Universitat de Girona
Facultat de Medicina

FINAL DEGREE PROJECT

Effects of a Mobile Phone Application on Medication Adherence in Homeless Patients with Type 2 Diabetes, Hypertension and Hypercholesterolemia.

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ABSTRACT

Background: Long-term adherence to chronic treatments remains exceptionally poor despite current effective therapeutic options. Current evidence suggests this trend is accentuated in cardiovascular disease chronic treatments, with an estimated non-compliance rate of 50% in high-income countries. Individuals experiencing homelessness have long been known to have a higher rate of non-adherence than the general population, and it's a growing and aging group, meaning it will see an increase in cardiovascular risk factors and disease in the following decades. There's little research on effective interventions for improving adherence in the homeless, and since new evidence demonstrates that their rate of mobile phone use is quickly aligning with that of the rest of the population, the application of adherence improvement interventions based on new technologies seems to be promising in this field.

Objectives: This study aims to use a mobile phone application designed to improve pharmacological treatment compliance, Medisafe®, to see its effects on medication adherence of the homeless population with Hypertension, Type 2 Diabetes, and Hypercholesterolemia. It will also look into the intervention effects on clinical attendance and disease control outcomes.

Study population: The eligible participants will be male and female aged $\geq$18 years registered in the ''La Sopa'' homeless database of Girona, owners of a compatible smartphone, and currently taking medication for their diagnosis of Hypertension, Type 2 Diabetes, or Hypercholesterolemia.

Design and methods: This is a randomized, pragmatic, controlled, open-label clinical trial. Each patient will be randomly allocated to one of two possible arms: control arm (receiving usual standard of care) or intervention arm (receiving the Medisafe app intervention along with the usual standard of care). The follow-up period of both groups will be of 12 months, measuring as primary outcome variables objective (Proportion of Days Covered) and subjective (Morisky Medication Adherence Scale) validated measurements of adherence. Secondary clinical outcome variables will be glycated hemoglobin, lipid panel, and blood pressure changes. For medical attendance, the number of clinical visits appointed and attended the year previous to the study will be compared to the ones during the year of the follow-up.

KEYWORDS: homeless, adherence, mobile phone, hypertension, diabetes, hypercholesterolemia.

ABBREVIATIONS

BP: Blood pressure

CAP: Centre d'Atenció Primària

CEIC: Clinical Research Ethics Committee

CI: Co-investigator

eCAP: Estació Clínica d'Atenció Primària

ETHOS: European Tipology of Homelessness and Housing Exclusion

EU: European Union

FEANTSA: European Federation of National Organisations working with the Homeless

GDPR: European General Data Protection Regulation

HbA1c: Glycated hemoglobin

HDL: High-density lipoprotein

HIV: Human Immunodeficiency Virus

ICF: Informed Consent Form

ICH: International Conference on Harmonization

ICT: Information and Communication Technologies

IEH: Individuals experiencing homelessness

IJERPH: International Journal of Environmental Research and Public Health

INE: National Institute of Statistics

IS: Independent statistician

LDL-c: Low-density lipoprotein cholesterol

MMAS-4: 4-item Morisky Medication Adherence Scale

MMAS-8: 8-item Morisky Medication Adherence Scale

NS: Nurse collaborators

PDC: Proportion of Days Covered

PI: Principal Investigator

SMS: Short message service

WONCA: International World Conference of Family Doctors

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1. INTRODUCTION

1. 1. CONCEPTUALIZING HOMELESSNESS

'Home' not only means a space to live in but also a place where safety, security, and a sense of belonging and emotional well-being are procured(1).

Homelessness can be concisely defined as the situation in which an individual lacks a stable and secure place to live. It represents the utmost expression of social exclusion(2) and reflects an infringement of basic human rights (3). This term is not only limited to those who sleep without a roof above their head: a more comprehensive view of the word encompasses a spectrum that goes from literal ''rooflessness''(sleeping rough), to housing precarity (living in inadequate, overcrowded, or transient accommodation). (4)

Research regarding individuals experiencing homelessness (IEH) has been perpetually hindered by the absence of consensus when it comes to a rigorous definition of the term. There are different criteria to define who is homeless and who is not, not only between countries but also inside of them, determining variable results in investigation and leading to great contrast in rates and data of IEH even in the same surroundings.

The most accepted characterization of the phenomenon nowadays is the one created by the European Federation of National Organisations working with the Homeless (FEANTSA), which receives the name of European Typology of Homelessness and Housing Exclusion (ETHOS). It was created to provide a shared language for transnational exchange(5), although many european studies still choose not to define homelessness according to ETHOS, and a majority of research outside of Europe also uses other definitions.

The **ETHOS model** identifies three domains that constitute a home *(see Figure 1)*, and when one or more of those domains are lacking one can talk about homelessness and housing exclusion. The physical domain is present when one has adequate space to meet the needs of the person and his/her family. The social domain is being able to maintain privacy and enjoy social relations; and finally, the legal domain is described as having exclusive possession, security of occupation, and legal title.

Furthermore, FEANTSA categorizes homelessness and housing exclusion into 4 groups: rooflessness, houselessness, insecure housing, and inadequate housing(4).

Therefore 'homelessness' understood through ETHOS' prism, not only refers to people who sleep rough, but also to those who stay in specialized services overnight, who have insecure or inadequate housing, or those who are temporarily institutionalized without a previous address of their own (e.g. in hospitals or prisons).

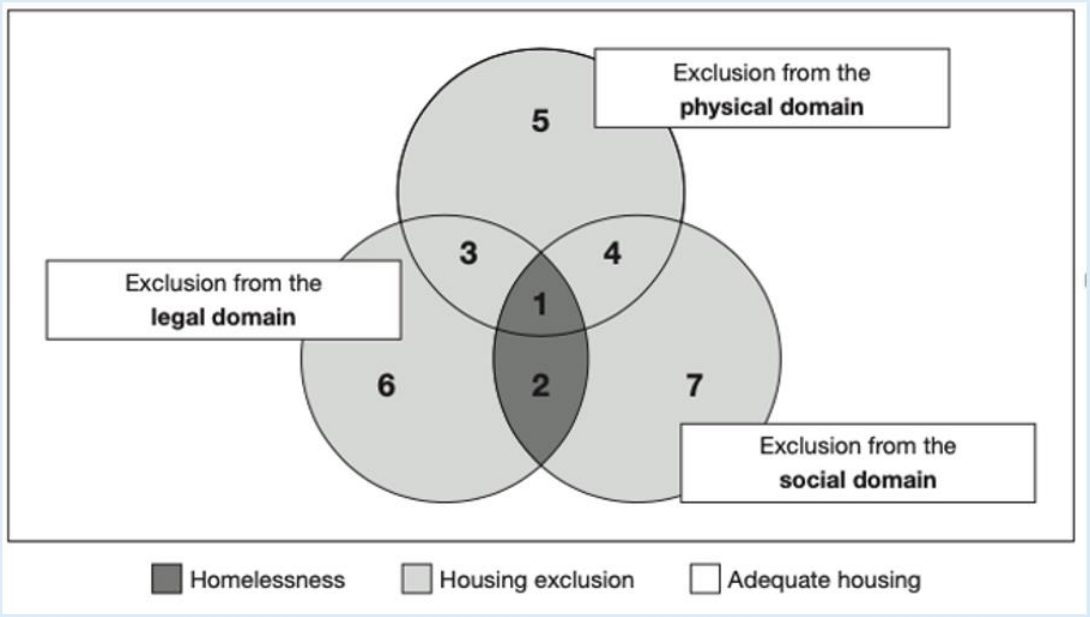

Figure 1: ETHOS model domains (4)

Although this conceptualization is more comprehensive, it nevertheless presents some difficulties when trying to establish reliable data on IEH, because people whose presence is not visible in the community are still excluded (e.g. individuals who do not accept services or suffer a mental health issue, sleep in illegally occupied housing, or are at risk of losing their house but have not informed the appropriate services). Furthermore, it doesn't provide a clear division between homelessness and housing exclusion; however, we cannot overlook the fact that they are interrelated and often affected individuals fluctuate between one another.

There are different types of homeless. In our research, we will focus on individuals experiencing long-term homelessness. **'Chronic homelessness''** is the term widely used for individuals who

have been homeless for at least a year continuously (or who have had 4 intermittent episodes of homelessness in 2 years), **and** who also have a disabling condition, whether it being mental or physical.

Controversy around this concept has emerged, because chronicity has incapacitating connotations, having the potential to pathologize IEH, since the idea of chronicity has an aspect of irreversibility in medicine (6). Having mentioned this, we will use the term with caution and only with descriptive purposes.

Other types of IEH that surpass the scope of this work are **intermittent homelessness** -individuals who cycle in and out of homelessness and institutional care repeatedly- and **crisis homelessness** -if experienced only once or twice for less than a year after an unexpected impasse such as job loss, eviction or divorce- (7).

1.2. CAUSES OF HOMELESSNESS

The comprehensive approach to understanding homelessness causation encompasses an interplay between **structural and individual factors** (*see figure 2*) that contribute to the process which leads to homelessness(8).

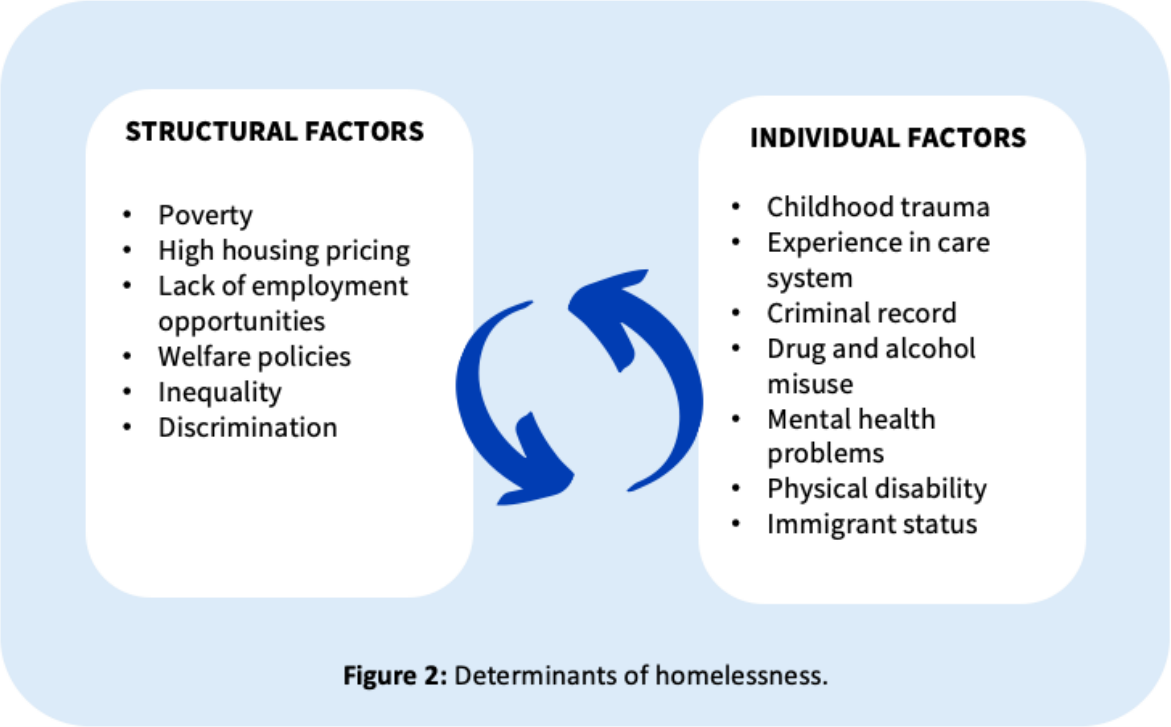

Figure 2: Determinants of homelessness.

Thus, certain individuals are predisposed to become IEH because of intrinsic characteristics that make them vulnerable to structural elements (9). Evidence suggests that drug and alcohol misuse are strongly associated not only with the commencement, but also the persistence of homelessness(7).

However, there's evermore agreement that structural causes (the biggest one being availability of low-cost housing) are the most impacting in this context, being aggravated by individual factors(10). Structural components increase the vulnerability of individuals in their context, hence augmenting the effect of individual determinants. Discrimination is a significant structural risk factor, as marginalized minority groups have been historically overrepresented among IEH (11).

Therefore, pathways into homelessness have to be comprehended as **interactive and interdependent.** Dichotomizing them into ''individual'' and ''structural'' fails to account for the complexity of the problem.

1.3. EPIDEMIOLOGY

The last time the United Nations attempted a **global** survey on homelessness was in 2005. Back then the number of homeless people in the world was estimated at roughly 100 million(12). As many as 1.6 billion people lacked adequate housing in 2015 (13). It can be stated that homeless data is systematically underestimated because of the lack of a standard definition of an IEH, the uneven offer of housing resources with different policies for accessibility in each territory, and considerable geographical mobility.

That being said, an estimated 400,000 people in the **European Union** experience homelessness on any one night. In the last decade, homelessness has been an increasingly serious social problem, because of residential exclusion, across high-income countries including Spain(14). Reasons for these augmenting rates are the rise in housing costs, migration, aging of the population, and changes in family structure(7).

The last survey on homelessness in **Spain** is from the National Institute of Statistics (INE) report of 2012 (15), which estimated that there were about 23,000 IEH in the country. Catalonia was

the Autonomous Community with a higher rate of IEH, accounting for 21% of the total of homeless people living in Spain. The numbers in this survey have to be taken with caution since the low homeless prevalence reported in Spain in comparison to other European countries has been attributed to methodological factors, not equating to social reality(16). The INE has a very strict definition of what constitutes an IEH, excluding all those who haven't reached out to professional aid or received accommodation directed to homeless people the week prior to the data gathering. Having a strict definition that omits a large sector of those affected by homelessness, minimizes the phenomenon and contributes to the stigmatization and invisibilization of the problem(10).

Lastly, **demographic changes** have to be mentioned, since there has been a shift in the average profile of a homeless person. In the past, it consisted on that of a white, single, ill-kempt middle-aged man, but nowadays there's a greater proportion of migrants (in 2012 they comprised almost half of IEH, being greatly overrepresented when compared to the 8,5% migrant sector present in the general population) (14). The proportion of young IEH and those who are 45 years old or more is increasing(15). Also, we should point out that although we do not have official data yet, social workers with experience in the sector have stated that the Covid-19 pandemic has especially affected female workers in precarious jobs who have sought help from homeless shelters, so we should be aware that the number of homeless women is probably rising. As time passes, IEH become more heterogenous, shedding light to the need for solutions adapted to different patient profiles, as overlooking the different cultural backgrounds and past experiences within the group is oversimplistic and ineffective.

Also, the aging of the homeless population implies the prevalence of age-related conditions and incidence of chronic diseases has increased in IEH (17), with such illnesses appearing 20 years earlier than in the rest of the population. Explanations found for this early acquisition of such diseases are poor treatment control and incremented rates of risk factors (e.g. tobacco, alcohol, illicit substance misuse)(7).

1.4. HOMELESSNESS AND HEALTH STATUS

Vulnerability denotes the possibility of being physically, psychologically, or morally harmed. IEH are highly vulnerable, especially when it comes to their health (10).

One cannot forget that though medical care is essential to well-being, **social determinants** play a bigger role when it comes to an individual's health (*see Figure 3*). Employment, education, housing, and social position have significant influence on clinical outcomes and prognoses(18). IEH have deficits in many of those factors. Numerous papers indicate a connection between social inequality and health inequity, while also suggesting that such inequities stemming from social deprivements may be increasing (19,20)

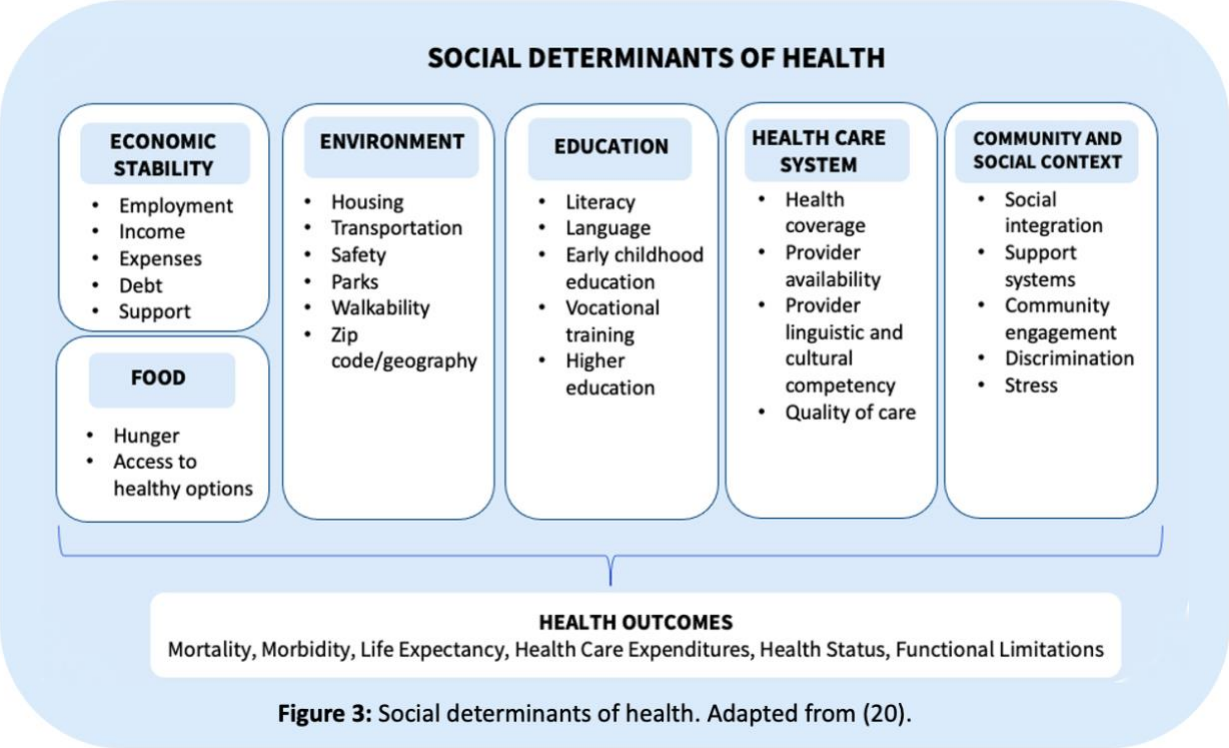

Figure 3: Social determinants of health. Adapted from (20).

While the Spanish health system provides universal access and coverage, IEH have **minimal clinical attendance,** perpetuating poor health status, and have lower perceived quality of health than the rest of the population(19). Contributing factors to this poor use of healthcare services are barriers to access, conflicting priorities, and physical and mental multimorbidity(21).

Homelessness is an important predictor to identify **high users of the emergency department**, characterized by visiting it more than three times per year (7). This high usage of emergency

settings is explained because health conditions in IEH are often not treated adequately, lack follow-up, and are difficult to manage since they require great coordination between social services and clinical practitioners. Moreover, 24% of Spanish IEH and 76% of migrant IEH do not have a health card, making their access to primary or preventive health care settings suboptimal(22), only reaching out to health care via emergency services. This pattern is consistent internationally(4). Being homeless also is an independent risk factor for higher rates of hospital admission and longer stays once admitted (23).

The experience of homelessness has a negative -and often long-term- impact on health, leading to a **rapid physical, psychological and social deterioration** (24). IEH have a higher risk of health complications, both physical and mental (25). IEH suffer from a higher prevalence of infectious and non-communicable diseases, mental and substance misuse disorders, and increased rates of premature mortality when compared to the general population (7,17).

Cardiovascular disease is one of the most frequent causes of death worldwide, with social factors being increasingly recognized as determinants of cardiovascular prognosis. Although outcomes of cardiovascular diseases in IEH are not widely studied (*See figure 4 for a comprehensive summary*), we know that this group of conditions is one of the 3 major causes of all-cause mortality among homeless adults(26,27)**.** Recent evidence suggests that age-standardized mortality rates due to all cardiovascular causes were 61 to 71% higher than in the general population. This disparity is even starker among the growing segment of homeless adults ≥45 years of age, for whom heart disease is the second-leading cause of death, with mortality rates 2- to 3- fold higher than in similarly aged adults in the general population (28). Higher rates of smoking, similarly to higher rates of **diabetes** have been reported in IEH from Europe and Canada (7,29). Poorer control of other cardiovascular risk factors has also been noted, but diabetes accounts for the highest non-adherence (27). Substantial evidence that indicates compliance and persistence with therapy are the limiting factors in the drive to achieve and maintain desirable management goals (30). One of the major impairments reported by homeless people is difficulties in prioritizing their cardiovascular conditions over the problems they may be experiencing (31). Non-adherent diabetic patients are at increased risk for the development of micro- and macrovascular complications, hospitalizations, and death (32)**.**

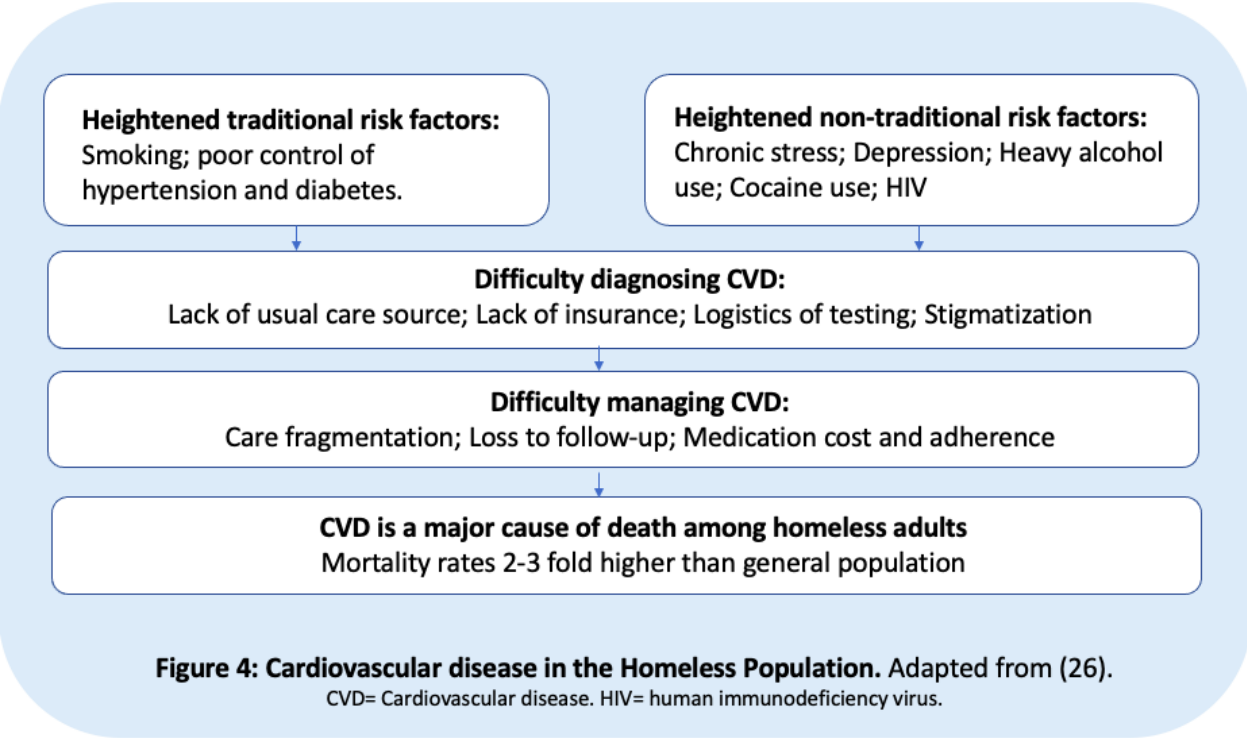

Figure 4: Cardiovascular disease in the Homeless Population. Adapted from (26).
CVD= Cardiovascular disease. HIV= human immunodeficiency virus.

Regarding **hypertension,** even though its prevalence among IEH is similar to that of the rest of the population, it often goes undiagnosed or untreated among homeless individuals(33)**,** contributing to poorer blood pressure control than that seen in the general population (34)**.** Studies of lipid profiles among homeless individuals have yielded mixed findings around the prevalence of **hypercholesterolemia** (26,33,35)**.** Although total cholesterol and triglyceride levels may be lower in some settings**,** potentially reflecting inadequate diet, high-density lipoprotein levels seem to also be lower in this population**.** Among those who qualify for lipid-lowering medications, few appear to be receiving them (26,33)**.**

Mortality age-adjusted rates of IEH in high-income countries are two to five times higher than those of the general population (7), with the mean age of death ranging from 34 to 47 years old (36). In Catalonia life expectancy of homeless individuals is 30 years lower than the national average, and type 2 diabetes has been highlighted recently as an important risk factor in IEH (19,37). When comparing the causes of death in the older IEH to that of the general population of equal age, the findings are relatively similar -with cardiovascular causes being the most common- yet they are fatal 10-15 years earlier among the homeless sector (38).

1.5. ON ADHERENCE AND HOMELESSNESS

Adherence is often defined as patients taking more than 80% of the prescribed medication.

Medication nonadherence is the failure to consume treatment as prescribed and has been pointed out as a paramount impediment to effective therapy, even more so in IEH (39). Poor adherence is linked to lower achievement rates in treatment target levels, increased adverse clinical outcomes, greater morbidity, and overall mortality (40). It has also been demonstrated that low adherence to medication leads to a significant increase in healthcare service use, reduction in patients' quality of life, and rising healthcare costs (41,42).

Long-term adherence to chronic medications has been estimated to be as low as 50% in high-income nations (43,44). However, in comparison to other variables being considered in therapeutics, research in this field has often been neglected. The socio-economic status of patients negatively impacts their adherence to medication (45).

Current evidence suggests that **homeless patients are less adherent** to their prescribed regimen and demonstrate poorer therapy results than the rest of the population, especially noted in cardiovascular disease (26). Although data on homeless adherence to treatment is limited, experienced clinicians and social workers agree with the evidence cited, emphasizing that the problem is greater in this sector of the population. A conservative estimation would be that 75% of IEH are currently not adhering to their chronic treatments adequately.

Given the higher morbidity and mortality rates amongst the homeless population, adherence to prescribed medicines is imperative in achieving better health outcomes.

In the general population, several **barriers to medication adherence** have been identified (*see Figure 5*), with forgetfulness being one of the most frequently cited (30,46,47).

Homeless patients face many additional barriers when it comes to adhering to prescribed pharmacologic treatments. In this population, **forgetfulness** or missed doses has been noted as the primary self-reported reason for medication non-adherence; that being explained in part because of the lack of daily structure and the irregular schedules of IEH. They often also point out having many other priorities that come before medication intake. Other specific factors

that increase non-adherence in homeless people are lost or stolen medication, lack of an area to store medications, and lack of privacy (48).

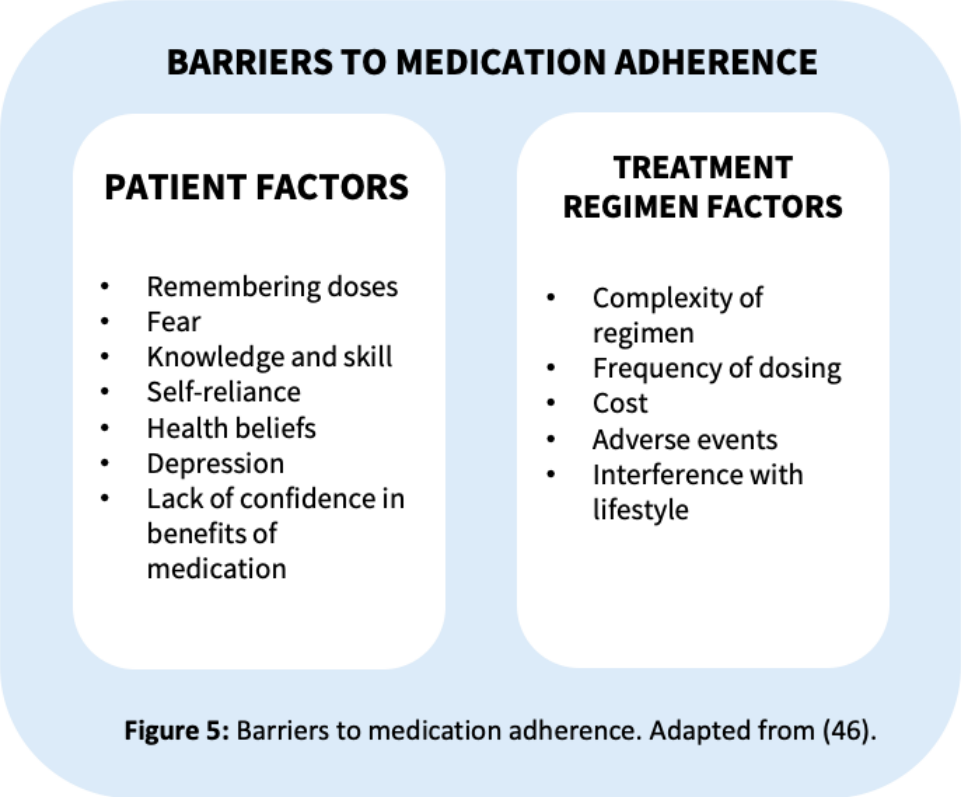

Figure 5: Barriers to medication adherence. Adapted from (46).

1.6. EVIDENCE ON MOBILE PHONE USE FOR ADHERENCE IMPROVEMENT

Many interventions aiming to improve adherence have been conducted, but often have been complex and not highly effective. Current knowledge points towards simpler interventions if one wants to achieve better results (49). Strategies using reminders are based on behavioral learning theory, suggesting that non-adherent conduct can be modified after sufficient repetition of external cues (e.g., reminders). Interventions focusing on behavioral change, rather than motivation or knowledge, have been found to have a greater impact on adherence(50).

Mobile phone interventions in healthcare are an emerging, rapidly-evolving practice, used to improve the delivery of health services in many countries of the world(51). They can present convenient, cost-effective ways of supporting self-management and improving patients' self-efficacy skills through medication reminders, therapy adjustments, or supportive messages (52). They do not require additional effort from health professionals and may be easily integrated in the patient's daily life.

With societal and economic trends, mobile phones have become a necessity rather than a luxury. **Cell phone use among the homeless has been increasing steadily** and currently the majority of IEH own and use a phone, with the prevalence of phone use not differing much from the general population, although exact numbers are not known at a large scale(53–55). Despite prevailing assumptions that homeless persons are cut off from many communication channels, a 2013 systematic review concluded that until mid-2012**,** between 44% and 62% of individuals experiencing homelessness owned a mobile phone, in comparison to 85% of the general population (53)**.** In 2016, a study on the feasibility of information and communication technologies (ICT) in the homeless population found that 89% of their participants owned a cell phone(54), and more recent studies have also pointed out that the generalized prevalence of phone ownership in this population is increasing (56).

One decisive factor in this rise of ICT in IEH has been the rapid drop in ICT prices over the past years, making them affordable even to those with incomes of a few hundred euros a month(53). Moreover, mobile phones are especially suited to the living situations of homeless and

unstably housed persons, who often carry their valuable possessions on themselves at all times.

Precedent literature regarding **electronic reminder strategies** has demonstrated improvements in medication adherence focusing on patients with conditions such as HIV(57), hypertension (58), and diabetes -where it was noted that reminder systems provided the best evidence for increasing adherence (59,60)-. A recent systematic review and meta-analysis on the use of mobile apps to improve cardiovascular disease medication adherence concluded that the overall effect of this type of intervention is positive, but research is widely heterogeneous and can differ greatly between populations(52). Conclusive data is still nonexistent to date, and the use of mobile phone interventions for improving adherence has barely been studied among the homeless population, with only one pilot trial with a sample of IEH published to this day (61).

Nonetheless, the **feasibility and potential of this type of strategies on homeless populations** have been stated (62): A number of studies have shown that mobile phone technologies improve communication between health care providers and traditionally vulnerable populations, such as persons of lower socioeconomic status and those with stigmatized health conditions (63,64)**.** In Girona, a study on a homeless count using Whatsapp saw great engagement from the IEH(56).

Besides adherence improvement benefits, these types of interventions could also aid in practitioner-patient communication: In Spain, about half of the homeless population are immigrants(14), and many of them have language difficulties, posing a challenge to healthcare providers when having to explain treatments to their patients. Mobile phone applications, such as the one in this study, come in a variety of languages, including French and Arabic, which are rarely spoken by sanitary personnel in Spain but frequently used by immigrant IEH.

2. JUSTIFICATION

Despite the development of effective therapies, **long-term adherence** to chronic disease treatments remains exceptionally poor, with approximately 50% of patients in the general population becoming non-compliant within a year of medication initiation(43,44). This problem has been especially noted in cardiovascular medication (65). Pharmacological nonadherence is a growing concern to clinicians, healthcare systems and patients, because it can lead to poor clinical outcomes and increased healthcare costs.

To this day, there has been limited success with strategies used to improve treatment compliance, because of the complexity of interventions, lack of adaptation to each individual's unique barriers to adherence, and the requirement of high implementation costs.

Although no exact numbers are known, current evidence and clinical experience point out that **individuals experiencing homelessness (IEH)** have a substantially higher non-adherence rate when compared to the rest of the population; and the main contributor reported for not taking medication adequately has been forgetting dose takes(48).

Because of socioeconomic trends, the number of IEH and people at risk of housing exclusion across high-income countries is augmenting. The homeless population is aging, meaning that the prevalence of age-related conditions and therefore the burden of cardiovascular disease will not cease to increase (17,66). **Cardiovascular disease** appears 20 years earlier in IEH than in the rest of the population, and nonadherence contributes to heightened healthcare costs and disability, and often results in the use of expensive treatments of their complications. Moreover, IEH access primary care less, using costly unscheduled emergency healthcare at a higher rate than housed populations, and prognosis of diseases that require long-term treatment are poorer among them (33). Equity in any healthcare system is of paramount value and should be ensured. Therefore, urgent and present-day solutions to non-adherence in IEH are imperative to face this growing trend and achieve better health outcomes.

Cell phone use among the homeless has been increasing steadily and currently the majority of homeless own and use one, with the prevalence of mobile phone use not differing much from the general population(53–55). The use of smartphone applications is starting to show its effectiveness as a tool for improving adherence in many healthcare settings, but has never been used in IEH with the intent of adherence improvement. Several studies have reported a good response and perception from

IEH to using information and communication technologies (ICT) for improving health in innovative ways(56,67).

In this study we aim to use a mobile phone application, Medisafe®, to improve medication adherence of chronic treatments in IEH, by tackling one of the main factors impairing adherence in this population, forgetfulness, through medication and clinical visit reminders. The focus will be on three highly prevalent chronic conditions in homeless individuals that are thought to present poorer adherence and prognosis than in the general population: Hypertension, Type 2 Diabetes, and Hypercholesterolemia.

If proven successful, this intervention can be cost-effective and easily integrable in daily life, whilst supporting self-management and empowering IEH, ultimately achieving progress in clinical outcomes. This strategy can also be a useful communication tool as it comes in many languages, eliminating the current language barrier that exists between healthcare providers and immigrant homeless patients, which constitute about half of IEH in Spain. The use of this type of technology could also decrease the work burden of medical and social services, paramount to care for IEH.

3. HYPOTHESIS AND OBJECTIVES

3. 1. HYPOTHESIS

The use of a mobile adherence application *(Medisafe®)* complementary to standard care, improves medication adherence, clinical appointment attendance, and clinical control of type 2 diabetes, hypertension, and hypercholesterolemia in comparison to standard care alone, in the homeless population of the city of Girona.

3.2. OBJECTIVES

- **The main objective of this trial** is to assess the effect of the mobile phone intervention in combination with standard care in the **adherence** to cholesterol-lowering, anti-hypertensive, and oral hypoglycemic agents compared to standard care alone in the homeless population of the metropolitan area of Girona.
- **A secondary objective** is to assess the effect of the mobile phone intervention in combination with standard care in **appointment attendance** compared to standard care alone in the homeless population with chronic hypertension, type 2 diabetes, and hypercholesterolemia of the metropolitan area of Girona.
- **Another secondary objective** is to assess the effect of the mobile phone intervention in combination with standard care in **glycated hemoglobin, blood pressure, and cholesterol levels**, compared to standard care alone in the homeless population with chronic hypertension, type 2 diabetes, and hypercholesterolemia of the metropolitan area of Girona.

4. METHODOLOGY

4.1. STUDY DESIGN

This is a **pragmatic, randomized, open-label, two-arm controlled clinical trial**. There will be follow-up assessments at months 3, 6, 9, and 12. The study period will end approximately 12 months post-randomization.

Computerised **randomization** will be used to minimize bias in the assignment of subjects to the 2 study arms, to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced across the 2 arms, and to enhance the validity of statistical comparisons between both groups.

After written informed consent and baseline assessment procedures, participants will be randomized to either the intervention or control group in a 1:1 ratio using an independent computerized randomization system; and will be informed of their group allocation. Neither participants nor the investigators will be masked to group assignment because of the nature of this trial. The independent statistician analyzing the data collected in the study will be blinded.

4.1.1. Intervention arm

The goal of the adherence intervention is to provide reminders and encourage the subject to take their medication every day through 2 primary mechanisms: 1) remind the subject to take the medicine when it is time; 2) remind the subject of clinical appointments. The Medisafe mobile application provides a real-time reminder that alerts the subject to take his or her medication and to attend clinical appointments. The application will also send an alert to the subject when a refill is needed based on calculated medication or pill supply. The intervention will focus on daily adherence to medication only used to treat hypertension, type 2 diabetes, and/or hypercholesterolemia.

5.1.2. Control arm

Subjects randomized to the standard care alone arm will receive physician- or nurse-guided standard of care. Patients in this arm will not access the Medisafe app during the trial.

4.2. POPULATION. SAMPLING AND SAMPLE.

4.2.1. Subject population:

The target population are the IEH in the city of Girona. ''La Sopa'' is a social and welfare public entity dedicated to people experiencing homelessness or in situations of extreme poverty or exclusion. The ''La Sopa'' database is constituted by people who do not have housing, live in the street, in illegally occupied houses, or temporarily in the municipal reception center of ''La Sopa'' and/or receive aid from this same center. The sample will be selected from this database, and the selection will be performed following a simple random sampling model.

Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Male or female, ≥18 years of age
2. Being registered in the Sopa database with a telephone contact.
3. Taking any oral medication to treat hypertension, type 2 diabetes mellitus, and/or hypercholesterolemia.
4. Possession of a compatible smartphone (iOS or Android) with an active phone number, text, and WiFi internet capability. The smartphone must be in continued possession of the subject during the study period and it may not be a shared device.
5. Willing to have the adherence application installed on a smartphone and use it every day during the entire study period.
6. Must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for the study, and is willing to participate in it, also authorizing the research team to access eCAP data on medication and refills.
7. Willing to provide oral confirmation indicating that he/she has not previously used a medication adherence application.
8. Ability to read or understand English, Spanish, or Catalan.

Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Anticipated inability to adhere to the mobile application (Medisafe) based on the opinion of site Principal Investigator (PI).
2. If the subject does not have a compatible iOS or Android smartphone, then the subject may not be enrolled in the study.
3. Cognitive or motor impairment that would prevent completion of study procedures or use of the mobile phone.
4. Employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.
5. Not having the intention of remaining in the province of Girona for the year that the study will last.

Therefore eligible participants will be male and female aged ≥18 years registered in the Sopa homeless database, owners of a compatible smartphone, and currently taking medication for their diagnosis of hypertension, type 2 diabetes, or hypercholesterolemia.

Subjects who meet the initial eligibility criteria and who consent to participate in this study will be asked to complete the modified 4-item Morisky Medication Adherence Scale (**MMAS-4**) (see Annex 1). The study population will include subjects who have answered ''yes'' to at least 1 of 4 questions from the MMAS-4, since answering ''Yes'' to ≥1 of 4 has 73% sensitivity to identify non-adherence. Answering ''No'' to all 4 questions has 75% sensitivity for high adherence. Therefore only individuals at risk for medication non-adherence will be included.

4.2.2. Sample Size Determination

The Sopa database had 1.627 people registered in 2020. This register was used to calculate the size needed for the sample of the study to be representative of the homeless population of Girona, using the ETHOS definition criteria of IEH. This definition not only includes those people without accommodation who live in open spaces (sometimes referred to as 'rooflessness') or in specific accommodation projects aimed at IEH, but also those in serious situations of unsafe and inadequate housing.

Adherence estimates in European countries are highly variable in literature, but recent estimates allocate a rate of non-adherence of approximately 50% in chronic treatments for the general population. Bearing in mind that available literature and clinical experience suggests that non-adherence is much higher in the homeless population by the various reasons described in section 1.5, we estimate a prevalence of non-adherence to the medications included in this study for the homeless population to be around 75%.

Existent data on clinical trials using SMS reminders for cardiovascular medication in non-homeless populations establish that these types of interventions have the potential to double the odds ratio (OR) of medication adherence (in a meta-analysis of randomized clinical trials using SMS reminders the result was OR= 2.11; 95% confidence interval [CI]=1.52-2.93; P<0.001). Based on the limited data available and clinical experience, it was expected that a high portion of the patients enrolled in the study would be lost to follow-up.

A **pilot test** will be performed before study sample enrollment (details in section 5), to ensure that the calculated drop-out rate and sample size equates to reality in our context, and if not it will be modified.

Assuming an alpha risk of 5%, and a beta risk of 0.20 in a two-sided test, and an anticipated **40% drop-out rate**, 252 individuals will be needed in each study arm. Therefore a total of 504 subjects have to be enrolled for randomization, to have a statistical power of 80% to detect a difference in PDC of 15% between both arms, which is the objective measure we are using for adherence.

Computations were carried out with GRANMO.

4.2.3. Subject completion/discontinuation from the study

Completion: a subject will be considered to have completed the study if he or she has completed assessments at End-of-Study Visit (Day 365 or Early Termination Visit).

Withdrawal from the study: A subject will be withdrawn from the study for any of the following reasons:

- Lost of follow-up
- Withdrawal of consent
- Death

4.3. VARIABLES AND MEASURING INSTRUMENTS

Primary dependent variable

Medication adherence of type 2 diabetes, hypertension, and hypercholesterolemia, measured with two methods: the subjective Morisky Medication Adherence Scale (MMAS-8) and the objective measure of Proportion of Days Covered (PDC).

The **PDC** methodology has been previously detailed and validated(68) against other direct adherence measures including drug levels(69,70).

The principal investigator will access the eCAP medication plan of included patients and go to the SIRE Management section, where information on the medication dispensed to the patient is available. The PDC will be computed using the date the prescription was filled, the ''days supplied'' field in dispensed drug data, and the dates on which the prescription was refilled.

PDC is calculated as non-hospitalized days during which medication was supplied and consumed(a+b+d+e+g)/Total observation time duration (number of days) during which medication should have been consumed(h-c-f).

$$\text{Proportion of days covered (PDC)} = \frac{a+b+d+e+g}{h-c-f}$$

a, b, d, e, g	days during which a subject took the medication of interest (every letter represents one medication refill).
h	total nomber of days
c	days of hospitalization
f	cancelled/discontinued/suspended treatment (by a doctor)

Overall medication adherence will be assessed as a binary variable defined as 1: if PDC is ≥80% and 0: otherwise. This is the most used threshold for determining adherence and non-adherence in research, and we consider it a decent cut-off for our study population. A positive difference in the total proportion of PDC at the end of the study of 15% will be considered clinically significant.

The **MMAS-8 questionnaire** (see Annex 2) will provide us with a widely validated albeit subjective measurement of non-adherence. It will be administered to subjects enrolled at the Day 0/Baseline Visit (prior to randomization) and at follow-up visits at 3, 6, 9, and 12 months. The data provided by the MMAS-8 will reinforce an accurate measurement of the primary study outcome, medication adherence, and will facilitate comparability with similar research.

Compared to the original 4-item Morisky scale used in the screening of subjects for study eligibility (see section 4.2.1), the MMAS-8 has an added 4 items related to medication use patterns, to try to identify and address the circumstances or situations related to adherence behavior; it has much better psychometric properties (sensitivity and specificity are 93% and 53%, respectively and Cronbach's alpha value is 0.83 that is above the acceptance threshold) (71).

A patient is considered ''adherent'' having MMAS-8 ≥6 and PDC ≥80%, or ''non-adherent'' if one or both of the previous conditions are not met.

Secondary dependent variables

- **Clinical appointment attendance:** measured using the number of attended visits divided by the total of visits programmed from the year before the study, collected from the eCAP register of each patient, as well as their non-attended and total visits programmed for the patient during the year studied. This discrete variable will be expressed in percentage, and a difference of 10% between the start and the end of the study will be considered clinically significant.
- **Clinical parameter control:** the mentioned parameters will be measured to determine if there are any changes in disease control at the end of the study in relation to the initial basal state, because of the medication adherence intervention:
    - HbA1c: For patients being treated for diabetes, glycated hemoglobin (%) will be determined from blood samples taken at CAP Santa Clara facilities. These HbA1c determination blood tests will be performed at baseline and at the End of Study

visit, to determine the control state of Type 2 Diabetes Mellitus patients. An HbA1c of <7% will be the threshold to consider a Type 2 Diabetes patient controlled.

- Lipid panel: For patients being treated for hypercholesterolemia, LDL-cholesterol (using the Friedewald formula) and HDL levels will be determined at baseline and at the End of Study visit from a blood sample taken at the CAP Santa Clara facilities after a 12-hour fast. An LDL-c lower than 100mg/dL will be considered optimal, 100-129mg/dL near-optimal, 130-159mg/dL borderline high and 160-189mg/dL as high.
- Blood pressure(BP): systolic and diastolic BP will be measured using standardized procedures at baseline and at every follow-up visit, using the validated automatic apparatus OMRON 705. The study subject will avoid any physical exercise at least an hour before measurement, abstaining also from copious amounts of food and drinks, smoking, or taking medications that could affect BP directly. BP measurement will be taken after 5 minutes of laying down. A controlled BP will be defined as systolic BP of <140mmHg and diastolic BP of <90mmHg.

All clinical control variables will be measured in the statistical analysis as dichotomous qualitative variables (controlled/not controlled).

Independent variable: Medisafe® mobile phone application intervention.

Mobile phone apps in medical research are a new phenomena, meaning that at the moment there isn't any application validated and extensively researched for adherence improvement purposes. However, the Medisafe mobile application has received the highest usability rating among medication adherence smartphone apps in several reviews, achieving the highest score in scientific and patient evaluations(52,72).

The **Medisafe mobile application** is publicly available on the iOS® and Android® application stores at no charge, has offline functionality (only requiring a smartphone with Wi-Fi capability for its installation) and can be configured in a variety of languages including Arabic, French, English, Spanish and Catalan. This provides a valuable provider-patient communication tool

since about half of IEH are immigrants and many don't have basic understanding of the official languages of Spain .

The app also has a feature of reminding clinical appointments to the user in a predetermined sequence. Medication intake reminders in the form of alarms and/or push alerts with visual dashboard notifications can be configured indicating the unit of measure, duration, frequency, time of take, and number of pills per box. When the time of taking a medication comes, the application reminder also showcases a question in which the patient has to indicate if the pill has been taken or not. The app generates weekly adherence reports. This can let the clinician follow closely compliance with treatment and detect early on adherence losses to avoid potential complications of the chronic disease being treated. When the moment of a pillbox refill comes, the application also can be configured to remind the subject.

The Medisafe app also allows for tracking of blood pressure and other biometric measurements, although in this study this feature will remain unused.

Covariates

- **Baseline characteristics:** age (expressed in years), sex(male/female), country of birth (Spain/other), years living in Spain, basic comprehension of the Spanish language (yes/no)
- **Smartphone use and habits:** uses mobile phone daily(yes/no), years of using a mobile phone.
- **Health behavior:** regular smoking, alcohol drinking, illicit drug use, physical activity. They will be yes/no answers.
- **Medical history of mental illness** (existent diagnosis depression, bipolar, schizophrenia, substance misuse).
- **Medical history of physical illness:** existent diagnosis of type 2 diabetes, hypertension, hypercholesterolemia, heart failure, chronic kidney disease, cancer.
- **Weight:** as an indirect measure of health behavior. This measurement will be collected during each follow-up visit.

- **Number of medications prescribed.** Polypharmacy is commonly considered a marker of poor glycemic control(30).
- **Current hypertension, type 2 diabetes and/or hypercholesterolemia medication:** type of medication, name, unit of measurement (e.g. mg, tbsp...), frequency of intake (as needed, or as planned), duration of medication (how many months/years has the patient been taking it), frequency (e.g. taken daily, two times a day...), time of take (e.g. at 9.00 am), existences (number of pills or units lasting).

4.4. DATA COLLECTION

Patient data collection will take place during a period of 1 year. All data will be collected via a face-to-face interview at the Nurse Office of the ''La Sopa'' reception center, except blood samples of patients with diabetes and/or hypercholesterolemia for determination of HbA1c and/or lipid profile, respectively. These blood samples will be drawn at the CAP Santa Clara via a previous clinical appointment.

With the help of the co-investigator for any comprehension difficulties, at the **baseline visit** and before randomization, patients will receive admission information about the study and informed consent will be provided. Once accepted, they will complete the MMAS-4 Questionnaire, and then they will be randomized to one of the 2 possible arms. Baseline characteristics, smartphone use patterns, and information on health behavior will be registered.

Physical and mental illness diagnoses, number of medications prescribed, current medication for hypertension, type 2 diabetes, and/or hypercholesterolemia, and number of clinical visits programmed and attended in the past year will be registered in the study database. This information will be obtained via a face-to-face interview with the patient and the principal investigator will ensure the data coincides with the one present in the eCAP register to clear any misunderstandings and avoid information bias.

With this database, the PDC will be calculated for each patient to establish objectively the adherence at the start of follow-up. The PDC will be complemented with the MMAS-8 Questionnaire that the patient will complete, to have more detailed information on the characteristics of each specific non-adherence pattern.

At this initial visit, blood samples will be drawn to determine the HbA1c in the case of diabetic patients, and/or lipid panel in those with hypercholesterolemia. This information will provide the baseline condition control of each patient.

Blood pressure and weight will be measured and registered for all patients in the study database.

All the information provided by the patient on this baseline visit will be initially collected using the baseline visit report form (see Annex 3) and then registered along with the other information already described in the database of the study.

At **follow-up visits at months 3, 6, and 9,** weight and blood pressure will be measured and registered. The patient will be asked to complete the MMAS-8 again to make sure data on adherence is collected in case of drop-outs to know the longevity of the intervention effect. The patient will also be asked if there are any problems with the Medisafe application, and any new clinical appointments or changes in the medications of interest will be configured in the mobile application.

At month 12 (day 365 or Early Termination Visit), weight, blood pressure, and the MMAS-8 will be registered as in the previous visits. Additionally, blood samples will be drawn from diabetic and/or patients with hypercholesterolemia to determine HbA1c and/or lipid panel levels, respectively. This information will allow us to compare if there have been any changes in the control of these diseases since the start of the study.

A new PDC will be calculated using each patient's eCAP register of the complete period of the study, to compare it with the basal PDC. The number of clinical visits appointed and attended during the study year will also be registered to assess if there have been any changes in clinical attendance with the study intervention.

To adhere to intent-to-treat principles, partially observed data from subjects who are lost to follow-up and not followed during all 12 months will also be used. Through the entire duration of the study, any information provided by patients on reasons for participation discontinuation will be also registered.

	Baseline	Month 3	Month 6	Month 9	Month 12
Informed consent, MMAS-4, baseline visit data (annex 3)	X				
PDC, number of clinical visits appointed and attended	X				X
Blood sample for HbA1c and/or lipid profile (CAP Sta Clara)	X				X
MMAS-8, Weight, BP	X	X	X	X	X

All the data collected will be recorded in the electronic database of the study.

4.5. STATISTICAL ANALYSIS

We will conduct all analyses according to the intention-to-treat principle, striving to collect data from all participants.

4.5.1. Descriptive Analysis

Dichotomous dependent variables (PDC and the control of clinical outcomes) will be summarized as frequencies. The median and the interquartile range will be used for discrete variables such as the MMAS-8, the number of clinical visits, and the number of medications prescribed.

The association between dichotomous dependent variables and the intervention will be assessed by means of contingency tables. In the case of discrete dependent variables, the association with the intervention will be assessed stratifying the descriptive analysis by the study arms. These analyses will be stratified by the covariates. Quantitative covariates will be categorized in quartiles.

4.5.2. Bivariate Inference

The effect of the intervention on the dichotomous dependent variables will be assessed by means of the Chi-Squared Test. If in any cell of the contingency table the frequency is expected to be lower than 5 the Fisher's exact test will be performed.

In the discrete dependent variables, the effect of the intervention will be evaluated using the Mann-Withney's U. The resulting analyses will be stratified for the covariates. In the case of quantitative covariates, they will be categorized (in quartiles).

4.5.3. Multivariate inference

The effect of the intervention on dichotomous dependent variables will be adjusted in logistic regressions, controlling for all the covariates.

For the discrete dependent variables, Poisson's regression will be performed, controlling for all covariates.

5. WORK PLAN

Personnel involved include:

- **Investigators: Principal Investigator or PI** (dr Rebeca Alfranca): general coordination, eCap data collection, economic management, analysis of results, publication, and dissemination.

  Co-investigator(CI) (Paula Buades Ribas): database creation, extraction and management of data, assessment of all follow-up data measurements in the Nurse Office of La Sopa Center, discussion and interpretation of results, publication, and dissemination.
- **Independent statistician(IS):** database control, data analyses, interpretation of results, publication.
- **Collaborators(NS)**: **2 nurses** working weekly at the Nurse Office of ''La Sopa'' Reception Center who will perform the blood sample extractions of the baseline and end of study visits from enrolled diabetic patients or those with hypercholesterolemia.

Study site: all data collection activities will take place at the Nurse Office of **''La Sopa''** reception center, except for blood extractions that will be performed at **CAP Santa Clara** (reference center of ''La Sopa'' Municipal Reception Center). All other study-related activities will also take place in CAP Santa Clara.

This study will be developed in a period of **22 months**. Publication and diffusion will take approximately a **further 7 months**. The study and will be divided in **4 phases**:

1) FIRST PHASE: Preparation and coordination (4 months):

- Initial meeting: the investigators will meet in order to explain the protocol and coordinate with the nurses participating in this study. Programmation of the chronogram will be performed and the methods for data collection will be explained: blood sample extractions will

be performed by the 2 nurse collaborators at CAP Santa Clara, and the rest of the data collected will be obtained by the co-investigator at the ''La Sopa'' reception center. During the time of the study, coordination between the Girona primary care center and ''La Sopa'' reception center will be established for the correct collection of data.

- Authorizations: before the trial starts, approval from the Ethics Committee will be solicited. Authorizations from the CAP Santa Clara and ''La Sopa'' reception center directories will be obtained.

- Database creation. After the PI has reviewed the centralized electronic records from the eCAP of IEH present in the ''La Sopa'' database, to select those who meet inclusion criteria, the CI will create the database for this study, and randomize from the eligible participants a sample of the needed size.

- Pilot test: prior to the actual trial initiation, a pilot test will be performed in 20 participants chosen randomly from the initial database, all receiving the intervention for two weeks. These patients will not be included in the final trial analysis. The trial's eligibility criteria and participation refusal ad drop-out rates will be assessed to ensure the attainability of the planned sample size. Medisafe software will be tested, monitoring for any systematic errors, and a risk management protocol will be prepared. All data collection forms will be assessed with regard to comprehensiveness for trial participants and practical use for clinical practitioners, respectively. Detected issues will be processed and the trial protocol will be revised, if necessary.

2) SECOND PHASE: Study Intervention and Data Collection (15 months)

- **Recruitment of patients and Baseline Visit/Day 0 of Follow-up(3 months):** patients will be contacted via telephone calls by the CI and cited at the Nurse Office of the ''La Sopa''. The study will be explained to the patient, orally and with a written information sheet (see Annex 4). The patient will be informed that withdrawal from the study can be done at any moment without any repercussion. No incentives will be given to any study subjects. After ensuring the subject meets the inclusion and exclusion criteria, a written Informed Consent Form will be signed if

the patient agrees (see Annex 5). Those who consent to participate in this study will be asked to fill out the MMAS-4 questionnaire (Annex 1). The MMAS-4 helps to identify subjects who are at increased risk for medication non-adherence. Subjects answering ''YES'' to at least 1 question in the MMAS-4, will continue to the Baseline Visit procedures, or if he/she so prefers, a new appointment will be made for the Baseline Visit.

In this initial visit, the following data will be collected from the patient by the CI and checked in the eCap by the PI whenever possible: baseline characteristics, smartphone use and habits, health behavior, medical history, number of medications prescribed, current hypertension, type 2 diabetes and/or hypercholesterolemia medication, number of clinical visits programmed and attended the year previous to this first visit. Weight and BP will be measured. The Baseline Visit Report Form will be completed (see Annex 3).

The PDC of the previous year will be calculated using the refill data on the eCap platform for every patient. If the patient has diabetes or a diagnosis of hypercholesterolemia, he/she will be cited in the following 4-5 days for a blood sample extraction in CAP Santa Clara to measure HbA1c and/or the lipid profile, respectively. These extraction visits will be programmed in turns of 10-15 patients per day to accommodate them to the capacity of the center.

All subjects will complete the MMAS-8 Questionnaire (Annex 2) with aid of the CI for any comprehension difficulty. Once all baseline data is collected and registered in the database, each patient will be randomly assigned to one of the study arms (Medisafe application or usual standard of care alone). The principal investigator or co-investigator will inform the patient of his/her pertinent arm allocation.

Patients allocated in the intervention arm will have the application installed on their smartphone by the study team to track only type 2 diabetes, hypertension, and hypercholesterolemia medications. Information uploaded to the application will be the unity of measurement, duration of treatment, frequency of dosage, pill existences in every box of said medication, and time of take. Any clinical appointments known at the time of configuration, and follow-up visits for this study will be also added in the Medisafe mobile application. The subject will then be educated on how to use and configure the Medisafe

application. The study team will make sure the language and settings of the application are set to the preference of the patient. The application will be linked with the PI application profile for following purposes, to ensure the patient is logging in data.

Subjects in this arm will also receive the usual physician- or nurse- guided standard care.

Subjects may call the study site, at any time, for assistance with troubleshooting the mobile application or their smartphone; and will be encouraged to also call if they desire to drop out from the study, to state the reason for withdrawal if they want to.

- Initial Week of Enrollment: to ensure that the subject's smartphone has been properly configured for use with the Medisafe mobile application and trial intervention, additional steps will be taken during the first 3 days after configuration, starting on Day 1, which is the day after Day 0/Baseline smartphone configuration. If the subject has not logged in the medication taken during the first 3 days of his/her participation in the study, then the CI will call the subject, to confirm the functionality of the mobile application and the smartphone and to assess and troubleshoot any barriers to use the mobile application or any technical issues with the device. If after multiple follow-up attempts, a participant is not responding, they won't be contacted further, and their anonymized data collected until that moment will be analyzed in the intent-to-treat analysis.

- Follow-up assessments (9 months): at months 3, 6, and 9 follow-up visits of the enrolled participants will take place in the ''La Sopa'' center. At each follow-up visit, the CI will reconfigure the application or ensure the patient has done it to showcase future clinical appointments and any changes in the medications relevant to this study. The patient will be asked orally if he is following the intervention correctly and if any problems have arisen, the Medisafe application will be reviewed to see if the patient is registering his/her medication intake daily (it is not an essential requirement but at the end of the study it can help with data interpretation) and the MMAS-8 Questionnaire (Annex 2) will be completed at every follow-up visit, along with measurements of weight and BP. The information collected will be registered in the informatic database of the study by the CI.

To minimize attrition of participants, pre-scheduled follow-up visit reminders will have been set in the Medisafe app at the baseline visit. Additionally, participants will receive telephone calls from the study team 7, 2, and 1 day prior to follow-up visits as reminders and encourage attendance. If participants are not able to attend the follow-up visit at all, they will receive a telephone call from the study team and the visit will be rescheduled.

-End of Study Visit or Early Termination visit (Day 365 of follow-up +/- 10 days): data will be collected as in the follow-up months (in ''La Sopa'' center), but blood extraction for HbA1c and lipid panel determination will be collected as well, in diabetics and/or patients with hypercholesterolemia, respectively. As in the baseline visit, patients will be cited in turns of 10-15 per day to the CAP Santa Clara for these extractions. eCAP electronic records will be consulted to calculate the PDC for each patient, and to calculate clinical visits appointed and attended during the study follow-up period.

3) THIRD PHASE: Statistical analysIs and interpretation of results (3 months):

Data will be entering the database during the second phase of the study. After database closure (at the end of 12 months of data collection) by the CI, the Independent Statistician will be conceded a period of time to perform the agreed analyses depending on the total data collected. Finally, the statistician will send the results to the PI, in order to interpret and discuss them.

4) FOURTH PHASE: Publication and result dissemination (7 months):

- Investigators will write the corresponding article in order to display the results and will publish them in the International Journal of Environmental Research and Public Health (IJERPH).
- Scientific outreach will also be favored by presenting the results of this work in the International World Conference of Family Doctors (WONCA) by the PI and CI. A sworn translator (See section 7) will translate the article in order to achieve international diffusion.

6. CHRONOGRAM

Work plan	Description	Responsible personnel	Months																										
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
STAGE 1 Preparation and coordination	Initial meeting	PI, CI, NS																											
	Authorizations	PI																											
	Database creation	CI																											
	Pilot test	PI, CI																											
STAGE 2 Study intervention + data collection	Recruitment+ baseline visit	CI, PI, NS																											
	Follow-up assessment	CI																											
	Termination visit	**CI, PI, NS**																											
STAGE 3 Statistical analysis and interpretation of results		CI, IS, PI																											
STAGE 4 Publication and result dissemination		PI, CI																											

7. BUDGET

CAP Santa Clara (and therefore the local government of Girona) will bear the cost of blood analyses requested, since all the IEH patients that we will include in our study already have this center of reference assigned for their periodic health controls. In total only two blood extraction appointments will be needed during the year of follow-up (at Baseline and End-of-Study Visits). Therefore we can integrate both analyses as part of the normal follow-up of patients in their periodic disease control measurements that already take place. Weight and BP measurements are already done weekly at the Nurse Office of ''La Sopa'' reception center (an intervention financed by the local government of Girona) by the 2 nurses that will collaborate in this study. This consult has OMRON validated monitors that are periodically calibrated, a portable computer, and a weight scale. Therefore these materials won't be included in the budget of the study.

Our sworn translator has collaborated with other studies for the ''Equip de Treball de Sensellarisme i Salut de Girona'', and will be needed for translating the published article to English for presenting it to the WONCA progress.

Type of cost	Description	Unit cost	Hours/unit	Subtotal
Personnel expenses	Independent statistician	30€	20h	600€
	Sworn translator	Fixed price per number of words		200€
Publication and dissemination	IJERPH publication	2000€	1	2000€
	WONCA congress: inscription, acommodation, travels	800€	2	1600€
TOTAL				4.400€

8. ETHICAL AND LEGAL CONSIDERATIONS

This investigation will be performed in accordance with the current International Conference on Harmonization (ICH) guidelines on Good Clinical Practice, consistent with the principles that originated in the **Declaration of Helsinki**.

The **4 ethical principles of medical research** will be respected throughout the entire duration of the intervention: Non-maleficence is ensured because no invasive procedures will be performed, and all data will be protected and confidential. Beneficence is respected because this project aims to achieve a positive impact on the chronic health problems of IEH. Justice will also be ensured, with both arms of the study receiving the usual standard of care. This research is being performed on IEH because its potential profits would be applicable to this specific population. All potentially benefited patients will be eligible for randomization, without discrimination. Finally, autonomy will be respected by obtaining the ICF(see Annex 5) after ensuring the patient's complete understanding using the written information sheet (see Annex 4).

This is in accordance with Spanish Organic Law 41/2002 regulating Patient Autonomy. A copy of both documents will be given to the patient. There will be no participation remuneration.

Before the start of the study, the investigation protocol will be provided for evaluation to the **Clinical Research Ethics Committee (CEIC)** of the University Hospital of Girona. Authorities of CAP Santa Clara and ''La Sopa'' reception center will be asked to approve the study as well.

Our clinical trial will be submitted to ClinicalTrials.gov and will be registered with an International Standard Randomized Controlled Trial Number.

Privacy of Personal Data: The Medisafe application is compliant with GDPR (European General Data Protection Regulation) and ISO 27001:2013. The collection and processing of personal data from subjects enrolled in this study will be limited to the necessary to fulfill the objectives of our research, and will be handled with adequate precautions to ensure confidentiality and compliance with Spanish Organic Law 15/1999, of Personal Data Protection. Study participants will have the right to consult, modify and delete all personal information from the records.

No conflicts of interest are declared by the investigators in charge of this study.

9. STUDY STRENGTHS AND LIMITATIONS

9.1. STUDY STRENGTHS

The study proposed is a **pragmatic randomized** clinical trial, meaning that inclusion and exclusion criteria are not very strict, conferring external validity to the results obtained. This study has a **representative** sample of the homeless population of Girona, as the database used for sample sizing is from ''La Sopa'' publicly funded homeless shelter, where all IEH of the city are domiciled, therefore all having their primary care services at CAP Santa Clara by default.

Previous studies on IEH have pointed out the importance to adapt the allocation of visits to this population for better engagement. By performing the follow-up visits at the ''La Sopa center'' we expect greater participation because the location is **convenient** for the majority of IEH who sleep in or around the area.

We will not only use as a measurement of adherence the MMAS-8 Questionnaire, which is a validated and widely used tool, albeit subjective and with the potential to overestimate adherence; instead we will take a multi-measure approach to reduce subjectivity using also the PDC, an **objective and more reliable assessment method**, minimizing the risk of information bias.

An added improvement in respect to previous adherence intervention studies is that the **duration of data collection will be of 1 year**, instead of the usual 3 or 6 months in current literature. By using this timeframe, after 6 months of follow-up, we expect to be able to discern if there can be sustained effects of the intervention in the future.

This is the **first** experimental study centered on applying mobile phone applications in a representative population of IEH. Therefore, all data that result from this research could serve as a reference point for future related investigations.

9.2 LIMITATIONS OF THE STUDY

The main difficulty of this study will probably be achieving an adequate **participation rate.** Although no data is available on this instance, and recent studies on the use of ICT in IEH have shown a very reassuring engagement from the homeless population, we expect a high rate of drop-outs, because of intrinsic characteristics of IEH (e.g. tendency to move and change residence places regularly, lack of schedules, distrust in authorities...). We have tried to counter this limitation by using a 40% nonadherence rate when calculating the sample size, and by performing a pilot test before recruiting the calculated sample necessary to confirm that our estimates are correct, and therefore we will have a window to solve any mismatch such as a drop-out rate higher than 40% or miscalculation of sample size.

Another problem we could encounter is **mobile phone losses.** IEH are always on the move, and studies that have given telephones to homeless participants have seen that many of those participants have to be removed from the study sample because they have lost their mobile phones or they have been stolen. We tried to avoid this complication by including in the sample only IEH who already have a mobile phone and use it regularly, since we hope they will be more habituated to their use, and by the phone being of their property and not gifted to them, they will be less likely to lose it.

By using a validated adherence survey instrument (MMAS-4) to enroll only people at increased risk for nonadherence, we attempt to minimize enriching for highly adherent participants, limiting the risk of voluntary bias. If we observe a high adherence through the study we should consider that it may be due to **Hawthorne Effect.** Because the study is **unblinded** (except for the statistician)**,** the intervention arm may have a greater awareness of being monitored due to the nature of the intervention, and the effect of the intervention may be magnified because of the placebo effect.

We must also note that mobile **applications do not address every barrier** to medication adherence. For example, cell phone reminders do not deal directly with mental health issues such as depression (demonstrated to be associated with nonadherence). If this intervention proves to be effective, caution should be taken to ensure that the app does not contribute to health inequalities for IEH who do not have access to compatible smartphones.

10. IMPACT ON THE NATIONAL HEALTH SYSTEM AND FUTURE RESEARCH

It is estimated that around 100 million people worldwide are homeless, and 1.6 billion lack adequate housing and are at risk of housing exclusion. Those numbers are only expected to intensify. Spain is one of the EU countries with a higher unemployment rate and greater housing crisis. Although there's increasing epidemiological research on IEH, very limited intervention studies have been designed with this population as a target. This is alarming since the homeless population is already being severely neglected and it is expected to increase in number in the upcoming years. Moreover, it is an aging population, therefore the management of chronic illness should be addressed as soon as possible, since we know that IEH have a much higher rate of nonadherence to chronic treatments, clinical non-attendance, preventable hospitalizations, poorer prognoses, and premature mortality.

All those aspects need to be improved as soon as possible, since the problem will not cease to expand, meaning an expensive increase in healthcare costs and a decrease in the quality of our healthcare system, considering equity is paramount to it.

Only by fitting solutions to the peculiarities of IEH, and by adapting to the exponential growth in mobile phone usage over recent times, we can start to glimpse some optimistic prospects for the future. Because of the low cost, simple implementation, and wide scalability of this nonpharmacological intervention, it has the potential to **save costs, resources and time**, and to improve massively the health of IEH and their empowerment through medication self-management. It may also provide a means to better address the burgeoning healthcare demand-capacity imbalance in the context of the growing burden of chronic conditions, not only in IEH but in other vulnerable and hard-to-reach populations.

The **conclusions and collected data of this investigation will be of high value for future research** since it is practically non-existent in this specific field to this day.

If this study turns out to be successful, an interesting follow-up would be to focus other related research on psychiatric and substance abuse pharmacological treatments, since they are very prevalent in IEH and are also affected by very high rates of nonadherence.

11. FEASIBILITY

The Primary Care Center participating in this study (CAP Santa Clara) is the health center of reference for all IEH registered in the Girona area, because all IEH in Girona have their residence address allocated by default on the geographical territory covered by this center.
Our principal investigator (dr Rebeca Alfranca Pardillos) has had more than fifteen years of experience as a healthcare provider for IEH and coordinating with the ''La Sopa'' center, and has participated in several published articles based on healthcare in the homeless population.

The ''La Sopa'' reception center has a Nurse Office, and a nurse from CAP Santa Clara visits weekly the center to assess the health evolution of IEH in the area. This is part of an intervention paid by Girona's local government. The nurse office has all the necessary material for this study (homologated OMRON blood pressure monitors which are periodically calibrated, and a digital weight scale). Blood samples for determining HbA1c or lipid panels in diabetic or patients with hypercholesterolemia, will be extracted in CAP Santa Clara. This center has the capacity of doing all the extractions needed because the study patients will be distributed at a rate of 10-15 extractions per day, and these extractions will only be needed 2 times, at the baseline visit and at the end of the study.

The PI is also a member of the ''Equip de Treball de Sensellarisme i Salut de Girona''. In this team, there is even a member with a thesis on the use of ICT in IEH. Therefore we can assure the centers and personnel have a lot of experience and have the capability of undertaking this intervention adequately.

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13. ANNEXES

ANNEX 1

Morisky Medication Adherence Scale (©MMAS-4)

You indicated that you are taking medication(s) for your hypercholesterolemia, diabetes mellitus or hypertension. Individuals have identified several issues regarding their medication-taking behavior, and we are interested in your experiences. There is no right or wrong answer. Please answer each question based on your personal experience with your hypertension, diabetes mellitus and/or hypercholesterolemia medication(s).

---------- (Please check 1 box on each line)-------

	YES	NO
1) Do you ever forget to take your medication(s)?	☐	☐
2*) Do you ever have problems remembering to take your medication(s)?	☐	☐
3) When you feel better, do you sometimes stop taking your medication(s)?	☐	☐
4) Sometimes if you feel worse when you take your medication(s), do you stop taking it?	☐	☐

*Modified item from original scale appearing in Medical Care, 1986

Measurement and scoring criteria: the MMAS is a generic self-reported, medication-taking behavior scale in which the specific health issue (high blood pressure, diabetes, elevated cholesterol...) is inserted for the "health concern". The MMAS consists of 4 items with a scoring scheme of "Yes"=0 and "No"=1. The items are summed to give a range of scores from 0 to 4.

ANNEX 2

Morisky Medication Adherence Scale (©MMAS-8-item)

You indicated that you are taking medication(s) for your hypercholesterolemia, diabetes mellitus or hypertension. Individuals have identified several issues regarding their medication-taking behavior, and we are interested in your experiences. There is no right or wrong answer. Please answer each question based on your personal experience with your hypertension, diabetes mellitus and/or hypercholesterolemia medication(s).

---------- (Please check 1 box on each line -------

	No=1	Yes=0
1) Do you sometimes forget to take your medication(s)?		
2) People sometimes miss taking their medication(s) for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your medication(s)?		
3) Have you ever cut back or stopped taking your medication(s) without telling your doctor, because you felt worse when you took it?		
4) When you travel or leave your residence, do you sometimes forget to bring along your medication(s)?		
5) Did you take your medication(s) yesterday?		
6) When you feel like your medical condition is under control, do you sometimes stop taking your medication(s)?		
7) Taking medication(s) every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your medical condition treatment plan?		

8) How often do you have difficulty remembering to take all your medication(s)?

(Please Circle your answer below):

Never/Rarely - 4

Once in a while - 3

Sometimes - 2

Usually - 1

All the time - 0

ANNEX 3

INFORME DE VISITA INICIAL (Baseline visit report form)

Data: **Número del participant:**

Sexe: **Edat:**

País de naixement: **Anys viscuts a Espanya:**

Sobre l'ús del telèfon mòbil:

- **És capaç de comprendre l'espanyol o català bàsic?**
- **Utilitza el telèfon mòbil diàriament?**
- **Quants anys fa que utilitza telèfon mòbil?**

Sobre la conducta en relació a la salut:

- **Fuma almenys un cop a la setmana?**
- **Amb quina freqüència beu?** (unitats d'alcohol per dia)

Sobre la història mèdica:

- Té algun/s diagnòstic/s de malaltia psiquiàtrica? Quin/s?
- Té algun/s diagnòstic/s de malaltia física? Quin/s?
- Marcar una creu en els diagnòstics existents del/la pacient:

Depressió	
Transtorn bipolar	
Esquizofrènia	
Transtorn per abús de substàncies	
Diabetis tipus 2	
Hipertensió	
Hipercolesterolèmia	
Insuficiència Cardíaca	
Insuficiència Renal Crònica	
Neoplàsia	

Nombre de medicacions prescrites (comprovat amb registre eCap):

Medicació per hipertensió, diabetis i/o hipercolesterolèmia:

Tipus de medicació	
Nom del fàrmac	
Unitats de mesura	
Freqüència d'ingesta (planejada o de conveniència)	
Durada del tractament (quants mesos/anys porta)	
Freqüència de les preses (ex: 2 cops al dia)	
Hora de la presa (ex: a les 9.00 AM)	
Existències (nombre de pastilles o unitats restants)	

Mesures basals:

- **Pes:**
- **Tensió arterial:**

ANNEX 4

FULL D'INFORMACIÓ AL PARTICIPANT

Agraïm la seva col·laboració en l'Estudi *Effects of the Medisafe Application on Medication Adherence in Homeless Patients with Type 2 Diabetes, Hypertension and Hypercholesterolemia.*. La seva participació està contribuïnt de manera important a millorar els coneixements i les eines que tenim per tractar malalties cròniques en la seva població.

FINALITAT DE L'ESTUDI

L'objectiu fonamental d'aquest estudi és estudiar els efectes d'una aplicació de telèfon mòbil, Medisafe, en l'adherència a tractaments crònics en població en situació o risc d'exclusió residencial de la població de Girona. El terme adherència fa referència al compliment d'un tractament correctament, de la manera en que està prescrit. Volem saber si aquesta aplicació pot ajudar als pacients amb hipertensió, diabetis i/o hipercolesterolèmia a millorar la seva adherència al tractament.

La meitat dels participants en l'estudi utilitzaràn aquesta aplicació, rebent les visites mèdiques de costum; i l'altra meitat dels participants només rebran les visites mèdiques de costum.

DESCRIPCIÓ DEL PROCÉS

Durant la seva participació en l'estudi l'informarem sobre els objectius del projecte i respondrem als dubtes que vostè pugui plantejar.

Les molèsties ocasionades per la seva participació són mínimes; Hi haurà un total de 5 visites distribuïdes al llarg d'1 any, que es duràn a terme al centre de La Sopa per conveniència dels participants, i es poden combinar si aquest ho desitja amb les visites setmanals que ja es realitzen a la consulta d'infermeria del centre. Durant uns 20 minuts per visita cada participant completarà amb l'ajuda de l'investigador un qüestionari curt i es mesuraran el pes i la pressió arterial.

Per als pacients diabètics o amb hipercolesterolèmia, a la primera visita i a la visita final (mes 12 de l'estudi) es concertarà una cita al CAP Santa Clara per extreure una mostra de sang i així conèixer l'estat de control de la seva diabetis o nivells de colesterol. Aquesta mostra sanguínia s'intentarà sempre que es pugui, ajuntar amb la mostra extreta per els controls normals de la malaltia periòdics que ja ha d'estar rebent el pacient.

En els participants assignats al grup que rebrà la intervenció, en la primera visita de l'estudi se'ls instal·làra al telèfon l'aplicació telefònica Medisafe, i rebràn una explicació detallada de com s'utilitza. L'aplicació permet enviar recordatoris al pacient de quan han de prendre la medicació, quan han d'anar a la farmàcia a buscar una nova capsa de medicació perquè l'actual s'està acabant, i quan han de visitar al seu metge. El pacient podrà triar si rebre

notificacions en pantalla o també alarmes sonores, i en cada recordatori de presa de medicament ha de contestar si ha pres la medicació o no.
El risc de totes les activitats en les que participaran els pacients d'aquest estudi és mínim, sent el mateix que s'experimenta quan es fa una extracció de sang per practicar una analítica normal.

La participació en l'estudi és totalment voluntària. A més, vostè té dret a sol·licitar als investigadors de l'estudi, en qualsevol moment, i sense necessitat d'especificar el motiu, l'eliminació de les seves dades. Per contactar amb aquests responsables en la primera visita se li proporcionaran les dades de contacte dels investigadors de l'estudi.
Li garantim que les seves dades seran tractades amb absoluta confidencialitat segons la Llei Orgànica que regula la confidencialitat de les dades informatitzades (Llei Orgànica 15/1999), també es respectarà la llei d'investigació biomèdica (14/2007) i qualsevol altra que resultés aplicable. Les dades seran utilitzades exclusivament amb finalitats d'aquesta investigació científica.

Rere la seva participació li enviarem un informe amb els resultats d'algunes de les exploracions relaitzades i que poden ser d'interès per vosté i el seu metge.
Per dur a terme el projecte que li hem exposat i atenent a les disposicions legals vigents li sol·licitem la seva autorització. Abans i després de firmar aquest document, del qual obtindrà vostè una còpia, pot preguntar qualsevol dubte que li sorgeixi als metges o personal sanitari responsable de l'estudi.

ANNEX 5

CONSENTIMENT INFORMAT

Estudi: ***Effects of the Medisafe Application on Medication Adherence in Homeless Patients with Type 2 Diabetes, Hypertension and hypercholesterolemia.***

DECLARACIÓ DEL PARTICIPANT:

He estat informat pel professional de salut a sota mencionat:
de les finalitats i implicacions del present estudi;
sobre el procés d'obtenció, emmagatzemament i processament de les dades personals;
que les dades obtingudes tenen com a objectiu la investigació biomèdica;
que la participació és voluntària i que la retirada pot ser en qualsevol moment, i que puc sol·licitar l'eliminació de les meves dades personals sense cap repercussió en l'atenció sanitària posterior;
a més, he pogut fer les preguntes que he considerat oportunes.

Accepto a que el personal mèdic relacionat amb l'estudi pugui accedir a les dades electròniques del meu registre sanitari, i accepto que les meves dades, en cas d'ésser assignat al grup d'intervenció, seràn també cedides a la base de dades de l'applicació Medisafe, que compleix la reglamentària Europea de protecció de dades electròniques.

Nom: _____

Signatura:_____ Data:_____

Declaració del professional de salut mèdica que ha informat degudament al pacient:
Nom: _____

Signatura:_____ Data:_____

APARTAT PER A LA REVOCACIÓ DEL CONSENTIMENT

Jo, _____, revoco el consentiment de participació en l'estudi indicat a dalt.

Signatura:_____ Data:_____