature of all studies is that, after participants' results were revealed, most resumed statins. Evidence suggests that current practice, which probably comprises explaining the benefits of statins and offering them leads to low uptake.<sup>7</sup> However, working with patients to acknowledge their concerns and testing these leads to high take-up of statins.

Implications

Our intervention capitalized on the common phenomenon that patients test their medication by stopping and starting it.<sup>36</sup> We asked physicians to acknowledge that the patient's concerns were valid and could be correct, but that the only way to ascertain this was using an n-of-1 experiment. Such an approach seems to have bridged the impasse that often develops when patients have experienced events that they are convinced are caused by a medication where doctors doubt this because of evidence from trials. This approach could extend to any other preventative medication. Current guidelines to manage perceived side-effects of statin comprise rechallenge with a different or lower dose statin.<sup>37</sup> Our study extends this using an unblinded



design for n-of-1 experimentation in which symptoms are recorded off statins. This may be crucial because symptoms occurring when not on statins may have gone unnoticed or not reflected upon, as a person is unlikely to think that symptoms off statin are salient in deciding whether or not to use a statin. The unblinded experiment simplifies n-of-1 administration compared with placebo-control, meaning it could be undertaken by any physician where the patient was willing to write down the adverse events daily and then total them for use and nonuse periods. In the future, generic phone apps could automate the analysis and feedback. Previous services to facilitate n-of-1 experiments in clinical practice have all folded because of lack of demand and because producing placebos is costly.<sup>38</sup> It cost UK£13 000 (US\$18 000) to create 36 patients' supplies of encapsulated placebos.

At least in the case of statins, the unblinded experimentation appeared to give similar results to the blinded, placebo-controlled n-of-1 experiment. Nocebo effects occur when taking medication that a person expects to cause adverse events and may be less likely when a person has been randomized to active or placebo treatment. As such, our data suggests that patient concern about the tolerability of statins stems mainly from misattribution of incidental adverse events to statins, rather than nocebo effects.

## Conclusions

A behavioral intervention encouraging patients with statin intolerance or who have declined statins to experiment with statins in n-of-1 experiments to test their beliefs led to a worthwhile increase in resumption of statins.

## ARTICLE INFORMATION

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### Disclosures

None.

## Supplemental Materials

Supplemental Methods I–III

Supplemental Results IV–VII

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