JRMO Non-CTIMP Protocol Template (Version 2 25/02/2016)

TITLE PAGE

Evaluation of tailored electronic reminders on compliance with removable orthodontic retention: a randomised controlled trial.

Full Title Evaluation of tailored electronic reminders on compliance with removable orthodontic retention: a randomised controlled trial.

Short Title/Acronym Evaluation of tailored electronic reminders on compliance with removable orthodontic retention.

Sponsor
Queen Mary, University of London

Contact person of the above sponsor organisations is:

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Contents Page

GLOSSARY of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
GAfREC	Governance Arrangements for NHS Research Ethics Committees
ICF	Informed Consent Form
JRMO	Joint Research Management Office
NHS REC	National Health Service Research Ethics Committee
NHS R&D	National Health Service Research & Development
Participant	An individual who takes part in a clinical trial
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee

SIGNATURE PAGE

Chief Investigator Agreement

The clinical study as detailed within this research protocol **(Version 2, dated 25 February 2016)**, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief Investigator Name: Dr Padhraig Fleming

Chief Investigator Site: The Dental Hospital, Barts Health NHS Trust

Signature and Date:

 (25/02/2016)

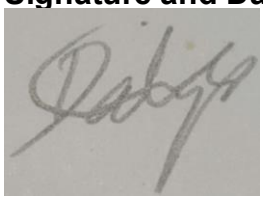
Principal Investigator Agreement *(Dalya Al Moghrabi)*

The clinical study as detailed within this research protocol **(Version 2, date 25 February 2016)**, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Principal Investigator Name: Dalya Al Moghrabi

Principal Investigator Site: The Dental Hospital, Barts Health NHS Trust

Signature and Date:

 (25/02/2016)

SUMMARY/SYNOPSIS

Short Title	Evaluation of tailored electronic reminders on compliance with removable orthodontic retention
Methodology	*Mixed methods design* Part 1: A Randomized Controlled Trial Part 2: Qualitative investigation using one-to-one interviews
Research Sites	*The Dental Hospital, Barts Health NHS trust*
Objectives/Aims	The primary objective is to analyse the effect of electronic reminders on compliance with removable orthodontic retention. The secondary objectives are to assess the subjective levels of retainers wear and to measure upper/lower anterior irregularity and transverse dimensions. We also aim to explore patients' experience with electronic reminders in a related qualitative element.
Number of Participants/Patients	Based on sample size calculation, patients referred into the orthodontic Department, Royal London Hospital will be recruited.
Main Inclusion Criteria	Inclusion Criteria: - Aged 12 to 21 years; - Planned for removable retention with Essix-type vacuum-formed retainers - Fit and well and on no medication; - In the permanent dentition.
Statistical Methodology and Analysis (if applicable)	Data analysis will involve descriptive and analytical statistics performed using

	software (SPSS, New York, NY, USA). Assessment of the reliability of the measures used in the study will be tested by assessing agreement between the measurements (Bland and Altman, 1986). Baseline characteristics will be summarised to ensure that all groups are similar with respect to potential confounding variables. Inferential statistics will be used to compare differences in the duration of appliance wear between the treatment groups. If the data follows a normal distribution, linear regression analysis will be used to assess the influence of retention protocol on the main outcome. This technique will allow for confounding factors including degree of crowding pre-treatment; age; and gender. The level of statistical significance will be pre-specified at $P<0.05$. Transcripts of the interviews will be entered in NVivo 10 TM qualitative data analysis software (QSR International) and anonymised for analysis. The Framework approach will be used to analyse the qualitative data (Gale *et al*., 2013). This approach facilitates the thematic analysis of qualitative data in a structured way around the key questions in the topic guide.
Proposed Start Date	May 2016
Proposed End Date	24 months after recruitment of the final participant.
Study Duration	24 months

INTRODUCTION

The introduction acts as the starting point for outlining the background and justification for the research, with clear concise objectives which have scientific merit and relate to existing literature.

Orthodontic retention following treatment is essential to resist the tendency of teeth to return to their pre-treatment positions. Removable retainers worn on full- or part-time basis are acceptable retention procedures. However, removable retention places an onerous premium on excellent long-term compliance.

Within the biomedical literature there is ample evidence alluding to the effectiveness of electronic and telecommunication systems in improving adherence to long-term use of medications (Reidel et al., 2008; Armstrong et al., 2009; Boland et al., 2014), self-monitoring of chronic conditions (Logan et al., 2007) and in terms of attendance at appointments (Gurol-Uranci et al., 2013). Specifically tailored approaches have proven particularly effective (Stacy et al., 2009). There is, however, no reported usage of these approaches within orthodontics. Moreover, electronic reminders to improve compliance with removable retention regimes among orthodontic patients have not been explored.

The primary aims of this study is to analyse the effect of electronic reminders on compliance with orthodontic retention at 3, 6 and 12 months following removal of fixed appliances.

The secondary aims are to assess the subjective levels of retainers wear, and to measure upper/lower anterior irregularity and transverse dimensions. We also aim to explore patients' experience with electronic reminders in a related qualitative element.

TRIAL OBJECTIVES

Primary /Secondary Objectives to be outlined as defined by the Primary/Secondary Endpoints which are also to be listed here.

The primary objective is to explore the effect of electronic reminders on compliance with orthodontic retention.

The secondary objectives are to assess the subjective levels of retainer wear and to measure upper/lower anterior irregularity and transverse dimensional changes during the retention phase. We also aim to explore patients' experience with electronic reminders in a related qualitative element.

- Primary Endpoint
Objective level of compliance with retainer wear at 6 months (T3) of orthodontic retention.

- Secondary Endpoints
Objective level of compliance with retainer wear at 3 months (T2) and 12 months (T4) of orthodontic retention.

METHODOLOGY

Inclusion criteria:

- Aged 12 to 21 years;
- Planned for removable retention with Essix-type vacuum-formed retainers;
- Fit and well and on no medication;
- In the permanent dentition.

The exclusion criteria:

- Inability to access or peruse electronic mail;
- Cleft lip and palate and other craniofacial anomalies.

Study Design / Plan – Study Visits

Subjects will be recruited for inclusion at a routine adjustment appointment prior to planned removal of the appliances in the Orthodontic Department at Institute of Dentistry, Barts and The London School of Medicine and Dentistry, UK. Following removal of the appliances, consenting participants will be randomly allocated to one of two groups by computer-generated random allocation. Allocation will be concealed from the treating clinician using of an opaque sealed envelope system. Study models will be available for all participants following removal of the appliances (T1).

Participants in both groups will have follow-up scheduled for 3 (T2), 6 (T3) and 12 (T4) months following removal of the appliances. All participants will be instructed to wear vacuum-formed (Essix-type) retainers on a full-time basis for 6 months, followed by night-time wear for a further 6 months (Gill et al., 2007). A Thera-MonTM micro-electronic timer will be integrated within the upper Essix-type retainer. All participants will be given standard advice at each recall visit. If any patient from both groups fails to attend their routine retainer check visit, another appointment will be arranged and posted through Royal Mail.

Participants in the intervention group will receive tailored electronic reminders. The frequency and content of the reminders will be informed by the qualitative findings of an ongoing trial, but are likely to include an intra-oral photograph taken pre-treatment and following removal of the active appliances, instructions on the necessary duration of retention, advice on maintenance of retainers, departmental details, advice on appropriate management for appliance breakages, and delineation of the implication of suboptimal retainer wear. Participants in the control group will not receive additional reminders.

Treating clinicians will be kept blind to the study group.

All patients failing an appointment will be sent another. Those wishing to withdraw from the trial may do so at any point without affecting continuing care with records taken at the point of withdrawal from the study with data analysis on an intention to treat basis.

One-to-one interviews will be undertaken by the researcher on subset of participants in confidential, non-clinical areas at the Institute of Dentistry. The interviews will be based on a topic guide, which will draw on existing literature and professional experiences. This will facilitate discussion based around the aims of the research. Themes to be explored are likely to be patients' acceptance and experience of electronic reminders. Discussions will be recorded digitally and transcribed verbatim. Transcripts will be entered in NVivo 10 TM qualitative data analysis software (QSR International) and anonymised for analysis.

Study Scheme Diagram

To reinforce the above and which demonstrates the life cycle of the study in a schematic form (see example below)

Please refer to figure 1.

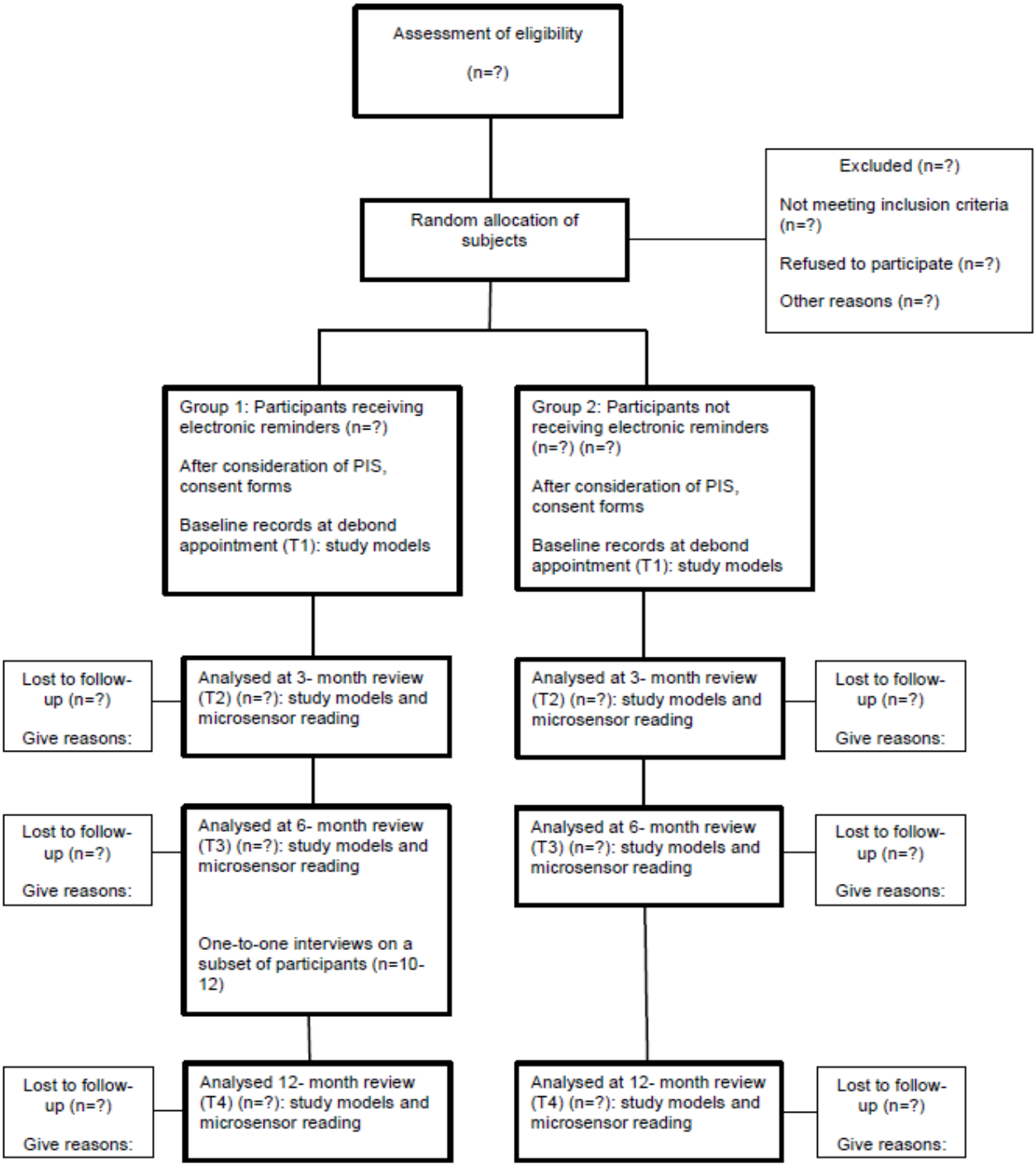


Figure 1. CONSORT chart showing the low of participants through each stage of the trial

STUDY PROCEDURES

Participants will be recruited by treating clinicians at Institute of Dentistry, Barts and The London School of Medicine and Dentistry. Potentially eligible participants will be given an information sheet detailing the study and its objectives at the visit prior to removal of their fixed appliances. Participants agreeing to be involved will be asked to sign a consent form for inclusion in the study at the following visit. Patients under 16-18 years can consent for themselves only if they were deemed mature to make a decision, this will be decided by the CI and PI. Otherwise, the parent will be asked to consent for their child.

Following removal of the appliances, consenting participants will be randomly allocated to one of two groups by computer-generated random allocation. Allocation will be concealed from the treating clinician using of an opaque sealed envelope system. Standard orthodontic study models will be available for all participants following removal of the appliances (T1).

Participants will then be reviewed at 3, 6 and 12 months for regular retainer checks and collection of records i.e. study models and microsensor readings.

One-to-one interviews will be undertaken in a confidential non-clinical areas. Interviews will continue until data saturation has been achieved characterized by a lack of new emergent themes.

All documents including models will be securely held in a locked office, photos will also be stored on an encrypted trust computer.

Schedule of Assessment (in Diagrammatic Format)
Please use a table format to detail the schedule of assessments that the participant will undergo at each visit (see example below).

Assessment	Randomization	Retention phase	Treatment phase	End of Study	Follow up visits
Enrollment, written information sheet, consent	Computer-generated random allocation. Allocation will be concealed from the treating clinician using of an opaque	3-monthly retainer check visits and records collation (study models and timer readings)	One-to-one interview with subset of recruited participants	End of retainer check visits	24 months

	sealed envelope system				

End of Study Definition
Follow-up of retention procedures will be undertaken over a 24-month period. The final retainer checks will be undertaken at 12 and 24 months in keeping with standard orthodontic practice. The study will be completed following the 24-month visit.

STATISTICAL CONSIDERATIONS

Summary
The study compares compliance levels in two groups. Only group one will receive an electronic reminder. The research question is therefore summarised as "does electronic reminders improve compliance levels with orthodontic retainers".

The research question is expressed as the following set of hypotheses:
Null hypothesis: *Periodic, tailored electronic reminders are ineffective in improving compliance with orthodontic retention.*

Alternative Hypothesis: *Periodic, tailored electronic reminders are effective in improving compliance with orthodontic retention.*

Sample Size Calculation

Based on previous research (Tsomos et al., 2014) alluding to a non-compliance rate of 31% characterized by wear of the appliance for less than 2 hours daily a minimum of 68 participants (34 in each group) is required with a power of 80% to detect a minimum difference of 25% in compliance rates at the 0.05 level of statistical significance. To compensate for a dropout rate of at least 10%, the final number to be enrolled in the trial is 84.

For the second part of the study, Initially, 10 one-to-one interviews will be undertaken. Interviews will continue until data saturation has been achieved characterized by a lack of new emergent themes.

Statistical Methods

Data analysis will involve descriptive and analytical statistics performed using software (SPSS, New York, NY, USA). Assessment of the reliability of the measures used in the study will be tested by assessing agreement between the measurements (Bland and Altman, 1986). Baseline characteristics will be summarized to ensure that all groups are similar with respect to potential confounding variables. Inferential statistics will be used to compare differences in

the duration of appliance wear between the treatment groups. If the data follows a normal distribution, linear regression analysis will be used to assess the influence of retention protocol on the main outcome. This technique will allow for confounding factors including degree of crowding pre-treatment; age; and gender. The level of statistical significance will be pre-specified at $P<0.05$.

For the second part of the study the Framework approach will be used to analyse the qualitative data (Gale *et al*.,2013). This approach facilitates the thematic analysis of qualitative data in a structured way around the key questions in the topic.

ETHICS

The Principal Investigator will ensure that the study will be carried out in accordance with the ethical principles in the Research Governance Framework for Health and Social Care, Second Edition, 2005 and its subsequent amendments as applicable and applicable legal and regulatory requirements.

Ethical approval shall be sought from Barts Health NHS Trust and sponsorship shall be sought from Queen Mary University of London. This is done via completion of appropriate protocol and any subsequent amendments along with an accompanying material provided to the patient, all will be submitted to an independent research ethics committee. Because this project involves treatment of children, ethical practice is of utmost importance. The treatment carried out in this trial will in no way differ from the standard routine care of patients ordinarily presenting in the same manner apart from one group receiving electronic reminders. The trial will compare a group of patients receiving electronic reminders and the other group not receiving any form of reminders. In terms of obtaining informed consent, the project will be thoroughly explained at the first visit (a brief will already have been given by referring practitioner), a written information sheet and consent form will be given and follow up arranged if the patient is happy to participate (at least 24 hours will be given to consider options) consent form will then be signed by the parent and patient. Patients under 16-18 years can consent for themselves only if they were deemed mature to make a decision, this will be decided by the CI and PI. Otherwise, the parent will be asked to consent for their child.

SAFETY CONSIDERATIONS:
There are no additional safety issues that are not present with routine orthodontic treatment surrounding the study. Possibility of harm to participants is minimal and most likely to be caused by misuse or mis handling of the appliance. Lab safety issues are not an issue as all lab work is quality assured, radiation protection is in line with local protocol and procedure and security of patients and records will be in line with hospital and departmental standards

DATA HANDLING AND RECORD KEEPING:

- Confidentiality

  Information related to participants will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldecott Principles, The Research Governance Framework for Health and Social Care, and the conditions of Research Ethics Committee Approval.

- Record Retention and Archiving

  When the research trial is complete, the records will be kept for a further 20 years. As this trial involves Barts Health Trust patients and is undertaken by Trust staff, and sponsored by QMUL, the approved

repository for long-term storage of local records is the Trust Modern Records Centre

LABORATORIES (if applicable)

- Central/Local Laboratories

Lab work will be processed in line with local departmental policy, as is the normal for standard provision of this appliance treatment.

SAFETY REPORTING

Adverse Events (AE)

An AE is any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with study activities.

Notification and reporting Adverse Events or Reactions

If the AE is not defined as SERIOUS, the AE is recorded in the study file and the participant is followed up by the research team. The AE is documented in the participants' medical notes (where appropriate) and the CRF.

Serious Adverse Event (SAE)

In other research other than CTIMPs, a serious adverse event (SAE) is defined as an untoward occurrence that:

(a) Results in death;
(b) Is life-threatening;
(c) Requires hospitalisation or prolongation of existing hospitalisation;
(d) Results in persistent or significant disability or incapacity;
(e) Consists of a congenital anomaly or birth defect; or
(f) Is otherwise considered medically significant by the investigator.

An SAE occurring to a research participant should be reported to the main REC where in the opinion of the Chief Investigator the event was:

• Related – that is, it resulted from administration of any of the research procedures, and
• Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

Notification and Reporting of Serious Adverse Events

Serious Adverse Event (SAEs) that are considered to be 'related' and 'unexpected' are to be reported to the sponsor within 24 hours of learning of the event and to the Main REC within 15 days in line with the required timeframe. For further guidance on this matter, please refer to NRES website and JRMO SOPs

Please note in the case of a blinded study, it is recommended the treatment code for the patient is broken in the reporting of an 'unexpected and related' SAE. Please seek advice on how this can be achieved whilst maintaining the team blind. The unblinding of single cases by the PI/CI in the course of a clinical trial should only be performed if necessary for the safety of the trial subject.

Urgent Safety Measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety. The measures should be taken immediately. In this instance, the approval of the REC prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the sponsor and Main Research Ethics Committee (via telephone) of this event immediately.

The CI has an obligation to inform both the Main REC in writing within 3 days, in the form of a substantial amendment. The sponsor (Joint Research Management Office [JRMO]) must be sent a copy of the correspondence with regards to this matter. For further guidance on this matter, please refer to NRES website and JRMO SOPs.

Annual Safety Reporting

The CI will send the Annual Progress Report to the main REC using the NRES template (the anniversary date is the date on the MREC "favourable opinion" letter from the MREC) and to the sponsor. Please see NRES website and JRMO SOP for further information

Overview of the Safety Reporting responsibilities

The CI/PI has the overall pharmacovigilance oversight responsibility. The CI/PI has a duty to ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements.

	Who	When	How	To Whom
SAE	Principle Investigator	-Report to Sponsor within 24 hours of learning of the event -Report to the MREC within 15 days of	SAE Report form for Non-CTIMPs, available from NRES website.	Sponsor and MREC

		learning of the event		
Urgent Safety Measures	Principle Investigator	Contact the Sponsor and MREC Immediately Within 3 days	By phone Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC and Sponsor Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.

MONITORING &AUDITING

The study will be monitored by the principle and chief investigator in keeping with Good Clinical Practice and the sponsor QMUL

Definition:
"A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)."

A study may be identified for audit by any method listed below:
1. A project may be identified via the risk assessment process.
2. An individual investigator or department may request an audit.
3. A project may be identified via an allegation of research misconduct or fraud or a suspected breach of regulations.
4. Projects may be selected at random. The Department of Health states that Trusts should be auditing a minimum of 10% of all research projects.
5. Projects may be randomly selected for audit by an external organisation.

Internal audits may be conducted by a sponsor's or funder representative.

TRIAL COMMITTEES

As this is a single centre trial, carried out solely by the chief and principle investigator there are no trial committees

FINANCE AND FUNDING

No additional costs will be incurred for the clinical study in view of the fact that the participants will attend their routine retainer check visits with no additional treatment being undertaken. An application for funding has been submitted to the European Orthodontic Society. The funding aims to facilitate the development and refinement of the electronic reminders. These costs are non-clinical but will provide professional expertise to facilitate the development of the reminders as part of a fully-funded PhD research project.

INDEMNITY

Our sponsor is QMUL who will indemnify this study subject to successful granting of ethical approval

DISSEMINATION OF RESEARCH FINDINGS:

Once the trial is complete study results will be disseminated via presentation at national meeting and publication in peer reviewed journal.

REFERENCES

Armstrong AW, Watson AJ, Makredes M, Frangos JE, Kimball AB, Kvedar JC. Text-message reminders to improve sunscreen use: a randomized, controlled trial using electronic monitoring. Arch Dermatol. 2009;145:1230-6.

Boland MV, Chang DS, Frazier T, Plyler R, Jefferys JL, Friedman DS. Automated telecommunication-based reminders and adherence with once-daily glaucoma medication dosing: the automated dosing reminder study. JAMA Ophthalmol. 2014;132:845-50.

Gurol-Uranci I, de Jongh T, Vodopivec-Jamsek V, Atun R, Car J. Mobile phone messaging reminders for attendance at healthcare appointments. Coch Database Syst Rev. 2013; 12: CD007458.

Logan AG, McIsaac WJ, Tisler A et al. Mobile phone-based remote patient monitoring system for management of hypertension in diabetic patients. AJH 2007; 20:942-48.

Reidel K, Tamblyn R, Patel V, Huang A. Pilot study of an interactive voice response system to improve medication refill compliance. BMC Med Inform Decis Mak. 2008;8:46.

Stacy JN, Schwartz SM, Ershoff D, Shreve MS. Incorporating tailored interactive patient solutions using interactive voice response technology to improve statin adherence: results of a randomized clinical trial in a managed care setting. Popul Health Manag. 2009;12:241-54.

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