Pragmatic randomised trial of a smartphone app (NRT2Quit) to improve effectiveness of nicotine replacement therapy in a quit attempt by improving medication adherence - results of a prematurely terminated study

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Abstract

Background

Nicotine replacement therapy (NRT) bought over the counter (OTC) appears to be largely ineffective for smoking cessation, which may be partially explained by poor adherence. We developed and evaluated the NRT2Quit smartphone app (for iOS) designed to improve quit attempts with OTC NRT by improving adherence to the medications.

Methods

A pragmatic double-blind randomized controlled trial with remote recruitment through leaflets distributed to over 300 UK-based community pharmacies. The study recruited adult daily smokers (≥10 cig/day) who bought NRT, wanted to quit smoking, downloaded NTR2Quit and completed the registration process within the app. Participants were automatically randomized within the app to the intervention (full) version of NRT2Quit or to its control (minimal) versions. The primary outcome was biochemically-verified 4-week abstinence assessed at 8-week follow-up using Russell Standard criteria and intention-to-treat. Bayes factors were calculated for the cessation outcome. Secondary outcomes were self-reported abstinence, NRT use, app use and satisfaction with the app.

Results

The study under-recruited with only 41 participants (3.5% of the target sample) randomly assigned to NRT2Quit (n=16) or the control (n=25) app versions between March 2015-September 2016. The follow-up rate was 51.2%. The intervention participants had numerically higher biochemically-verified quit rates (25.0% vs 8.0%, p=0.19, OR=3.83,0.61-24.02). The Bayes factor calculated was 1.92, suggesting anecdotal level of support for the hypothesis that the intervention app version aided cessation, but showed the data were insensitive. The intervention participants had higher median logins (2.5 vs. 0, p=0.01), were more likely to use NRT at follow-up (100.0% vs. 28.6%, p=0.03) and recommend NRT2Quit to others (100.0% vs. 28.6%, p=0.01).

Conclusions

Despite very low recruitment there was preliminary but inconclusive evidence that NRT2Quit may improve short-term abstinence and adherence among smokers using nicotine replacement therapy.
Well-powered studies on NRT2Quit are needed, but different recruitment methods will be required to engage smokers through community pharmacies or other channels.

Background
High quality evidence from randomised trials shows that nicotine replacement therapy (NRT) is effective when provided with at least some professional support (Stead et al., 2012). However, large scale surveys and prospective studies have found that smokers who buy NRT over the counter (OTC NRT) and do not receive any processional support have quit rates that are similar to, or lower, than smokers who quit unaided, even when adjusting for a range of potential confounding variables (Kasza et al., 2013; Kotz, Brown, & West, 2014a, 2014b). One explanation for the discrepancy between NRT effectiveness in trials and when bought over the counter is low adherence (Apollonio & Glantz, 2017; Beard, Bruguera, McNeill, Brown, & West, 2015; Carpenter, Ford, Cartmell, & Alberg, 2011; Curry, Ludman, & McClure, 2003; Hughes, Fanshawe, & Stead, 2017; Raupach, Brown, Herbec, Brose, & West, 2014; Stanley & Massey, 2016). There is some research to suggest that better adherence is associated with better cessation outcomes (Cropsey et al., 2017; Ma, Kendzor, Poonawalla, Balis, & Businelle, 2016; Raupach et al., 2014; Schlam et al., 2018). Smartphone applications (apps) could improve NRT adherence and thus success rates in smokers, especially among those using NRT-OTC (Kotz, Fidler, & West, 2009; Pulverman & Yellowlees, 2014; Raupach, West, & Brown, 2013).

Smartphone apps have become an increasingly popular medium to deliver support for a range of health conditions (Higgins, 2016) and for medication use (Ahmed et al., 2018; Morrissey, Corbett, Walsh, & Molloy, 2016; Santo et al., 2016). Apps have also been developed to promote smoking cessation, but many of these have been shown to offer only limited support with quitting, and as yet none has been developed specifically to promote NRT adherence (Abroms, Lee Westmaas, Bontemps-Jones, Ramani, & Mellerson, 2013; Abroms, Padmanabhan, Thaweethai, & Phillips, 2011; Ahmed et al., 2018; BinDhim, McGeechan, & Trevena, 2018; Bricker et al., 2017; Bricker et al., 2014; Buller, Borland, Bettinghaus, Shane, & Zimmerman, 2014; Cheng, Xu, Su, Fu, & Bricker, 2017; Choi, Noh, & Park, 2014; Haskins, Lesperance, Gibbons, & Boudreaux, 2017; Hoeppner et al., 2016; Iacoviello et al., 2017; Jacobs, Cobb, Abroms, & Graham, 2014; Thornton et al., 2017; Ubhi et al., 2016; Ubhi, Michie,
Kotz, Wong, & West, 2015).

We developed an app for iOS phones, called NRT2Quit, that aimed to support smokers who are using NRT to quit smoking, with a focus on those who purchase OTC NRT. NRT2Quit was developed following the methods outlined in the Behaviour Change Wheel (S Michie, Atkins, & West, 2014), was informed by the COM-B model (Capability, Opportunity, Behaviour (Jackson, Eliasson, Barber, & Weinman, 2014; S. Michie, van Stralen, & West, 2011)) and Theoretical Domains Framework (TDF, version 2 (Atkins et al., 2017)), as well as the framework of intentional and non-intentional non-adherence (Lehane & McCarthy, 2007), the Necessity Concerns Framework (Horne et al., 2013), the Compliance and Persistence Framework (Cramer et al., 2008), PRIME Theory of Motivation (West, 2007b), and best clinical practice identified through consultations with the UK’s National Centre for Smoking cessation and Training (NCSCT).

NRT2Quit was designed to deliver easily accessible general advice on quitting, as well as detailed guidelines about NRT, including instructions on medication use, information addressing intentional and modifiable reasons for poor adherence, such as limited knowledge and concerns (Horne et al., 2013; Pacek, McClernon, & Bosworth, 2017), as well as features for monitoring and feedback on NRT use. NRT2Quit delivered 25 behaviour change techniques (BCTs) directly addressing NRT use, and 27 BCTs addressing quitting in general (S. Michie et al., 2013), in comparison with an average of 12 BCTs found in apps supporting adherence to other medications (Morrissey et al., 2016). It was expected that NRT2Quit would aid cessation by offering advice, reassurance and encouragement to use NRT according to best clinical practice during a quit attempt.

Choosing the right control conditions for the evaluation of apps remains challenging (S. Michie & West, 2016). It was decided that the most appropriate and realistic comparison to NRT2Quit would be a version of the app that offered a minimum credible intervention (S. Michie & West, 2016) by being similar to the intervention in many respects (e.g. the registration flow and design), but providing only limited support. There were two main reasons for this approach. First, from an ethical point of view it was important to offer at least brief advice to smokers who were interested in using an app to help them quit. Second, the similarities between the two arms increase credibility of the control app,
potentially minimising the seeking of alternative apps or support, which would have likely increased attrition from the trial and reduced power to detect an effect (S. Michie & West, 2016).

Finally, given that the effectiveness of OTC NRT is low (Kotz et al., 2014a, 2014b), it was important to evaluate NRT2Quit in an OTC setting and with no involvement of the researchers, pharmacists or other healthcare professionals (HCPs). It was judged that promoting the study among community pharmacies would offer the best chance to reach smokers who have just purchased OTC NRT and who might not have received additional support with NRT use.

Aims

The main aim of this pragmatic trial was to evaluate the short-term effectiveness of NRT2Quit. We hypothesised that in comparison with the control app version, the intervention app would lead to increases in (1) biochemically-verified 4-week-long abstinence assessed at 8-week follow; (2) self-reported use of NRT, (4) app usage, and (5) satisfaction with the app.

Materials And Methods

Design

The study was a pragmatic remote two-arm parallel double-blind randomized controlled trial (RCT) in the UK, with 1:1 automatic randomization to the intervention and control versions based on random numbers function embedded within the registration process within the app, and with 8-week follow-up. The study received ethical approval from UCL Research Ethics Committee (ID: 5398/001), and was prospectively registered (ISRCTN33423896). The reporting follows CONSORT (Ruano-Ravina, Figueiras, Montes-Martinez, & Barros-Dios, 2003) (See Supplementary Material 1) and TiDieR guidelines (FDA, 2018). Two changes to the protocol were made after the trial initiated: 7-month follow-up was suspended, and participants using NRT on prescription were included (see Supplementary Materials 2 for details). Additionally, due to very slow recruitment, the trial was terminated after 18 months.

Participants
Participant recruitment

Recruitment was through self-identification and self-selection, was conducted remotely, with no contact with the researcher (Eysenbach & Group, 2011). The recruitment campaign lasted between 23rd March 2015 and 15th September 2016. Recruitment materials were delivered to around 300 UK community pharmacies, mostly through their central managerial offices, with instructions to display and distribute them among smokers who purchase NRT (see Supplementary Materials 3 for recruitment materials). The materials directed potential participants to the study website with a detailed study information sheet, information about data processing, End User Licence Agreement, and links to download the app for free (www.nrt2quit.co.uk). The app could also be found through online searches and on iTunes.

Note on recruitment via community pharmacies

In order to recruit the target sample of participants (i.e. smokers who have already obtained OTC NRT as part of quitting but without being supported by HCPs, rather than smokers in general who are interested to quit but who have not purchased NRT yet and have no interest in NRT), the recruitment campaign was planned to be conducted only in the community pharmacies across the UK, and not online or through HCPs. The majority (n=250) of the pharmacies belonged to one large pharmacy chain and were identified through the central managerial office who was supportive of the study. Additional 50 pharmacies were recruited from other major pharmacy chains by communicating with their communications teams and by directly approaching several independent pharmacies. However, no training or direct communication between the researchers and the pharmacy staff were planned (to limit staff burden and to ensure the context of recruitment of smokers remains as ecological as possible) nor possible.

The study promotion could take place only outside of the busy periods, such as Christmas and New Year’s. Only leaflets, rather than larger posters, could be distributed in the participating pharmacies. The leaflets delivery was preceded by internal email communication and accompanied by a printed letter for the head pharmacists instructing them to place the leaflets near the counters and NRT displays, and to provide leaflets to customers purchasing OTC NRT. No professional company was
involved in developing the recruitment campaign, and it was not possible to trial the recruitment materials or procedures. Visits to few of the pharmacies after study initiation identified potential barriers to recruitment, including: (i) the leaflet displays not being sufficiently prominent; (ii) in case of pharmacies embedded within larger supermarkets, the OTC NRT was more prominently displayed on the general supermarket floors (managed by different managerial offices), rather than the pharmacy sections that supported the study; (iii) other cessation campaigns concurrently run in the pharmacies; (iv) lack of training and no direct involvement of the pharmacy staff might have resulted in the staff not being effective or engaged in study promotion or insufficiently knowledgeable about the study and the app.

**Eligibility criteria**

Only iPhone users (with iOS 8+) could participate. Eligibility for the trial was assessed based on the information provided during registration via the app: (a) UK-based, (b) aged ≥18 years, (c) daily smoking ≥10 cigarettes/day, (d) use at least one NRT product, (e) downloaded the app to quit, (f) completed registration process, including providing plausible and complete contact details (these were assessed manually by the researcher), and (g) provided consent to participate that also implied no contraindications for NRT use.

**Sample size**

The target sample size was calculated *a priori* to be 1186 participants (with alpha=0.05, two-tailed) to have 80% power to detect an expected effect size of OR=1.7, translating to 5% difference in self-reported abstinence rates at 8-week follow-up (8% in the control and 13% in the intervention. The expected cessation rates for intention-to-treat were low as it was expected that attrition from the study will be as high as 50% from each group (Eysenbach, 2005). The expected effects were small, but potentially cost-effective (West, 2007a). However, due to very slow recruitment, the trial was terminated and the analysis involved only 41 eligible participants recruited.

**NRT2Quit platform and intervention and control arms**

NRT2Quit intervention and control app versions were delivered through a single NRT2Quit app platform that could be used offline except for changing the quit date or NRT use to ensure data were
synchronised with the server. Both versions of NRT2Quit were developed to be automated and standalone interventions. The advice offered was tailored to the type of NRT product used and the quit date (control and intervention), and to dependence level (intervention only, see 2.3.2). The support was offered for up to two weeks before the quit date and eight weeks post-quit date. Functionality, BCTs, screenshots, and user journeys of the intervention and control are provided in Supplementary Materials 4. The app was not modified during the trial.

**NRT2Quit – Control (minimal) version**

The control version of the app provided only minimal support with quitting and NRT use: (1) setting of a quit date in the next 2 weeks, (2) very brief advice on the use of selected NRT, (3) brief advice on quitting and managing nicotine withdrawal, (4) progress monitoring (days to and since the quit date), (5) a calendar that displays the quit date and the 8-week questionnaire. It also included (6) brief information about the study and the app. Users could (7) change the quit date and the NRT used.

**NRT2Quit – Intervention (full) version**

The intervention version of NRT2Quit offered the same support as the control version, and in addition provided (1) more comprehensive information about NRT in general and about each of products (e.g. detailed instructions on use, short articles about key misconceptions, e.g. overdosing), (2) an interactive dashboard for monitoring and feedback on NRT use, (3) daily diary on smoking and NRT use followed by tailored feedback, (4) a more detailed advice on quitting, (5) daily tips, (6) additional information about the study team and study rationale, and (7) daily reminders to engage with the app. Feedback and advice on NRT use were minimally tailored to dependence levels (heavy smokers were all those who were smoking 11-19 CPD and smoking the first cigarette within 5 min since waking, or all those smoking ≥20 CPD; moderate smokers: everyone else). The app was designed to encourage daily use (e.g. through app reminders and new daily tips). However, in anticipation of high attrition from the app (Eysenbach, 2005) and given the different preferences for usage of digital interventions among smokers (Herbec et al., 2014), the core content and behaviour change techniques were delivered immediately following the registration.

Procedures
After downloading the app, participants were guided through a tunneled registration process that included a summary of study information sheet and links to study website with detailed information, provided informed consent and contact details, completed baseline assessment, entered data on the NRT purchased, and set their quit date (see Supplementary Material 5). After registering participants were automatically randomized to the intervention or control versions of the app and were assigned a unique ID. Participants received an email confirming registration with a link to study website and contact details to the researchers. Duplicate registrations were excluded following a manual check.

The follow-up took place at 8 weeks after the registration (18 May 2015-22 November 2016) through an online survey as opposed to within the app in anticipation of participants deleting the app or switching off notifications. The links to the survey were distributed through an e-mails (up to 3 reminders) that were personalized (Jamie Brown et al., 2014). Participants failing to complete the survey were contacted over the phone (up to three calls) to assess smoking status only (a longer survey was judged to be infeasible to conduct over the phone). Participants self-reporting prolonged abstinence were posted a saliva kit with instructions, a £20 high street gift voucher as reimbursement, and a freepost envelope addressed to the laboratory, and asked to post the samples as soon as possible (Jamie Brown et al., 2014).

Due to slow recruitment it was decided in early August 2016 to prepare for termination of the trial. Bayes factors were calculated on the primary outcome on 18th August 2016 (after 39 eligible participants were recruited), but no hypothesis testing or other analyses were performed. Before NRT2Quit was removed from iTunes on 15th September (the current app users could still access it) two additional participants meeting eligibility criteria joined the study and were included in the analyses reported here. All study procedures, including the follow-up for all participants, were conducted blind to study arm allocation.

Measurements
Baseline assessment

The baseline questionnaire assessed socio-demographic characteristics (age, gender, having post-16 years of age education vs. not), smoking and quitting history (items from the Heaviness of Smoking Index (Etter, Duc, & Perneger, 1999); when the last quit attempt was made, past use of cessation aids) and reasons for joining the study (to quit smoking/other). Participants also provided information about the NRT type purchased (NRT patch/fast acting NRT/combination), how they obtained NRT (OTC/on prescription/both); and whether they received any support with NRT use from HCPs (yes/no).

Primary outcome

The primary outcome was self-reported 4-week prolonged abstinence assessed at 8-week follow-up, and verified by saliva cotinine levels of <15ng/mL (West, Hajek, Stead, & Stapleton, 2005) or, among participants reporting using NRT or e-cigarettes: anabasine levels of <1ng/mL (Benowitz et al., 2002) (Jamie Brown et al., 2014). The pre-registered salivary anabasine cut-off value was based on discussions with the processing lab and the information available at the time of trial set up (2011-2014). However, as the lab has conducted more studies since, it now recommends a lower cut-off value for salivary anabasine of <0.2ng/mL. Results for the lower cut-off are reported in the footnote of Table 2. Participants lost to follow-up were assumed to have resumed smoking, as per intention-to-treat principle (ITT).

Secondary outcomes

Secondary outcomes were: (1) the follow-up parameters: follow-up rate, the re-contact channel (survey/phone), proportion of saliva samples returned. The online survey at 8-week follow-up assessed: (2) total number of cigarettes smoked in the past 4 weeks (none/<5/≥5); (3) adherence to NRT: (i) use of NRT on the follow-up day (yes/no), (ii) weeks NRT was used (<5/≥5 weeks), (iii) number of days in those weeks NRT was used (every day/not every day); (4) use of other cessation support, e.g. other medications, behavioural support, or self-help support (yes/no); (5) satisfaction: how helpful was NRT2Quit app for (i) quitting smoking and (ii) using NRT (1=not at all, 5=extremely helpful), (iii) whether would recommend the app to others wanting to quit (yes/no). Additionally, (5) data on app usage: (i) number of logins, and (ii) number of days users logged in on. Due to the
structure of app database, data on time spent using the app or on accessing individual app features were not saved.

**Data Analysis**

The primary outcome was analysed using Fishers’ exact test. Additionally, unadjusted logistic regressions were conducted for the dichotomised cessation outcomes, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. In exploratory sensitivity analyses participants who reporting using only Rx NRT (n=14) or for with that data missing (n=3) were excluded. All other analyses were pre-planned. For smoking outcomes, participants with missing data were assumed to be smoking.

Bayes Factors were calculated for the smoking outcomes as they can distinguish between the likelihood of both the null and alternative hypotheses, and assess whether the data provide an insensitive test of the hypotheses (J. Brown, Michie, Walmsley, & West, 2016; Dienes, 2008, 2014; West, 2016). Bayes Factors were calculated using an online calculator that is available for free at http://www.lifesci.sussex.ac.uk/home/Zoltan_Dienes/inference/Bayes.htm. We used a uniform H1 distribution with a possible expected effect size between OR=1 and OR=3 versus an H0 of OR=1. In sensitivity analyses, we used a conservative H1 with a half-normal distribution with the mean of the log OR of 0, and the standard deviation corresponding to expected effect sizes of OR=1.2, OR=1.7, and OR=2.5 (Rigotti et al., 2017; West, 2016). This distribution means that plausible values have been represented between zero and twice the effect size, with smaller values more likely.

Descriptive statistics are presented for baseline and all secondary outcomes. Categorical variables were compared using Fisher’s exact test, and chi-square test and Linear-by-Linear association for ordered categories, and continuous data using independent t-test or Mann-Whitney U-test for data that were not normally distributed. Data on app usage were not normally distributed, but both medians (IQR) and means (SDs) are reported to enable comparison with other studies. All tests were 2-sided, and alpha was set to 5%.

**Results**

Participants
In total 41 participants met eligibility criteria for the study, of which 16 (39.0%) were randomized to the intervention app. Figure 1 (based on the Consort flow diagram) shows the flow of participants, and Table 1 presents baseline characteristics. A significant minority (came across the app through online searcher or other channels. About half of participants were female, had post-16 years of age education, and made an attempt to quit in the past 12 months. Almost all participants had used some cessation assistance before, with NRT (41.5%) and e-cigarettes (24.4%) being the most common. At baseline 43.9% of participants reported they were using a fast acting NRT product on its own, and 26.8% were using combined NRT. A quarter of participants obtained advice form HCPs on NRT use.

Follow-up
At 8-week follow-up 51.2% of participants were successfully contacted (43.8% among intervention and 56.0% among control, see Table 3). The online follow-up survey that assessed additional secondary outcomes was completed by 12 (29.3%) participants. The rates were similar across study arms.

Cessation outcomes
Table 2 presents cessation outcomes assessed at 8-week follow-up. In the ITT analysis, abstinence was biochemically verified for 14.6% of trial participants (25.0% among intervention and 8.0% among control, p=0.19). The results changed only minimally when the <0.2ng/mL cut-off for salivary anabasine was used. Self-reported abstinence was reported by 17.1% of participants (25.0% among intervention vs. 12.0%, among control p=0.40). The Bayes factors calculated for biochemically-verified and self-reported abstinence suggested the data were insensitive to distinguishing between the null and experimental hypotheses. The results did not change when the analysis was limited to participants who bought at least one of their NRT OTC (not reported here).

NRT use
Among participants who completed the online survey (n=12), adherence rates were relatively high, and the differences between study arms were not statistically significant except for having used NRT on the survey day (100% vs. 28.6%, p=0.03, see Table 3 for details).

**App usage**

App usage (see Table 3 for details) was low and positively skewed in both conditions, but there was an indication that the intervention participants engaged more (e.g. median number of logins: 2.5 vs. 0, p=0.01). This is an underestimation, however, as offline use might not have been saved on servers.

**Satisfaction**

Among the 12 participants who completed the survey (see Table 3), the intervention participants gave higher median ratings of the app as being helpful with NRT use (p=0.02). Additionally, all intervention participants stated they would recommend the app to others, compared with 28.6% among the control participants (p=0.01).

<Table 3 about here>

**Discussion**

**General summary**

Due to very challenging recruitment through community pharmacies the study was terminated with 41 participants. Nevertheless, it resulted in some promising findings. First, the full app version (intervention) led to numerically greater self-reported (25.0% vs 12.0%) and biochemically-verified short-term quit rates (25.0% vs 8.0%), although the differences were not significant when assessed using traditional statistics (p-values). However, Bayes factors for the primary outcome suggest ‘anecdotal’ evidence that NRT2Quit could aid cessation, but demonstrate that that data were not
sensitive to distinguish between experimental and null hypotheses, and more research is needed.
Secondly, the intervention participants had statistically significant greater engagement and satisfaction with the app. On some indicators of NRT use, e.g. duration, there was an indication that intervention participants used more of it. Taken together, these findings suggest that the support offered by NRT2Quit app may aid cessation and warrants conducting an adequately powered study, but establishing a feasible recruitment channel in the real world may be a major challenge.

The cessation rates reported in this study are similar to those found in other research, but biochemical verification of abstinence was rarely conducted in most other trials (BinDhim et al., 2018; Bricker et al., 2017; Bricker et al., 2014). The findings suggesting greater effectiveness of the intervention version of the NRT2Quit app are all the more encouraging as the control app version already included several evidence-based BCTs that were shown to improve cessation, including goal setting and monitoring (Lorencatto, West, & Michie, 2012). It must be also acknowledged, however, that since NRT2Quit was a complex intervention offering both generic support with smoking cessation, as well as dedicated support with NRT use, the trial could not identify specific active ingredients that may be driving the effect. Due to the small sample it was also not possible to explore predictors of cessation. In line with other findings from digital cessation interventions, attrition from the study was high, and app engagement was relatively low, although the mean number of logins was in line with usage data from other digital interventions (Bricker et al., 2014; Jamie Brown et al., 2014; Taylor et al., 2017). However, NRT2Quit offered access to the core content immediately following the registration, and it is therefore possible that participants had accessed relevant advice already during their first visit, which might had been sufficient to optimise NRT use and improve cessation. The slow recruitment and high attrition could be at least partially explained by the lack of contact with the researchers at the enrolment and lack of incentives at follow-up data (except as part of the saliva sample collection) (Bricker et al., 2014).

Low recruitment rate
Despite securing access to more than 300 community pharmacies across the UK and extending the recruitment window, the study seriously under recruited with only 4% of the target sample enrolled. Relying on recruitment via printed materials distributed in community pharmacies, but with no researcher or healthcare professionals’ engagement proved infeasible. A recent interview study (Herbec, Tombor, Shahab, & West, 2018) with smokers and ex-smokers who used NRT while quitting found that while they viewed NRT2Quit as potentially beneficial, they reported many barriers in terms of capability, opportunity and motivation to engaging with any support and information about NRT use (e.g. leaflets, healthcare professionals, information on how to use the medications). These findings offer partial explanation for the possible low interest in downloading NRT2Quit and the trial.

There were also other potential causes of low recruitment. First of all, NRT2Quit was available only on iOS devices, and therefore a considerable proportion of smartphone users who have Android phones could not enrol. However, it is unlikely that developing an Android version of NRT2Quit would improve the recruitment. Research shows that iOS and Android users differ on a range of socio-demographic characteristics app use. For example, iOS users are more likely to download and use health apps and engage with more content (BuildFire, 2017; Ubhi, Kotz, Michie, van Schayck, & West, 2017). iOS users also tend be better off financially (Schonfeld, 2011) and thus might have more disposable income to purchase OTC NRT. On the other hand, given that lower socio-economic status is associated with higher smoking rates, future app developments should also include versions compatible with Android devices.

Secondly, recruiting participants into an online and remote trial as this one required concealing the differences between the two app versions and prevented promoting the features and advice offered within the intervention app, thus likely leading to a less attractive offer in comparison to other commercially available stop smoking apps. Furthermore, the trial took place during a phase marked by a decline in NRT popularity and an increase in popularity of electronic cigarettes, which was reducing an already small pool of potential participants who use NRT to quit (Beard, West, Michie, & Brown, 2016).

Study Limitations
The response rate to the online survey was low, which limited the availability of data on NRT use and satisfaction. We were also unable to assess adherence to NRT in detail or account for changes to the patterns of use. Due to the structure of the app database it was also not possible to assess engagement with individual app components and fidelity of intervention delivery (Kruse et al., 2017). Additionally, the burden of joining the current trial was higher than that associated with accessing other cessation apps available on the market (e.g. it involved providing contact details and agreeing to follow-up procedures). It is likely that the recruited participants, as well as those who responded to the follow-up, were more motivated than the general population of smokers. While this should not have impacted the main results (as motivation would have been similar in the control and intervention groups), the findings should be interpreted with caution and their generalisability is limited.

Another limitation is that, if the app did improve quit rates we cannot be sure that this was through improved NRT adherence. It is possible that it might have been through more general support for quitting. The sample size was too small to conduct meaningful mediation analysis involving NRT adherence.

Study strengths

We collected contact details through the app and followed-up participants outside of the app, as well as conducted biochemical validation of self-reported abstinence, which had a good response rate, and which was not done in other studies (e.g. (BinDhim et al., 2018; Ubhi et al., 2015)). The study also enabled us to make important methodological observations about recruitment and engagement of smokers with smartphone-based support for NRT use. Finally, we evaluated the app in a setting that had higher ecological validity that earlier studies – namely one involving no contact with the researchers at enrolment or incentives for app engagement and survey-based follow-up, some of which have been used in other studies (Bricker et al., 2017; Bricker et al., 2014; Buller et al., 2014).

Future directions

The findings warrant further development of NRT2Quit and conducting a well-powered study. However, it will be necessary to establish better recruitment channels and methods for such a trial,
which in the case of community pharmacies may require engaging the pharmacy staff in active recruitment into the trial, and possibly offering incentives (Corelli et al., 2013). Additionally, it would be relevant to evaluate NRT2Quit as part of face-to-face support to establish if the app could augment cessation and medication use in this context. Moreover, it is possible that actively promoting the benefits of the full NRT2Quit and offering only this version could lead to better uptake among the smokers. Thus, assessing NRT2Quit in a study with a waitlist control or in an observational study may be a possible future direction, especially if the recruitment relies on campaigns in the social media.

Conclusions
In a limited evaluation disrupted by extremely poor recruitment, there was preliminary evidence, but not conclusive, that the NRTN2Quit smoking cessation app has a promising effect on short-term quit rates, and also on medication use, app use, and satisfaction, but this would need to be confirmed in definitive studies. Future research will need to implement more effective recruitment strategies.

Author Disclosures

Ethics approval and consent to participate

The study received ethical approval from UCL Research Ethics Committee (ID: 5398/001). All participants provided informed consent before participating.

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
Conflict of Interest

AH led the development of NRT2Quit app and the NRT2Quit trial as part of her PhD funded by British Heart Foundation 4-year PhD at UCL, has conducted certain administrative tasks for NRT2Quit trial in a paid capacity from the GRAND, and has received unrestricted funds as part of a project Global Bridges at Mayo Clinic and Pfizer Independent Grants for Learning and Change Request for Proposals (RFP): EUROPEAN PROGRAM. LS has received honoraria for talks, an unrestricted research grant and travel expenses to attend meetings and workshops from Pfizer and Johnson&Johnson, and has acted as paid reviewer for grant awarding bodies and as a paid consultant for health care companies. Other research has been funded by the government, a community-interested company (National Centre for Smoking Cessation) and charitable sources. JB received an unrestricted research grant from Pfizer. RW undertakes research and consultancy and receives fees for speaking from companies that develop and manufacture smoking cessation medications (Pfizer, J&J, McNeil, GSK, Nabi, Novartis, and Sanofi-Aventis). JB & RW are both unpaid members of the scientific steering group of the Smoke Free mobile application. TR has received honoraria from Pfizer, Novartis, Glaxo Smith Kline, Astra Zeneca and Roche as a speaker in activities related to continuing medical education. He has also received financial support for investigator-initiated trials from Pfizer and Johnson & Johnson. The views presented are not necessarily the views of the funders.

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of the data, preparation of the manuscript or the decision to submit it.

Authors’ Contributors

TR prepared the initial trial protocol and obtained the funding, AH, JB and RW contributed to revising and finalizing the final trial design. AH has conducted formative research that informed NRT2Quit development, guided the work of IT teams that developed the NRT2Quit app and has lead on all aspect of the trial, including setting up, data collection and analysis, in consultation with JB, RW, LS and TR. AH drafted the first version of the manuscript, and JB, LS, RW and TR revised the manuscript. All authors approved the final version of the manuscript.

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List Of Abbreviations

HCP – healthcare professional

NRT – nicotine replacement therapy
OTC – over the counter

RCT – randomised controlled trial

Rx – on prescription

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Tables
Due to technical limitations, Tables 1-3 are only available as a download in the supplemental files section.

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