Title:
Effects of Remote Patient Monitoring on Chronic Disease Management

NCT Number:
NCT03127852

Document Date:
May 29, 2019

University Health Network

Research Study Protocol

Title	Randomized controlled trial of a mobile phone-based telemonitoring application for self-management and clinical decision support for patients with complex chronic conditions
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Abstract

The rising prevalence of chronic illnesses threatens the sustainability of the healthcare system, especially due to the high cost of frequent hospitalizations. Effective self-management of chronic disease can reduce the need for urgent care but helping patients to master complex decision-making and to implement lifestyle changes is difficult. Telemonitoring systems are a promising adjunct in this regard. Such systems allow patients to monitor their physiological state (e.g. weight, blood pressure) and to receive both automated and real-time feedback from health care providers. Current systems tend to be inconvenient and costly to implement in existing clinical settings and are often limited to the monitoring of one chronic condition. We believe that delivering telemonitoring through a mobile phone will enable patients with complex chronic conditions to track their health, receive automated feedback relevant to their unique situations, and improve communication with their health care team in a cost effective and intuitive way.

In order to test the effectiveness of the intervention, we propose a 6-month randomized controlled trial of 146 patients. The study will include patients with a diagnosis of any of the following conditions or combinations of these conditions: heart failure, chronic obstructive pulmonary disease, chronic kidney disease, and/or uncontrolled hypertension. Insulin-requiring diabetes will be included as a co-morbidity to be supported by the telemonitoring application if the patient also has at least one of the four above chronic conditions. Patients will be assigned to either (1) the control group receiving usual care, or (2) the group using the mobile telemonitoring system in addition to usual care. We hypothesize that our mobile intervention will be a cost-effective and scalable tool that will improve health outcomes and quality of care, while empowering and reassuring patients and their family.

Background

Patients with chronic illnesses, including those with multiple chronic conditions (MCCs), face numerous challenges in the self-management of their conditions, particularly complex decision-making, varying and often contradictory clinical management advice, and frequent hospitalizations. A 2011 Canadian Institute for Health Information study found that three out of four Canadians age 65 and older reported having at least one chronic condition, while one in four seniors reported having three or more (1). While 75% of health care dollars are solely devoted to managing chronic illnesses, 5% of the population **consumes > 50% of all dollars devoted to healthcare** (2). With the increasing prevalence of chronic illnesses and MCCs (1), the sustainability of our healthcare system is threatened. However, through enhanced patient self-care and clinical management, significant reductions in healthcare spending and improved health outcomes could be achieved.

eHealth tools may empower patients and their informal caregivers in more effective self-management of MCCs, and serve as a critical decision-support tool for their healthcare providers (HCP). In particular, telemonitoring enables patients to track their vital signs and symptoms, and also to receive automated instruction and clinical intervention during "teachable moments" (i.e., clear actions are provided when the context is most appropriate). The automated instructions can be based on current physiological measurements, self-monitored symptoms, and readily analyzed trends in both (3). Automated real-time alerts and frequently collected and analyzed physiological data can also support clinical decisions by healthcare providers (3).

A growing body of research on telemonitoring interventions for single chronic conditions exists, but it focuses on singular conditions such as diabetes, hypertension, or heart failure (4-6). Several studies and systematic reviews have shown that the use of telemonitoring interventions for the management of chronic conditions (e.g., heart failure, hypertension and diabetes) lead to positive health outcomes and significant reductions in healthcare costs (7-11). Contradictory studies that did not find improvements often excluded a self-care component, were difficult to use, or did not target patients who were the most ill and frequently hospitalized (12-15). Due to the added complexity involved, very few studies have focused on the use of telemonitoring amongst high-risk patients with MCC, even though these patients may benefit the most from such an intervention (16-21).

Based on our existing telemonitoring tools and extensive experience in evaluating such technologies focused on patients with chronic conditions, we propose conducting an investigation of the use of mobile phone-based telemonitoring for the self-management of complex patients. The rationale for the use of mobile phones is that it enables a cost-effective data hub that allows

patients to transmit physiological and symptom information from any location with cell phone reception.

For our project, complex patients will be defined as those who are at high-risk for hospitalization, exacerbations, and disease progression, as well as patients with multiple chronic conditions. In particular, heart failure (HF) and chronic obstructive pulmonary disease (COPD) are among the most common causes of avoidable hospitalizations (22), and CKD patients incur very high costs when hemodialysis is required (23, 24). Thus, delaying the need for hemodialysis through eHealth tools would improve patient quality of life and defer substantial health service utilization. In addition, improving self-care of patients prior to requiring hemodialysis may result in patients later opting for more independent interventions, such as home hemodialysis.

Objectives

The objective of the randomized controlled trial (RCT) is to evaluate a mobile phone-based telemonitoring system for management of a variety of chronic conditions, including HF, COPD, CKD, insulin-requiring diabetes and uncontrolled hypertension in specialty clinic settings. The RCT will be registered into clinicaltrials.gov and ISRCTN.org prior to commencement.

The telemonitoring system, named *"Medly"*, has been developed through leveraging technology and accumulated expertise in the development and clinical trials of mobile telemonitoring systems in the areas of hypertension, diabetes, asthma, heart failure (HF), chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD) (3, 4, 25-32). The development and usability testing of *Medly* for this RCT was completed under the University Health Network research ethics board approval number 13-7085-BE. Research ethics board approval numbers for trials using this telemonitoring platform that have been conducted at the University Health Network include 08-0192-BE (HF RCT), 14-7638 (CKD pilot), and 14-7756-AE (COPD pilot).

Central Research Question: What is the impact of a telemonitoring system for patients with complex chronic illnesses on health status, cost, self-management, clinical management, health outcomes, and health service utilization?

Patient Population

Inclusion Criteria

Patients who meet the following criteria will be considered for inclusion in the study:

- Adults (age 18 years or older)
- Diagnosed with HF, COPD, CKD, insulin-requiring diabetes and/or uncontrolled hypertension
- Followed by at least one of the following physicians:
    - Followed by a cardiologist at the Heart Function Clinic, University Health Network, who has primary responsibility for management of the patient's HF
    - Followed by a respirologist at the Asthma and Airway Centre, University Health Network, who has primary responsibility for management of the patient's COPD
    - Followed by Dr. Alexander Logan or another hypertension specialist at the Mount Sinai Hospital, who has primary responsibility for management of the patient's CKD and/or hypertension
    - Followed by an endocrinologist at the Endocrinology Clinic at UHN, such as Dr. Phil Segal.
- Patients with HF as the primary chronic disease:
    - Patients with HF with reduced ejection fraction (EF<0.40)
- Patients with COPD as the primary chronic disease:
    - Spirometrically confirmed diagnosis of COPD of GOLD Stage II or higher (defined as post-bronchodilator FEV_1 < 80% predicted and FEV_1/FVC ratio < 70%) and,
    - smoking history of ≥ 20 pack-years or homozygous alpha-1 antitrypsin deficiency and,
    - Prescribed an action plan for the early self-treatment of acute exacerbations
- Patients with CKD as the primary chronic disease:
    - Grade 3-5 (eGFR < 60mL/1.73 m^2)
- Patients with uncontrolled hypertension as the primary chronic disease:
    - For non-diabetics: blood pressure >=140/90 mmHg auscultatory (manual measurement) or >=135/85 mmHg oscillometric (automated measurement)
    - For diabetics: blood pressure >=130/80 mmHg
- Patient or their caregiver speaks and reads English adequately to provide informed consent and understand the text prompts in the application.
- Ability to comply with using the telemonitoring system (e.g, able to stand on the weight scale, able to answer symptom questions, etc.).

Exclusion Criteria

Patients will be excluded from participating in the pilot study for any of the following reasons:

- Patients on mechanical circulatory support
- Patients on the heart transplant list
- Terminal diagnosis with life expectancy < 1 year
- Dementia or uncontrolled psychiatric illness
- Resident of a long term care facility

Patient Recruitment

Patients will be recruited during regularly scheduled visits to the UHN and Mount Sinai Hospital clinics associated with their chronic illnesses. After the clinician determines that the patient is eligible for recruitment, he/she will ask the patient if they are willing to speak to the study coordinator regarding the study. All eligible participants, based on the inclusion/exclusion criteria above, will be asked to sign a written consent form prior to being enrolled in the study (Appendix 1).

An additional recruitment strategy to asking patients if they are interested in participating in the study during their regularly scheduled clinic visit may be employed to speed up patient enrolment. This recruitment strategy has previously been used with great success for a completed and a current study at the University Health Network by Dr. Alexander Logan (co-investigator) at the Renal Clinic. It involves identifying interested patients prior to their clinic visit. The research study coordinator, an independent third party who is not part of the clinical care team, will generate an eligible patient mail out list. This list will be derived from the general clinic roster at the Hypertension Clinic (Mount Sinai Hospital) and at the Heart Function Clinic (UHN); the list will be screened and verified by the clinic nurses/physicians to ensure appropriateness (as determined by the study inclusion criteria) for mailing out invitations about the study. A separate REB amendment will be sent to the Mount Sinai Hospital REB. The mail out study invitation will be used in order to determine interest of patients who are not scheduled for an upcoming clinic visit at UHN. After identifying eligible patients, the research coordinator will mail out an invitation letter including a study description and consent form along with a pre-addressed and stamped envelope to return the signed consent form to the clinic (see Appendix 2). This will be mailed only to potential participants who have been reviewed by the clinic staff as “appropriate to be approached”. The letter will be mailed to the potential participants on behalf Dr. Alexander Logan for the Hypertension Clinic patients at Mount Sinai Hospital and Dr. Heather Ross for the Heart Function Clinic patients at the University Health Network. Each will sign the letter as they are the clinician leads in the respective clinics. The patients will also be provided with the

coordinator's phone number in case they require additional information or want to discuss aspects of the study, as well as to indicate interest in the study. For those who did not respond to the letter within two weeks of mailing, the study coordinator will contact them over the phone to explain the study and determine interest in participating. For all those interested in participating, the study coordinator will arrange a date and time to meet in the clinic. Details of the study and the consent form will be reviewed in-person at this time to ensure that patients are fully informed about all aspects of the study and are freely providing their consent to participate.

To perform a sample size calculation, the primary outcome measure SF-36 was used. Assuming a moderate effect size on the general health dimension of the SF-36 of 10.5 points (39), a score of 57 +/- 21 for the control group (40), 80% power, and alpha=0.05 (two-sided), the sample size per group was calculated to be 63 (http://clincalc.com/Stats/SampleSize.aspx). Assuming 15% of patients will be lost to follow-up (including mortality) (36, 37), the sample size per group is 73. Hence 146 patients will be enrolled during the trial and randomized 1:1 into control and telemonitoring groups.

To perform the randomization, the online computer generated randomization tool, Research Randomizer, will be used (www.randomizer.org). The study coordinator performing the recruitment will be blinded until the patient has consented to participate. The participants will be blocked randomized (blocks of 4) and stratified into groups according to their primary condition (HF, COPD, hypertension, insulin-requiring diabetes, and CKD). The HF group will further be stratified based on NYHA classification (NYHA class 2-3, NYHA class 4), and the hypertensive patients will be stratified to those with and those without diabetes.

A member of the clinical care team (e.g., physician or nurse) will briefly introduce the study to the patient and ask if the patient would be willing to meet with the study coordinator. If the patient agrees, the study coordinator will meet with the patient to discuss the study in more detail. If the patient is interested in participating in the study, the coordinator will evaluate the patient for inclusion/exclusion criteria and obtain written consent for participation. Once this is completed, the study coordinator will provide the patient and, if appropriate, his/her caregiver with training on the telemonitoring system.

Telemonitoring Technology

Medly will enable patients with complex chronic illnesses, including MCCs, to take clinically relevant physiological measurements with wireless home medical

devices and to answer symptom questions on the mobile phone. The measurements will be automatically and wirelessly transmitted to the mobile phone and then to a data server. Specifically, patients with HF will monitor daily weight and blood pressure/heart rate, CKD patients will monitor blood pressure, diabetes patients will monitor blood glucose and HF, COPD, and CKD patients will monitor symptoms. Hypertension patients will monitor their blood pressure. Automated self-care instructions/messages that have been carefully developed with healthcare specialists will be sent to the patient based on the readings and reported symptoms. If there are signs of their status deteriorating, an alert will be sent to a clinician that is responsible for the particular chronic condition of concern (i.e., in the specific specialty clinic). The clinicians will have all the relevant patient data sent to them and will be able to access (through a secure web portal) to view historical and trending data for their patients. Additional app features will also be available, such as educational videos for proper inhaler use for COPD patients.

Methods

The control group will receive usual care, and the intervention group will receive usual care plus the telemonitoring intervention. Both groups will be followed for 6 months. Study data collection will occur during regularly scheduled visits, no additional study visits beyond what patients experience in usual care, it is anticipated that patients will be recruited, randomized, and trained during a routine scheduled clinics. If this proves inconvenient for the patient, an additional study visit may be scheduled at their convenience. Similarly, we anticipate collecting the study equipment and administer the follow up questionnaire at a regularly scheduled visit. Each intervention study participant will be provided with a smartphone. This phone will be loaded with the application and a limited data plan to enable data transfer. Patients will also be provided with relevant home medical monitoring devices (e.g., weight scales and blood pressure monitors for HF patients, blood pressure monitors for CKD and hypertension patients, and blood glucose meters for diabetes patients). Patients will be asked to take measurements and record symptoms at a specified frequency at their homes. Home measurement depends on the specific chronic condition(s). HF, COPD, and diabetes are generally monitored daily whereas hypertension and CKD are generally monitored several times per week as specified by the algorithm developed in conjunction with specialists. Patients will be notified when they should take at home measurement through the application.
The research team, as informed by the patient's clinician(s), will enter patient-specific baseline information into the telemonitoring system dashboard, such as individual target weight ranges, target blood pressure ranges, medication lists, COPD action plan, etc.

Outcome Measures:

The primary outcome will be health status as measured with SF-36 because this metric will be relevant to all chronic conditions under investigation. A secondary

outcome measure will be the cost (from the health system and patient perspectives). The cost of healthcare will include hospitalizations, emergency department (ED) visits, clinic visits, delay of hemodialysis commencement, medications, and telemonitoring program, as relevant to the different chronic illnesses and will include disease-specific sub-analyses.

Other secondary outcome measures will include combined hospitalization for any reason or death from any cause within 6-months after enrolment, hospitalization, mortality, days in hospital, number of emergency department (ED) and clinic visits, and medications. Secondary outcome measures will also include general quality of life as measure by the EuroQol 5D-RL, anxiety and depression as measure with the Hospital Anxiety and Depression Scale (41) and patients' self-efficacy to self-manage their disease as measured with the Self-Efficacy for Managing Chronic Disease Scale (42) (Appendix 3).

Disease specific outcome measures will include:

- HF
    - left ventricular ejection fraction (LVEF)
    - brain natriuretic peptide (BNP)
    - self-care as measured by the Self-Care of Heart Failure Index (43) (Appendix 4)
    - Heart-failure specific quality of life as measured by Minnesota Living with Heart Failure Questionnaire (44) (Appendix 4)
    - Shortness of breath as measure using a visual analogue scale (VAS) for dyspnea (Appendix 4)
    - Blood work: creatinine, sodium, potassium, hemoglobin, urate
    - Prognostic score as determined by the Seattle Health Failure Model (requires: age, gender, NYHA class, weight, ejection fraction, systolic BP, medication list (including diuretics), lab results (hemoglobin, lymphocytes, uric acid, total cholesterol, sodium) and QRS interval)
- COPD
    - forced expiratory volume in one second (FEV_1)
    - symptoms score from the telemonitoring system
    - COPD Assessment Test (CAT) score (45) (Appendix 5)
    - COPD-specific knowledge after 6-months of application usage, as measured by the Bristol COPD Knowledge Questionnaire (BCKQ)(46) (Appendix 5)
    - patient self-efficacy at 6 months as measured by the COPD Self-Efficacy Scale (CSES)(47) (Appendix 5)
    - COPD severity as measured by the BODE Index(48) at 6 months (Appendix 5)

- CKD
    - estimated glomerular filtration rate (eGFR)
    - symptoms score from the telemonitoring system
    - blood pressure as measured by an automatic blood pressure monitor
- Hypertension
    - blood pressure as measured by an automatic blood pressure monitor
    - average 7-day blood pressure
- Diabetes
    - HgbA1c

Data Acquisition: Number of hospitalizations, days in hospital, number of ED and clinic visits, and medications will be determined through the hospital EMR and a manual chart review of all participants' clinical records. Combined hospitalization will be verified by patient participants through self-report with the help of a questionnaire. The cost of the intervention will be tracked, including for equipment costs and human resources for clinical support, technical support, and program management. Standard cost values for a day in-hospital, ED visit, etc. will be used to estimate net cost savings or expenditures. Values for pre- and post-trial health outcome measures (eg, blood test results) will be obtained through hospital clinical records or through the *Medly* database for symptoms. Pre- and follow up questionnaires (baseline, 1-month, and 6-months), will be administered to both control and intervention groups that contain the validated survey tools listed above. Participants will be able to complete the questionnaires at the clinic or complete it at home. Participants that chose to complete the questionnaire at home will be given a pre-paid self-addressed envelope to mail the questionnaire back to the study team. The 1-month questionnaire will be given to participants upon enrolment with instructions to complete the questionnaire one month after starting the trial and to mail it back to the study team using the pre-paid envelope. The study coordinator will call each participant at the 1-month period to remind participants to complete the questionnaire. In addition to the baseline and follow up questionnaires that are applicable to all patient participants (Appendix 3), patients with HF and/or COPD will also receive the validated survey tools listed above (Appendix 4 and 5). Average 7-day blood pressure will also be recorded from patients with a primary diagnosis of hypertension during their first week in the study (baseline) and their last week in the study (6-months). To do this, patients will be provided with a digital blood pressure monitor which they will use to take blood pressure 4 times per day (2 times in the morning and 2 times in the evening) over each 7-day period. Patients will return the blood pressure monitor to the study team who will download the

data and calculate the average 7-day blood pressure value. Usage data, in terms adherence to taking measurements and use of the different features, will also be data-mined from the servers.

In addition to the quantitative metrics, all participants will be asked basic questions such as their self-care practice and their thoughts on remote patient monitoring at the start of the study. A subgroup of the intervention arm will also be interviewed individually to assess their experiences and perceptions regarding the use of *Medly* at the end of the study. The number of patients that will interviewed will depend on when saturation of information is reached, typically 15-20 participants. The interviews will be conducted in a quiet and private space within a clinic (e.g., consultation room or education room). Prior to the interview, participants will be informed that notes will be taken and they will be audio taped for data analysis. See Appendix 6 for sample patient interview questions. The clinicians involved in the trial will also be asked to participate (see Appendix 7 for clinician consent form) in interviews to determine their perceptions of *Medly*. See Appendix 8 for sample clinician interview questions.

All study data will be kept for 10 years after the completion of the study and then destroyed by shredding of paper or erasing of digital information.

Data Analysis: Post-trial data and change scores will be compared between the control and intervention groups using independent Student t tests and Mann–Whitney tests (for normally and not normally distributed data, respectively). Paired Student t tests and Wilcoxon signed rank tests will be performed to compare baseline and post-study data within the control and telemonitoring groups. The statistical analyses will be performed using the statistical software application SPSS (IBM Corporation, USA). The cost evaluation will be performed by comparing any savings through reductions in hospitalization, emergency and clinic visits, through the use of the intervention. This will further include amortizing the equipment costs and factoring in additional clinical, technical, and management resources. An analysis of indirect costs will also be performed, such as days absent from work. Interview data will be analyzed using a conventional content analysis approach (49). Two researchers will analyze the transcripts independently and code the transcripts with the software program NVivo (QSR International, Doncaster, Victoria, Australia).

The Principle Investigator will keep all study data in a secure and confidential location for 10 years after the completion of the study and then they will destroyed by shredding of paper or erasing of digital information. All participants will be assigned a unique identifier, which will replace any identifiable information contained in the research data. A list linking the study number with the participants' name will be kept by the Principle Investigator in a secure place in a locked cabinet.

Benefits to Being in the Study

By participating in this study, patients will have the opportunity to experience using a new application that is not yet available on the market and is part of an original approach to improving chronic illness management. Patients will also have the opportunity to learn more about their chronic conditions and its treatment as well as strategies to improve their health and quality of life. The intervention itself may or may not provide benefits to their health outcomes.

Benefits to Society

The information gathered during this study will help us learn if and how a mobile telemonitoring system improves the self-care, clinical management, and health outcomes of those with complex chronic conditions. This trial may lead to evidence that supports sustained telemonitoring programs that improves health outcomes and reduces costs to our healthcare system for management of chronic conditions.

Compensation

Patients will be compensated for their participation in the study with a $25 Shoppers Drug Mart gift card, this will be offered once at the time of recruitment. Clinicians will not receive any form of compensation for participating in this study.

Dissemination Strategy

We plan to disseminate our findings through publications in appropriate scientific journals and through presentations at appropriate scientific conferences. We also plan to disseminate summarized results understandable to a lay audience to study participants directly and through general media so that those outside the study may take advantage of any such tools developed as a result of this study.

Budget

Funding for this project is available through a successful grant application to the CIHR eHealth Catalyst Grant. For a detailed budget for this RCT, please see Appendix 9.

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