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Title: A randomized trial to determine the impact on compliance of a psychophysical peripheral cue based on the Elaboration Likelihood Model

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Keywords: Compliance; Elaboration Likelihood Model; Dosing Frequency; Peripheral Cues; Patient Diaries; Interactive Voice Response System (IVRS).

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Abstract: Objective: Non-compliance in clinical studies is a significant issue, but causes remain unclear. Utilizing the Elaboration Likelihood Model of persuasion, this study assessed the psychophysical peripheral cue 'Interactive Voice Response System (IVRS) call frequency' on compliance.

Methods: 71 participants were randomized to once daily (OD), twice daily (BID) or three times daily (TID) call schedules over two weeks. Participants completed 30-item cognitive function tests at each call. Compliance was defined as proportion of expected calls within a narrow window (±30 min around scheduled time), and within a relaxed window (-30 min to +4 hour). Data were analyzed by ANOVA and pairwise comparisons adjusted by the Bonferroni correction.

Results: There was a relationship between call frequency and compliance. Bonferroni adjusted pairwise comparisons showed significantly higher compliance (p=0.03) for the BID (51.0%) than TID (30.3%) for the

narrow window; for the extended window, compliance was higher (p=0.04) with OD (59.5%), than TID (38.4%).

Conclusion: The IVRS psychophysical peripheral cue call frequency supported the ELM as a route to persuasion. The results also support OD strategy for optimal compliance. Models suggest specific indicators to enhance compliance with medication dosing and electronic patient diaries to improve health outcomes and data integrity respectively.

Response to Reviewers: Sincerest thanks to the reviewers for providing feedback. Each comment has been addressed either in the manuscript or is shown below.

Review comment - Response Reviewer 1

1. Authors present 'A sample size calculation' should be '75' (Line 22 P9), but in fact it was just '71'.

Although the sample size calculation indicated that 75 participants were required, time and resource implications resulted in recruitment being closed after the enrolment of 71 participants. It was not possible to extend the recruitment further as access to the IVRS was limited. The shortfall of four participants is felt unlikely to impact the overall results. Additional text has been added to pages 12 (results) and 16–17 (discussion).

2. 'Participants (N=71), were randomized using an IVRS in the ratio 1:1:1 to a OD, BID or TID call schedule'. How did authors divide them according to 1:1:1?

Explanatory text has been added to page 8. Please note that randomization was not stratified.

3. '44 (62%) completed the study (Fig.1). Participants who prematurely discontinued were not followed up, so reasons for withdrawal are unknown'. Just 44 of 71 participants completed study, the quality of it should be susceptible.
The authors recognize that the completion rate is lower than perhaps might be considered ideal. However it should be noted that 78% of participants randomized to once-daily calls completed the study compared to 43% of participants randomized to three-times daily calls. This difference in completion rates supports our findings for the primary endpoint, given that the once-daily call schedule was associated with the highest rate of compliance (with the relaxed window). Additional text has been added to the discussion (page 16) to raise this point.

4. The discussion should be concise; the conclusion should be cautious.

The discussion and conclusion have been shortened, to ensure that only the key points from the study are discussed, and to remove some of the aspects of the conclusions that generalised the findings of the study in a clinical study context. See pages 15–20.

Reviewer 2
1. Define "electronic patient diaries "

A definition has been added to page 5.

2. Define "Interactive Voice Response systems "

A definition has been added to page 5, along with supporting references (one of which is taken from this journal).

3. Reason to do the study?

In this study, we sought to examine one of the potential causes of sub-optimal compliance – dosing frequency. There is some evidence (although inconsistent) that reducing dosing frequency may enhance compliance. However, this evidence generally comes from clinical trials, where the results can be influenced by the efficacy or adverse effects of the drugs being studied. This study therefore utilised a novel design, in which an IVRS system was used to model dosing frequency. The stated aim of the study (page 6) was ‘to provide an insight into causes of sub-optimal compliance, with a particular focus on compliance to medication regimen and patient diaries’.

Additional explanatory text has been added to the introduction (pages 5–6)

4. The researchers’ review of literature is weak done.

The introduction has been expanded to include additional literature reviews and supporting references. See pages 5–7.

5. Define "psychophysical peripheral cue "

A definition has been added to page 6.

6. Why are participants females and males ?

Recruitment was open to either men or women, with no stratification. This sentence (page 8) has been rephrased for clarity.

7. Why didn't compare the results?

The results for the male participants were not compared with the female participants. The study was not powered for such a comparison (given that randomization was not stratified by gender), and thus interpretation of the results could be challenging. However, it should be noted that the distribution of gender in each group was approximately even. The authors acknowledge that this would be an interesting area for future study. Additional text has been added to the discussion (pages 19–20).

8. The discussion section was too long

The discussion section has been significantly shortened. See pages 15-20.

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19 May 2008

Beth Kazol
Managing Editor
211 East Chicago Avenue
Suite 1450
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IL 60611, USA

Dear Dr Kazol

Please find enclosed a manuscript entitled 'A randomized trial to determine the impact on compliance of a psychophysical peripheral cue based on the Elaboration Likelihood Model' for your consideration.

This manuscript describes the results of a novel study examining various aspects of compliance and which is therefore of great relevance to both healthcare practice and pharmaceutical research.

The design of this study was based around a dual-process psychological model of persuasion. The psychophysical peripheral cues examined the effect of task frequency (therefore modeling medication dosing frequency) on compliance. A particularly novel aspect of this study was the use of Interactive Voice Response System (IVRS) commonly used in clinical trials.

The study demonstrates a clear relationship between reduced task frequency and improved compliance and therefore builds on existing research.

Rachael Jane Horton was previously employed by Clinphone, and Damian McEntegart is currently employed by Clinphone, who provided assistance with the IVRS facilities and database used in this study. There are no other known conflicts of interest or financial arrangements regarding the companies featured in this manuscript. All authors have seen and approved the final manuscript.

The five suggested peer reviewers include: Stone AA, Shiffman S, Schwartz JE, Broderick JE, Hufford MR

I very much look forward to hearing from you in the near future.

Yours sincerely

Miss Rachael Horton
encs.

Dr Antonietta Minniti

Dr Stewart Mireylees

Damian McEntegart

Figure

FIGURES

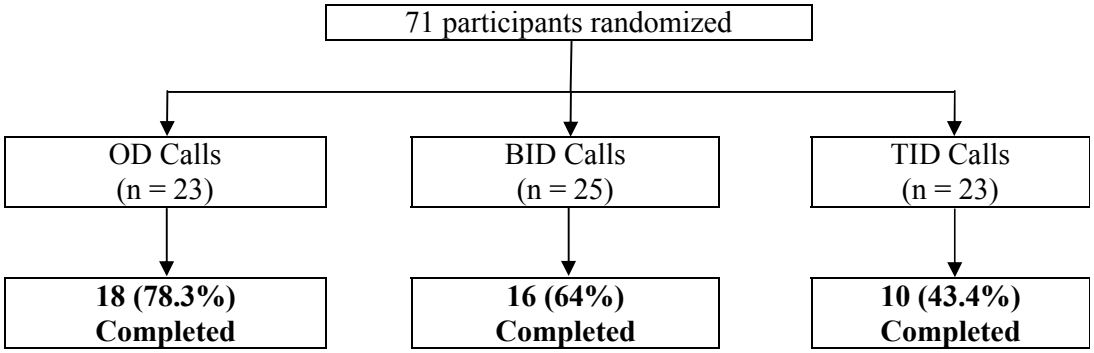

Fig. 1: Patients completing the trial with each call strategy

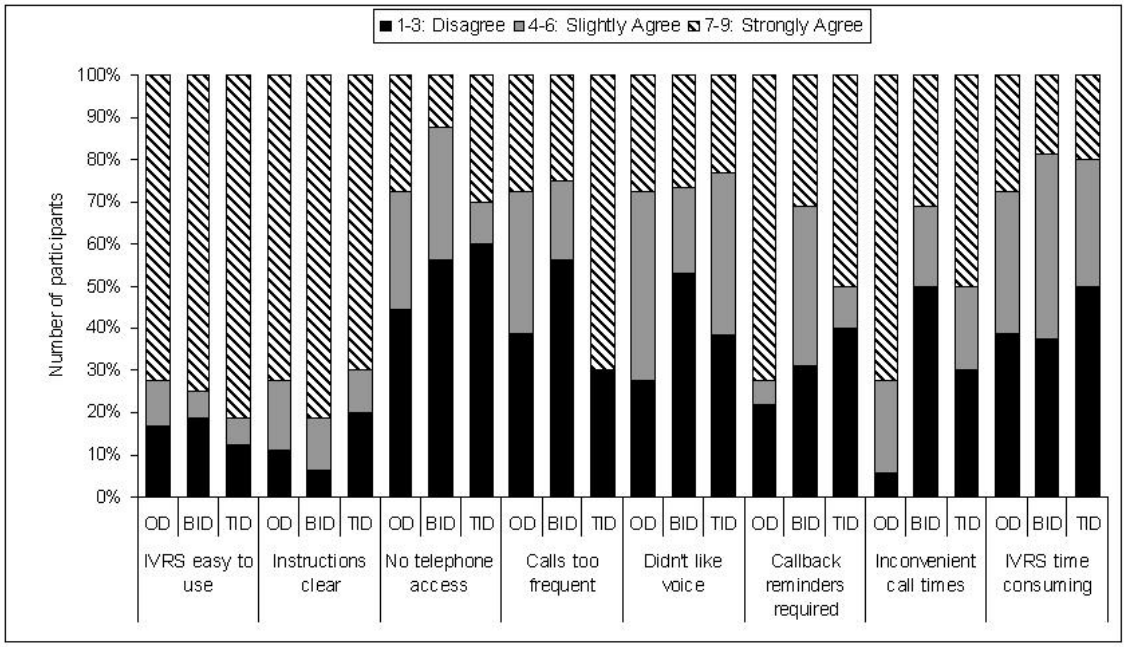

Fig. 2: End of study phase results for randomized trial participants (N=71).

FIGURE LEGENDS

Fig. 1: Patients completing the trial with each call strategy

Fig. 2: End of study phase results for randomized trial participants (N=71).

Title: A randomized trial to determine the impact on compliance of a psychophysical peripheral cue based on the Elaboration Likelihood Model

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Acknowledgements: Input regarding choice of psychological model of persuasion included in this research was provided by Dr K. Umeh. The author was assisted by D. Young who reviewed this manuscript prior to submission. Funding was supplied in part by ClinPhone and part by the author. IVRS Facilities were supplied by ClinPhone and cognitive function tests provided by Cognitive Drug Research (CDR; Goring-on-Thames, UK). There are no known conflicts of interest.

ABSTRACT

Objective: Non-compliance in clinical studies is a significant issue, but causes remain unclear. Utilizing the Elaboration Likelihood Model of persuasion, this study assessed the psychophysical peripheral cue 'Interactive Voice Response System (IVRS) call frequency' on compliance.

Methods: 71 participants were randomized to once daily (OD), twice daily (BID) or three times daily (TID) call schedules over two weeks. Participants completed 30-item cognitive function tests at each call. Compliance was defined as proportion of expected calls within a narrow window (±30 min around scheduled time), and within a relaxed window (-30 min to +4 hour). Data were analyzed by ANOVA and pairwise comparisons adjusted by the Bonferroni correction.

Results: There was a relationship between call frequency and compliance. Bonferroni adjusted pairwise comparisons showed significantly higher compliance ($p=0.03$) for the BID (51.0%) than TID (30.3%) for the narrow window; for the extended window, compliance was higher ($p=0.04$) with OD (59.5%), than TID (38.4%).

Conclusion: The IVRS psychophysical peripheral cue call frequency supported the ELM as a route to persuasion. The results also support OD strategy for optimal compliance. Models suggest specific indicators to enhance compliance with medication dosing and electronic patient diaries to improve health outcomes and data integrity respectively.

Keywords: Compliance; Elaboration Likelihood Model; Dosing Frequency; Peripheral Cues; Patient Diaries; Interactive Voice Response System (IVRS).

1. Introduction

Patient compliance can be defined as the extent to which an individual's behaviour coincides with medical advice [1] or more generally to their compliance with clinical trial procedures. Suboptimal compliance to treatment regimens has been observed in approximately 50% of patients with chronic diseases [2]. It has been reported to impact treatment efficacy, resulting in poor clinical outcomes, increased hospitalizations, reduced overall quality of life and increases overall healthcare costs [3]. If health outcomes are to be assessed in clinical trials, high levels of patient compliance are vital [4] – to the intervention under examination (such as a prescribed medication) [5], to protocol assessments and procedures [6], and to the completion of patient reported outcomes (PRO) tools such as electronic patient diaries (electronic devices that can be used by patients to capture events such as symptoms and quality of life outcomes) [7]. Despite this, high levels of non-compliance have been reported in all these areas [5,6,7]. Of particular interest to this study are patient diaries, which are increasingly used in clinical trials to assess both quantitative (e.g., number of doses of 'rescue' medication) and qualitative (e.g., quality of life) parameters. Here the evidence about compliance is mixed with both poor [8] and high [9] compliance noted for diaries administered by telephone using Interactive Voice Response Systems (IVRS). In IVRS, study participants use a touch-tone telephone to respond to pre-recorded messages; responses are transmitted in real-time to a central database for later analysis [10–12]. Little is known about the cause of this variable behaviour [2].

In this study, we sought to examine one of the potential causes of sub-optimal compliance – dosing frequency. There is some evidence (although inconsistent) that reducing dosing frequency may enhance compliance [13–17]. However, this evidence generally comes from

clinical trials, where the results can be influenced by the efficacy or adverse effects of the drugs being studied. This study therefore utilized a novel design, in which an IVRS system was used to model dosing frequency and patient diary compliance by varying the parameter 'IVRS call frequency'. Such a model will support targeted development and meaningful evaluation of interventions to enhance compliance in clinical trials.

1.1. Models for understanding suboptimal compliance

The Elaboration Likelihood Model (ELM) of persuasion, developed by Petty & Cacioppo [18] is a dual-process model that proposes two routes to persuasion along an elaboration continuum and comprise the peripheral route, and the central route. The ELM is a useful model for enhancing compliance because by understanding aspects of persuasion, compliance can be optimized. Since, in general, compliance relies on superficial peripheral cues under conditions of low elaboration (i.e., encouraging participants low in motivation to complete an assessment under potentially distracting conditions) [19], IVRS is therefore an ideal model for compliance – with a previous study providing evidence of good compliance and high participant acceptability of the technology employed [20]. Our design was based on the study of psychophysics, which theorizes that it is possible to physically measure the impact of various psychological parameters [21]. We accomplished this by manipulating a peripheral cue (call frequency) and determined the impact on the psychological parameter 'compliance'. This peripheral cue is therefore described as a 'psychophysical' peripheral cue.

1.2. Study aim and hypothesis

The study sought to provide an insight into causes of sub-optimal compliance, with a particular focus on compliance to medication regimen and patient diaries. The main aims were to assess the level of compliance to the completion of an IVRS patient diary over 13 days, and to act as a model of medication dosing by varying the peripheral cue 'call frequency'. The null hypothesis was that compliance is not associated with call frequency.

The primary objective was to assess the effect of the IVRS psychophysical peripheral cue variable 'call frequency' (OD [once daily], BID [twice daily], TID [three times daily]) on rates of compliance over 13 days. Secondary objectives included an assessment of the impact of these call frequencies on the cognitive function variables Simple Reaction Time (SRT) and Choice Reaction Time (CRT), and the effect on variables of the Eysenck Personality Questionnaire (EPQ).

2. Methods

2.1. Design

This was a single centre, randomized study in healthy adults aged over 18 years. On Day 1, participants called into IVRS to complete a set of baseline assessments. They were then randomized to one of three call frequencies (OD, BID, TID). Post-randomization, participants contacted the IVRS daily for 13 days, with a study completion call on Day 15 to assess participant experiences and acceptability of IVRS diaries.

The study received local ethics committee approval and all participants gave written informed consent prior to the start of the study.

2.2. *Inclusion and exclusion criteria*

~~Male and female~~ Participants aged 18 years or over were enrolled. There were no restrictions with regards to medical history or gender, and no other inclusion / exclusion criteria were applied. Recruitment was by open invitations distributed to internal staff at The ClinPhone Group Ltd and external participants already known to the authors.

2.3. *Procedure*

Participants (N=71), were randomized using an IVRS automated sequential selection from a blocked randomization list in the ratio 1:1:1 to a OD, BID or TID call schedule. IVRS facilities were provided by The ClinPhone Group at their Head Office, Nottingham, UK. During the call on Day 1, as part of the randomization transaction, baseline demographics and EPQ variables (including a measure of extraversion and neuroticism) were collected. The EPQ is an example of a 101-item validated research tool that measures three major components of personality, namely extraversion, neuroticism and psychoticism [22]. The purpose of collecting EPQ data was to investigate the effect of personality dimensions extraversion and neuroticism on compliance.

During the call on Day 1, participants specified their preferred IVRS call times and were requested to call as close as possible to those times. Participants randomized to a BID or TID schedule were required to allow a minimum of 4 hours between each IVRS call to model as close as possible a medication dosing schedule. Where a call was made more than one hour prior to a scheduled call time, participants were advised to call back at the scheduled date / call time. Calls more than 4 hours after the scheduled call time were defined as missed.

Where a call was missed, on next logging into the system, participants were presented with an automated missed call questionnaire for each missed diary transaction. This assessed reasons for the missing call, such as 'forgot' and 'lack of access to a telephone'.

Each IVRS call, irrespective of randomized assignment, consisted of two cognitive function tests – Simple Reaction Time (SRT) and Choice Reaction Time (CRT). These were developed and validated for use with IVRS by Cognitive Drug Research (CDR; Goring-on-Thames, UK) as components of patient diaries.

SRT measures the power of concentration and alertness, where a faster response indicates more processes are being called upon to action the task. This 30-item test involved pressing the '9' key on the telephone keypad in response to an audible "Yes" prompt. CRT measures continuity of attention, where a higher score reflects ability to sustain concentration. In this 30-item test, participants were instructed to press the '9' key in response to the audible "Yes" prompt or the '7' key in response to the word "No". In both tests, the intervals between prompts varied to avoid a learned response. The total time required to complete the SRT and CRT tests was approximately 2 minutes. On completion of the tests, participants were advised of the date and time of their next scheduled call.

The final transaction on Day 15 was the end of study (completion) phase call to obtain participants perceptions about the ease of use of IVRS, and their experiences of the study design. No follow-up data were obtained from participants who discontinued the study; these participants were classified as 'lost to follow-up'.

2.4. Statistical analyses

A sample size calculation was performed with a crude estimate of the variability where the SD was assumed to be one quarter of the range i.e. 25%; in the event this turned out to be quite accurate. Then with a two-tailed test adjusted for multiple comparisons, it was calculated that 75 patients would be required to detect differences of 25% with 90% power.

Compliance variables were analyzed for all randomized participants including those who discontinued prior to Day 15. Compliance was defined by two key variables, namely:

- Proportion of calls within a narrow window around the scheduled time points (defined as the period from 30 minutes before until 30 minutes after each specified time point)
- Proportion of calls within the relaxed window (defined as the period from 30 minutes before until 4 hours after each specified time point, thereby also incorporating the narrow window).

These values were expressed as the percentage of the expected calls that were actually made/recorded/completed, where the number of expected calls was calculated by multiplying the number of participants randomized into each group by the IVRS call frequency of that group for the entire scheduled length of the study. Thus if a participant dropped out prematurely, his/her expected number of calls was not reduced.

Data were analyzed using an ANOVA, where the independent factor was the call strategy group (OD, BID or TID), and dependent variables were respectively the percentage of calls within the narrow window, and percentage of calls within the relaxed window. Significance was determined with respect to the 5% level (two-sided); the Bonferroni correction was applied to adjust for multiple comparisons. A two-sided test was employed because it was not

known whether the increased frequency could aid memory and thus compliance even though of course the compliance burden was greater as the call frequency increased. The influence of the continuous scale covariates measured (EPQ, SRT and CRT) were examined by analysis of covariance (ANCOVA) with call group strategy as an independent factor. It was realized that SRT and CRT were post randomization variables which could complicate the interpretation of any significant results and so this was seen as an exploratory analysis.

3. Results

3.1. Participants

Participants were recruited to a single call centre in Nottingham, UK. Of the 71 randomized participants, 44 (62%) completed the study (Fig.1). As a result of the length of time required to recruit 71 participants, and the resource implications of extending the recruitment period further, recruitment had to be closed before the enrolment of all 75 participants required according to the sample size calculation. Participants who prematurely discontinued were not followed up, so reasons for withdrawal are unknown. Demographic and baseline characteristics were well balanced between the randomized groups (Table 1). For the EPQ, mean scores of extraversion and neuroticism between the three groups were also well balanced.

3.2. IVRS compliance

For the narrow window (32.1% of calls made), the overall ANOVA analysis revealed a statistically significant difference between the three call frequency groups (p=0.03). Similarly for the relaxed window (67.9% of calls made), there was an overall difference (p=0.03).

In the Bonferroni adjusted pairwise comparisons for the narrow window, compliance was significantly enhanced with a BID schedule compared with a TID schedule (Table 3). For this window the OD schedule showed no statistical difference from BID or TID schedules. In contrast, with the relaxed window the OD call schedule revealed the highest levels of compliance when compared to the BID or TID call schedule with the difference between OD and TID being statistically significant.

In response to the missed call questionnaire, the majority reason given (in 10–13% of cases) for missing the scheduled call was due to participant forgetfulness. Other reasons included 'too busy to call', 'no access to a telephone', 'lack of interest in the trial', 'system issues', 'data confidentiality concerns', 'don't remember reason for failure to call' and 'other'.

3.3. SRT and CRT

There was evidence within the groups that task repetition increased accuracy, where the percentage of correct responses for the CRT test improved slightly with increasing the daily call frequency (Table 4); the SRT test was virtually always correct in all instances. However, ANOVA analysis showed no statistically significant effect of SRT or CRT performance on compliance (Table 5).

3.4. EPQ

ANOVA analysis showed no statistically significant relationship between baseline EPQ Extraversion or EPQ Neuroticism scores and compliance, whether using the narrow window or the relaxed window (Table 5).

3.5. End of study phase

In the end of study evaluation, participants generally scored the IVRS system highly for ease of use and clear instructions (Fig. 2). Participants liked the use of reminders at the end of each call, although a need for further improvements in IVRS speed and reliability was highlighted, as was the ability to alter selected daily call times.

With the exception of the number of calls made per day, there was good agreement in the feedback received from the three groups.

4. Discussion and Conclusion

4.1. Discussion

~~The first objective of this study was to examine the effect of three different call schedules on compliance while using IVRS diary data capture as a model of medication dosing. The secondary aims of the study were to explore the effect of call frequency on cognitive function variables and the effect of personality variables on compliance. Two key variables were used to assess compliance: the proportion of calls completed within a narrow window around the specified calls times; and the proportion of calls completed within a relaxed window.~~

In this study ~~provide a number of important contributions to the literature. Firstly~~, changes in the peripheral cue 'IVRS call frequency' were shown to influence compliance. This result partly supported the hypothesis that reduced call frequency would be associated with increased rates of compliance. Thus with the relaxed window, the overall (numerically) highest rate of compliance was observed with the OD schedule – consistent with the theory that once-daily dosing is superior to more frequent dosing regimens [13–17]. Indeed, the rate of completed calls within the relaxed window was considerably higher (38% to 60%) for the OD schedule than for the TID schedule. For the narrow window, although the percentage of calls completed was numerically higher with the OD schedule than the TID schedule, the highest rate of compliance was observed with the BID frequency.

It is also clear from the results that imposing a narrow time window reduces compliance, regardless of call frequency, when compared with an expanded window. This accords with published data, in which compliance nearly doubled with a relaxed completion window of 90 minutes, compared with a strict 30-minute completion window [7]. The slightly higher

compliance rate observed in this study for the BID schedule in contrast to the OD schedule for the narrow window may suggest that, at least when participants are able to select their own call times, a more regular, structured frequency has some advantages. However, the differences in compliance between the OD and BID schedules were marginal, and so care should be taken in any such interpretation. The much-reduced rate of compliance with the TID schedule suggests a lifestyle element to compliance whereby OD schedules may fit in better with daily routines than TID schedules.

The low overall rates of compliance in this study (up to 60%), and the relatively high discontinuation rate make the interpretation of the results of the study challenging. ~~Previously reported rates of compliance with electronic diaries, particularly IVRS, are variable [5].~~ This may be, at least in part, due to the recruitment of healthy volunteers who had little incentive to participate in, or complete, the study. However, participants reported little difficulty with the diary procedures and were not unduly burdened by the call strategies, and so it would appear that the design of the study *per se* was not the cause of the lower than anticipated compliance and completion rates. Given that rates of compliance observed in clinical trials are generally acknowledged to be better than those observed in clinical practice, the current study may in fact represent a more accurate compliance rate than has previously been observed. Indeed, rates of persistence (a measure of compliance) with chronic medication as low as 60% have been reported [23]. It is also of note that 78% of participants randomized to once-daily calls completed the study compared to 43% of participants randomized to three-times daily calls. This difference in completion rates supports our findings for the primary endpoint, given that the once-daily call schedule was associated with the highest rate of compliance (with the relaxed window). The number of participants recruited into the study

(71) was lower than the required number according to our sample size calculation (75). However, a shortfall of just four participants is felt unlikely to impact the overall results.

When researching compliance, the psychological literature describes dual-process models of persuasion than can be used as a framework to determine components of compliance. The Elaboration Likelihood Model (ELM) of persuasion, developed by Petty & Cacioppo, 1981 [18] is a dual-process model that proposes two routes to persuasion along an elaboration continuum – the peripheral route and the central route. ~~Under conditions of high elaboration, e.g., where an individual is motivated and has the ability to scrutinise the message text, persuasion occurs via the central route. Conversely, when elaboration is low e.g., where the message is not personally relevant or where motivation / ability to process are low, processing occurs via a peripheral route.~~ Peripheral route persuasion allows processing to occur under highly distracting conditions and relies on a variety of 'peripheral cues' that, when present, induce an attitude change without message scrutiny [24]. Examples of persuasive peripheral cues include aspects of source credibility (such as high expertise), where the perceived expert is more credible than the non-expert [25], a high fear message [26], a short message length [27] and low dosing frequency [28]. The design of this study matches the criteria for the ELM of persuasion with low elaboration, given that calls to IVRS were made under distracting conditions, that participants had low motivation to process and no incentive, and that the study involved ephemeral behavior change over 2 weeks. ~~The results suggested that IVRS call frequency acts as a peripheral cue to persuasion and hence compliance behaviors are influenced by this variable even under highly distracting conditions. Nevertheless, despite good evidence that peripheral cue call frequency impacts compliance in healthcare, these results should be considered with caution. There was no~~

~~evidence from this study to suggest that peripheral route processing occurred in the absence of central route processing. Future studies should challenge the ELM model and investigate whether peripheral route processing does occur in isolation. It is recommended that future work examines the effect of intermittent dosing (weekly) to determine if a psychophysical threshold can be found above which compliance is significantly compromised.~~ However, the study was not designed to determine whether peripheral route processing occurred in the absence of central route processing – this would be an interesting area for future research.

IVRS acted as a suitable model of medication dosing since, in accordance with the literature, OD dosing was associated with improved compliance compared with BID or TID dosing [13–17]. A key advantage of this model is that the selected SRT and CRT modules took approximately 2 minutes each to complete – simulating the time required to take a dose of medication. SRT results throughout the study were high, which might be a reflection of the participants who largely had prior experience with the use of IVRS and good concentration and alertness for the task. Similarly, correctness of CRT results was high, particularly with increasing call frequency. While the SRT and CRT findings did not reach statistical significance, it is well recognized in the literature that repetition increases persuasion [19]. In the past, PRO measures (including patient diaries) have traditionally used paper-based instruments. One of the issues with such methods is that it has been shown that 75 to 80% of dates and times are falsified [7]. An advantage of IVRS over such paper-based systems is that such 'data falsification' can be prevented, and the high SRT and CRT results in this study suggest that IVRS can be a reliable and accurate model for data collection. ~~Furthermore, IVRS was generally considered easy to use, which highlighted the acceptability of this method for data capture.~~

~~It is proposed that whilst peripheral route processing may offer a route to persuasion, dimensions of personality, namely extraversion and neuroticism (anxiety proneness) have also shown some effect on compliance, such that compliance correlates positively with neuroticism and negatively with extraversion [19]. In accordance with Eysenck's original two-dimensional framework (neuroticism-stability and introversion-extraversion), compliance is highest among unstable introverts and lowest among stable extraverts [19]. Whilst the EPQ is good to use in conjunction with IVRS in that it asks Yes/No questions, this is also a limitation of the model in that it can force inaccurate responses and hence be psychometrically inferior.~~

~~Future work is needed on compliance in the current study. This might be because extraversion and neuroticism scores of the EPQ were well balanced between the groups, and the finding is perhaps a reflection of the chosen sample population.~~

~~Future work is needed to enhance persistence, and findings should be extended in further research to follow-up with and ascertain the reasons for participants' premature discontinuation. Finally, these findings are based on conducting a controlled trial. Real-world data may differ from results obtained in such a controlled study. Further work is required to monitor compliance in a real-life clinical practice and in large-scale studies.~~

The results for the male participants were not compared with the female participants. The study was not powered for such a comparison (given that randomization was not stratified by gender), and thus interpretation of the results could be challenging. However, it should be noted that the distribution of gender in each group was approximately even. Given that other

research has suggested a gender bias to compliance but with very inconsistent findings (in some studies, compliance was higher in females; in other studies compliance was higher in males) [29,30], this would be an interesting area for future research with our IVRS model. Future work is also recommended on the impact of dimensions of personality on compliance (the lack of extremes in baseline EPQ score prevent detailed analysis), and into the reasons for premature discontinuation. Finally, it would be interesting to study whether these (controlled trial) results are replicated in a 'real world' setting.

4.2. Conclusion

In conclusion, the results suggest that a once-daily diary call or dosing regimen is preferential for compliance compared to a twice-daily or three-times daily schedule, when dosing or diary calls must occur as close as possible to the scheduled time point. Repetition may encourage better compliance where a more relaxed time window of up to 4 hours is permitted. If these findings are substantiated in large-scale, controlled clinical trials, reduction of call frequency may represent a significant improvement in overall rates of compliance of the trial.

~~The practice implications of this research suggest that reducing IVRS diary transactions and medication dosing to a once-daily regimen increases compliance in clinical studies when such assessments are to be completed as close as possible to a scheduled time. Limiting the number of daily doses / IVRS transactions can avoid compromising data reliability and integrity and, hence, provide more assurance of the accuracy of safety, tolerability and efficacy of treatments. In terms of development of the ELM theory, findings support the use of the IVRS psychophysical peripheral cue variable 'call frequency' as a route to persuasion;~~

~~thus, awareness of the ELM contributes to the maximisation of compliance. Furthermore, an awareness of various aspects of compliance helps to maximize data integrity of patient-reported outcomes, and of assessments of the safety, tolerability and efficacy of treatments in clinical studies. Future work with such an IVRS model is proposed to study how to maximize compliance in healthcare and, in turn, reduce the burden to society of spiraling healthcare costs.~~

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TABLES

Table 1: Demographics and personality characteristics of randomized trial participants (N=71).

	Call Schedule		
	OD	BID	TID
	n=23	n=25	n=23
Median age (yr) (range)	29 (20-50)	29 (23-51)	29 (23-58)
Sex, n (%)			
Male	11 (47.8)	12 (48.0)	9 (39.1)
Female	12 (52.1)	13 (52.0)	14 (60.9)
Smoking History, n (%)			
Never smoked	14 (60.9)	13 (52.0)	16 (69.6)
Ex-smoker	4 (17.4)	7 (28.0)	2 (8.7)
Current smoker	5 (21.7)	5 (20.0)	5 (21.7)
EPQ Extraversion			
Mean (SD)	13 (5.9)	13 (5.9)	14 (4.9)
EPQ Neuroticism			
Mean (SD)	10 (5.5)	11 (6.1)	10 (5.6)

Demographics of study participants where OD = Once daily, BID = Twice daily, TID = Three-times daily calls.

Table 2: Compliance variables (%) by call schedule of randomized trial participants (N=71).

	Call Schedule		
	OD	BID	TID
	N=23	N=25	N=23
Calls (as % of expected) within narrow ±30-min window of specified call times[1]			
Mean (SD)	44.5 (22.48)	51.0 (28.54)	30.3 (24.69)
Calls (as % of expected) within relaxed window between -30-min & 4-hour[2]			
Mean (SD)	59.5 (23.68)	57.9 (29.45)	38.4 (29.35)

[1]ANOVA F= 3.87; df=2,68;p=0.03

[2]ANOVA F=3.89; df=2, 68, p=0.03

Mean calls within the narrow (30 minute) and relaxed (4 hour) time windows by call strategy (OD, BID and TID)

Table 3: Bonferroni post-hoc regression analysis of compliance variables (%) by call schedule for randomized trial participants (N=71).

Dependent Variable	(I) Call Strategy	(J) Call Strategy	Mean Difference in compliance (I-J)	Std Error	P[a]
Calls made within narrow	OD	BID	-6.30	7.22	1.00
(±30-mins) window	OD	TID	13.52	7.21	0.20
	BID	TID	19.83	7.29	0.03(*)
Calls made within relaxed	OD	BID	2.08	7.79	1.00
(-30 min to +4 hours) window	OD	TID	19.86	7.78	0.04(*)
	BID	TID	17.78	7.87	0.08

(*) indicates $p<0.05$

[a]Pairwise comparisons adjusted according to Bonferroni comparing the call strategies for the narrow and relaxed compliance windows.

Table 4: SRT and CRT Performance (% correct responses for randomized trial participants (N=71)

	Call Schedule		
	OD	BID	TID
	n=23	n=25	n=23
SRT Correct Responses (%)			
Mean (SD)	100 (0.06)	100 (0.02)	100 (0.000)
CRT Correct Responses (%)			
Mean (SD)	95.1 (3.6)	97.3 (2.3)	97.6 (2.8)

Cognitive performance (SRT & CRT) in terms of correct responses given over the study period by call strategy.

Table 5: Results of the ANCOVA analysis of relationship between compliance and average SRT,CRT and baseline EPQ scores for randomized trial participants (N=71)

Covariates	Dependent Variable	F	p
Average SRT	Percentage calls (30-min window)	0.24	0.63
	Percentage calls (4-hour window)	0.34	0.56
Average CRT	Percentage calls (30-min window)	0.04	0.84
	Percentage calls (4-hour window)	0.08	0.78
Baseline EPQ N Score	Percentage calls (30-min window)	0.02	0.90
	Percentage calls (4-hour window)	0.01	0.94
Baseline EPQ E Score	Percentage calls (30-min window)	1.26	0.27
	Percentage calls (4-hour window)	0.07	0.79

Degrees of freedom = 1,64 for all

Describes the effect of key covariates on compliance with both the relaxed and narrow windows

*** Revision Notes**

Title: A randomized trial to determine the impact on compliance of a psychophysical peripheral cue based on the Elaboration Likelihood Model

First Author: Rachael Jane Horton

Response to review comments

Review comment	Response
Reviewer 1	
1. Authors present 'A sample size calculation' should be '75' (Line 22 P9), but in fact it was just '71'.	Although the sample size calculation indicated that 75 participants were required, time and resource implications resulted in recruitment being closed after the enrolment of 71 participants. It was not possible to extend the recruitment further as access to the IVRS was limited. The shortfall of four participants is felt unlikely to impact the overall results. Additional text has been added to pages 12 (results) and 16–17 (discussion).
2. 'Participants (N=71), were randomized using an IVRS in the ratio 1:1:1 to a OD, BID or TID call schedule'. How did authors divide them according to 1:1:1?	Explanatory text has been added to page 8. Please note that randomization was not stratified.
3. '44 (62%) completed the study (Fig.1). Participants who prematurely discontinued were not followed up, so reasons for withdrawal are unknown'. Just 44 of 71 participants completed study, the quality of it should be susceptible.	The authors recognize that the completion rate is lower than perhaps might be considered ideal. However it should be noted that 78% of participants randomized to once-daily calls completed the study compared to 43% of participants randomized to three-times daily calls. This difference in completion rates supports our findings for the primary endpoint, given that the once-daily call schedule was associated with the highest rate of compliance (with the relaxed window). Additional text has been added to the discussion (page 16) to raise this point.
4. The discussion should be concise; the conclusion should be cautious.	The discussion and conclusion have been shortened, to ensure that only the key points from the study are discussed, and to remove some of the aspects of the conclusions that generalised the findings of the study in a clinical study context. See pages 15–20.
Reviewer 2	
1. Define "electronic patient diaries "	A definition has been added to page 5.
2. Define "Interactive Voice Response systems "	A definition has been added to page 5, along with supporting references (one of which is taken from this journal).

Title: A randomized trial to determine the impact on compliance of a psychophysical peripheral cue based on the Elaboration Likelihood Model

First Author: Rachael Jane Horton

Response to review comments

Review comment	Response
3. Reason to do the study?	In this study, we sought to examine one of the potential causes of sub-optimal compliance – dosing frequency. There is some evidence (although inconsistent) that reducing dosing frequency may enhance compliance. However, this evidence generally comes from clinical trials, where the results can be influenced by the efficacy or adverse effects of the drugs being studied. This study therefore utilised a novel design, in which an IVRS system was used to model dosing frequency. The stated aim of the study (page 6) was 'to provide an insight into causes of sub-optimal compliance, with a particular focus on compliance to medication regimen and patient diaries'. Additional explanatory text has been added to the introduction (pages 5–6)
4. The researchers' review of literature is weak done.	The introduction has been expanded to include additional literature reviews and supporting references. See pages 5–7.
5. Define "psychophysical peripheral cue "	A definition has been added to page 6.
6. Why are participants females and males ?	Recruitment was open to either men or women, with no stratification. This sentence (page 8) has been rephrased for clarity
7. Why didn't compare the results?	The results for the male participants were not compared with the female participants. The study was not powered for such a comparison (given that randomization was not stratified by gender), and thus interpretation of the results could be challenging. However, it should be noted that the distribution of gender in each group was approximately even. The authors acknowledge that this would be an interesting area for future study. Additional text has been added to the discussion (pages 19–20)
8. The discussion section was too long	The discussion section has been significantly shortened. See pages 15-20.