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SMIT-CKD: A MOBILE APP TO IMPROVE ADHERENCE TO THERAPY IN CKD PATIENTS. A PILOT STUDY.

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***Abstract*— Chronic Kidney Disease is a major public health issue, with about 13% of the general adult population and 30% of the elderly affected. Patients in the last stage of this disease have an almost uniquely high risk of death and cardiovascular disease, probably because kidney and cardiovascular system share the same risk factors, such as hypertension, high blood glucose and body weight. Reduced adherence to therapy represents an additional risk factor for cardiovascular morbidity and mortality in renal patients. Considering the wide spreading of mobile phones, an app could be a possible solution to self-monitor cardiovascular risk factors and to improve adherence to therapy**

We developed an integrated system made by a server and an app within the SMIT-CKD project, with the aim to improve self-monitoring of risk factors of both renal and cardiovascular disease and to improve adherence to therapy. The integrated system was tested with the help of 22 volunteers.

The level of compliance with the use of the app and data entering was quite high, being "malfunctioning due to obsolete versions of the operative system" the main cause of scarce use. After 6 months of use, the percentage of regular intake of medications rose from 64 to 82%. User satisfaction was high, as both the server and the app obtained high scores in the questionnaires administered to general practitioners and patients

Our pilot study demonstrated that the use of a simple Mobile APP may improve adherence to therapy in patients affected by Chronic Kidney Disease. Further studies, specifically designed to test this app in a larger population, are required to clarify if the use of the SMIT-CKD integrated system will have long-term effects on therapy adherence, and if self-monitoring of risk factors will improve clinical outcomes in this population.

Keywords—SMIT-CKD, mHealth, eHealth, CKD, therapy adherence, risk factors

I. INTRODUCTION

Alarming epidemiological data produced during last year suggest that Chronic Kidney Disease (CKD) is now a major public health problem. Looking at literature, about 13% of the general adult population has evidence of CKD, falling into one of the 5 stages identified by the K / DOQI classification [1]. The prevalence of this chronic disease increases up to 15-30% in the elderly, and exceeds 50% in subjects with cardiovascular and metabolic comorbidities [1], [2].

Additionally, patients in the last stage of this disease have an almost uniquely high risk of death and cardiovascular disease, with a rate of incident cardiovascular events strongly associated with the level of renal function both in community-based studies and in selected populations with established cardiovascular disease [3]. Data available so far clearly indicate that heart disease is the first cause of death for this category of patients. The reason is to be found in the risk factors of chronic renal failure which are largely common to those of cardiovascular disease [4]. The pathogenic mechanisms underlying the close relationship between renal failure and cardiovascular syndrome are not fully elucidated; however, it is known that diabetes mellitus, arterial hypertension and excess of body weight are the leading causes of the high frequency of cardiovascular events common to both renal failure and ischemic heart disease [5]–[7]. Finally, reduced adherence to therapy (low compliance) represents an additional risk factor for cardiovascular morbidity and mortality in renal patients [8], [9]. Low adherence, especially in chronic patients treated with multiple drugs, may be due to the difficulty of reminding days and time of medicine intake. Considering the wide spreading of mobile phones, an app could be a possible solution to improve adherence to therapy [10] even in this population.

The SMIT-CKD project aimed at developing an integrated system consisting of a Web-based platform (SMIT-CKD-SERVER) and an APP (SMIT-CKD-APP, available for Android and iOS), designed for both general practitioners (GPs) and patients. General practitioners was able to manage the patients' therapy, improving compliance, and to educate the patient about self-diagnosis (through the SMIT-CKD-

SERVER interface). Patients were allowed to monitor the main modifiable risk factors of kidney disease, such as blood pressure, body weight and blood glucose, in a completely autonomous way, and to monitor drug intake (through the SMIT-CKD-APP interface).

The integrated system has been recently tested in a small number of volunteer, in order to determine the ease of use and the willingness of using it. Additionally, the potential usefulness of the system in improving therapy adherence was also verified.

II. METHODS

A. Development of the SMIT-CKD-SERVER and SMIT-CKD-APP

The development methodologies for the software infrastructure fall within the standard web oriented development methodologies. The reference model is the agile methodology or agile software development called "agile software development" (ASD). In particular, the Agile Unified Process (AUP) was use for modeling, implementation, test, deployment, configuration management, project management, environments. "Open source" tools, when available, was preferred to have a minimal impact on project costs. They were chosen from a list of tools widely known in the web oriented developer community, including RAD tools for editing of source code, tools for managing the data in the database engine; tools for managing the interfaces and related graphics; version control and source code sharing tools. For the app development, the following tools were evaluated: RAD for code editing, client for managing the data in the database engine, graphics management tools, version control and source code sharing tool.

More specifically, for the development of the web platform, the team of developers focused on operating systems of the "Linux" family, choosing the CentOS “Distribution / Distro”. This decision obviously guided most of the subsequent choices. As a consequence of this basic selection, it was evaluated which programming languages, web servers and database servers could be used.

For what concerns the programming languages, Java, PHP and Rails were evaluated together with the related usable web servers (Apache, Tomcat and Ngnix respectively); the MySQL and Oracle database servers were also evaluated. After careful evaluation, the choice fell on:

- PHP programming language

- Apache web server

- MySQL database server

Having made this choice, the team analyzed and configured a whole series of "Tools", i.e. tools oriented to development for this type of infrastructure, and proceeded to select from the "Editor" type tools, to the "Continuos integration ”and finally to the“ Team collaboration ”platform.

The “Agile” development methodology that the team has decided to implement is based on short development cycles and rapid implementation. These cycles, provided in a continuous iteration, are related to production, testing, debugging and back to production.

To be highly productive with this methodology, instead of carrying out a procedural development, we chose to rely on a “framework” type tool in which the entire part of the ORM (Object Relation Manager) was already structured. This made it possible to shorten development times compared to pure code, releasing versions continuously in collaboration with the team members who took care of the tests.

The "framework" tools on the market use a series of libraries shared by the developer community and can be integrated into any development project using standard managers such as "Composer" and "NodeJs". This allows to have a robust platform that is always subject to revisions, improvements and corrections and above all to use the software reuse techniques that are the basis of “Agile” development. The team took into consideration some of the most used frameworks in the web field written in PHP language. Among these Laravel was chosen as a tool, as it offers the best synthesis for the required development. This framework can be integrated with the most modern and consolidated technologies in the field of web-oriented software production. For this reason we were able to use javascript libraries for the dynamic part of the pages managed through NodeJS and NPM package manager. Also, Bootstrap was chosen as a reference for CSS styles.

Finally, for data storage, MySQL was chosen as the DBMS. Reference point as a database server for years, it provides a system perfectly integrated with the development tools chosen and has a robust, easily installed and scalable structure.

The same criteria were chosen for the creation of the Mobile App for smartphones. The two major "Stores" on which our App was published require the use of specific languages for the creation and distribution of native apps: Java for Android, Swift for iOS. This technological bifurcation, in the case of implementation in native language, would consequently have doubled the production times of the Mobile part, with the risk to follow two paths not completely identical or convergent. The choice was therefore oriented towards those platforms that allow the development of multi-platform “Mobile App” starting from a single source code. Among those available, the platform called "Ionic" was chosen.

B. Questionnaire to measure adherence to therapy

The questionnaire to measure adherence to therapy used in the SMIT-CKD project was derived by modeling existing questionnaires, such as the Morisky scale [11] and the Renal Treatment Satisfaction Questionnaire (RTSQ) [12], the latest designed to be used by people suffering from chronic kidney disease. Using as starting point tools already reported in the literature, and adding the necessary changes in order to define a set of questions suitable and understandable by subjects suffering from chronic kidney disease, a questionnaire was created consisting of 13 questions (4 concerning demographic information, 9 concerning satisfaction with treatment and adherence to therapy) (Table 1). As foreseen by the project, the questionnaire was administered to 10 volunteers, having the same characteristics as the patients to be recruited in the study, in order to identify and correct possible errors of interpretation and confused or inappropriate ways of responding. Volunteers were asked to check the comprehensibility of the questions and verify their logical structure. All the volunteers positively evaluated the questionnaire, not having difficulty in interpreting the questions and their respective answers, so the questionnaire was used during the pilot phase and administered to all the

QUESTIONNAIRE FOR ADHERENCE TO THERAPY
DEMOGRAPHIC INFORMATION
1. What is your marital status?
2. Do you live with?
3. What is your highest educational qualification?
4. What is / was your source of income?
SATISFACTION WITH TREATMENT / ADHERENCE TO THERAPY
1. How long have you been on therapy for your kidney disease / hypertension / diabetes? (expressed in years)
2. How satisfied are you with your current treatment?
3. How well do you think your kidney disease is controlled?
4. How often do you experience side effects from therapy?
5. Does your therapy satisfy you in terms of side effects?
6. How easy / comfortable did you find your therapy in the last period?
7. How satisfied are you with the knowledge of his state of health?
8. Have you taken the prescribed doses of the medications in the past two weeks?
9. Why did you not take the prescribed doses?

Tab. 1. Questionnaire designed to measure adherence to therapy in the SMIT-CKD study

participants at baseline and during the follow-up visits.

C. Patient enrolment and pilot study

The protocol of this study was approved by the Ethical Committee of our institution. All participants gave their informed consent.

The enrolment phase started in June 2019 and lasted 2 months. Patients were randomly selected from the list of patients by 4 GPs who accepted to join the study. Inclusion criteria were age 18-75 years; creatinine 1.5-4.0 mg / dL (men) or 1.3-3.5 mg / dL (women); antihypertensive therapy; possession of a Smartphone with an Android or iOS operating system or assisted by family or care-givers, written informed consent. Patients with AKI (Acute Kidney Disease), rapidly progressive nephropathies or neoplasms, included in other clinical trials, visually impaired or with impaired cognitive abilities were excluded.

Visits were performed at baseline, after 3 months and after 6 months. The SMIT-CKD-APP was downloaded at baseline from Google Play or Apple Store. During this same visit, GPs set days and the time of measurement of blood pressure, body weight and blood glucose (the latter for diabetics only), according to patient's conditions. Clinical data, laboratory data and therapy were recorded by the GPs in the SMIT-CKD-SERVER at baseline and at the follow-up visits. After the baseline and during the entire follow-up, patients received on their APP alerts, according to GPs settings, reminding them to measure clinical data and take medications. Feedbacks were sent in real time to the SMIT-CKD-SERVER via internet connection.

After the end of the study both patients and GPs filled the satisfaction questionnaire that investigated the user satisfaction about functioning, ease of use and performance of both SMIT-CKD-SERVER (GPs) and APP (patients).

III. RESULTS

A. Architectural features and functionality of the web platform

The SMIT-CKD Server (Fig. 1) is accessible through the registered domain "smit-ckd.org", after authentication. Access to the system is granted with three different profiles (System administrator; Medical supervisor; Doctor), with each operator able to access all or only some parts of the portal, according to their role.

Once the patient has been enrolled, the referring GP is able to access and enter medical history, anamnesis and ongoing therapies. The doctor establishes, for each patient enrolled, which are the therapeutic prescriptions to be followed, choosing from the list of drugs pre-entered in the database. The dosage and methods of administration of the drugs, which have been chosen, are stored in the database so that the app installed on the patient's smartphone can manage the "alarms" and "reminders".

In accordance with therapies and clinical conditions the GP establish the rules of measurement to be performed by the patient (blood pressure, weight, blood glucose), creating measurement rules in the dedicated section of the platform.

B. Architectural features and functionality of the mobile app

The Smit-CKD-APP (Fig. 1) has been developed for the use by Android and iOS. An internet connection allows the APP and the Server to communicate; for this reason, it is mandatory that the smartphone has a working and active internet connection. The Smit-CKD-APP has several functions, including the management of alarms and notifications. Access is granted by username and password after accepting use conditions. The activities of the APP are reported below:

- Home: this is the "basic" activity after the login. It contains: the patient's name, the pop-up menu and the project logos.

- Configure Blood Pressure Monitor: this activity is used only to pair the smartphone with a blood pressure monitor equipped with a Bluetooth interface.

- Therapy: on this activity there is a global display of the therapy prescribed by the doctor to the patient. This is organized to display the days of the week and times of drug administration. In this activity the patient has a global view of the drugs prescribed and their administration doses.

- Control data: this activity is used by the patient to enter control data such as weight and blood glucose, to be entered manually. As for the blood pressure measurement, Smit-CKD-APP will first try to take the measurement from the paired Bluetooth monitor. Only if data are not received the patients are allowed to enter them manually. All data entered via APP are transmitted in real time, if active internet connection available, to the referring GP.

- History: this activity contains the history of all the measurements made and / or entered in the "control data" activity, since the patient was enrolled. It reports whether or not the measurements was sent to the remote server.

In addition to the activities, the APP is designed to send personalized notifications to the patient

- To remind, at a certain date and time, the administration of the prescribed drug;

- To remind, at a certain date and time, the measurements of weight, blood glucose, pressure.

Fig. 1. Functioning of the integrated system SMIT-CKD-SERVER/APP. The GP register in the platform the days of the week and the time at which the patient has to measure blood pressure, body weight and blood glucose and take the prescribed medications. This record produces an alert on the mobile APP. The patient receives the reminder and enters the required measurements or give the feedback for have taken the therapy. Measurements and feedbacks are transmitted to the server.

After receiving the notification, the patient select from an input box "YES" or "NOT" to indicate if the required action (for example "take the pill xxx") has been performed. This allows the GPs to monitor the progress of the treatment.

C. Pilot study

The integrated system SMIT-CKD-Server and Mobile APP was tested with the help of 22 patients, enrolled by 4 GPs supervised by VP. Mean age was of 70±11 years, 59% were male. The analysis of the family situation highlighted that 64% of them were conjugated, 27% were widowers, 1 patient was separated / divorced and 1 was never married. The analysis of the educational level of the patients participating in the trial showed that 59% of patients had a low/medium education, 23% a high school diploma, 9% a university degree, 9% did not have any education. Eighty-two per cent of patients had / had had an employee income.

Patients were treated with antihypertensive drugs for a median time of 10 years (IQR 6.50 - 21). According to the questionnaire administered during the study, before using the APP, 64% regularly took all drugs. Forgetfulness was the most common cause of non-intake. The percentage of regular intake rose to 82% after 6 months of using the App, confirming, albeit in small numbers, the usefulness of the APP in remembering to take the prescribed drugs.

The level of compliance with the use of the app was quite high, with 16 subjects entering clinical data (blood pressure, body weight, glucose) regularly and sending feedbacks of drug intake. Among the 6 low compliant patients, 4 encountered technical problems, as the version of the Android installed in their smartphone was too obsolete.

Among users, the percentage of satisfaction, expressed on a scale with possible values from 1 to 5 (with 1 equivalent to poor satisfaction - 5 to high approval), was very high, as shown in the graphs below (Fig. 2). The same questionnaire, administered to general practitioners, to investigate the level of satisfaction with the use of the SMIT-CKD-SERVER, gave even better results, as all the GPs involved indicated, for each of the questions asked, a score equal to 5.

IV. DISCUSSION

According to the Ericsson Mobility Report published in June (https://www.ericsson.com/en/mobility-report) 5.9 billion people have access to cell phones worldwide. The number of apps currently available in Google Play or App Store is 2.87 million and 1.96 million, respectively (https://www.statista.com/statistics/276623/number-of-apps-available-in-leading-app-stores/), with health and fitness apps among the ten most popular categories (https://www.statista.com/statistics/270291/popular-categories-in-the-app-store/). According to the World Health organization, the use of mobile and wireless technologies to support the achievement of health objectives (mHealth) may change the approach to health systems worldwide. This is not only due to rapid progress in mobile technologies and applications, but also to the growth in coverage of mobile cellular network and to the increasing opportunities for the integration of mobile health into existing eHealth services (https://www.who.int/goe/publications/goe_mhealth_web.pdf).

mHealth can be applied to several field of medicine. A review published in 2016 suggests that mobile apps may be useful for changing health behavior and promoting self-management [13], [14]. *Pacifica*, a self-help app, has been demonstrated to be effective in reducing self-reported symptoms of depression, anxiety, and stress, and this effect was more evident among subject non treated with psychiatric medication [15]. Apps designed to control symptoms of

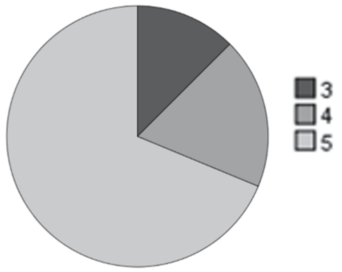

Fig. 2 Satisfation level of the users of the SMIT-CKD-APP. The number reported in the legend correspond to the overall evaluation, in a rating scale from 1 (low satisfaction) to 5 (high satisfaction), given by patients to the use of the SMIT-CKD-APP.

diabetes mellitus, chronic lung disease and cardiovascular disease may improve clinical outcomes among those affected by chronic diseases [16]. *Bluestar*, for example, an app validated in a clinical trial, helps reducing blood sugar providing a database for food intake monitoring and including personalized advice according to the goals indicated by the customers [17]. Other mobile apps are helpful in reducing body weight, as reported by Mateo et al. [18].

The increase in life expectancy has led to a parallel increase in chronic diseases [19], most of them treated with several medication simultaneously [20], [21]. Remembering days and timing of intake may be seriously challenging for elderly people [22], [23], and this may explain the wide spreading of apps for medication monitoring both for Android and iOS [10]. However, most of these apps are not focused on specific diseases, and has no medication monitoring as main purpose. Conversely, the vast majority of apps focused on a specific disease are for diabetic [10] or oncologic patients [24] or for patients affected by respiratory diseases [25].

Among apps specially designed for CKD patients, *My Kidneys, My Health handbook*, developed by Kidney Health Australia, aims at both educating and supporting patients affected by CKD. This app provides the user with educational information about detection of kidney disease and advices for a healthier life. A risk calculator is also included. *H2O Overload: Fluid Control for Heart-Kidney Health*, was designed by the National Kidney Foundation (NKF) to help fluid intake control; a fluid tracker, weight tracker, blood pressure tracker, nutrition tips, appointment diary are some of the features of this app. *CKD Go!*, developed from the CKD Management in Primary Care handbook, allows to create personalized action plans based on the eGFR and urine albumin:creatinine ratio, well known risk factors of CKD progression.

CKD patients are often subject to dietary restrictions in order to control the progression of the disease. *My Food Coach*, designed by NKF, offers nutritional advices thanks to the involvement of health care professionals, who provide personalized support about dietary requirements and modifications. *AAKP myHealth Nutrition Guide* is an interactive app which features the nutrient values of more than 300 commonly consumed foods as well as many fast food restaurant options. Similarly, *Kidney APPetite*, developed by Sanofi US, helps monitoring daily nutrient and fluid intake. *Wholesome* collects healthy recipes from the web, and contains personal recommendations to optimize nutrition.

Other apps are focused on specific dietary restrictions. Oxalator, for example, comprises a list of products with low or high oxalate levels, helping the user following a low oxalate diet, while *Phosphorus Foods Diet Guide* lists food according to phosphorous content.

To our knowledge, no apps specifically targeted on CKD patients, aiming at monitoring the basic risk factors of disease progression, and designed to improve therapy adherence are available. The SMIT-CKD-APP allows the self-monitoring of blood pressure, blood glucose and body weight, and at the same time is able to transmit clinical information to the GP. Alerts remind the patients to register the measurements and to take the prescribed medications. Thanks to feedback transmitted via internet, the GP can access patient's data and check the adherence to the prescriptions. Real-time communication between server and app on one hand allow the patient to self-monitor risk factors of CKD; on the other hand it allows the GPs to intervene if transmitted data are out of the normal range or if adherence to therapy is low.

In this pilot study, the use of the integrated system was well tolerated by both GPs and patients, who appreciated the ease of use. Most importantly, the alerts were helpful in reminding to take medications, as demonstrated by the fact that in only 6 months the adherence to therapy rose of 18%.

Our study has limitations, the most evident represented by the small sample size. However, subjects involved in the study were representative of the CKD population, in term of age, social status and other demographic features. For this reason, we are confident that it will be possible, in the near future, to test the SMIT-CKD integrated system in a larger population, and that it will be positively welcomed by these patients.

Our pilot study demonstrated that the use of a simple Mobile APP may improve adherence to therapy in patients affected by CKD. Furthermore, the use of the natural counterpart, SMIT-CKD-Server, by general practitioners may help tracking the evolution of the disease in real time, preventing clinical outcomes and making patients more involved in the management of their clinical condition. Further studies, specifically designed to test this app in a larger population, are required to clarify if the use of the integrated system will have long-term effects on therapy adherence, and if self-monitoring of risk factors will improve clinical outcomes in this population.

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REFERENCES

[1] N. R. Hill et al., "Global prevalence of chronic kidney disease - A systematic review and meta-analysis," PLoS ONE. 2016, doi: 10.1371/journal.pone.0158765.

[2] N. Lameire, K. Jager, W. Van Biesen, D. De Bacquer, and R. Vanholder, "Chronic kidney disease: A European perspective," Kidney Int., vol. 68, pp. S30–S38, Dec. 2005, doi: 10.1111/j.1523-1755.2005.09907.x.

[3] C. Zoccali, "Traditional and emerging cardiovascular and renal risk factors: an epidemiologic perspective.," Kidney Int., vol. 70, pp. 26–33, 2006, doi: 10.1038/sj.ki.5000417.

[4] M. J. Sarnak et al., "Kidney Disease as a Risk Factor for Development of Cardiovascular Disease," Circulation, vol. 108, no. 17, pp. 2154–2169, Oct. 2003, doi: 10.1161/01.CIR.0000095676.90936.80.

[5] S. M. Grundy et al., "Diabetes and Cardiovascular Disease," Circulation, vol. 100, no. 10, pp. 1134–1146, Sep. 1999, doi: 10.1161/01.CIR.100.10.1134.

[6] S. E. Kjeldsen, "Hypertension and cardiovascular risk: General aspects," Pharmacol. Res., vol. 129, pp. 95–99, Mar. 2018, doi: 10.1016/j.phrs.2017.11.003.

[7] P. Poirier et al., "Obesity and Cardiovascular Disease: Pathophysiology, Evaluation, and Effect of Weight Loss," Circulation, vol. 113, no. 6, pp. 898–918, Feb. 2006, doi: 10.1161/CIRCULATIONAHA.106.171016.

[8] S. Baroletti and H. Dell'Orfano, "Medication Adherence in Cardiovascular Disease," Circulation, vol. 121, no. 12, pp. 1455–1458, Mar. 2010, doi: 10.1161/CIRCULATIONAHA.109.904003.

[9] K. H. Leslie, C. McCowan, and J. P. Pell, "Adherence to cardiovascular medication: a review of systematic reviews," J. Public Health (Bangkok)., vol. 41, no. 1, pp. e84–e94, Mar. 2019, doi: 10.1093/pubmed/fdy088.

[10] K. Tabi et al., "Mobile Apps for Medication Management: Review and Analysis," JMIR mHealth uHealth, vol. 7, no. 9, p. e13608, Sep. 2019, doi: 10.2196/13608.

[11] Morisky DE, Green LW, and Levine DM. "Concurrent and Predictive Validity of a Self-Reported Measure of Medication Adherence and Long-Term Predictive Validity of Blood Pressure Control." Medical care 1986; 24 (1) pp. 67-74

[12] Barendse SM, Shalleen M. et al. "The Renal Treatment Satisfaction Questionnaire (RTSQ): A measure of satisfaction with treatment for chronic kidney failure", American Journal of Kidney Diseases, 2005; 45 (3), 572 - 579

[13] J. Zhao, B. Freeman, and M. Li, "Can Mobile Phone Apps Influence People's Health Behavior Change? An Evidence Review," J. Med. Internet Res., vol. 18, no. 11, p. e287, Nov. 2016, doi: 10.2196/jmir.5692.

[14] I. Rudolf et al., "Assessment of a Mobile App by Adolescents and Young Adults With Cystic Fibrosis: Pilot Evaluation," JMIR mHealth uHealth, vol. 7, no. 11, p. e12442, Nov. 2019, doi: 10.2196/12442.

[15] C. Moberg, A. Niles, and D. Beermann, "Guided Self-Help Works: Randomized Waitlist Controlled Trial of Pacifica, a Mobile App Integrating Cognitive Behavioral Therapy and Mindfulness for Stress, Anxiety, and Depression," J. Med. Internet Res., vol. 21, no. 6, p. e12556, Jun. 2019, doi: 10.2196/12556.

[16] L. Whitehead and P. Seaton, "The Effectiveness of Self-Management Mobile Phone and Tablet Apps in Long-term Condition Management: A Systematic Review," J. Med. Internet Res., vol. 18, no. 5, p. e97, May 2016, doi: 10.2196/jmir.4883.

[17] P. Agarwal et al., "Mobile App for Improved Self-Management of Type 2 Diabetes: Multicenter Pragmatic Randomized Controlled Trial," JMIR mHealth uHealth, vol. 7, no. 1, p. e10321, Jan. 2019, doi: 10.2196/10321.

[18] G. Flores Mateo, E. Granado-Font, C. Ferré-Grau, and X. Montaña-Carreras, "Mobile Phone Apps to Promote Weight Loss and Increase Physical Activity: A Systematic Review and Meta-Analysis," J. Med. Internet Res., vol. 17, no. 11, p. e253, Nov. 2015, doi: 10.2196/jmir.4836.

[19] W. Raghupathi and V. Raghupathi, "An Empirical Study of Chronic Diseases in the United States: A Visual Analytics Approach to Public Health," Int. J. Environ. Res. Public Health, vol. 15, no. 3, p. 431, Mar. 2018, doi: 10.3390/ijerph15030431.

[20] E. D. Kantor, C. D. Rehm, J. S. Haas, A. T. Chan, and E. L. Giovannucci, "Trends in Prescription Drug Use Among Adults in the United States From 1999-2012," JAMA, vol. 314, no. 17, p. 1818, Nov. 2015, doi: 10.1001/jama.2015.13766.

[21] R. A. Payne, A. J. Avery, M. Duerden, C. L. Saunders, C. R. Simpson, and G. A. Abel, "Prevalence of polypharmacy in a Scottish primary care population," Eur. J. Clin. Pharmacol., vol. 70, no. 5, pp. 575–581, May 2014, doi: 10.1007/s00228-013-1639-9.

[22] J. Aston, K. A. Wilson, and D. R. P. Terry, "The treatment-related experiences of parents, children and young people with regular prescribed medication," Int. J. Clin. Pharm., vol. 41, no. 1, pp. 113–121, Feb. 2019, doi: 10.1007/s11096-018-0756-z.

[23] E. Millar et al., "Pill for this and a pill for that: A cross‐sectional survey of use and understanding of medication among adults with multimorbidity," Australas. J. Ageing, vol. 38, no. 2, pp. 91‐97, Jun. 2019, doi: 10.1111/ajag.12606.

[24] J. C. Y. Jupp, H. Sultani, C. A. Cooper, K. A. Peterson, and T. H. Truong, "Evaluation of mobile phone applications to support medication adherence and symptom management in oncology patients," Pediatr. Blood Cancer, vol. 65, no. 11, p. e27278, Nov. 2018, doi: 10.1002/pbc.27278.

[25] E. Menditto et al., "Adherence to treatment in allergic rhinitis using mobile technology. The MASK Study," Clin. Exp. Allergy, vol. 49, no. 4, pp. 442–460, Apr. 2019, doi: 10.1111/cea.13333.