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Improving treatment adherence in people with diabetes mellitus

Submission date	Recruitment status	[X] Prospectively registered
27/01/2020	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
05/02/2020	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
05/09/2022	Nutritional, Metabolic, Endocrine	[_] Record updated in last year

Plain English summary of protocol

Background and study aims

People with type 2 diabetes mellitus (T2DM) have an increased risk of problems with their eyes and kidneys caused by high levels of sugar in their blood. Medicines are usually used to lower these sugar levels but around one half of people with T2DM don't take their medicines as prescribed. Researchers have had little success in helping people with T2DM to take their medicines as prescribed. This could be because the things they have tried are usually a 'one size fits all' approach but everyone is different and so will need and want different ways to help them take their medicines as prescribed. Researchers have been working for several years on developing different ways to help people take their medicines as prescribed. They have tested each of these different ways so know that they work for some people. What they plan to do in this study is put them all together and allow the patient and pharmacist to sit together and select which ways are likely to be best for the individual.

The researchers will only be testing their ways on people with T2DM who have not been taking their medication as prescribed. The aim of this study is to develop and investigate the (cost-) effectiveness of a personalised intervention program to analyse and improve medication adherence in people with T2DM using oral blood glucose and/or blood pressure lowering drugs. (i.e. to find out if people can be helped to take their medicines as prescribed by using things like messages to their smartphone).

Who can participate?

People aged 35-75 with T2DM prescribed oral blood glucose lowering medication who are non-adherent to oral blood glucose and/or blood pressure lowering drugs

What does the study involve?

Participants are randomly allocated to the new personalised intervention program or usual services. The patient's GP will measure blood sugar readings at the start and end of the service to find out whether the service improves blood sugar and whether it is good value for money to the NHS.

What are the possible benefits and risks of participating?
Overall, for participants, no specific risks for possible damage or potential harm are foreseen. Moreover, the study will not include vulnerable participants and therefore involves a negligible risk to participants and is justified.

Where is the study run from?
The University of East Anglia (UK)

When is the study starting and how long is it expected to run for?
January 2019 to April 2022

Who is funding the study?
1. The European Foundation for the Study of Diabetes (Germany)
2. National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Prof Debi Bhattacharya, d.bhattacharya@leicester.ac.uk

Study website
https://www.uea.ac.uk/groups-and-centres/patient-care-group/intense

Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
270673

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 43936, IRAS 270673, NL8747

Study information

Scientific Title
Towards the development of a personalised E-Health intervention for use in community pharmacies to analyse and improve medication non-adherence in people with type 2 diabetes mellitus, who are non-adherent to oral blood glucose and blood pressure lowering drugs

Acronym
INTENSE

Study objectives
Principal research question/objective:
To develop and investigate the (cost-) effectiveness of a pharmacist-led personalised intervention to improve medication adherence in people with type 2 diabetes mellitus who are non-adherent to oral blood glucose and blood pressure lowering medicines

Secondary research questions/objectives:
1. To identify the non-adherence profiles based on individual factors, barriers, needs and preferences related to medication adherence of people with T2DM who are non-adherent to oral blood glucose and/or blood pressure lowering drugs
2. To perform a process analysis of the personalised intervention program in order to assess the extent to which the intervention has been performed according to the study protocol and to gain insight into the barriers and facilitators of the intervention program
3. To develop and refine non-adherence algorithms after evaluation of the personalised intervention program in order to further improve the intervention for future use

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 30/10/2019, Wales REC 5 (Health and Care Research Wales; Email: Wales.REC5@wales.nhs.uk), REC ref: 19/WA/0275

Study design
Randomised; Interventional; Design type: Process of Care, Education or Self-Management, Device, Management of Care

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)

Community

Study type(s)
Treatment

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Type 2 diabetes mellitus

Interventions
Current interventions as of 27/08/2020:
This study will include people known to be not regularly taking their prescribed tablets or capsules for managing their type 2 diabetes. These people will be identified by the person's GP practice who will search their records to find patients who have not ordered enough of their medication to allow them to be able to take them as prescribed over the previous 2 years. These people will get an invitation letter, participant information leaflet and an expression of interest form. The medical practice will send one reminder after 2 weeks. If a patient is interested, they will then contact their community pharmacy team by telephone or in person. Eligible participants may also be approached opportunistically by the practice team members when visiting the GP to check whether they received the letter sent by the practice and encourage them to notify their regular pharmacy if interested in the study.

The community pharmacy team will be trained by the researchers so that they know what to do when approached by a patient expressing interest in study participation. The pharmacy team will also opportunistically approach potential participants who contacts the pharmacy of whether they received the study invitation letter from their GPs and whether they would like to participate. A trained member of the community pharmacy team will ask the patient some questions to make sure that they are definitely right for the project for example, they must have a mobile phone that allows them to get text messages. If having been satisfied that they have enough information and still want to be involved in the project, the pharmacy team member will ask the patient for permission to share their contact details with the research team. If the patient agrees, the pharmacy team member will add the patient's contact details onto an electronic database to which the research team have access. The pharmacy team member will also provisionally book the patient into a consultation that will be conducted according to practice employed by the pharmacy at the time of the study, i.e. the consultation could be conducted face-to-face, virtual or by telephone, whatever practice employed by the pharmacy. The consultation will be booked at a mutually agreeable date and time within the next two to three weeks (ideally aligning with when the patient would next be in the pharmacy to collect their medication).

Once the pharmacy team member enters the patient's contact details onto the shared database, the research team will send to the patient by post or e-mail (depending upon which the patient prefers) a consent form and baseline questionnaire which includes a diagnostic medication adherence tool called the Adapted Quick Barrier Scan questionnaire. This is the tool that will allow the patient and pharmacist to work together to develop an intervention tailored to the needs and preferences of the patient in terms of adherence support. A reminder will be sent after one to two weeks to non-respondents (after 1 week for those who received the consent materials by email and after 2 weeks for those who received them by post). If the signed consent form is not returned using the prepaid envelope (yet answers to questionnaire one are

returned), the researcher will inform the pharmacy team to follow up with patient participants and collect their signed consent form when they come the pharmacy for the appointment/or to remind them to return it if the consultation is held virtual or through the phone.

After receiving informed consent and responses to the AQBS and questionnaire-1, participants will be randomised one to intervention and one to control at the level of patient participant. The researcher will inform the pharmacy team and the patient participant's GP about their enrolment in the study. The researcher will also request baseline routinely collected data from GP held medical notes; the participant's blood sugar levels (HbA1c), blood pressure and current prescribed medications. A researcher will also telephone the patient to find out how many blood glucose and if prescribed, blood pressure lowering tablets/capsules the patient has in their possession. This will enable a follow-up pill count to be used to estimate whether the participant has taken the expected number of tablets/capsules during the study period.

Patients allocated to the intervention group will have a 15-minute consultation with their pharmacist. The consultation will be conducted according to practice employed by the pharmacy, i.e. it could be conducted face-to-face, virtual or by telephone, whatever the approach used by the pharmacy at the time of conducting the study. During the consultation, the patient and pharmacist will work together to select the supporting programmes that are deemed to be the most effective and acceptable based on the AQBS results and patient preference. Pharmacists will be trained in using the AQBS to inform decision making and have a pre-set profiling algorithm to further guide decision making. All of the supporting programmes have been previously tested on their own but not as an available package from which to select. The programmes are summarised below:
i) To address insufficient knowledge or negative perceptions e.g. information provision by pharmacist or by text messages
ii) To address practical problems e.g. reminder text messages or a compliance aid
iii) To address side effects e.g. referral to prescriber for medication review or guidance on how to manage side effects
iv) To address negative mood and beliefs e.g. unguided self-help online application or motivational text messages.

Participants will receive £8.50 to cover internet costs associated with receiving the online/text message based intervention. After having received the selected supporting programs for one month, the pharmacist will telephone the participant to establish the extent to which they are satisfied with the supporting program and if needed, to further tailor the intervention appropriately. For example, if the patient opted for daily text messages but is finding the frequency too great, they may decide to change them to weekly. The average duration of this phone call will be approximately 10 minutes. This agreed combination and configuration of supporting programs will be delivered for a total of 6 months.

In order to maintain allocation concealment to the patient, they will also receive a consultation (either face-to-face or virtual) using the same process as for intervention participants. However, the consultation will be with a pharmacy assistant trained by the research team. The pharmacy assistant will not have access to the AQBS information but during the consultation, they will introduce the patient to an already available general T2DM information website. The general T2DM information website in the UK will be the Diabetes UK website. During the consultation, the pharmacy assistant will direct the patient to the different sections on the website including information about the condition and their prescribed medications. They will also guide participants on how to make a link of this website available on their mobile phones should they wish.

Both intervention and control participants will be asked to complete a questionnaire after 3 months and then one final questionnaire after 6 months. These questionnaires will be sent either via an email invitation generated from the electronic database system or by post from the research team (depending upon patient preference). The questionnaire content is the same as the baseline questionnaire that the participants completed with the addition of information about any health services that they may have used e.g. visits to the GP practice, hospital and any loss in their own productivity e.g. missed working days if they are in employment. The average time to complete these questionnaires is 15 to 30 minutes. Three automated follow-up reminders will be sent (two weeks apart):

"Please click on the link at the end of this message to complete the xxx questionnaire if you are still interested in the study.
If you are having technical problems or would like help with completing the questionnaire, please give us a call on 01603592020. We will send you reminders to complete the questionnaire. You are free to withdraw from the study without stating a reason, but, we would be grateful if you could tell us why you want to withdraw as this might help us improve the service that we are testing. You can do this by contacting us on the phone number above, or by emailing h.al-jabr@uea.ac.uk.
[Copy and paste if you can't click on the link below]
URL"
If the participant does not respond after three follow-up messages, he/she will be withdrawn from the study.

After 6 months and as part of their standard care, participants will be asked to visit their GP to have their blood pressure and blood sugar levels (HbA1c) checked. People with T2DM should have their blood sugar and blood pressure checked at least annually or more frequently if their condition is poorly controlled or fluctuating. Given our patient population with poor adherence, the additional test will be of clinical value to the medical practice and not out of the ordinary for the patient. At 6 months, the researchers will additionally collect from the medical practice the details of the patient's prescribed medication to establish whether there have been any changes during the patient's study participation. They will also conduct the final telephone pill count which will be the same process as baseline; the researcher will telephone the patient and ask them to tell us exactly how many tablets/capsules they have of each of the diabetes and if relevant, their blood pressure medication.

This will be the end of the participant's involvement in the study and the researchers will send them (email or paper) a summary of the study findings once the data have been analysed and the report prepared.

To be able to detect an improvement in medication adherence of 20% in the intervention group compared to the control group, this study will need 98 persons per group. To allow for attrition, the researchers intend to recruit a total of 300 patients: 150 in the UK (75 intervention and 75 control) and 150 in the Netherlands.

Previous interventions:
This study will include people known to be not regularly taking their prescribed tablets or capsules for managing their type 2 diabetes. These people will be identified by the person's GP practice who will search their records to find patients who have not ordered enough of their medication to allow them to be able to take them as prescribed over the previous 2 years. These people will get an invitation letter, participant information leaflet and an expression of interest form. The medical practice will send one reminder after 2 weeks. If a patient is interested, they will then contact their community pharmacy team by telephone or in person.

The community pharmacy team will be trained by the researchers so that they know what to do when approached by a patient expressing interest in study participation. A trained member of the community pharmacy team will ask the patient some questions to make sure that they are definitely right for the project for example, they must have a mobile phone that allows them to get text messages. If having been satisfied that they have enough information and still want to be involved in the project, the pharmacy team member will ask the patient for permission to share their contact details with the research team. If the patient agrees, the pharmacy team member will add the patient's contact details onto an electronic database to which the research team have access. The pharmacy team member will also provisionally book the patient into a consultation at the pharmacy for a mutually agreeable date and time within the next two to three weeks (ideally aligning with when the patient would next be in the pharmacy to collect their medication).

Once the pharmacy team member enters the patient's contact details onto the shared database, the research team will send to the patient by post or e-mail (depending upon which the patient prefers) a consent form and baseline questionnaire which includes a diagnostic medication adherence tool called the Adapted Quick Barrier Scan questionnaire. This is the tool that will allow the patient and pharmacist to work together to develop an intervention tailored to the needs and preferences of the patient in terms of adherence support. A reminder will be sent after one to two weeks to non-respondents (after 1 week for those who received the consent materials by email and after 2 weeks for those who received them by post. if the signed consent form is not returned using the prepaid envelope (yet answers to questionnaire one are returned), the researcher will inform the pharmacy team to collect participants' signed consents when they come to the pharmacy visit.

After receiving informed consent and responses to the AQBS and questionnaire-1, participants will be randomised one to intervention and one to control at the level of patient participant. The researcher will inform the pharmacy team and the patient participant's GP about their enrolment in the study. The researcher will also request baseline routinely collected data from GP held medical notes; the participant's blood sugar levels (HbA1c), blood pressure and current prescribed medications. A researcher will also telephone the patient to find out how many blood glucose and if prescribed, blood pressure lowering tablets/capsules the patient has in their possession. This will enable a follow-up pill count to be used to estimate whether the participant has taken the expected number of tablets/capsules during the study period.

Patients allocated to the intervention group will have a 15-minute consultation with their pharmacist. During the consultation, the patient and pharmacist will work together to select the supporting programmes that are deemed to be the most effective and acceptable based on the AQBS results and patient preference. Pharmacists will be trained in using the AQBS to inform decision making and have a pre-set profiling algorithm to further guide decision making. All of the supporting programmes have been previously tested on their own but not as an available package from which to select. The programmes are summarised below:
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iv) To address negative mood and beliefs e.g. unguided self-help online application or motivational text messages.
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month, the pharmacist will telephone the participant to establish the extent to which they are satisfied with the supporting program and if needed, to further tailor the intervention appropriately. For example, if the patients opted for daily text messages but is finding the frequency too great, they may decide to change them to weekly. The average duration of this phone call will be approximately 10 minutes. This agreed combination and configuration of supporting programs will be delivered for a total of six months.

In order to maintain allocation concealment to the patient, they will also receive a consultation at the community pharmacy using the same process as for intervention participants. However, the consultation will be with a pharmacy assistant trained by the research team. The pharmacy assistant will not have access to the AQBS information but during the consultation, they will introduce the patient to an already available general T2DM information website. The general T2DM information website in the UK will be the Diabetes UK website. During the consultation, the pharmacy assistant will introduce the patient to the different sections on the website including information about the condition and their prescribed medications. They will also help participants place a link to the website onto their mobile phone should they wish.

Both intervention and control participants will be asked to complete a questionnaire after 3 months and then one final questionnaire after 6 months. These questionnaires will be sent either via an email invitation generated from the electronic database system or by post from the research team (depending upon patient preference). The questionnaire content is the same as the baseline questionnaire that the participants completed with the addition of information about any health services that they may have used e.g. visits to the GP practice, hospital and any loss in their own productivity e.g. missed working days if they are in employment. The average time to complete these questionnaires is 15 to 30 minutes. Three automated follow-up reminders will be sent (two weeks apart):

1st reminder: “we noticed you haven’t completed questionnaire(s) x, this is a brief reminder for you to complete and return it. If you have technical problems or would like help with completing the questionnaire(s), please give us a call at 01603591996. A final reminder will be sent after 2 weeks. You are free to withdraw from the study without stating a reason, however, we would be grateful if you tell why you want to withdraw”

2nd reminder message: “we haven’t received your answers to the questionnaires, if you are still interested in the study, please complete and return the questionnaire(s). If you have technical problems or would like help with completing the questionnaire(s), please give us a call at 01603591996. A final reminder will be sent after 2 weeks. You are free to withdraw from the study without stating a reason, however, we would be grateful if you tell why you want to withdraw”

3rd reminder: “This is a final reminder to complete questionnaire(s) x. if you are still interested in the study, please complete and return the questionnaire(s). You are free to withdraw from the study without stating a reason, however, we would be grateful if you tell why you want to withdraw”.
If the participant does not respond after three follow-up messages, he/she will be withdrawn from the study.

After 6 months, participants will be asked to visit their GP to have their blood pressure and blood sugar levels (HbA1c) checked. People with T2DM should have their blood sugar and blood pressure checked at least annually or more frequently if their condition is poorly controlled or fluctuating. Given our patient population with poor adherence, the additional test will be of clinical value to the medical practice and not out of the ordinary for the patient. At 6 months,

the researchers will additionally collect from the medical practice the details of the patient's prescribed medication to establish whether there have been any changes during the patient's study participation. They will also conduct the final telephone pill count which will be the same process as baseline; the researcher will telephone the patient and ask them to tell us exactly how many tablets/capsules they have of each of the diabetes and if relevant, their blood pressure medication.
This will be the end of the participant's involvement in the study and the researchers will send them (email or paper) a summary of the study findings once the data have been analysed and the report prepared.

To be able to detect an improvement in medication adherence of 20% in the intervention group compared to the control group, this study will need 98 persons per group. To allow for attrition, the researchers intend to recruit a total of 300 patients: 150 in the UK (75 intervention and 75 control) and 150 in the Netherlands.

Intervention Type
Behavioural

Primary outcome measure
Medication adherence measured with a telephone pill count at baseline and the end of the trial (after 6 months)

Secondary outcome measures
1. Blood pressure measured by the GP at baseline, 3 and 6 months
2. HbA1c level measured by the GP at baseline, 3 and 6 months
3. Medication adherence measured using Medication Adherence Report Scale (MARS-5) questionnaire at baseline, 3 and 6 months
4. Attitude and beliefs toward medication measured using Beliefs about medicines questionnaire (BMQ specific questionnaire) at baseline, 3 and 6 months
5. Satisfaction with diabetes treatment measured using Diabetes Treatment Satisfaction Questionnaire (DTSQs+c) at baseline, 3 and 6 months
6. Quality of life measured using Quality of Life Questionnaire (EQ-5D-5L) at baseline, 3 and 6 months
7. Medical and productivity costs measured using Institute of Medical Technology Assessment (iMTA costs questionnaire) at 3 and 6 months

Overall study start date
01/01/2019

Completion date
01/04/2022

Eligibility

Key inclusion criteria
1. People with T2DM prescribed oral blood glucose lowering medication that are non-adherent to oral blood glucose and/or blood pressure lowering drugs
2. Aged 35-75 years
3. Smartphone user and willing to use platform facilities (digital health resources) or have access

to an electronic device (e.g. computer)
4. All ethnicities
5. Able to understand text messages in English

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
Planned Sample Size: 300; UK Sample Size: 150

Total final enrolment
23

Key exclusion criteria
1. People with T2DM that use parenteral medication (e.g. insulin) for diabetes
2. People in which, according to screening data collected, adherence data is not valid due to hospital admission or in which medication is dispensed by different pharmacies
3. People who use medication-intake supporting services provided by the pharmacy (i.e. repeat dispensing and pill packaging)
4. People who indicate in the questionnaire that they suffer from the following major mental health disorders: depression, schizophrenia, psychosis or suicidality
5. Any significant medical reason for exclusion as determined by the researchers
6. Unable or not willing to provide written informed consent
7. Not willing to accept information transfer concerning participation in the study, and/or information regarding a participants' health (like laboratory results or physical examination) and /or eventual adverse events to and from his GP and/or pharmacist
8. People who are involved in current research or have recently been involved in any research prior to recruitment

Date of first enrolment
01/12/2020

Date of final enrolment
08/10/2021

Locations

Countries of recruitment
England

Netherlands

United Kingdom

Study participating centre
NIHR CRN: Eastern
United Kingdom
NR1 1QQ

Study participating centre
Grove surgery
Thetford Healthy Living Centre
Thetford
United Kingdom
IP24 1JD

Study participating centre
Lime Pharmacy
Grove Surgery
Grove Lane
Thetford
United Kingdom
IP24 2HY

Sponsor information

Organisation
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Sponsor type
University/education

Website
https://www.uea.ac.uk/

ROR
https://ror.org/026k5mg93

Funder(s)

Funder type
Research organisation

Funder Name
European Foundation for the Study of Diabetes; Grant Codes: EFSD INTENSE project 2017

Alternative Name(s)
The European Association for the Study of Diabetes, EFSD

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Germany

Funder Name
National Institute for Health Research (NIHR) (UK)

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Research protocol of the INTENSE study: June-July 2020
2. Adaptation of research across culturally and linguistically diverse communities: June-July 2020
3. Validation of a telephone pill count for measuring medication adherence: July-September

2020
4. Profiling of non-adherent patients based on the underlying cause of non-adherence (development of a profiling algorithm): September-November 2020
5. (Cost-)effectiveness of the INTENSE intervention: After the end of the trial
6. Process evaluation of the INTENSE study: After the end of the trial
7. Learning article - April 2021 (added 15/12/2020)

Intention to publish date
28/02/2023

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version v3	24/10/2019	05/02/2020	No	Yes
Protocol article		02/09/2022	05/09/2022	Yes	No
HRA research summary			28/06/2023	No	No