A multicenter, assessor-blinded, controlled, randomised, parallel group, superiority, pragmatic trial assessing the effectiveness of daily **S**MS-reminders in **P**harmaceutical Care of older adults with hypertension on improving **P**atients' **A**dherence to blood pressure-lowering medication

SPPA Trial

Trial registration: NCT03105687
Protocol Version: Final Version 2.1

Date: 05-Jun-2017

The SPPA Clinical Trial Protocol was designed and developed in accordance with the SPIRIT 2013 guidelines (1, 2) (for the SPIRIT 2013 Checklist please, refer to ***Appendix 24***) and using the PRECIS-2 tool (3) (for the PRECIS-2 table of score for trial domains and wheel scheme please, refer to ***Appendix 25***).

SUMMARY OF CHANGES TO PROTOCOL (AFTER INITIAL SUBMISSION):

Summary of Changes to the Clinical Study Protocol CSP Ver. 1.0 to CSP Ver. 2.0 10-Apr-2017	Acknowledged by the Ethics Committee on 19-Apr-2017
Summary of Changes to the Clinical Study Protocol CSP Ver. 2.0 to CSP Ver. 2.1 05-Jun-2017	

ROLES AND RESPONSIBILITIES

Title of the trial: A multicenter, assessor-blinded, controlled, randomised, parallel group, superiority, pragmatic trial assessing the effectiveness of daily SMS-reminders in Pharmaceutical Care of older adults with hypertension on improving Patients' Adherence to blood pressure-lowering medication (SPPA Trial)

Trial Code: NCT03105687

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Role of the Sponsor in the SPPA trial

The sponsor had no role in the design of this trial and will have no role in the conduct of the trial, data analysis, results interpretation and dissemination.

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Title of the trial: A multi-center, assessor-blinded, randomised, parallel-group, superiority, pragmatic trial assessing the effectiveness of daily SMS-reminders in Pharmaceutical Care of older adults with hypertension on improving Patients' Adherence to blood pressure-lowering medication (SPPA Trial)

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Name	Date	Signature
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SIGNATURE PAGE - INVESTIGATORS

Title of the trial:	A multi-center, assessor-blinded, randomised, parallel-group, superiority, pragmatic trial assessing the effectiveness of daily SMS-reminders in Pharmaceutical Care of older adults with hypertension on improving Patients' Adherence to blood pressure-lowering medication (SPPA Trial)
Trial Code :	NCT03105687

I have read and understood the SPPA trial protocol and agree that it meets all the ethical, legal and scientific requirements necessary for my participation in this clinical trial.

With my signature, I agree to conduct the SPPA trial in accordance with the protocol (including other manuals and documents referenced within this protocol), International Conference on Harmonization and Good Clinical Practice guidelines and in accordance with the applicable local regulatory requirements.

Moreover, all information obtained from the participation in this study will be kept confidential unless otherwise agreed in writing.

Name of the Investigator (Trial Pharmacist): _____

Address of the trial centre: _____

Signature: _____

WHO TRIAL REGISTRATION DATA SET

1. Primary Registry and Trial Identifying Number:	NCT03105687
2. Date of Registration in Primary Registry:	07-Apr-2017
3. Secondary Identifying Numbers	PRECIS-2 database registration: https://www.precis-2.org/Trials/Details/251
4. Source(s) of Monetary or Material Support	Sponsor Application for the Grant for young researchers from the Comenius University submitted Provider of Pharmaceutical Care, Dr. Max
5. Primary Sponsor	Faculty of Pharmacy Comenius University in Bratislava Odbojarov 10 832 32 Bratislava
6. Secondary Sponsor(s)	N/A
7. Contact for Public Queries **8. Contact for Scientific Queries**	Dr. Zuzana Haramiova address: Department of Organization and Management of Pharmacy, Faculty of Pharmacy, Kalinciakova 8, 832 32 Bratislava e-mail: haramiova@fpharm.uniba.sk phone number: +421 944 19 01 19
9. Public Title	SPPA trial of the effectiveness of SMS reminders of blood pressure-lowering drugs intake (Slovak: SPPA klinická štúdia účinnosti SMS pripomienok užívania liekov na vysoký krvný tlak)
10. Scientific Title	A multicenter, assessor-blinded, controlled, randomised, parallel group, superiority, pragmatic trial assessing the effectiveness of daily SMS-reminders in Pharmaceutical Care of older adults with hypertension on improving Patients' Adherence to blood pressure-lowering medication (SPPA Trial)
11. Countries of Recruitment	Slovak Republic
12. Health Condition(s) or Problem(s) Studied	Adherence to antihypertensive drugs
13. Intervention(s)	Personalised daily SMS reminders of medication intake provided by pharmacists
14. Key Inclusion and Exclusion Criteria	Inclusion Critetia: 1. Age ≥ 55 years (from the day of the 55. birthday inclusive) 2. Diagnosis of primary (essential) hypertension (I10 according to ICD-10) 3. Filling of blood pressure-lowering prescription(s) at trial recruitment (Visit 1) 4. Duration of antihypertensive drug treatment for at least 1 year without any discontinuation

	5. Ownership of a mobile phone for personal use with the ability to open and read SMS 6. Understanding of Slovak language on native-speaker level 7. Informed consent for participation in the clinical trial and personally signed Informed Consent Form Exclusion criteria assessed prior to patient enrolment (by trial pharmacists): 1. Planned hospitalisation during the trial period (3 months) 2. Biological impairment affecting the ability to read the SMS (e.g. loss of vision, visual field cuts, aphasia) 3. Living in the same household with another trial participant 4. Participation in another clinical trial Exclusion criteria assessed after patient enrolment (by trial pharmacists and project leader): 1. Hospitalisation during the trial period 2. Patient informs he/she won't be able to participate in the trial 3. Withdrawal of Informed Consent
15. Study Type	Interventional trial multicentre assessor-blinded, controlled, randomised, superiority, pragmatic, parallel-group clinical trial
16. Date of First Enrollment (anticipated)	May/June 2017
17. Target Sample Size	300
18. Recruitment Status	Pending: participants are not yet being recruited or enrolled at any site
19. Primary Outcome	Proportion of adherent patients (%) at Visit 2
20. Key Secondary Outcomes	1. change in medians of MMAS-8 after 3 months; 2. mean AR (%) after 3 months calculated via pill count; 3. mean change in sBP after 3 months; 4. patients' satisfaction with SMS reminders.

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PROTOCOL SYNOPSIS

Rationale

Hypertension belongs to the main risk factors of cardiovascular diseases, which are the leading cause of morbidity and mortality in the world and in the Slovak Republic. Despite the availability of effective antihypertensive treatment, blood pressure control remains a serious problem. Poor adherence to blood pressure-lowering medication is considered to be the key factor for uncontrolled blood pressure. Studies estimate the overall adherence to medication in patients with chronic diseases at around 50%. Slovak studies report even significantly lower adherence rates (15-19%), which underlines the urgency to address this health problem in the Slovak Republic. The majority of interventions aimed at increasing patients' adherence are associated with substantial costs and health care professionals capacity, both lacking in the current Slovak health care system. Several studies have shown the efficiency of SMS reminders to improve patients' adherence and health outcomes at very low cost. Since mobile phones are frequently used among Slovak inhabitants and SMS messages are a popular mean of communication, this approach could be feasible also in Slovakia. Pharmacists are highly trained drug experts who have the knowledge, skills and time to address patients' nonadherence using a simple SMS reminder system.

Objectives

The primary objective of the SPPA trial is to ascertain if daily SMS reminders of blood pressure-lowering medication intake provided by pharmacists, in addition to the standard pharmaceutical care, increase the proportion of adherent older hypertensive ambulatory patients.

Secondary objectives of the SPPA trial include: 1) comparing the change of self-reported adherence (using the *eight-item Morisky Medication Adherence Scale*) after 3 months in the intervention and the control group; 2) comparing adherence rates (measured via pill count) after 3 months in the intervention and control group; 3) comparing the change of systolic blood pressure after 3 months in the intervention and the control group; 4) investigating the effect of SMS reminders on improving patients' adherence and systolic blood pressure control (treatment effects) across subgroups; 5) collecting and reporting patients' satisfaction with daily SMS reminders of blood pressure-lowering drugs.

To other objectives of the SPPA clinical trial belong: reporting up-to-date adherence rates in older patients with hypertension in Slovakia and assessing the impact of sociodemographic characteristics on patients' adherence to blood pressure-lowering drugs; evaluation of the *eight-item Morisky Medication Adherence Scale* questionnaire in our trial population; carrying out a cost-effectiveness analysis of SMS reminders of medication intake; active surveillance and collection of adverse events associated with patients' medication and reporting anonymised reasons for refusal to participate in the trial or withdrawal from the trial.

Clinical trial design

The SPPA trial is designed as a pragmatic, randomised, controlled, assessor-blinded, multicentre, superiority trial with two parallel groups (1:1 allocation ratio) to assess the effectiveness of daily

SMS reminders of blood pressure-lowering medication provided by pharmacists in addition to the usual pharmaceutical care compared to the usual pharmaceutical care only. Patients will be randomised into two groups: the intervention group (receiving daily SMS reminders of medication intake) and control group (receiving usual pharmaceutical care only, no SMS reminders of medication intake).

Clinical trial setting and duration

The trial will be conducted in community pharmacies in Slovakia (multicentre, national clinical trial). The intervention (SMS reminders of medication intake) will be delivered to the participants for 3 months (intervention phase). With additional 2 months of the recruitment phase the trial is planned to last 5 months.

Trial population

The trial population consists of hypertensive patients of 55 years of age or older who are taking blood pressure-lowering medication for a minimum of 1 year.

Sample size justification

Based on the results of national adherence studies, we assume an adherence prevalence of 30% in the control group. Findings of the latest meta-analysis of randomised clinical trials assessing the effect of SMS reminders on medication adherence in cardiovascular diseases, report that odds of being adherent in the group receiving SMS reminders was 168% higher than in the control group (odds ratio, 1.68; 95% CI, 1.18-2.39). The weighted mean effect size was d=0.41 (95% CI, 0.23-0.59). Therefore, we hypothesise that SMS reminders of blood pressure-lowering medication intake can increase the proportion of adherent older patients in Slovakia from 30% to 49% given an effect size of w=0.2 (equivalent to d=0.4). Thus, a total of 264 patients (132 in each group) are needed to reject the null hypothesis that the adherence proportions in both groups are equal with a power (probability of type II error) of 0.9 and alpha (probability of type I error) of 0.05 (using a χ^2 test of independence). Considering approximately a 10% attrition rate, we plan to enroll 300 patients (150 in each group).

Intervention

In this trial, patients will be randomised either to the control group or the intervention group. Patients in the control group will receive the standard pharmaceutical care provided by the trial pharmacists, while patients in the intervention group will additionally receive daily SMS reminders of their blood pressure-lowering medication for a period of 3 months.

Outcomes

Our primary outcome is the proportion of adherent patients in the intervention group after 3 months of receiving SMS reminders of medication intake compared to the control group. For these purposes we will assess patient's adherence via the combined adherence endpoint

consisting of self-reported medication adherence measured on the *eight-item Morisky Medication Adherence Scale* and pill count rate (%).

To our secondary outcome belong: 1) change in medians of adherence score measure via the *eight-item Morisky Medication Adherence Scale* after 3 months; 2) mean adherence rate (%) after 3 months calculated via pill count; 3) mean change in systolic blood pressure after 3 months; 4) patients' satisfaction with SMS reminders.

Other outcomes of the SPPA trial include: direct treatment costs associated with blood pressure-lowering medication; signals of adverse events associated with blood pressure-lowering medication and anonymous data on refusal to participate in the trial or withdrawal from the trial.

Statistical methods

All statistical analyses will be carried out according to the intention-to-treat principle. We will compare the proportion of adherent patients according to the combined adherence endpoint after 3 months (primary outcome measure) in the control and intervention group using chi-square test. For our secondary outcome analysis, we will calculate the difference in medians of adherence reported as adherence score measured via the *eight-item Morisky Medication Adherence Scale* after 3 moths in the control and intervention group; and the mean difference between control and intervention group in medication adherence reported as adherence rate (%) measured via pill count. Furthermore, mean change in systolic blood pressure will be compared using the results of a mixed ANOVA and ANCOVA. Finally, we will analyze patient satisfaction with the SMS reminders and we will perform a simple cost-effectiveness analysis from the payer's perspective.

Safety of patients

The SPPA trial does not involve any trial medication. Due to the simple and safe trial intervention (SMS reminders of medication intake), no harms associated with participation in the trial are expected.

KEY WORDS: mHealth, SMS reminders, adherence, antihypertensive drugs, pharmacists, cost-effectiveness

LIST OF ABBREVITIONS

ANCOVA = Analysis of covariance

ANOVA = Analysis of variance

AR = Adherence Rate

BP = Blood Pressure

CeVD = Cerebrovascular Disease

CRF = Case Report Form

CTR = Clinical Trial Report

CVD = Cardiovascular Disease

dBP = diastolic Blood Pressure

EBPC = Evidence-Based Pharmaceutical Care

euTP = external unblinded Trial Pharmacist

GCP = Good Clinical Practice

CONSORT = Consolidated Standards of Reporting Trials

GPP = Good Pharmaceutical Practice

GSM = Global System for Mobile Communication

ICD-10 = International Statistical Classification of Diseases and Related Health Problems (10^{th} Revision)

IHD = Ischemic Heart Disease

IQR = inter-quartile ratio

ISF = Investigator Site File

MEMS = Medication Electronic Monitoring Systems

mERA = mobile health Evidence Reporting and Assessment

mHealth = mobile Health

MMAS-4 = Morisky Medication Adherence Scale – 4 items

MMAS-8 = Morisky Medication Adherence Scale – 8 items

PC = Personal Computer

PCNE = Pharmaceutical Care Network Europe

sBP = systolic Blood Pressure

SD = standard deviation

SIM = Subscriber Identification Module

SMS = Short Message Service

sPhC = standard Pharmaceutical Care

SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials

SRQ = Self-Reported Questionnaires

TMF = Trial Master File

V4 = Visegrad Four (countries)

WHO = World's Health Organization

1. BACKGROUND AND RATIONALE

Hypertension

Hypertension is defined as systolic blood pressure (sBP) values >140 mmHg and/or diastolic blood pressure (dBP) values >90mmHg (4). Estimated overall prevalence of hypertension in Europe is 30-45% with significant differences among countries and steep increase with aging (4, 5). Individual national studies report similar prevalence of hypertension in the Slovak population (6-9). Since hypertension is the primary cause of stroke, mortality due to stroke is considered to be one of the most accurate indicators for hypertension prevalence (10, 11). A total of 5 062 deaths caused by stroke and 825 caused by hypertension were registered in Slovakia in 2014 (12). Hypertension represents a major global health burden causing 9.4 million deaths and 7% of disability-adjusted life-years (DALY) in 2010 (13). Hypertension also belongs to the main risk factors of cardiovascular diseases (CVD), such as ischemic heart disease (IHD), myocardial infarction and cerebrovascular diseases (CeVD)(5, 14). In 2012, World's Health Organization (WHO) reported 1.1 million, 7.4 million and 15.2 million deaths due to hypertension, IHD and CeVD respectively (15). CVD are the main cause of mortality and hospitalization and count to the most common reasons for invalidity in Slovakia. Despite a decrease in CVD mortality over the last decade, CVD still account for 25 198 deaths in 2014. In comparison to other V4 countries, Slovakia has shown the smallest decrease in CVD mortality. Additionally, currently the standardized CVD mortality in Slovakia reaches numbers that are 3.6, 2.0 and 1.5 times higher in comparison to France, Austria and Czech Republic respectively (12, 16). According to the Slovak Register of Acute Coronary Syndromes (SLOVAKS), 73.6% of women and 63.4% of men with acute heart infarction have been previously diagnosed with arterial hypertension (17). It is known that CVD mortality can be prevented with interventions aimed at lowering CVD risk factors, such as efficient blood pressure control. However, the recent results of EURIKA study report that 50% of hypertensive patients have uncontrolled blood pressure despite adequate treatment (18), which is in accordance with earlier results (19). In Slovakia, a similar study carried out by Gajdoš identified only 31% of treated patients with controlled blood pressure (20), while results from earlier screening programs CINDI and MONICA showed even lower control of only 21% (21). Although both efficient and cost-effective antihypertensive therapy is available for Slovak patients, the control of hypertension is highly insufficient. Antihypertensive treatment cannot by limited only to pharmacological treatment. International and national guidelines stress

the importance of overall hypertension management, which includes but is not limited to: education, life-style changes and risk factors management (4, 22, 23). The 2014 update of the National Health Promotion Programme in Slovakia, which implements the principles of the European Health 2020 policy framework and the Slovak national strategic framework for health for 2014-2030, calls for implementation of both motivational and educational interventions focused on lowering the prevalence of main CVD risk factors, especially in high-risk populations (16, 24, 25).

Medication adherence

WHO precisely defines adherence as "the extent to which a person's behaviour – taking medication, following a diet and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider." A meta-analysis including 733 studies carried out between 1948-1998 reported a non-adherence rate of 24.8% with and increasing trend over the last reported period (26). Later studies estimate overall adherence to medication in patients with chronic diseases at around 50% (27, 28). Results from a recent study, assessing nonadherence to antihypertensive medication, vary among European countries from 24% in The Netherlands up to 70% in Hungary (29). Local studies report alarmingly low medication adherence (15%-19%) among Slovak patients (30-32). The latest Slovak study reported an average medication adherence in chronic disease patients to be 4.066 (±1,795) on the *eight-item Morisky Medication Adherence Scale (MMAS-8)* (33).

Poor adherence is considered the key factor for uncontrolled blood pressure (34) resulting in increased risk of stroke, hospitalisation and premature death (35-37). It has been proven that poor medication outcomes may be decreased by 26% achieving high medication adherence (38).

The following factors were identified as the reasons for nonadherence to antihypertensive treatment: length of the treatment, high number of medication, lack of apparent symptoms, side effects of antihypertensives, low knowledge of disease management as well as patients' individual health believes and motivation (39). The majority (25%) of patients in a national study stated that nothing could influence them to intentionally not adhere to the antihypertensive treatment prescribed by their physician, which indicates that the main reason for nonadherence of Slovak patients is forgetfulness (40).

The complexity of reasons leading to patients' nonadherence to pharmacotherapy needs to be targeted by the cooperation of all interested health professionals and society (41). WHO

statement for action concludes that improving patients' adherence may have greater effect on the health than any other improvement in therapy (28). Thus, developing interventions aimed at increasing adherence, especially to long-term medication treatment, is essential in improving the overall health status of the population.

Measures of medication adherence

Adherence to medication can be measured using self-reported questionnaires (SRQ), pill counts, pharmacy refill rates or medication event monitoring systems (MEMS). All of these measurements are quantifiable and have specific advantages and limitations (42-44). Some studies point out that SRQ, unlike MEMS, are subjective tools and as such may lead to overestimated and biased results (45-47). Others consider them good estimates of medication adherence, showing that the results of SRQ are correlated to the results of MEMS, underlining their significance in identification of nonadherent patients (26, 48-50). MEMS enable long-term detailed analysis of patient's adherence to medication and allow the identification of white-coat hypertension (4). However, the main limitations of MEMS include: substantial costs, requirement of an electronic monitoring device for each drug, interference with patients and devices, technical problems and the inability to identify reasons of patient's nonadherence. Additionally, a study using MEMS to measure medication adherence reported the following difficulties: intake of no medication even though the electronic monitoring device was opened (26%), inconsistent use of the electronic monitoring device (36%) and intake of more than one dose of medication during one opening of the electronic monitoring device (41%) (43). Validated SQR present a simple, practical, fast and inexpensive tool for medication adherence measurements that are able to identify the reasons of patient's nonadherence.

Interventions improving medication adherence

Many different interventions for improving patients' adherence to medication have been developed and studied. Consultancy from health professionals, interventions enhancing behavioural changes, telephone calls, social support activities, remote pill count devices, automated reminder systems and drug diaries are some of them (51). In a cohort of 196 Slovak patients the initial mean adherence of 15% (or 0.43 on the *four-item Morisky Medication Adherence Scale (*MMAS-4 score)) was improved to 85.2% (or 2.89 on the MMAS-4) by means of personal consultations with community pharmacist over 24 months (31).

However, the majority of these interventions are associated with high cost, time and health professional capacity resources, providing promising, but uncertain and variable results highly dependant on the extend of patients' self-motivation and prescription literacy (52). Due to low financial resources in health care system and lack of health professionals, these are not manageable as state of art practice in Slovakia.

Mobile Technologies Use in Health Care (The concept of mHealth)

Worldwide usage of mobile phones has resulted in the development of Mobile Health technologies (mHealth), which comprises of all services of mobile phones to support, promote and improve health of individuals. These include phone calls, apps, telemonitoring systems and other services available on smartphones and tablets aiming at providing medical and health-related information and advice, social networking and decision support among patients and health care providers. Their primary goal is to improve the efficacy of health systems as well as health outcomes (53-55). Follow up using phone calls has already shown to improve patients' health outcomes. The interest in evaluating SMS reminders as effective tools for improving patients' adherence and other health outcomes is increasing worldwide, especially in low- to middle- income countries with limited resources. According to the results of previous studies, SMS services are as effective as phone calls in the management of chronic diseases. To the advantages of SMS reminders count: time efficiency, cost effectiveness and function without limitations due to location (56). A number of studies in different therapeutical fields have shown promising results (56-72). The most robust results were reported from studies investigating the effect on antiviral therapy (73-83). Findings of the latest systematic reviews conducted by Yasmin, Banu (84), Thakkar, Kurup (85) confirmed that using SMS messages effectively improves both the adherence with medicine taking, as well as health outcomes also in patients with chronic diseases.

Bobrow, Farmer (58) recently presented the results of a randomised trial, which to our knowledge included the largest sample size of patients (1372) so far. SMS reminders were successful in improving patients' adherence to therapy, but showed only a modest impact on lowering systolic blood pressure. Several limitations of this study as well as causes that might have led to non-significant results were identified (86).

As Thakkar, Kurup (85) together with Lauffenburger and Choudhry (84) point out, it is essential to identify the types of patients who will benefit the most of mHealth interventions. To our current

knowledge, older people have not been yet a specifically targeted population to assess the impact on SMS reminders in improving medication adherence. Yet this group of patients has usually the highest CVD risk and thus could benefit from the strengthening of adherence to antihypertensive medication the most.

Mobile phone usage in the Slovak Republic

The Global System for Mobile Communication network covered 92.0% of the territory of Slovak Republic and 100.0% of the Slovak population in 2015 (87). Cellular phones are frequently used among the inhabitants of Slovakia. There were 6 675 553 active mobile telephone numbers in Slovakia in 2015, which exceeds the overall population by 23.07%. A small increase by 10.57% since 2007 demonstrates that the use of mobile phones for communication is well established and accepted in the Slovak Republic (88). In average, 496.41 SMS per one inhabitant were sent in 2015. Compared to the data from 2007, when only 233.25 SMS per one inhabitant were sent, this recent increase (by 112.82%) (89) indicates large popularity of this form of communication among Slovak population.

Intervention frequency selection and choice of comparator

The latest meta-analysis of controlled randomised trials showed that the frequency of SMS reminders has no influence on the results (85). We have decided to send daily SMS reminders due to the nature of hypertension, which requires regular daily medication.

The SPPA trial is the first study to investigate the potential of mHealth intervention (daily SMS reminders of medication intake) provided by community pharmacist in enhancing patients' adherence in Slovakia. Therefore, we will compare the intervention to the current Pharmaceutical Practice of patient consulting during drug dispensing in Slovakia, which includes no mHealth intervention.

Older adult hypertensive patients

The prevalence of hypertension increases sharply with age. A Slovak national clinical-epidemiological study showed hypertension prevalence to be 51.6%; 66.7% and 85.3% in adults aged 45 to 54 year, 55 to 64 years and 65 to 74 years respectively (9). In the CoSMO study 48.3% of elderly patients had low to medium adherence to antihypertensive medication (36). Due to the fast aging of population, the prevalence of hypertension in elderly will increase over the next

years. Nonadherence to antihypertensive medication in elderly patients leads to therapeutic failure, secondary complication and increased costs due to high medical resources utilization (such as medicaments and medical devices, physician appointments, nursing homes and hospitalizations). Therefore, it is important to lower non-adherence in this group of patients by developing and implementing effective interventions.

With increasing age, drug regiments become more complex. Elderly patients bear other comorbidities and take more different medications, which have higher probability to interact and/or cause adverse effects. All of these factors have been proven to be associated with higher risk of patient's non-adherence (90-94).

The investigation of the relationship between adherence and blood pressure values in older patients, as well as the clinical impact of improvement in their adherence to antihypertensive medication, will significantly guide therapeutic decision in the future (52).

The role of pharmacists in the therapy-management of patients

Pharmacists are specially educated and trained health care professionals authorized for the distribution and management of medicines. They are responsible for safe and efficacious use of medicines. Substantially increasing costs of medicines potentiate also the role of pharmacists in assuring cost-effectiveness of the pharmacotherapy so that it is available for as many patients as possible (95). The new concept of the Pharmaceutical Care concentrating on the interaction with patient has been developed in pharmaceutical practice since 1975, when it was first mentioned by Mikeal, Brown (96). Experts from Pharmaceutical Care Network Europe (PCNE) revised previous definitions of Pharmaceutical Care and agreed on the following re-definition: "Pharmaceutical Care is the pharmacist's contribution to the care of individuals in order to optimise medicines use and improve health outcomes" (97). Professional organizations and experts emphasize that pharmacists play a vital role in health care systems all over the world and can substantially improve the value of pharmacotherapy (95, 97, 98). The Good Pharmacy Practice (GPP) Guidelines define the mission of pharmacy practice via contribution to health improvement and helping patients with health problems assuring the best use of their medicines (95).

The new Slovak Act No. 362/2011 Z. z. on medicines and medical devices defines Pharmaceutical Care in a broad and complex way, focusing also on clinically- and patient-oriented health-services. These include: 1) provision of professional information and guidance on drugs, medical

devices and dietetic food in order to provide a high-quality health care according to safe and rational pharmacotherapy; 2) carrying out of physical and chemical examinations focused on primary prevention and monitoring of the effectiveness of pharmacotherapy that do not require further laboratory processing (99). The process of drug dispensation and information provision describes in more detail the Decree No. 129/2012 Z. z. on the Requirements of Pharmaceutical Practice (100).

Pharmacists are considered to be important health care professionals who can significantly contribute to the therapeutical management of patients with chronic diseases, such as hypertension and other cardiovascular diseases (101, 102).

The findings of national studies conducted in community pharmacies within Slovak Republic underline the importance of pharmacists in the antihypertensive therapy of elderly patients. These results showed that regular and qualitative pharmaceutical care has the potential to improve both the adherence to medication as well as blood pressure levels (31, 103).

We believe that pharmacists have the required knowledge, training and capacity to provide certain mHealth services as a part of their daily pharmaceutical care. These include, but are not limited to: improving patients' adherence to medication, awareness of essential health-related information, strengthening prevention against diseases and forming of health-promoting habits. This concept is supported not only by the recommendations of international pharmaceutical associations, but also by Slovak national legislation.

Similar to other fields and disciplines, Evidence-Based Pharmaceutical Care (EBPC) needs to be encouraged, implemented and supported in order to improve the quality of pharmaceutical care services (104, 105). Studies evaluating attitudes of pharmacist towards EBPC show that pharmacist have substantial interest in developing their role in pharmaceutical research (106-108).

Balážová and Kuželová (109) set forward the options of pharmaceutical care in management of patient with hypertension in Slovakia as follows:

- regular blood pressure measurements;
- guidance regarding correct measurement of blood pressure at home;
- life-style recommendations: weight reduction, lowering salt-intake and alcohol consumption, enhancing physical activity;

- counselling on correct use of drugs, their possible adverse effects, interactions and contraindications;
- communication of possible treatment problems with the physician.

Our current trial aims at assessing the feasibility, effectiveness and patients' acceptance of SMS reminders of medication provided by community pharmacists along with the standard Pharmaceutical Care (sPhC), as described above. Additionally, we attempt to assess the cost-effectiveness of this mHealth service in the selected setting considering local conditions of Slovak Republic.

Cost-effectiveness

Hypertension remains a significant disease burden to the society both in clinical and economic terms (110, 111). In 2014, Slovakia had the third highest cardiovascular drugs utilization within OECD countries (683.4 DID; 37.6% of total drug consumption) (112). A total of 6 506 258 prescriptions were realized in the diagnosis of primary hypertension (113). The expenditures on cardiovascular drugs amounted 155.9 million EUR (11.8% of total sales on pharmaceuticals) (112), while complications resulting from insufficiently treated hypertension are even more expensive (114). Due to lack of centralized information system of direct and indirect costs, it is not possible to calculate the overall economic burden of hypertension in Slovakia. However, in the USA expenditures on antihypertensive drugs were estimated to account only for 24% of the overall costs associated with cardiovascular and chronic kidney diseases resulting from hypertension in 2011 (115).

High adherence to antihypertensive drugs is associated with lower health care costs (116). SMS reminders have been proven to effectively increase medication adherence in patients with a large variety of diseases across different countries and settings. At the same time they present a highly cost-effective and relatively simple tool (86).

In conclusion, hypertension is a medical condition with very high prevalence in the Slovak population and also belongs to the major risk factors of other CVDs which account for approximately 50% of all deaths in Slovakia (12). Even though effective treatment is widely

available and affordable for the Slovak patients, accurate adherence to blood pressure lowing medication is far from ideal. As a result, high numbers of hypertensive patients have uncontrolled blood pressure despite adequate treatment. Older hypertensive patients are at higher risk of medication nonadherence as well as associated complications.

SMS reminders of medication intake showed promising results both in increasing patients' adherence as well as improving health outcomes. However, there is need for further trials evaluating the effectiveness and benefits of SMS reminders in specific groups of patients, personalized settings and local conditions, consequently addressing their cost-effectiveness.

Pharmacists are highly trained health care professionals, who we believe have the education and capacity to efficiently address patients' adherence to medication treatment through mHealth technologies.

Mobile phones are widely used in the Slovak Republic, GSM network covers 92,0% and SMS are a very popular and frequently used means of communication. Additionally, 4 419 professionally trained community pharmacists currently provide pharmaceutical care in Slovakia (117).

Hence, the potential of SMS reminders of medication provided by community pharmacists to improve patients' adherence and outcomes is very high in Slovakia. Therefore, in the current study we are aiming at assessing the efficiency and cost-effectiveness of SMS reminders in older hypertensive patients in Slovakia provided by qualified community pharmacists as a part of their Pharmaceutical Care provision.

2. TRIAL HYPOTHESIS AND OBJECTIVES

2.1. Research question

Do personalized daily SMS reminders of blood pressure-lowering medication intake provided by pharmacists in addition to standard Pharmaceutical Care (sPhC) reduce the proportion of nonadherence to blood pressure-lowering medication among older ambulatory patients with hypertension in Slovakia?

2.2. Trial hypothesis

We hypothesize that personalized daily SMS reminders of blood pressure-lowering medication intake provided by pharmacists in addition to sPhC increase the proportion of adherence to blood pressure-lowering medication among older ambulatory patients with hypertension in Slovakia from 30% to 49% in the intervention group compared to the control group.

2.3. Primary objective

Our primary objective is to determine if daily SMS reminders of blood pressure-lowering medication intake provided by pharmacist in addition to the sPhC reduce the proportion of nonadherence to blood pressure-lowering medication among older hypertensive ambulatory patients. Whereas adherence to blood pressure-lowering medication will be measured as **combined adherence endpoint** consisting of self-reported medication adherence assessed by the eight-item Morisky Medication Scale and adherence rate (AR) measured via pill count.

2.4. Secondary objectives

Our secondary objectives are as follows:

1) to compare the change of adherence after 3 months in the intervention and control group using self-reported MMAS-8 scores;
2) to compare AR of patients in the intervention and control group after 3 months measured via pill count;
3) to compare the change of systolic blood pressure (sBP) after 3 months in the intervention and control group;
4) to investigate the effect of SMS reminders on improving patients' adherence and systolic blood pressure control (treatment effects) across subgroups;
5) to collect and report patients' satisfaction with daily SMS reminders of blood pressure-lowering drugs.

2.5. Other objectives

To the other objectives of the SPPA clinical trial belong: reporting up-to-date adherence rates in older patients with hypertension in Slovakia and assessing the impact of sociodemographic characteristics on patients' adherence to blood pressure-lowering drugs; evaluation of the MMAS-8 questionnaire in our trial population; carrying out a cost-effectiveness analysis of SMS reminders of medication intake; active surveillance and collection of adverse events associated with patients' medication and reporting anonymised reasons for refusal to participate in the trial or withdrawal from the trial.

3. TRIAL DESIGN

The SPPA trial is designed as a multicentre assessor-blinded, controlled, randomised, superiority, pragmatic trial with two parallel groups (1:1 allocation ratio) to assess the effectiveness of daily SMS reminders of blood pressure-lowering medication provided by pharmacists in addition to the sPhC compared to the sPhC only.

Patients will be randomised into two groups: the intervention group (receiving daily SMS reminders of medication intake) and control group (receiving sPhC only, no SMS reminders of medication intake). The intervention (SMS reminders of medication intake) will last for 3 months.

Our trial was designed to fit in a daily practice of a community pharmacy. Eligibility criteria are fairly liberal and can be assessed solely using the information available to the pharmacists.
For further details about the pragmatic design of the SPPA trial, please see the PRECIS-2 table of scores for trial domains and the PRECIS-2 wheel scheme (3) of the SPPA trial in ***Appendix 25.***

4. TRIAL SETTING

The SPPA trial will be carried out in six community pharmacies (=trial centres) in Slovakia. To maintain generalizability of the results for the whole Slovak population of older hypertensive patients, selected trial pharmacies will be evenly distributed to cover the whole territory of Slovakia. Additionally, half of the selected community pharmacies will be located in rural and the other half will be located in urban region. All pharmacies will enrol an equal number of patients. Map of all 22 selected trial pharmacies is provided in Appendix 26. A detailed list of trial sites along with responsible principal investigators will be also included in the Appendix of the Protocol.

In case a trial centre won't be able to enrol the agreed number of patients, an additional trial centre comparable in region characteristics will be trained and initiated to complete the enrolment.

5. TRIAL POPULATION AND ELIGIBILITY CRITERIA

The trial population consists of hypertensive ambulatory patients of 55 years of age or older who are taking blood pressure-lowering medication for at least 1 year without any discontinuation.

5.1. Inclusion Criteria

Patients eligible for the trial must comply with all of the following inclusion criteria at randomisation:

1. Age ≥ 55 years (from the day of the 55. birthday inclusive)
2. Diagnosis of primary (essential) hypertension (I10 according to ICD-10 (118))
3. Filling of blood pressure-lowering prescription(s) at trial recruitment (Visit 1)
4. Duration of antihypertensive drug treatment for at least 1 year without any discontinuation
5. Ownership of a mobile phone for personal use with the ability to open and read SMS
6. Understanding of Slovak language on native-speaker level
7. Informed consent for participation in the clinical trial and personally signed Informed Consent Form

5.2. Exclusion Criteria

Patients cannot participate in the trial if they meet at least one of the following exclusion criteria at randomisation or at any point of the trial period.

Exclusion criteria assessed prior to patient enrolment *(by trial pharmacists):*

1. Planned hospitalisation during the trial period (3 months)
2. Biological impairment affecting the ability to read the SMS (e.g. loss of vision, visual field cuts, aphasia)
3. Living in the same household with another trial participant
4. Participation in another clinical trial

Exclusion criteria assessed after patient enrolment *(by trial pharmacists and project leader):*

1. Hospitalisation during the trial period
2. Patient informs he/she won't be able to participate in the trial
3. Withdrawal of Informed Consent

The rationale behind the eligibility criteria is as follows:

*Age ≥ 55 years (*from the day of the 55. birthday inclusive)

In the SPPA trial we are evaluating the impact of SMS reminders of antihypertensive medication intake in older adult patients who are at higher cardiovascular risk. Therefore, according to our hypothesis strengthening their adherence as well as improving systolic blood pressure control might have substantial effect on their health prognosis.

Diagnosis of primary (essential) hypertension (I10)

We decided to focus on patients with primary (essential) hypertension to limit the confounding influence of secondary hypertension causes both on patients' adherence to medication and resulting blood pressure control.

Filling of blood pressure-lowering prescription(s) at trial recruitment (Visit 1)

According to the Slovak Act No. 362/2012 Z. z., §120, d), the number of prescribed packages of a drug is not allowed to exceed the number of doses required for three months of treatment for patients who are taking the drug on a regular basis (i.e. not for the first time)[5] (119). Hence patients who are collecting their medicines at the day of the recruitment can begin to take the collected package on the next day (first day of the intervention), enabling the precise calculation of pill count rates.

Duration of antihypertensive drug treatment for at least 1 year without any discontinuation

Patients who are using their medication more than one year are considered to have reached their acceptance phase of pharmacotherapy treatment. These patients are at lower risk of early discontinuation of their therapy due to non-acceptance which might potentially bias the trial results (120). Moreover, doctors in Slovakia usually prescribe medication for 3 months to these patients, which is the longest, legally allowed period of time (119).

[5] *for drugs containing narcotic or psychotropic substances the number of prescribed doses is not allowed to exceed the number of doses required for 30 days of treatment.*

Ownership of a mobile phone for personal use with the ability to open and read SMS

As the main intervention of the SPPA trial are SMS reminders, the patients need to possess a mobile phone and be able to open and read the SMS reminders.

Understanding of Slovak language on native-speaker level

All SPPA-trial material and documentation for the participants, including Inform Consent Forms, Patient Cards and Questionnaires will be available in Slovak language, thus eligible patients need to speak Slovak language on native speaker level.

Trial participants who will be hospitalized during the trial duration will be excluded from the trial, since while hospitalized, health care providers will manage their medication, which might bias their results. Patients who live in the same household with another study participant or are enrolled in a different clinical trial will be also excluded from the trial as this could influence the final results. All patients have the right to withdraw their Inform Consent at any time during the trial duration.

6. TRIAL CENTRE REQUIREMENTS AND TRIAL INVESTIGATORS TRAINING

Community pharmacies located in Slovak Republic with a valid authorization for providing pharmaceutical care services in Slovakia are eligible trial centres for the SPPA trial.

Eligible trial investigators are pharmacists that must have successfully completed pharmaceutical education (at least with the Master Degree in Pharmacy) with at least two years experience working as a pharmacist. Additionally, all trial investigators must have successfully completed a training on the principles of Good Clinical Practice (ICH GCP), covering the following topics: Investigators' responsibilities, Compliance with Trial Protocol, Informed Consent Procedures, Randomisation, Trial Blinding and Procedures of Unblinding, Investigator Site File, Safety Reporting, Communication with the Ethic Committee. Authorization List (***Appendix 19***) with all trial centre members and their responsibilities within the SPPA trial will be available for each trial centre.

Prior to trial initiation of each trial centre, all trial investigators will be fully trained on all trial-related procedures by the project leader. Their training will be documented on a trial specific Training Log (***Appendix 20***), dated and countersigned by the trial investigator and project leader.

7. INTERVENTIONS

Eligible patients will be randomised in a 1:1 ratio between control group and intervention group. Participants in the control group will receive sPhC only, while participants in the intervention group will additionally receive daily SMS reminders of their blood pressure-lowering medication intake.

7.1. Control group

Participants in the control group will receive sPhC according to the principles of GPP and national Slovak legislation requirements (97-100, 102) only. Trial pharmacists will provide the sPhC to the patients while dispensing their medicines at the trial pharmacy. Participants in the control group will also receive a welcome SMS one day after enrolment and an end-of-trial SMS three months after the enrolment (***Figure 1***). Additionally, prior to their scheduled follow-up visit (Visit 2), three months following the enrolment, trial pharmacists will call the participants to remind them of their follow-up visit.

7.2. Intervention group

Participants in the intervention group will also receive sPhC provided by the trial pharmacist, the welcome SMS and the end-of-trial SMS. Additionally, they will receive daily SMS reminders of their blood pressure-lowering medication intake from a trial pharmacist for a period of 3 months after the enrolment.

Behavioural perspective of the content and the framing of SMS reminders are not yet sufficiently understood (86). Thus, we will focus on simple and plain provision of information, in accordance with the national and international pharmaceutical regulations and guidelines (95, 97, 99, 100). The content of the SMS reminders will be personalized for each participant in terms of drug name, strength, dosage, frequency and other specifications, if applicable according to their blood pressure-lowering medication schedule recorded at trial enrolment (Visit 1). The structure of the SMS reminder will follow the information provided as a part of the usual drug dispensation and counselling process as described in the Slovak national Decree No. 129/2012 (100). Thus, most of the data are available on the prescription and all of the collected data are already a well-established and required part of the sPhC in Slovakia (121-123). The simple structure of the SMS reminder will allow for future reproducibility. Sample SMS reminder for the SPPA trial participants is included in ***Figure 1.***

Delivery times of the SMS reminders will be customized to patients' individual preferences and will be defined at the enrolment with each patient.

Figure 1: SMS messages in the SPPA clinical trial

SMS	Time of receipt	Content of the SMS
Welcome SMS	day after enrolment	"Welcome in the SPPA trial. Thank you for your participation that might help to improve health of other patients as well as the Slovak health care system. Your SPPA trial research team."
Sample SMS reminder (intervention group only)	daily for 3 months; starting the day after enrollment	"Please, be reminded to take your blood pressure-lowering drug(s): <DRUG NAME & STRENGHT>: <DOSAGE>, <FREQUENCY>, <FURTHER INSTRUCTIONS, IF APPLICABLE>. Thank you."
End-of-trial SMS	3 months after the enrolment	Thank you for your participation in the SPPA trial. Your prescheduled appointment at the trial pharmacy is on XX. XX. XXXX. Please, bring your marked drug package with you. We will be looking forward to your visit. Your SPPA trial research team."

We chose the length of the intervention to be 3 months for two main reasons. First, it has been shown by previous studies that it is a sufficiently long time to detect a significant change in medication adherence (56, 60, 62). Second, since according to the Slovak law (119), chronic patients can receive their medication for a maximum of 3 months, after which they have their regular medical appointment, receive a new prescription and thus visit the pharmacy usually in 3 months cycles. We believe this will increase the retention rates. Furthermore, to minimize attrition of participants, trial pharmacists will contact all participants via phone call one day prior to their pre-scheduled follow-up visit as a reminder. During this phone call, the follow-up visits can be rescheduled if need be. In case the participants are not able to attend the follow-up visit at all, they will be asked to perform the MMAS-8 questionnaire and the satisfaction questionnaire, if applicable via phone call. Additionally, anonymised reasons for not attending the follow-up visit will be collected (please refer to Contact Report Form, Trial Pharmacists-Participants in ***Appendix 16***). These data will present a valuable source of information for the research teams of the following pharmaceutical clinical studies in Slovakia.

Should there be an urgent medical appointment in between Visit 1 and Visit 2 that leads to change in blood pressure-lowering medication, the patient will be asked to inform either the trial pharmacist at the trial pharmacy or the project leader of the SPPA trial via phone call of this change. This way we strive to ensure the relevancy and usefulness of the SMS reminders.

The participants will also be informed that they can decide to discontinue their participation in the trial at any time, after which they will stop receiving the intervention (SMS reminders). Due to the nature of the intervention, no harm is expected ascribable to patient's discontinuation.

7.3. Technology platform for the intervention

We will use the SMS Connector® software for the dissemination and coordination of the SMS reminders. SMS Connector® is an open-access online platform that can be operated via a personal computer (PC). It will be connected to the local phone network using an aggregator phone number obtained from a local phone operator (124).

The external unblinded trial pharmacist (euTP) will set personalised SMS reminders using the SMS Connector® software according to the information recorded in Case Report Form Visit 1 - PART A (***Appendix 1***). The euTP will not have any direct contact with the trial participants or with the trial pharmacists. SMS Connector® will automatically send these SMS reminders according to the pre-defined schedule to trial participant with no cost to the participants. All contacts, SMS-messages and allocation information will be stored on a remote secure server and will be removed after trial termination. An overview of all sent messages (including sent and delivery times and dates) with coded mobile phone numbers will be downloaded and filled in the Trial Master File documentation.

7.4. Concomitant care and interventions

The SPPA trial is designed to be a pragmatic trial that imitates the real-life circumstances in routine pharmaceutical practice. Furthermore, the SPPA trial includes neither an investigational medicinal product nor investigational drug. Thus, no concomitant care or interventions are prohibited for the trial participants.

7.5. Additional trial services for the participants

Participants in both groups will be provided with patient cards on which a telephone contact on the Project Leader will be listed (please, refer to sample Patient Card in ***Appendix 22***. Trial pharmacists will inform all participants at the enrolment that they need to call this number (at no cost for them) in case of: telephone number change/loss, hospitalization, change in blood pressure-lowering medication, they won't be able to participate in the trial or informed consent withdrawal. They are also welcome to call anytime they have further questions related to their participation in the SPPA trial. Project Leader will keep a Contact Report Form, listing all contacts

with trial participants and their reasons, resolution and time invested in each contact from the initiation of the contact up to the resolution (please, refer to Contact Report Form, Participants – Project Leader in ***Appendix 18***). Herein also information concerning withdrawal from the trial will be recorded.

8. TRIAL OUTCOMES

8.1. Primary outcome measure

Our primary outcome is the proportion of adherent patients in the intervention group after 3 months of receiving SMS reminders of medication intake compared to the control group. For these purposes we will assess patients' adherence via combined adherence endpoint consisting of self-reported medication adherence measured via MMAS-8 and pill count rate (%).

Some object that self-reported adherence measures, such as the MMAS-8, tend to be subjectively biased (42, 44). On the other hand, they use a highly patient oriented approach that enables provision of feedback regarding adherence behaviour and pointing out reasons for poor medication adherence (34). Pill count represents a semi-objective adherence measurement, which may also be biased by patient's manipulation. We believe that combining both adherence measurements will provide a more reliable and stronger outcome.

No specific guidelines exist on how to assess medication adherence (125), therefore we based our categorization of a patient as being "adherent" or "non-adherent" on the previous literature and expert opinions. Our study team agreed that a patient at the end of the trial will be considered as either "adherent", having MMAS-8 ≥ 6 (34) and pill count rate ≥80% (126) or "non-adherent" if one or both of the previous conditions are not met.

Table 1: Primary outcome: Combined adherence endpoint

Level	
Domain	combined medication adherence
Specific measurement variable	adherence status (dichotomous) adherent: MMAS-8 score ≥6 and pill count rate ≥80%; non-adherent: MMAS-8 score <6 and/or pill count rate <80%
Analysis Metric	final value (Visit 2)
Method of aggregation	proportion of adherent patients (%)
Time point of measurement	at Visit 2 (follow-up visit after 3 months of intervention period)

Morisky Medication Adherence Scale (MMAS-8)

The eight-item MMAS questionnaire on which the scale is based, was designed from a previous four-item questionnaire (127) and evaluated by Morisky, Ang (34) in hypertensive patients. It showed good reliability (α=0.83) as well as sensitivity (93%) and specificity (53%) in identification of lower versus higher adherence to antihypertensive medication. Additionally, the association between MMAS-8 and blood pressure control was proved statistically significant (p<0.05). Each

question aims at assessing a specific medication-taking behaviour. First seven questions have dichotomous answers (yes/no), whereas the last question offers a 5-points Likert response. The maximum score is 8 points (for each question 1 point) indicating full medication adherence (34, 128).

Pill count rate

Pill count is a simple measurement of patients' adherence to medication intake (42). The correlation between adherence rates calculated by pill count and reported by MEMS was proved to be significant ($r = 0.29–0.39$; $p < 0.01$) in hypertensive patients (129).

Trial pharmacists will count the number of doses of the antihypertensive drug(s) taken since Visit 1 at the follow-up visit (Visit 2). They will calculate the adherence rate (AR) of each subject using Equation 1, adopted from Vik, Maxwell (130):

Equation 1:

$$AR\ (\%) = \left(\frac{No.\,of\ pills\ actually\ taken}{No.\,of\ pills\ that\ should\ have\ been\ taken}\right) x\ 100$$

If the participants were taking more antihypertensive drugs than one, pill count rate will be calculated for each drug separately and averaged so that each participant will have a single AR (%).

To help the patient remember which drug packages they should bring at Visit 2 to the pharmacy, trial pharmacists will visibly mark them at Visit 1 (please, refer to Medication Label in ***Appendix 23***). In cases, where participants still have remaining pills of these blood pressure-lowering drugs at home, the number of them will be obtained form the participants (either at Visit 1 or during a brief phone call thereafter). Patients will be instructed to finish taking these remaining pills and continue with the new drug package (marked with the SPPA label) Additionally, participants will be asked not to share their blood pressure-lowering medication with any relatives or friends.

8.2. Secondary outcome measures

To our secondary outcome belong:

1) change in medians of MMAS-8 after 3 months (Table 2);
2) mean AR (%) after 3 months calculated via pill count (Table 3);
3) mean change in sBP after 3 months (Table 4);
4) patients' satisfaction with SMS reminders.

Change in medians of MMAS-8 after 3 months

Some previous studies have calculated the mean change of MMAS-4 or MMAS-8 scores (60, 64, 131), however, we have decided to calculate the change in medians of MMAS-8 scores between the control and intervention group since the MMAS-8 score is an ordinal variable for which the median is a more suitable measure of central tendency. This secondary outcome is intended to show the approximate potential of SMS reminders in improving patients' adherence (in terms of self-reported MMAS-8 scores).

Table 2: Secondary outcome: Change in medians of MMAS-8

Level	
Domain	self-reported medication adherence (via MMAS-8 questionnaire)
Specific measurement variable	MMAS-8 (categorical, ordinal)
Analysis Metric	change from baseline (Visit 1)
Method of aggregation	median
Time point of measurement	at Visit 1 (at the enrolment) at Visit 2 (at follow-up visit; 3 months after Visit 1)

Mean AR (%) after 3 months calculated via pill count

Table 3 describes in detail our secondary adherence outcome calculated based on adherence rates calculated via pill count.

Table 3: Secondary outcome: Mean adherence rates after 3 months calculated via pill count

Level	
Domain	medication adherence (measured via pill count)
Specific measurement variable	adherence rate (%), continuous variable
Analysis Metric	final value (at Visit 2)
Method of aggregation	mean
Time point of measurement	at Visit 2 (at follow-up visit; 3 months after Visit 1)

Mean change in systolic BP

Blood pressure was proved to be a direct and strong predictor of cardiovascular morbidity and mortality in middle- and older-aged patients (132, 133).

The importance of measuring blood pressure as a secondary outcome in trials evaluating interventions for increasing adherence to blood pressure-lowering drugs is strongly emphasized since it provides valuable information on the relationship between adherence and blood pressure control (52). Results from a large meta-analysis including over 1 million patients demonstrated that systolic BP is much more predictive than diastolic BP in regard to age-stratified stroke deaths (89% vs. 83%) and coronary heart disease deaths (93% vs. 73%) (133). In another meta-analysis, 11 studies found mortality as well as morbidity outcomes to be associated with reduction of systolic BP but not diastolic BP (134). Systolic BP is especially important in people over 55 years of age. Systolic BP rises with age unlike diastolic BP that rises only approximately until the age of 55 years and decreases in the following years (14, 135).

Table 4: Secondary outcome: Mean change in systolic blood pressure

Level	
Domain	blood pressure
Specific measurement variable	systolic blood pressure in mmHg (continuous variable)
Analysis Metric	change from baseline (Visit 1)
Method of aggregation	mean
Time point of measurement	at Visit 1 (at the enrolment) at Visit 2 (at follow-up visit; 3 months after Visit 1)

Trained trial pharmacists will measure systolic BP of all participants at the enrolment and during the follow-up visit using a pre-calibrated certified sphygmomanometer according to the ESC/ESH Guidelines 2013 (4). The average systolic BP from two to three measurements, if deemed appropriate, will be calculated. SPPA Scheme for Blood Pressure Measurement (***Appendix 21***) describes the step-by-step BP measurement process and will be a part of the Investigator's Operational Manual.

Patients' satisfaction with SMS reminders

We plan to collect information on satisfaction of Slovak patients with the daily, personalized SMS reminders of their medicine intake. For these purposes we have designed a brief questionnaire consisting of nine questions focusing on the main aspects of the SMS reminders as additional

health care service provided by the pharmacists. We have based our questionnaire on previous studies (59, 62, 75, 136) stressing out the most important aspects for tailoring future studies to reflect the needs of the patients. First eight questions are provided with answers on a five-point Likert scale, the ninth question offers five answers. Patients will have also the possibility to leave any comment regarding their experience with the SMS reminders of medication intake and we will report them all in a cumulative fashion. Four pharmaceutical professionals and a social psychologist, all members of the research team, assessed face validity of the questionnaire. Furthermore, five patients above 55 years of age have assessed the questionnaire for clarity, simplicity and understanding. The questionnaire was adjusted according to their recommendations and comments. The final Satisfaction Questionnaire is included in ***Appendix 8.***

8.3 Other outcomes

Direct treatment costs associated with blood pressure-lowering medication will be collected for each participant according to the current List of categorized drugs issued by the Ministry of Health of the Slovak Republic on monthly basis (137).

Adverse events associated with the intake of blood pressure-lowering medication will be actively collected from the patients at Visit 2 (follow-up visit). Patients will have the opportunity to report any adverse events during the whole trial duration either to the trial pharmacist personally or the project leader via phone call.

Also, anonymous data on refusal to participate in the trial will be collected to evaluate the feasibility and acceptance of SMS reminders by older hypertensive patients in Slovakia. Moreover, participants will have the opportunity to provide a reason for ceasing their participation in the trial (by withdrawal of their Informed Consent) to help improving the intervention to best address patients' needs in the future.

9. RANDOMISATION, INTERVENTION ALLOCATION AND BLINDING

9.1. Randomisation

Participants will be randomly assigned to either control or intervention group with a 1:1 allocation ratio.

9.2. Intervention allocation and allocation concealment

Allocation Sequence Generation

The euTP will generate a simple Randomisation and Allocation List stratified by gender for each trial pharmacy independently. The random allocation sequence will be generated using computer-generated random numbers (trial codes). Free-available online software, Research Randomizer (Version 4.0 or updated version, if applicable) will be used for this purpose (138). The full Randomisation and Allocation list for each trial centre will be stored in a separate locked drawer with the euTP, who will have no personal contact neither with the trial participants nor with the trial pharmacists (blinded). The treatment allocations won't be disclosed before the termination of the trial. After trial termination, final analysis and Clinical Trial Report completion, euTP will provide the Allocation and Randomisation list for filing into the TMF (for sample Randomisation and Allocation List, please refer to ***Appendix 9***).

Allocation Concealment and Implementation

Each pharmacy will receive 25 sequentially numbered, opaque, sealed randomisation envelopes for male participants (blue) and 25 sequentially numbered, opaque, sealed randomisation envelops for female participants (red) from the euTP (for sample Randomisation Envelopes, please refer to ***Appendix 10***).

Trial pharmacists will recruit patients at the pharmacy in the natural, unpredictable order as they enter the pharmacy. Allocation of trial participants to either intervention or control (via randomised numbers – trial codes) will be carried out as follows:

1) After the patient signs the Informed Consent Form, trial pharmacist will randomly allocate one randomisation envelope (red in case the participant is female; blue in case the participant is male) to the trial participant;
2) Trial pharmacist takes one randomisation envelope (red in case of female patients; blue in case of male patients) and unseals it;

3) Trial pharmacist writes patient's name and mobile phone under the trial code on the inner side of the randomisation envelope;
4) Afterwards, trial pharmacist fills patient trial code in the ***Case Report Form Visit 1***; and stores randomisation envelope in a safe locker in the room of the Head of the Pharmacy.

9.3. Blinding

Trial Participants

Due to the nature of the trial, it is not possible for the participants to be blinded. Trial pharmacists will inform the participants about the purpose of the trial and their random allocation to either receiving daily SMS reminders or not.

Trial Pharmacists (Investigators)

Trial pharmacists, performing blood pressure measurements, pill count calculations and completing the MMAS-8 questionnaires with the participants (the assessors) will be blinded to the allocation of the intervention. The participants will be strongly inculcated not to disclose the allocation status to the trial pharmacists or other pharmacy staff until completing the follow-up visit. At the end of the follow-up visit, trial pharmacists will ask the participants, if they have been receiving SMS reminders and if so, they will kindly ask them to fill out the Satisfaction Questionnaire (***Appendix 8***). The euTP will assign the intervention (SMS reminders) to the participants centrally.

Other members of the research team

The statistician, unblinded to the trial allocation, will receive the final anonymised data after the end of trial and database lock. Since the project leader is the main contact person for trial participants, it is possible that during these contacts patient allocation may be disclosed to the project leader, should the nature of the discussed issue require such disclosure. However, since the project leader is not involved in the assessment of the trial outcomes or in the final statistical analysis, this potential partial unblinding has no impact on the trial results.

Emergency unblinding procedure

Since the trial does not involve an investigational product and no harms to the participants are expected, there is no need for emergency unblinding procedures.

10. TRIAL PROCEDURES

10.1. Sample size justification

The prevalence of nonadherence among hypertensive patients varies from 24% to 70% in European countries (29), whereas in Slovakia it is reported even higher (30, 31). According to the latest study of medication adherence in hypertensive patients in Slovakia, only 18,67% of 150 patients were fully adherent measured on the four-item Morisky Medication Adherence Scale (MMAS-4) (32, 139). Thus, we assume an adherence prevalence of 30% in the control group. According to findings of the latest meta-analysis of randomised clinical trials assessing the effect of SMS reminders on medication adherence in cardiovascular diseases, SMS had the potential to approximately double the odds ratio of medication adherence (odds ratio 2.11; 95% CI 1.52-2.93; p< .001). The weighted mean effect size was d=0.41 (95% CI 0.23-0.59). After adjusting for publication bias the odds of being adherent in the group receiving SMS reminders was 168% higher than in the control group (odds ratio 1.68; 95% CI 1.18-2.39) (85). These results are supported also by the results of the StAR trial with hypertensive patients, which reported odds ratio of 1.86 (95% CI 1.20-2.16, p = 0.002) (58). for improved adherence in patients receiving SMS reminders compared to patients receiving usual care only. Therefore, we hypothesise that SMS reminders of blood pressure-lowering medication intake can improve the proportion of adherent older patients in Slovakia from 30% to 49% given an effect size of w=0.2 (equivalent to d=0.4). A total of 264 patients (132 in each group) are needed to reject the null hypothesis that the adherence proportions in both groups are equal with a power (probability of type II error) of 0.9 and alpha (probability of type I error) of 0.05 (using a χ^2 test of independence). Considering approximately a 10% attrition rate, we plan to enroll 300 patients (150 in each group).

The planned sample size is sufficient to detect a difference in adherence of 1 point on the MMAS-8 scale, which is our secondary outcome. Provided that the median MMAS-8 score in the control group is 4 and in the intervention group 5 (SD=1.8) (33), we need 172 subjects (86 in each group) to achieve a power of 95% and significance level of 5% using a two tailed t-test.

For our secondary clinical outcome (mean change in systolic blood pressure), this sample size does not provide sufficient power to detect a clinically meaningful change of at least 5mm/Hg (SD=20) with a power = 0.9, alpha=0.05 (using either mixed ANOVA or ANCOVA test), but a larger sample is currently not feasible. In the current trial we focus on medication adherence. If the

SPPA trial provides sufficient evidence of a positive effect of SMS reminders on patients' adherence to blood pressure-lowering medication in older Slovak population, and patients' satisfaction with this additional mHealth service is high, we will conduct a larger study to test the effect of SMS reminders also on systolic blood pressure.

Sample size calculations were carried out using G*Power software version 3.1.9.2.

10.2. Patient Recruitment and enrollment

Maintaining the pragmatic design of the study, the recruitment will take place in trial pharmacies (community pharmacies) while patients fill their prescription and collect their antihypertensive drugs. The trial pharmacist will screen the patients according to the information available on the prescription (age, diagnosis and medication) and if deemed eligible, he/she will inform the patient about the possibility of participation in the SPPA trial. Furthermore, poster introducing the study and leaflets with important information for patients about the purposes and aims of the study and their participation will be distributed to each trial pharmacy. This is to ensure that patients are transparently informed about the trial and do not feel pressured. Trial pharmacists will record the screening process and enrolment status of each patient into the Screening & Enrolment Log (***Appendix 11***). Anonymous data on refusal to participate in the trial will be collected to evaluate the feasibility and acceptance of SMS reminders by older hypertensive patients in Slovakia.

Trial pharmacies will be selected in order to be able to recruit 50 patients (recruitment target) in the intended 2 months recruitment period (40 working days) based on the average number of hypertensive patients visiting the pharmacy per month. We expect a cumulative rate of participation refusal and failure to meet the inclusion criteria and/or meeting the exclusion criteria of 75%. Therefore, feasible pharmacies need to have 5 potentially eligible patients per day to be able to meet recruitment target within 40 working days. However, if the recruitment target won't be reached (due to the variable nature of patients' visit rates per month), the recruitment period will be extended until 50 participants in each pharmacy are recruited. In case a trial centre won't be able to enrol the agreed number of patients, an additional trial centre (community pharmacy), comparable in region characteristics, will be trained and initiated to complete the enrolment.

All participants must sign written informed consent to participate in the trial before any trial related procedures are initiated.

10.3. Participant Timeline

All trial procedures and related information are summarized in the Participant Timeline on ***Figure 2.***

Figure 2: Participant Timeline

Participant Timeline SPPA Trial				TRIAL PERIOD				
				Visit 1 (Enrollment)	Intervention / No Intervention			Visit 2 (Follow-up visit)
Trial Procedures	Form available	Team member	Time (min)	t_0	t_W	t	t_L	t_1
ENROLLMENT:								
Screening Assessment of inclusion & exclusion criteria	Yes	TP	2	x				
Information Process, Informed Consent & Enrolment	Yes	TP	15	x				
Allocation	No	TP	2	x				
Scheduling of SMS reminders and Visit 2	Yes	TP	2	x				
INTERVENTIONS:								
Standard Pharmaceutical Care	No	TP	2	x				
CG: Welcome SMS	Yes	euTP	3		x			
IG: Welcome SMS & first SMS reminder								
CG: No intervention during 3 months	Yes	euTP	5			x		
IG: daily SMS reminder during 3 months								
Phone call reminding the follow up visit	Yes	TP	5			x (1 day prior last SMS reminder)		
CG: End-of-trial SMS	Yes	euTP	3				x	
IG: End-of-trial SMS & last SMS reminder								
ASSESSMENTS:								
Sociodemographic and Health Information	Yes	N/A (participant)	N/A	x				
MMAS-8 questionnaire	Yes	TP	4	x		(x) via phone if V2 not possible		x
Blood Pressure Measurement	Yes	TP	10	x				x
Inquiry regarding signals of adverse events	Yes	TP	0-2			(x) via phone if V2 not possible		x
Satisfaction Questionnaire	Yes	N/A (participant)	N/A			(x) via phone if V2 not possible		x
Pill count	Yes	TP	3			(x) via phone if V2 not possible		x

Abbreviations: TP – Trial Pharmacist; euTP – external unblinded Trial Pharmacist; CG – Control Group, IG – Investigation Group; t_0 – Time of enrollment in the trial t_W - Time of Welcome SMS (one day after enrollment); t – Intervention duration (trial period); t_L – Time of the last SMS reminder; t_1 – Time of the Follow-Up visit at the trial pharmacy

10.4. Pilot test

Prior to trial initiation, we will perform a pilot test in one of the trial pharmacies with 20 patients, of which all will be included in the intervention group for 2 weeks (these patients will not be included in the final analysis). All procedures will be performed the same way as planned for the SPPA trial. We will test the eligibility criteria and the refusal to participation rate and thus if the planned sample size is achievable. Furthermore, we will evaluate the smooth run of the software with active monitoring for any systematic errors. We will assess the data collection forms for comprehensiveness for trial participants and practical use for trial pharmacists. Also, the intervention will be evaluated in regards to comprehensiveness, practicality and satisfaction in cooperation with pharmacists and participants. The data management team will test the data

management pathway. All detected problems will be processed and the protocol will be re-evaluated accordingly if deemed necessary.

11. DATA MANAGEMENT

11.1. Data collection methods

Trial data will be collected at Visit 1 (day of patient enrolment) and at Visit 2 (follow-up visit after 3 months). Data collected during Visit 1 will be entered into Case Report Form Visit 1 - PART A (***Appendix 1***), Case Report Form Visit 1 - PART B (***Appendix 2***), Case Report Form Visit 1 - PART C (***Appendix 3***), Case Report Form Visit 1 - PART D (***Appendix 4***). Data collected during Visit 2 will be entered into the Case Report Form Visit 2 – PART A (***Appendix 5***), Case Report Form Visit 2 – PART B (***Appendix 6***) and Case Report Form Visit 2 – PART C (***Appendix 7***). Additionally, any data regarding adverse event will be entered in the Adverse Events Report Form - Sites (***Appendix 12***) by the trial pharmacists and in the Adverse Events Report Form – Project Leader (***Appendix 13***) by the project leader during the whole trial duration. Trained trial pharmacists, blinded to the allocation of the participants, will collect all the data from the participants.

We will strive to collect all data from trial participants and thus we will reschedule the date of Visit 2 if need be. However, in case participants are not able to attend Visit 2, trial pharmacist will ask them to complete the data collection over phone call in the following extend: MMAS-8 questionnaire, report of potential adverse events, satisfaction questionnaire, in case of intervention group. For participants, who discontinue their participation in the SPPA trial, data collected until the date of their discontinuation as well as the reason for their discontinuation will be collected on the Discontinuation Log - Sites (***Appendix 14***) (by the trial pharmacists) and on the Discontinuation Log – Project Leader (***Appendix 15***) (by the Project Leader). We will establish a Trial Master File (TMF) for the complete trial documentation and an Investigator Site File (ISF) for trial documentation of each trial pharmacy according to the principles of GCP. Any relevant contact between participants and trial pharmacists or pharmacy stuff (not members of the trial research team) outside the Visit 1 and Visit 2 will be recorded by the trial pharmacists in the Contact Report Form, Participants - Sites (***Appendix 17***) kept in the ISF of each trial pharmacy.

11.2. Data Handling Procedures

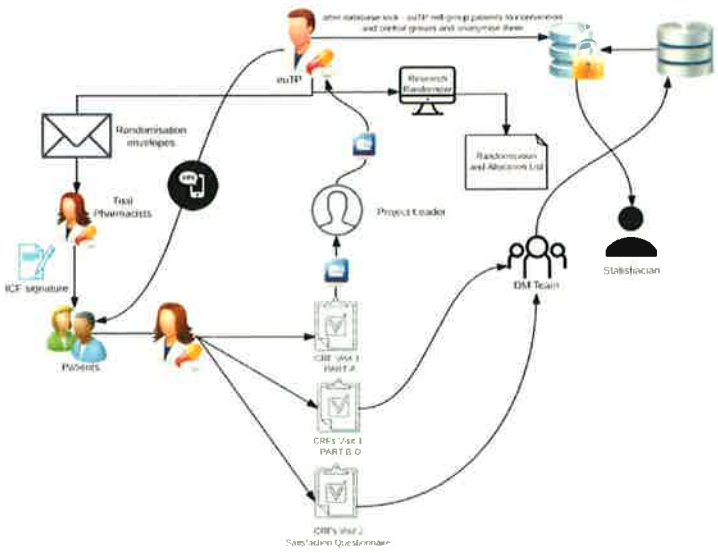
Study pharmacists will be trained prior to trial initiation on all Case Report Forms (CRFs) used in the trial. Trial pharmacists will not leave any data entry incomplete. All completed paper CRFs will be filed in the ISF at the pharmacy, locked in the room of the Head of the Pharmacy.

During the recruitment period, trial pharmacist will send password-protected scans of the Case Report Form Visit 1 PART A and the Screening & Enrollment Log to the project leader via e-mail. The project leader will then forward the antihypertensive medication specification, mobile phone number and preferred time for SMS reminder in a password-protected document to the euTP via e-mail.

The project leader will contact each trial pharmacist once a week to discuss all potential complications, questions or details of the trial. Trial pharmacists will address all questions on the project leader anytime during the trial conduct.

Each month, copies of all CRFs except Case Report Form Visit 1 - PART A from each trial pharmacy will be sent to the research office in sealed envelopes via recorded delivery. A separate data management team (DM Team), whose members are not part of the research team, will enter the data into the pre-prepared password-protected Microsoft Access Database. Two members of the DM Team will do the data entry on a double-entry basis independently. The DM Team will be blinded to the allocation of all participants. These copies of the CRFs will be filed into a separate Data File, which will be kept looked in the administrative office at Department of Organization and Management of Pharmacy of the Faculty during the whole trial duration, with restricted access only to the DM Team. At the end of the trial they will be filled into the TMF. ***Figure 3*** shows in detail all trial data procedures and data workflow.

Figure 3: Trial data procedures and data workflow diagram



11.3. Data confidentiality

All trial related documentation will be kept in ISF, stored locked in the office of the Head of the Pharmacy with limited access to the trial pharmacists. Trial pharmacists will ensure that no personal information violating the anonymity of trial participants will be forwarded to the sponsor of research team. Project leader and euTP will receive the following personal data of the participants: mobile phone number, blood pressure-lowering medication information necessary to perform the trial intervention. Furthermore, birth certificate number and address of residency will be collected since these information are required for the regular enrolment reports of trial participants to insurance companies in Slovak Republic. All parties (investigators, regulatory authorities, ethical committee, insurance companies, auditors) with direct access to personal information of trial participants must take all reasonable precautions, within the constraints of the applicable regulatory requirements, to maintain the confidentiality of the subject's identity. Participants' trial information won't be released outside of the trial without the written permission of the participant neither during the trial nor after trial termination. No personal information of the potential participants, who will not be enrolled in the trial, will be collected. Anonymised reasons for refusal to participate in the trial will be obtained.

11.4. Data storage

After trial termination, final analysis and Clinical Trial Report (CTR) completion, all trial related documentation will be filed in the TMF. Finally, the euTP will provide the Randomisation and Allocation list for filing into the TMF. Afterwards, the TMF will be sealed, securely locked and archived in the archive of the Department of Organization and Management of Pharmacy of the Faculty, Comenius University in Bratislava with limited access to the Sponsor. Investigator Site Files will be securely locked and archived in each trial pharmacy with limited access to the Head of the Pharmacy. The archival period for trial related documentation is 15 years, according to the national regulations of the Slovak Republic (140). In case the pharmacy archival place moves within this period, the Sponsor needs to be informed about this situation within 3 months.

11.5. Access to data

All trial data will be saved in a password-protected Microsoft Access database. During trial analysis, access to the database will be restricted to: DM Team, euTP and trial statistician. After final database lock euTP will anonymise the data and trial statistician will carry out the statistical

analyses. The anonymised datasets will be available in Appendix of the CTR as well as on the Open Science Framework platform (141).

12. STATISTICAL METHODS

All statistical analyses will be carried out according to the intention-to-treat principle. We will strive to collect data from each participant. In case of missing data from Visit 2 (adherence and/or sBP), we will use missing data imputation techniques from the R package "MICE" (Multivariate Imputation via Chained Equations). For continuous variable (sBP) we will use predictive mean matching and for categorical variable (adherence) we will use logistic regression (142). Additionally, a per-protocol analysis will be carried out for comparison. We will report all missing data along with the reasons why these data are missing and explore their patterns. This information will help us to appropriately adjust future studies. No interim analysis is planned only final analysis will be carried out after all data have been collected. Prior to data unblinding the statistician will complete a structured and detailed analysis plan.

We will report descriptive statistics as means (SD) or medians (IQR) for continuous variables and the categorical variables as proportions for categorical variables. All statistical analysis will be carried out with and 5% type I error rate.

Primary outcome analysis

We will compare our primary outcome measure (proportion of adherent patients according to the combined adherence endpoint after 3 months) in the control and intervention group using chi-square test. Also odds ratios and their effect sizes together with the corresponding 95% confidence intervals will be calculated. We will report the absolute effect size as the number needed to treat adjusted for the purposes of our trial to "number needed to remind". To accommodate our pre/post design for our primary binary outcome we will also use a two sample McNemar test (143).

Secondary outcomes analysis

Change in medians of MMAS-8 after 3 months

We will calculate the difference in medians of adherence reported as MMAS-8 after 3 moths between the intervention and the control group (secondary outcome). We will report the effect size and the 95% confidence interval. We will use a specific independent sample t-test on robust location measure (median) implemented in the function „medpb2" in Randy Wilcox´s R package WRS2 (144).

Mean adherence rates after 3 months calculated via pill count

We will calculate the mean difference in adherence reported as AR (%) measured at Visit 2 between the intervention and the control group (secondary outcome). We will report the effect size and the 95% confidence interval. We will use a two-tailed t-test to compare difference between these independent means as well as their robust versions that are recommended when conditions for these tests are violated while preserving high statistical power.

Mean change in systolic blood pressure

For our clinical secondary outcome, mean change in systolic blood pressure, we will compare the results of a mixed ANOVA (suitable to assess change in pre and post measurements) and ANCOVA (suitable to assess the differences in pre and post measurements) as well as their robust versions that are recommended when conditions for these tests are violated while preserving high statistical power (145).

Subgroup analysis

We will conduct a sub-group analysis of the effect on improving adherence and sBP control (treatment effect) of SMS reminders across subgroups based on sex; baseline systolic blood pressure; number of years with hypertension; education level; number of daily blood pressure-lowering medications; frequency of blood pressure-lowering medication intake and baseline self reported adherence rate according to MMAS-8. The QUINT (Qualitative INteraction Trees) package in R will be used for a qualitative subgroup analysis to detect different direction of impact for various sub-groups. (146).

Patients' satisfaction with SMS reminders

Firstly, we will analyse the psychometric quality of the designed questionnaire items using Cronbach's alfa, McDonalds's hierarchical omega as well as Mokken scale analysis (147) in order to find out if all items have sufficient quality to be included in the final scale. In case of significant deficiencies, item(s) will be excluded.

Secondly, using the final scale, we will analyse the impact of patient satisfaction level on the change of adherence and systolic blood pressure values via multivariate linear regression, controlling for impact of sex, age, education, etc. This way we strive to find out if the overall

satisfaction level of patients is a significant predictor variable for the change in adherence rates and/or systolic blood pressure values.

Other outcomes

Our study will also provide current lacking up-to-date data on the adherence of older hypertensive patients in Slovakia, including evaluation of the internal consistency and reliability of the MMAS-8 questionnaire. Internal consistency of MMAS-8 scale will be assessed by Cronbach's alpha coefficient and the reliability of the summed score will also be assessed by McDonalds hierarchical omega (148), which has been shown to be a superior measure to Cronbach's alpha. We will also provide the measures of sensitivity and specificity of MMAS-8 related to correct prediction in regards to high blood pressure. Of interest is also the relationship between two measures of adherence by MMAS-8 and pill count (AR), which will be analysed by correlation coefficient (Pearson and Kendall tau).

Additionally, we will apply regression techniques to analyze the impact of co-variables, such as: **age, gender, education level, social status, place of residence, number of daily doses, co-medication and pharmacy** on patients' adherence.

We plan to realize a simple cost-effectiveness analysis from the payer's perspective. Since we are interested in providing relevant information for the decision making process, we will focus only on the differential costs that depend on the choice of alternative therapy (usual pharmaceutical care or SMS reminder). The steps are as follows: 1) identification of all differential costs; 2) measurement of resources (provided as quantities in case of products, such as SMS; or working time of a health care professional, in case of provided health care services); 3) costs for both therapeutical strategies will be calculated.

We also plan to actively seek for, collect and report any adverse events associated with patients' medication that may occur during SPPA trial.

Finally, we will collect, report and perform a qualitative analysis of the refusal to participation in the trial and withdrawal from the trial rates.

Results of the SPPA trial will be reported following the CONSORT (Consolidated Standards of Reporting Trials) 2010 statement (149, 150) and the Guidelines for reporting of health interventions using mobile phones: mobile health (mHealth) evidence reporting and assessment (mERA) checklist (151). All analyses will be conducted using R (152) using the basic statistical functions as well as robust functions from the package WRS2 (153), and for plotting and graphs the ggplot2 package (154).

13. DATA FIDELITY ASSURANCE, MONITORING AND AUDITING

Prior to SPPA trial initiation at each trial centre, Project Leader will train all trial pharmacists on the SPPA trial protocol and all related procedures including data collection, storage and applicable regulatory requirements. All activities from the initiation of trial centre will be documented in the Initiation Visit Report. Project leader will be in contact with all trial centres (pharmacies) on a regular basis during the whole trial; hence all identified problems will be reported and discussed during these contacts (phone calls). Project leader will document in detail each reported problem a including the resolution and preventive actions taken. The final summary for each site will be provided in the Close Out Visit Report written by the project leader for each trial pharmacy after trial termination. Also, the Project Leader will perform the final audit of trial documentation at close out visit at each trial centre. All activities, observations and finding along with all corrective actions will be reported in detail in the Close out Visit Report.

Due to a relative simple trial procedure schedule and a short trial period, there is no need for a Data Monitoring Committee or other internal trial audit.

14. HARMS

The SPPA trial does not involve any trial medication. Due to the simple and safe trial intervention (SMS reminders of medication intake), no harms associated with participation in the trial are expected.

15. ETHICS AND HUMAN SUBJECTS PROTECTION

The clinical trial will be conducted in accordance with the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) (155), ICH GCP E6 (R1) (156) and the applicable Slovak national regulations: Act No. 362/2011 Coll. on drugs and medical devices (140), Act No. 576/2004 Coll. on health care (157), Act No. 372/1990 Coll. on violations (§29 Violations in health care sector) (158), Act No. 300/2005 Coll. Penal Code (§161 Unauthorized experiment on humans and cloning of human beings; §170 Menace to health with unauthorized drugs, medical devices and equipment) (159) and Act No. 460/1992 Coll. Constitution of the Slovak Republic (160).

15.1. Ethical Committee and submission procedures

Approval of the research ethics

Ethical Committee of the Pharmaceutical Faculty at the Comenius University in Bratislava (Ethical Committee) will review the SPPA Clinical Trial Protocol, the Informed Consent Form and all other required documents. The clinical trial will be evaluated with respect to scientific content and compliance with all applicable international and national guidelines on biomedical research involving human subjects. No trial-related procedure will be initiated prior to the approval of the Ethical Committee.

Protocol modifications

Any subsequent modifications to the clinical trial protocol which may impact the conduct of the clinical trial or the safety of trial participants will be submitted to the Ethical Committee in form of a substantial amendment. Minor clarifications or corrections (such as administrative changes) that do not impact the conduct of the clinical trial will be summarized in the Appendix of the Clinical Trial Report. The Ethical Committee will be notified of these minor modifications in a timely manner. The Project Leader will send a detailed End of Trial Report to the Ethical Committee within three months of clinical trial termination. Furthermore, Clinical Trial Report will be sent to the Ethical Committee upon finalization.

15.2. Informed Consent Process and Information for the participants

Trained trial pharmacists will inform all participants about the purposes and processes of the SPPA clinical trial. During this process or afterwards, patients will have the opportunity to ask further questions regarding their participation in the trial. Additionally, all trial participants will receive Information sheets (as a part of the Informed Consent Form) with detailed information on the clinical trial. During the information process, trial pharmacists will stress the right of the patients to withdraw their Informed Consent at any time during the trial, without providing any reason for their decision. However, trial pharmacists will ask them to provide such reason, if they would like to, since this may help improving the investigated health care intervention for future patients. If a patient decides to participate in the SPPA clinical trial, the trial pharmacist will obtain signed and dated written Informed Consent Form in Slovak language from him. Informed Consent Form will be obtained in two original copies, one will be provided to the trial participant and one will be filed in the ISF at each trial pharmacy locked in the office of the Head of the Pharmacy.

Sample Patient Information Sheet and Informed Consent Form are enclosed to this Clinical Study Protocol as separate documents.

16. DECLARATION OF INTERESTS AND TRIAL FUNDING

All members of the SPPA clinical trial research team, their function in the SPPA clinical trial and declaration of interests are listed in Figure 4.

Figure 4: Member of the SPPA clinical trial research team

ZH[1]	Project Leader Main author of the Clinical Trial Protocol
MK[2]	Contributed to the development of the Clinical Trial Protocol
DM[3]	Contributed to the development of the Clinical Trial Protocol
TT[1]	Contributed to the development of the Clinical Trial Protocol
MS[1]	External Unblinded Trial Pharmacist (euTP) Contributed to the development of the Clinical Trial Protocol
MH[4]	Trial Statistician Contributed to the development of the Clinical Trial Protocol

No member of the research team has received any financial compensation for her trial related activities.

A separate document (Declaration of interests of Investigators) will be finalized upon completion of all initiation visits and finalization of the List of the SPPA trial centres and Principal Investigators (Trial Pharmacists).

The Sponsor has provided financial support for the payment of the MMAS-8 Questionnaire Licence. ZH, as a PhD student, has also applied for a Grant for young researchers offered by the Comenius University in December 2016 to cover other trial related expanses (requested amount of financial funds: 1000 EUR). Information materials for patients will be financed by the provider of pharmaceutical care, Dr. Max, who is the official partner of the trial.

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3 UCLA Fielding School of Public Health, Department of Community Health Sciences
[4] *Research Institute for Child Psychology and Pathopsychology*

17. DISSEMINATION POLICY

The whole SPPA clinical trial is first and foremost part of the dissertation project of ZH. Clinical Trial Protocol, Clinical Trial Report and anonymised trial results will be part of the dissertation thesis of ZH. We plan to publish the Clinical Trial Protocol before initiation of the clinical trial and Clinical Trial Report after completion and final analysis of the clinical trial. Afterwards, clinical trial forms and anonymised data sets will be made publically available in the Open Science Framework database. Furthermore, validation analysis of the MMAS-8 questionnaire in our trial population, cost-effectiveness analysis of the investigated intervention as well as the qualitative evaluation of the acceptance of SMS reminders of medication intake by Slovak hypertensive older patients will be published separately. A qualitative analysis of the attitudes towards clinical trials in Pharmaceutical Practice and readiness of the pharmacists to carry them out; as well as their attitudes towards the use of mHealth technologies in Pharmaceutical Care will be conducted with all SPPA trial investigators (pharmacists) and coordinators (phramceutical technicians) after trial completion and will be published separately. ZH will be the first author of these publications and will cooperate with the whole research team of the SPPA clinical trial on the completion of the publications.

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