How can we best use SMS prompts for ensuring compliance with study procedures?

A Protocol for a 'Trial Within A Study'

BACKGROUND AND RATIONALE

Retention in clinical research is important for the validity of studies yet , there are few robust, evidence based strategies for improving retention beyond questionnaire response [1,2], particular in longitudinal studies [3]. Therefore methodological research into improving retention strategies is warranted and remains a research priority [4,5].

We are conducting a longitudinal observational study of lifestyle measures in people with Huntington's Disease (DOMINO-HD). A fundamental part of the study involves participants wearing an activity tracker for a 12-month follow up period, where they are required to regularly sync their tracker with an app on their smartphone thus transmitting data to a cloud server. As high data completion rates are vital for the intended analysis, we want to ensure that we obtain as much of the intended data as possible. To do this we intend on sending participants reminders using a short message service (SMS), however, the optimal strategy for ensuring high levels of compliance, whilst simultaneously achieving high levels of acceptability and hence overall retention in study participants, is unknown. This aligns with two of the top ten research questions regarding retention in clinical research as determined by the PRioRiTy II study [5] ; 1) What are the best ways to encourage trial participants to complete the tasks [required by the study]? and 2) how could technology be best used in trial follow-up processes?

The use of mobile technologies, including the use of SMS in healthcare settings is collectively referred to as mHealth [6]. The widespread use of mobile devices provides equality of access, which has led to a marked increase in the use of mHealth technologies in healthcare and health related research, with SMS being particularly popular due to its low cost. The use of SMS in various healthcare and research settings has been investigated for several purposes but often with the common goal of improving engagement of the recipient with a service or procedure. Studies of SMS have demonstrated effectiveness and good acceptability in improving attendance of patients at health services [7,8], as a method for delivering health interventions for both acute [9,10] and chronic disorders [8,11,12], including behaviour change interventions [13], and for data collection [14–17] in clinical research.

There is evidence to suggest that electronic prompts such as SMS can improve participant retention in clinical research [18] with specific reference to tailoring or personalising messages [9,19] and the timing of said prompts [20]. However, there are no reports on the use of SMS in the long term for promoting participant retention and how the frequency of SMS in this scenario may impact on their effectiveness.

Here we plan to investigate the relative effectiveness of a routine versus a data driven approach to prompting participants to comply with study procedures in a longitudinal

observational study. This protocol was designed in consultation with our Public and Patient Involvement (PPI) group with particular reference to the frequency and content of message prompts. The opinions of the PPI group as to what would be acceptable to participants, and the language that should be used guided study design. We plan to perform a process evaluation using follow-up questionnaires with both participants and researchers to explore the feasibility and acceptability of both approaches.

OBJECTIVE

To determine the optimum strategy for sending SMS prompts to participants to maximise compliance with study procedures.

INTERVENTION AND COMPARATOR

Comparator Group (Routine messaging): This group will receive a routine SMS sent on the 8th day following recruitment and then weekly thereafter. The content of the message will remain constant throughout and will remain neutral in tone. An example of such a message would be;
"Please remember to wear your FitBit continuously and sync with the app on your mobile regularly. Thanks very much, the DOMINO-HD team"

If a participant fails to upload more than 50% of the expected data, that is more than 50% of activity data in the preceding 7 days is missing, for a continuous 4 week period, this will prompt a telephone call from the recruiting site to the participant. This will be to see if;

a) the participant is having any technical issues wearing the activity tracker or syncing the data that can be remedied or
b) if the participant no longer wishes to continue in the study.

An example of how this would work can be found below.

Scheduling type: Weekly routine messaging																															
day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Example day	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We
collected (grey if retrospectively collected due to sync lag)	X	X	X		X	X	X	X	X	X				X	X					X	X	X							X	X	
missing				X							X	X	X			X	X	X	X				X	X	X	X	X	X			X
Prompt																															
Escalation prompt																															

Scheduling type: Weekly routine messaging with triggered call to participant																															
day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Example day	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We
collected (grey if retrospectively collected due to sync)	X					X	X	X	X						X	X															
missing		X	X	X	X					X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X		
Prompt																															
Phone call from site																														ES2	
	routine SMS																														
	Phone call from site																														

Intervention Group (Data driven messaging): In this group participants will receive a weekly SMS sent on the 8th day following recruitment and weekly thereafter as in the comparator group. However, the content of this message will be dependent on their compliance with uploading data. If the participant has uploaded more than 50% of the expected data in the preceding 7 days, they will receive a positive message of thanks:

"We have received your data for xx days this week. Thank you for wearing your FitBit and for syncing with the App on your mobile phone. We value your ongoing participation in the DOMINO-HD study."

However, it the participant fails to upload more than 50% of the expected data in the preceding week they will receive a prompt reminding them of the need to wear the FitBit and sync the data:
"We have received your data for xx days this week. Please remember to wear your FitBit continuously and sync with the app on your mobile regularly. Thanks very much, the DOMINO-HD team"

This message will be sent for two consecutive weeks if the participant continues to upload less than 50% of the data required. After the third week of receiving less than 50% of the expected data, the message will be altered again:
"We are having trouble locating data from your FitBit. Please wear your FitBit continuously and remember to sync with the app on your mobile. If you are having problems please contact the research team on xxxxxxx. Thanks very much, the DOMINO-HD team"

If the participant continues to fail to upload at least 50% of the expected data for four consecutive weeks, as in the comparator arm they will receive a telephone call from the participating site.

An example of how this will work can be found below.

Schedulling type: Weekly individualised summary **minor escalation**

day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Example day	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We
collected (grey if retrospectively collected due to sync lag)	X	X	X		X	X	X	X	X					X	X						X	X	X	X		X	X		X	X	
missing				X						X	X	X	X			X	X	X	X	X					X			X			X
Prompt																															

Scheduling type: Weekly individualised summary **with full escalation**

day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Example day	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We
collected (grey if retrospectively collected due to sync)	X					X	X	X	X						X	X															
missing		X	X	X	X					X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X		
Prompt																						Es1								Es2	

Positive SMS giving thanks
SMS reminder to sync
SMS highlighting missing data
Phone call from site

OUTCOME MEASURES:

Primary Outcome:

Total number of wear hours logged (up to and including the 9th week following randomisation [where week 1 data is excluded from analysis])

Secondary Outcomes

Total number of wear hours logged (across the 12 months study period)

Average number of data synchronisation events per week (Fitbit App with cloud server)

Average number of days data synchronisation events occur after SMS sent (Fitbit App with cloud server)

Average number of escalation phone calls made per participant

Number of 'withdrawals' from DOMINO-HD observational study

Participant user experience

Researcher user experience

METHODOLOGY

Participants will be enrolled into the TWAS automatically on registration to the DOMINO-HD longitudinal study. Once registration and the baseline assessments have been completed participants will be randomised to either the comparator or intervention groups of the TWAS. Participants will be randomly allocated via the DOMINO-HD clinical study database in a 1:1 ratio, stratified by recruiting site. Participants will receive information about receiving reminders in the participant information given to them for the DOMINO-HD longitudinal study, in particular, it will be highlighted that they need to provide their mobile telephone number for this and how it will be used and stored. The consent for the DOMINO-HD longitudinal study specifically references this and additional consent will not be required for the TWAS. Participants and site staff will remain blind to the allocation of participants to either the comparator or intervention arm of the TWAS.

The TWAS will be managed centrally by the Cardiff team. They will be responsible for ensuring that weekly SMS prompts are sent, and also for the data monitoring required to tailor the message in the intervention arm. SMS prompts will be sent using an automated messaging platform, Esendex. Esendex stores information on an Amazon server which holds an ISO certification for data security and is compliant with the General Data Protection Regulation.

Mobile telephone numbers for participants will be entered into the clinical database by local site staff. Access to this information will be restricted to specific, delegated users. Delegated members of the Cardiff team will access these numbers for input into the Esendex platform. Within Esendex, telephone numbers will be linked to the participant identification number (PID) and names will not be stored in the platform to maintain confidentiality.

The Cardiff team will continue to monitor data upload for all participants and send SMS prompts according to the participant's preferred language (English, Spanish, German, French or Polish), allocation and compliance with study procedures. Should a participant upload less than 50% of the expected data for 4 consecutive weeks, the Cardiff team will alert the relevant site to the need for a phone call to the participant.

If a participant is contacted due to non-compliance and they indicate that they wish to withdraw from the study, the site staff should follow the withdrawal procedure documented in the DOMINO-HD study protocol.

At the end of the 12-month observational study, participants will be asked to complete a short questionnaire about the messages they received. Researchers involved in the delivery of the TWAS will also receive a questionnaire about their experiences.

DESIGN AND SAMPLE SIZE

To allow for early stopping of the TWAS if data driven messaging proves to be the superior strategy, we will use a group-sequential design with two interim analyses and O'Brien-Fleming stopping boundaries. Conservatively assuming a total sample size of 300 for DOMINO-HD (i.e. 150 randomised to each TWAS arm), the TWAS has 90% power to detect a small-to-medium effect size (Cohen's d=0.3786) based on a one-sided type I error rate of 2.5% (calculated with rpact version 2.0.6 [21,22]; see Appendix).

ANALYSIS

Primary outcome: The first interim analysis will be performed once 100 participants have provided primary outcome data (total wear hours logged between the 2nd and 9th week following randomisation). We will calculate a p-value based on a one-sided t-test for the mean difference in the primary outcome between the randomised groups. If the p-value is below 0.00026, we will stop the TWAS, conclude that data driven messages increase total wear hours logged, and switch all participants over to the superior method of prompting. If not, the analysis will be repeated after 200 participants have provided primary outcome data, this time using a p-value threshold of 0.00706, and if the TWAS is not stopped at this point, again after all 300 participants have provided primary outcome data, now with a p-value threshold of 0.02253. We will present the point estimate of the mean difference alongside a 95% confidence interval (CI).

Secondary outcomes: We will present descriptive summaries (e.g. means, frequencies, ranges) by arm and will estimate mean differences between the two arms alongside 95% CIs. Reasons for withdrawal, if known, will be tabulated by arm.

Questionnaires used to evaluate participant perceptions of the SMS messages will use a mix of quantitative and free text questions. Summary quantitative data from the questionnaires will be tabulated by study arm. Qualitative analysis of free text comments in the questionnaires will be conducted using thematic analysis.

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APPENDIX

The following code was executed in R to compute the group-sequential design:

```
library(rpact)

obf <- getDesignGroupSequential(kMax=3, alpha=0.025, beta=0.1, sided=1,
typeOfDesign="OF")

getSampleSizeMeans(design=obf, groups=2, alternative=0.3786)
```