UNIVERSITE DE GENEVE
Section des sciences pharmaceutiques
Unité de pharmacie communautaire

FACULTE DES SCIENCES
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Implementation and Effectiveness Study of an Interprofessional Support Programme for Patients with Type 2 Diabetes in Swiss Primary Care

THÈSE

présentée aux Facultés de médecine et des sciences de l'Université de Genève
pour obtenir le grade de Docteur ès sciences en sciences de la vie,
mention sciences pharmaceutiques

par
Noura BAWAB
de
Belgique

Thèse N°: 71

LAUSANNE
2020

LIFE SCIENCES PhD SCHOOL GENEVA

DOCTORAT ÈS SCIENCES EN SCIENCES DE LA VIE DES FACULTÉS DE MÉDECINE ET DES SCIENCES

MENTION SCIENCES PHARMACEUTIQUES

Thèse de Madame Noura BAWAB

intitulée :

«Implementation and Effectiveness Study of an Interprofessional Support Programme for Patients with Type 2 Diabetes in Swiss Primary Care»

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Genève, le 26 octobre 2020

Thèse - 71 -

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N.B. - La thèse doit porter la déclaration précédente et remplir les conditions énumérées dans les "Informations relatives aux thèses de doctorat à l'Université de Genève".

Acknowledgements

First of all, the realisation of this thesis was made possible thanks to the generous financial support of the Swiss Federal Office of Public Health and the Quality and Research Fund (RBP IV/1); and thanks to the participation of the advisory group, patients, physicians, pharmacies, Sispha, Ofac and Odys.

I am thankful to my direct supervisor, Clémence Perraudin, who guided me throughout my PhD and was always available to me. I am especially grateful for her encouragement, and even more so these past few months. I would also like to thank Marie-Paule Schneider for accepting to be my deputy thesis director and for her expertise on medication adherence and interprofessionality.

I would like to extend my thanks to the members of my jury, Dr Victoria Garcia Cardenas, Dr Alexandre Gouveia, Prof Alice Panchaud, and Prof Pascal Bonnabry, also for his role as President. I am particularly grateful to my thesis advisory committee (TAC) members, Prof Carine De Vriese and Prof Eric Allemann.

I acknowledged the wonderful colleagues with whom I collaborated for their different skills: Joanna Moullin in implementation science; Aurélien Georges in qualitative research; Pierluigi Ballabeni and Isabella Locatelli in statistics, Sébastien Jotterand and Christophe Rossier in interprofessional collaboration; Jérôme Berger, Emilie Antille, and Isabelle Peytremann on the CoDiab Study. Moreover thanks to special aids during my thesis for data treatment and collection to Dahlia Busch (master student), Carolane Pernatozzi, Carlo Moyano, Morgane Coquoz (student assistants), Duy Nguyen (pharmacy assistant), Alain Vuille, Jules Gisclon, Mehdi Isoz, Marc Rochat, Simon Zaslawski, Jérôme Viroux, Paul Thoueille (civil servants), IT assistants; for interview transcripts to Hélène Maireau Patuel; and for administrative parts to Nadia Martel, Aline Christinat, Gwenaëlle Botton, and Mirka Rebetez.

Thanks to all my colleagues at Unisanté for their hospitality and kindness, and in particular to Anne and Denise for my research and pharmacy activities respectively, and to Mélanie, Stéphanie, Carole, Patricia, and Talitha for meals, walks, runs, or tennis sessions during lunch or after work.

I would also like to thank my friends for their generosity and especially Wassim, Sarah, Inês, Rahma, and Raquel. Special appreciation goes to my family members, my parents, and my brother who keep me progressing in my personal and professional goals. Thanks to my partner, Patrick, who pushes me forward every day. I am glad to have shared the doctoral experience together, and especially to have you as a colleague during the last months of home-office due to the sanitary situation.

Finally, I would like to thank my thesis director, Professor Olivier Bugnon. On Wednesday afternoon, May 13, 2020, we had our meeting, which you scheduled at the last minute, to discuss my thesis and papers. We ended it with a few jokes and your good mood. In the evening, your heart did not hold out and you left abruptly. My sadness remains immense and my pain intense, but I feel lucky to have shared this journey with you. You gave me the keys, and you pushed me like a cyclist is pushed to resume a race. Thank you Olivier for sharing your vision and trusting me during these five years. And most of all, thank you for your personal and professional spirit. Your deeply human values will stay with us forever.

Abstract

Background (Chapter 1) : In 2016, Swiss Health Authorities recognised the value of expanding the role of community pharmacists in primary care, particularly in the interprofessional management of patients with chronic diseases. For the first time, they acknowledged the need to evaluate the effectiveness of an interprofessional patient support programme (Siscare) and to formulate recommendations for its effective implementation and sustainability in primary care in the French-speaking part of Switzerland (FrCH). Siscare aims to optimise medication adherence and patient safety and promotes interprofessional collaboration with the intervention of the community pharmacist as a trigger factor. Siscare includes (i) regular patient-pharmacist motivational interviews, (ii) the monitoring of medication adherence (electronic pillbox) as well as clinical and patient-reported outcomes, and (iii) pharmacist-physician interactions. Therefore, this PhD thesis illustrates the use of implementation science and clinical research to support and assess the implementation of Siscare with a focus on patients with type 2 diabetes (T2D) due to the widely recognised burden, morbidity and mortality associated with this disease.

Objective: To assess the implementation and effectiveness of Siscare for patients withT2D (Siscare-DT2) through three research questions: (1) Is the implementation of Siscare-DT2 possible in primary care in the FrCH, and which strategies are appropriate for such an implementation? (2) Is Siscare appropriate and effective in patients with T2D? (3) How does interprofessional collaboration through Siscare-DT2 occur in primary care in the FrCH?

Method: Chapter 2 details the research protocol. A 15-month prospective, multicentre, observational, mixed-method cohort study was conducted with a hybrid type 2 implementation-effectiveness design and using the Framework for the Implementation of Services in Pharmacy (FISpH). Outcomes were assessed at the implementation stages: exploration, preparation, operation, and sustainability. Measures of implementation included the process (indicators of progress through the stages), outcomes (e.g., reach, fidelity), and impact (influencing factors, implementation strategies, provider and patient satisfaction). Effectiveness was assessed for patients with T2D taking at least one oral antidiabetic medication (OAD) by measuring their medication adherence to OADs, estimated as a product of implementation (Generalised Estimating Equations model) and persistence (Kaplan-Meier survival curve), clinical outcomes, quality of life (QoL, linear mixed-effect models), and patient satisfaction. Interprofessionality was operationalised through four progressive levels of interrelationship practices between the pharmacist and the referent physician of the patient.

Results: Chapter 3 presents the results of the implementation from a pharmacy's perspective. Twenty-seven of 41 volunteer pharmacies provided Siscare to 212 patients with T2D. The mean inclusion was 8 patients per pharmacy (SD 6, min-max: 1-29). An orderly three-step implementation process was observed in the pharmacies: internal organisation at the pharmacy, preparation of interprofessional collaboration, and relationship building with patients. The operational success in the implementation of Siscare-DT2 in pharmacies implies a global corporate project involving a clear project management strategy, human and financial investments, precise documentation of performance indicators, commitment of the entire staff team and good coordination of the local healthcare provider network. Chapter 4 presents the results of the intervention. The percentage of persistent patients taking their OADs appropriately was estimated to be 90% at baseline and 88% at month 15. The average HbA1c level at baseline was 7.5% and decreased from 0.3 to 0.5 units (%) after 15 months. QoL remained stable, and 75% of patients would recommend Siscare to another person with diabetes. Chapter 5 presents the results of the interprofessional collaboration. Collaboration primarily occurred through the unidirectional transmission of information from the pharmacist to the physician (level 1); bidirectional exchange of information occurred sometimes (level 2); and concerted measures of treatment objectives took place occasionally (level 3).

Conclusion: This PhD thesis provided evidence regarding the ability to implement and the acceptability of Siscare among pharmacy teams, effective support for patients with T2D, and a promising start towards interprofessional collaborative practices. Broader implementation of this intervention is still tentative due to the need for fundamental changes in practices as well as economic and political uncertainties influencing healthcare providers in primary care.

Résumé (French)

Contexte (Chapitre 1) : En 2016, les autorités sanitaires suisses ont reconnu l'intérêt d'étendre le rôle des pharmaciens d'officine dans les soins primaires, en particulier dans la gestion interprofessionnelle des patients chroniques. Pour la première fois, elles reconnaissaient la nécessité d'évaluer scientifiquement l'efficacité d'un programme de soutien aux patients chroniques (Siscare) et de formuler des recommandations pour son implémentation et sa pérennisation dans les soins primaires en Suisse romande (FrCH). Siscare vise à optimiser l'adhésion thérapeutique et la sécurité des patients chroniques, et favorise la collaboration interprofessionnelle avec l'intervention du pharmacien d'officine comme déclencheur. Siscare comprend (i) des entretiens motivationnels réguliers entre le patient et le pharmacien, (ii) le suivi de l'adhésion thérapeutique (par pilulier électronique) ainsi que des résultats cliniques et des résultats rapportés par le patient, et (iii) des interactions entre le pharmacien et le médecin référent du patient. Par conséquent, cette thèse de doctorat illustre l'utilisation des sciences de l'implémentation et de la recherche clinique pour soutenir et évaluer l'implémentation de Siscare pour les patients atteints de diabète de type 2 (DT2), en raison du fardeau, de la morbidité et de la mortalité largement reconnus associés à cette maladie.

Objectif : Évaluer l'implémentation et l'efficacité de Siscare pour les patients DT2 (Siscare-DT2) par le biais de trois questions de recherche : (1) l'implémentation de Siscare-DT2 est-elle possible dans les soins primaires en FrCH, et quelles stratégies sont appropriées pour cela ? ; (2) Siscare est-il approprié et efficace chez les patients atteints d'un DT2 ? ; (3) comment la collaboration interprofessionnelle se construit-elle à travers Siscare-DT2 dans les soins primaires en FrCH ?

Méthode : Le chapitre 2 détaille le protocole de recherche. Une étude de cohorte prospective, multicentrique, observationnelle avec une méthode mixte (données quantitatives et qualitatives), d'une durée de 15 mois, a été menée avec un design hybride implémentation-efficacité de type 2 et en utilisant le cadre théorique FISpH (*Framework for the Implementation of Services in Pharmacy*). Les résultats ont été évalués tout au long des quatre étapes du processus d'implémentation : exploration, préparation, réalisation, maintenance. Les mesures d'implémentation comprenaient le *processus* (indicateurs de progression à travers les quatre étapes), les *outcomes* (p. ex., portée, fidélité) et l'*impact* (barrières/facilitateurs, stratégies d'implémentation, satisfaction des patients et professionnels). L'efficacité a été évaluée pour les patients avec un DT2 prenant au moins un médicament antidiabétique oral (ADO) en mesurant : l'adhésion aux ADOs, estimée comme le produit de l'implémentation (modèle d'équations d'estimation généralisées) et de la persistance (courbe de survie de Kaplan-Meier) ; les valeurs cliniques et la qualité de vie (modèles linéaires à effets mixtes) ; et la satisfaction des patients. L'interprofessionnalité a été opérationnalisée par quatre niveaux d'interrelations croissants entre le pharmacien et le médecin référent du patient.

Résultats : Le chapitre 3 présente les résultats de l'implémentation du point de vue de la pharmacie. Vingt-sept des 41 pharmacies volontaires ont délivré Siscare à 212 patients atteints de DT2. La moyenne d'inclusion était de 8 patients par pharmacie (SD 6, min-max : 1-29). Un processus d'implémentation structuré en trois étapes a été observé dans les pharmacies : une organisation interne de la pharmacie, la préparation de la collaboration interprofessionnelle, et l'établissement de relations avec les patients. Le succès opérationnel de l'implémentation de Siscare-DT2 dans les pharmacies implique un projet d'entreprise global qui comprend une stratégie de gestion de projet claire, des investissements humains et financiers, une documentation précise des indicateurs de performance, l'engagement de toute l'équipe de la pharmacie et une bonne coordination du réseau local des acteurs de santé. Le chapitre 4 présente les résultats de l'intervention. Le pourcentage de patients persistants qui prenaient leurs ADOs de manière appropriée a été estimé à 90% au début du suivi et à 88% au 15ème mois. Le taux moyen d'HbA1c au début du suivi était de 7,5% et a diminué de 0,3 à 0,5 unité (%) après 15 mois. La qualité de vie est restée stable et 75% des patients recommanderaient Siscare à une autre personne diabétique. Le chapitre 5 présente les résultats de la collaboration interprofessionnelle. La collaboration interprofessionnelle s'est principalement traduite par la transmission unidirectionnelle d'informations du pharmacien au médecin référent (niveau 1), l'échange bidirectionnel d'informations a parfois été observé (niveau 2), et une action concertée sur les objectives du traitement n'a eu lieu que très occasionnellement (niveau 3).

Conclusions : Cette thèse de doctorat a fourni des preuves concernant la capacité d'implémentation et l'acceptabilité de Siscare au sein des équipes de pharmacies, un soutien efficace aux patients DT2, et un début prometteur vers des pratiques de collaboration interprofessionnelle. Une implémentation

plus large de Siscare reste toutefois fragile en raison de la nécessité de changements fondamentaux dans la pratique professionnelle ainsi que des incertitudes économiques et politiques qui influencent les prestataires de soins de santé dans les soins primaires.

Preface

This thesis is presented under the requirements of the doctoral degree (Doctor of Philosophy) of the Pharmaceutical Sciences programme of the School of Life Sciences, Faculties of Medicine and Science, University of Geneva, Switzerland. Noura Bawab carried out the doctoral program at the Center for Primary Care and Public Health (Unisanté), University of Lausanne, Switzerland.

The thesis is organised by papers and is based on the scientific research report developed for the funders. Chapter 1 provides background and rationale for the topic, including the results of a literature review on medication adherence and its clinical and economic impacts on patients with type 2 diabetes, and the findings of a parallel study on the interest in and use of pharmacy services for patients with diabetes. This chapter also presents the general objective and research questions. Chapter 2 details the research protocol by describing the mixed methods that were used. The protocol was approved by the ethics committee and published in a peer-review journal. Chapters 3 to 5 include the results, which are presented in the form of papers and are in the submission process in peer-reviewed journals. They focus on the implementation results from a pharmacy's perspective, the intervention effectiveness outcomes, and the interprofessional collaboration outcomes. Chapter 6 discusses the results, provides some recommendations for the implementation and sustainability of Siscare in the given context, and comments on the methodological aspects. Finally, future research directions are provided.

Articles are displayed as copies, with the corresponding bibliography and appendix, as published, to be submitted, or in preparation in each peer-review journal.

Most parts of the thesis were edited for proper English language, grammar, punctuation, spelling, and overall style by one or more of the highly qualified native English speaking editors at American Journal Experts.

Noura Bawab is the primary author of each paper. In addition, the papers have co-authors, including thesis directors and supervisors, and collaborators who contributed to the conceptualisation, method design, data collection, data analysis, data interpretation, and/or manuscript review.

Contents

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Abbreviations

ADO	Médicament antidiabétique oral
CHF	Swiss francs
CiS	Interprofessional simulation centre (*Centre interprofessionnel de simulation*)
CMG	Continuous measure of medication gaps
CoDiab-Vd	Cohort of patients with diabetes in the canton of vaud (Switzerland)
EM	Electronic monitoring
FOPH	(Swiss) Federal Office of Public Health
FrCH	French speaking-part of Switzerland (Suisse romande)
HbA1c	Glycated haemoglobin
IMAP	Interprofessional medication adherence programme
MARS	Medication adherence report scale
MMAS	Morisky medication adherence scale
MPR	Medication possession ratio
OAD	Oral antidiabetic medication
PDC	Percentage of days covered
Siscare	Interprofessional patient support programme
Siscare-DT2	Interprofessional patient support programme for patients with type 2 diabetes
Sispha	(Network) Smart and innovative solutions for pharmacy
T2D	Type 2 diabetes
Unisanté	Center for Primary Care and Public Health, University of Lausanne, Switzerland
WHO	World Health Organization

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Chapter 1. General Introduction

Chronic Diseases and Type 2 Diabetes

Chronic diseases are a major public health issue and are estimated to affect 57% of the world's population in 2020 [1]. In Switzerland, there are approximately 2.2 million patients with chronic diseases, and the prevalence increases with age, affecting 10% of people over 50 years and 30% of people over 80 years [2]. Chronic diseases account for more than 50% of premature deaths before the age of 70 years and 80% of total healthcare costs [2]. The consequences of chronic diseases are manifold and include mobility difficulties, impaired cognitive function, undernutrition, unmet therapeutic goals, complex multiple drug regimens resulting in medication non-adherence, avoidable emergency rooms visits, hospitalisations and overcosts for healthcare systems, etc. [3-6]. Among chronic diseases, type 2 diabetes (T2D) has a widely recognised impact on morbidity and mortality and socio-economic impacts [7].

T2D is a metabolic disease. Insulin, produced by the pancreas, regulates blood glucose levels by promoting the absorption of glucose into cells. In T2D, insulin secretion is insufficient, and/or the body's response to this hormone is decreased. Cells in the peripheral tissues of the liver, muscle and fat are less sensitive to insulin and do not absorb enough glucose into the bloodstream, resulting in hyperglycaemia [8]. Glucagon secretion and the effect of incretins are also disturbed [8,9]. In addition, oxidative stress and an inflammatory process have negative consequences [10]. T2D is the most common type of diabetes in the population and accounts for 90-95% of diabetes diagnoses. The *Diabetes Atlas* has estimated that the number of adults (aged 20 to 79 years) with diabetes was 463 million worldwide (9.3% prevalence) in 2019 (and 59 million in Europe) and predicts a 51% increase to 700 million in 2040 [7]. In Switzerland, the current prevalence of diabetes among these adults is estimated to be 7.7%, representing 496,900 people [7].

The risk of developing T2D is influenced by genetic and environmental factors. Lack of physical activity and poor diet leading to overweight and obesity are associated with the development of this disease [9]. Other factors may also contribute to this risk such as ethnicity, family history, chronic stress, smoking, age, excess alcohol consumption and lack of sleep [9]. Currently, the disease also appears in young populations, particularly in relation to lifestyle [9].

Diabetes can cause complications leading to micro- and macrovascular damage, especially in the case of long-term hyperglycaemia. Microvascular complications include retinopathy, nephropathy, and peripheral neuropathy, while macrovascular complications include stroke, ischaemic heart disease and lower limb arterial insufficiency [11]. These complications are associated with major risks for the patient, such as loss of vision, kidney failure and amputation, and are even more severe if the treatment is not optimal [11]. Glucose control (blood glucose and glycated haemoglobin levels), prevention of cardiovascular risks (such as blood pressure and cholesterol levels) and patient support are therefore necessary to reduce and delay the onset of these complications to improve patients' quality of life [9,11].

Medication therapy plays an important role in preventing complications of T2D, disease progression and symptom reduction when hygiene and dietary measures are not sufficient [12]. Oral antidiabetic medications (OADs) are the main treatments prescribed to patients with T2D. Many classes are currently on the market: biguanides (represented by metformin, which is used in first-line treatment),

sulfonylureas, glinides, thiazolidinediones (or glitazones), dipeptidyl peptidase-4 inhibitors, alpha-glucosidase inhibitors, and sodium-glucose co-transporter type 2 inhibitors [13,14]. To achieve therapeutic goals, combinations of these classes may also be prescribed by physicians [14]. Other antidiabetic treatments, such as glucagon-like peptide 1 receptor agonists and insulin in injectable form are also used in patients with T2D [14]. The treatment regimen is rapidly becoming complex, especially since a large proportion of patients with T2D are also being treated for other chronic diseases. Patients with T2D often have comorbid diseases (e.g., obesity, dyslipidaemia, hypertension) and require polypharmacy, which explains the results of the literature showing that daily intake of their medications is often difficult [14].

Diabetes is one of the most widespread diseases in the world with a rapidly increasing prevalence, which makes it a priority for action, including the promotion of adherence to medications in primary care [7]. Primary care is a key process in the health system where first-contact care is available when needed and ongoing care is provided for a person's long-term health, including comprehensive care through a range of services appropriate for common problems and populations and coordinated care with other specialists that the patient may require [15]. One of the nine global goals for the control of noncommunicable diseases set for 2025 by the World Health Assembly (decision-making body of World Health Organization (WHO)) includes targets such as a 25% relative reduction of global diabetes mortality (when compared with 2013) and halting the progression of diabetes and obesity [16]. In Switzerland, diabetes is also one of the priorities of the National Strategy for the Prevention of Noncommunicable Diseases (NCD strategy) 2017-2024 [12] with health promotion and prevention in healthcare, which includes goals such as reducing the disease burden and premature mortality [2].

Patient Support Programmes

Delaying the effects of chronic disease is essential if more people are to remain healthy and maintain their quality of life despite illness. People with chronic diseases can be supported by patient support programmes to reduce the risk of further illness, avoid complications, and reduce the need for intensive care [17]. Patient support programmes refer to different types of services supporting patients with a variety of diseases that can be delivered by different healthcare professionals [18]. Ganguli et al. defines patient support programmes as “self-management support programs that include interventions such as individualized medication counselling, training, support, and virtual reminders to improve medication-taking behaviour” and say “the underlying objective is to help patients better manage their disease and complex medication regimens, improve medication adherence, and reduce complications and related costs” [19]. In 2016, a systematic review assessed 64 patient support programmes showed a great diversity of the pathologies concerned, the types of interventions, the healthcare providers involved and the targeted outcomes [19]. The most frequently targeted diseases states were type 2 diabetes/metabolic syndrome, HIV and cardiovascular disease. The majority of programmes offered a face-to-face support, sometimes including telephone or home support and mail reminders, and only few (5%) included in-pharmacy consultations. Programmes were delivered by providers from a variety of disciplines, with first pharmacists, second nurses, third physicians, and lastly and multidisciplinary teams. The services were aimed at improving clinical, economic, humanistic and/or adherence outcomes. Forty-one studies (64.1%) reported at least one significantly positive clinical outcome. The most frequent outcome impacted was adherence, with 66% of the studies (27 of 41) reporting a positive outcome.

Pharmacist's Role & Interprofessional Collaboration

Internationally, the pharmacist's role has evolved over time to become a provider of services. Pharmacies represent an easily accessible gateway to the health system, and the increased use of their expertise is expected to improve the quality of drug therapy. Pharmacists play an important role in terms of observation, advice and coordination in the field of prevention of diseases or their complications. The WHO and the International Pharmaceutical Federation (FIP) jointly defined the guidelines on Good Pharmacy Practice (GPP). The purpose of these guidelines is to describe ways in which pharmacists can improve access to healthcare, health promotion and medicine use for patients they serve through optimal, evidence-based care [20].

Within the healthcare system, chronic patients are managed by different healthcare professionals. The care provided by healthcare professionals is usually specific and complementary but remains largely fragmented, requiring interprofessional collaboration to ensure optimal care [21]. *Interprofessionality* can be defined as the collaboration between distinct professions that manifests itself in various forms of increasing interrelationship practices [22]. The positioning of pharmacies in primary care must therefore be considered from an interprofessional perspective [23].

In Switzerland, the Confederation has been interested for several years in the tasks that different healthcare professionals can assume to ensure safe and effective basic care [24]. In 2012, following National Councillor[1] Ruth Humbel's postulate on the position of pharmacies in basic care, the Federal Council[2] was invited to study what tasks pharmacies can fulfil in the health system and how their area of competence could be extended to guarantee basic care [24]. In this context, two external expert reports were commissioned in 2014. They provide an overview of existing interprofessional collaboration models between pharmacists and other healthcare providers in Switzerland and abroad, determine whether and how they could lead to an improvement in the quality of care, and investigate the factors of success and failure [26,27]. Both expert reports indicated that interprofessional care focusing on the individual needs of patients (e.g., chronic care models) leads to an increase in the quality of care but that these models are not sufficiently widely implemented in Switzerland compared to other countries. Success factors included programmes addressing the needs of specific risk groups (e.g., for chronic diseases), structured information exchange, clearly defined professional roles, planned interprofessional education, certified/labelled health professionals, and remunerated services. To date, patient-centred models have only been able to develop locally in Switzerland, mainly due to a lack of cooperation and acceptance by service providers for fear of overcoming interprofessional barriers and financial conflicts of interest. Broader implementation cannot be achieved through state-imposed obligation to cooperate (top-down) and must be launched based on individual initiatives by service providers in a bottom-up process. Both reports therefore recommended that the Confederation should support pilot projects launched gradually and scientifically evaluated with the participation of all stakeholders [28].

In response to the postulate, the Federal Council drew up a report published in October 2016 [28]. The report confirms that pharmacists' skills should be better used within the framework of interprofessional, coordinated, and patient-centred models. Several federal government strategies such as the Health2020 strategy and the support programme "Interprofessionality in healthcare" 2017-2020 are

[1] A National Councillor is a member of the National Council, which is part of the Federal Assembly (Switzerland's highest legislative authority) that discusses and makes decisions on important issues to the country and amends laws or makes new ones [25].
[2] The Federal Council is one of the three Swiss powers implementing the laws [25].

moving in this direction [29,30]. The Federal Council therefore wishes to focus its efforts on promoting such projects on a larger scale. In this context, two pilot projects have been selected by the Federal Office of Public Health (FOPH) for financial support, of which one focuses on T2D (see Objective - p.17).

Pharmacy Services in Diabetes

To support patients with T2D in the day-to-day management of their treatments, pharmacies can offer pharmacy services tailored to the needs and interest of patients. *Moullin* et al. (2013) defined professional pharmacy service as one or more actions organised or provided in a pharmacy to optimise the process of care, with the goal of improving health outcomes and the value of healthcare [31]. In Switzerland, community pharmacies can provide pharmacy services including basic cognitive services (e.g., counselling services, prescription/dosage/drug-drug interaction checks, and checks of patient records), medication intake support (directly observed therapy, fractioned delivery or provision of a pillbox filled with medication for one or more weeks), or individual consultation with the pharmacist [32]. Some of these services are remunerated and covered for patients by basic health insurance according to the tariff headings.

Alongside this thesis and in partnership with another research team from the Center for Primary Care and Public Health (Unisanté), University of Lausanne, a study was undertaken to evaluate the interest in and use of pharmacy services among a population-based cohort of patients with diabetes in the canton of Vaud (CoDiab-Vd) in Switzerland [33]. The full article is available in Appendix 1 and is in review in *BMC Health Services Research*. Noura Bawab contributed to this article through formal analysis, manuscript writing, and data presentation.

The cross-sectional study analysed self-reported data from 790 people with diabetes included in the CoDiab-VD cohort recruited by pharmacies who responded to the 2017 annual questionnaire, which included a thematic module about pharmacy services [34]. The questions addressed sociodemographic and economic characteristics, diabetes and its management, and interest in and use of pharmacy services related to (1) medication intake and adherence and (2) diabetes and general health. Descriptive analyses were first conducted. Logistic regression analyses were then performed for pharmacy services that were of interest to ≥50% of respondents.

The mean age of participants was 66 years, the sample included more males (59%) than females, and had predominantly T2D (72%). The pharmacy services that interested the most respondents were individual consultation, pillboxes, treatment plans, checks of all medications, first medical opinions from pharmacists and counselling on devices. Factors significantly associated with interest in pharmacy services were being older, having a lower self-efficacy score, taking more than three medications and having a positive opinion about pharmacists.

This study provides key information on interest in and use of pharmacy services among patients with diabetes in Switzerland, which may help pharmacists individualise their services for patients.

Medication Adherence

Appropriate medication can reduce symptoms and the risk of complications. However, to achieve this goal, adherence to treatment is necessary.

Concepts of Medication Adherence

Medication adherence is a complex process that characterises a patient's daily treatment intake and management [4]. A patient is considered "adherent" if he or she takes the treatment as prescribed, in terms of duration and intake. Adherence is a dynamic process that can be broken down into three dimensions (Figure 1): (i) initiation: starts the therapeutic process and corresponds to the moment when the patient takes the first dose of the prescribed treatment; (ii) implementation: characterises the quality of the patient's treatment performance from initiation to the last dose in relation to the prescribed dosing regimen; (iii) persistence: characterises the duration of the treatment from its initiation to discontinuation [35]. Discontinuation marks the end of treatment when the next dose to be taken is missed and no dose is subsequently taken.

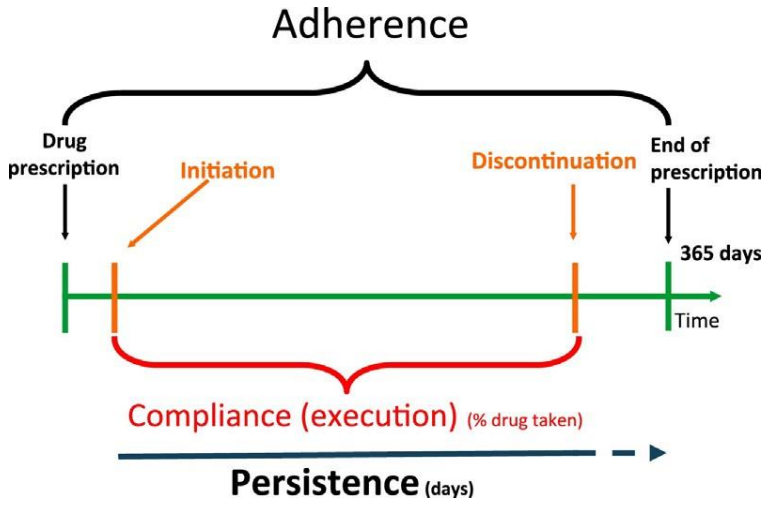

Figure 1 - Illustration of medication adherence components
From *Burnier* (2017) [36]

The support and accompaniment of medication adherence is based on a multidimensional approach involving both the policy and the organisation of the health system, the healthcare actors, the patients and their social network [35]. The forms of non-adherence (Figure 2) do not have the same impact on the patient's state of health [35].

Time

	Phases		
	Initiation	**Implementation**	**Persistence**
Non-adherence	The patient does not start the treatment	The patient defers, misses or takes extra doses of medication	The patient stops the treatment
Measurement	Binary variable: Yes/No	Regimen history	Length of time until discontinuation

Figure 2 - Medication non-adherence forms
Adapted from *Vrijens* et al. (2012) [35]

According to the WHO, 50% of chronic disease patients do not adhere to their treatments [4]. Causes of medication non-adherence are diverse and vary over time depending on a wide range of factors. Seven hundred factors have been identified [37] and grouped into five dimensions: social and economic factors and healthcare team and system-, condition-, therapy-, and patient-related factors that interact with each other [4]. Medication non-adherence may be either voluntary and based on the patient's decision and influenced by his/her perception, beliefs, experiences and knowledge and/or involuntary and dependent on his/her skills and resources [38].

Various methods can measure medication adherence. There is no gold standard measure of adherence as each measure provides an approximation of unique aspects of medication use [39]. In contrast to direct methods, which measure drug ingestion (e.g., via biological markers such as glycated haemoglobin (HbA1c) determined by blood tests), indirect measurements are proxies for medication adherence [39]. The four main indirect (subjective or objective) methods are as follows:

1. Self-report measures such as questionnaires, diaries or interviews that provide a picture of medication adherence at a given time. The two most commonly used questionnaires that have been validated in several languages are the Morisky Medication Adherence Scale (*MMAS*, consisting of four or eight binary questions that characterise the patient's overall medication-taking behaviour [40]) and the Medication Adherence Report Scale (*MARS*, which includes five or ten questions that reflect intentional and unintentional non-adherence) [41,42].
2. Electronic measures (e.g., weekly pillbox, blister pack or pillbox equipped with microchips) allow longitudinal measurement of the frequency and timing of medication intake by recording the date and time at each opening [39].
3. Databases available from pharmacy refills or prescription claims can be used to estimate the number of days a patient is or is not supplied with medication. The three main measures derived from these data are the Medication Possession Ratio (*MPR*, total number of days of medication supply divided by the number of days the patient should have taken the medication), the Percentage of Days Covered (*PDC*, number of days of drug supply since the first prescription and over a specified period) and the Continuous Measure of Medication Gaps (*CMG*, number of days the patient did not have medication available divided by the number of days the patient should have had medication) [39,43].
4. Pill counting (e.g., number of tablets remaining in a week's supply) can also determine an adherence rate [39].

The use of methods will depend mainly on their availability, cost, performance (specificity/sensitivity) and potential biases in the specific clinical context (over/underestimation, positive bias in use, etc.), while their combination will allow complementarity and increase the validity and reliability of the data collected [44]. The estimation of the prevalence of medication adherence is therefore influenced by the measurement method applied. Any synthesis of the results of a literature review about adherence must therefore describe precisely the clinical context and the method of measurement used.

Current Knowledge in Type 2 Diabetes

As part of this thesis, a systematic literature review on medication adherence in patients with T2D was conducted in 2016 and updated in 2020 to synthesise current knowledge (i) on OAD adherence including methods, prevalence, and determinants and (ii) on associations between medication adherence and clinical outcomes, healthcare services utilisation and costs, and health status/quality of life. The literature review was entirely conducted by Noura Bawab and is in preparation for submission in a peer-reviewed journal. The complete methodology and detailed results of the literature review are available in Appendix 2.

A literature search was undertaken in PubMed and Embase combining MESH/Emtree terms with keywords covering the following topics: *type 2 diabetes*, *medication adherence*, *clinical impact*, and *economic impact*. First, systematic literature reviews or meta-analysis evaluating the determinants, clinical and/or economic impact of medication adherence with at least reported outcomes in T2D using OADs (with or without injectable treatment) published from 2004 were identified (review of reviews). Then, studies from the reviews were selected if they included adult patients (≥18 years) in addition to the criteria for selecting the reviews or meta-analysis.

Nine literature reviews including 192 different studies were selected, and 106 studies met the inclusion criteria. These studies, published between 2004 and 2016, were mostly conducted in the United States (68%, n=72). Only 14% of the studies (n=15) were conducted in Europe, mainly in the Netherlands, and one study was conducted in Switzerland [45]. The studies were most often conducted retrospectively (55%, n=58) or cross-sectionally (33%, n=35) and rarely prospectively (12%, n=13). The number of participants in the studies ranged from 20 to over one million (large cohort with insurance data). Most studies included patients with T2D only (89%, n=94), 3% (n=3) included patients with both type 1 and 2 diabetes, and in 8% (n=9) of studies, the type of diabetes was not specified. Medication adherence was measured for OADs alone in 64% (n=68) of the studies, OADs and injectable forms in 24% (n=25), and in 12% (n=13) of studies the medications used were unspecified. Of all studies, 18% (n=19) focused on newly diagnosed patients with treatment initiation.

The two following sections give an overview of the findings of the methods, prevalence, determinants and impact of medication adherence in T2D.

Methods, prevalence and determinants of medication adherence

Interpretation and comparison of the results should be treated with caution due to the heterogeneity of studies in terms of the population, design, type of adherence measure outcomes, and risk of bias, etc. For instance, the level of adherence measured could represent a 'mean' score of medication adherence in a given population or the proportion of patients considered 'adherent' according to a defined threshold level. In addition, some studies report adherence results according to different subgroups within the study (e.g., type of facility consulted, type of OAD treatment) without information on prevalence for the entire cohort.

Among 106 studies, 118 adherence measures were reported (Table 1). Prescription refills or reimbursements (64%, n=78/118) with a majority of 12-month monitoring and self-report questionnaires (34%, n=40/118) were the main data sources, but these do not allow for an assessment of actual medication intake in relation to the prescribed regimen. Only one study used electronic monitoring (EM) and over a short time [46] although tools such as electronic pillboxes provide a more accurate measurement of medication adherence [35].

Table 1 - Medication adherence measures by method and monitoring duration in type 2 diabetes

	Monitoring duration				
Data sources	**<6 months** (n=4)	**6-9 months** (n=5)	**12 months** (n=46)	**>12 months** (n=22)	**n/s** (n=1)
Prescription refill or reimbursement data (n=75)	n=1 • Initiation: 1	n=5 • MPR: 3 • PDC: 2	n=46 • MPR: 24 • PDC: 9 • CMG: 2 • Others: 11	n=22 • MPR: 13 • PDC: 4 • CMG: 2 • Others: 3	n=1 • MPR: 1
Pill count (n=2)	n=2	-	-	-	-
Electronic monitoring (n=1)	n=1	-	-	-	-
Self-report questionnaires* (n=40) • Morisky Medication Adherence Scale (MMAS): 21 • Medication Adherence Report Scale (MARS): 4 • Other scales: 15					

CMG: Continuous Measure of Medication Gaps, MPR: Medication Possession Ratio, PDC: Proportion of Days Covered, n/s: not specified, *Cross-sectional studies: no duration of monitoring.

Concerning the prevalence of medication adherence, the measure of the MPR ranged from 0.56 to 0.82 over 12 months (n=6 studies) and from 0.48 to 0.78 over 24 to 60 months (n=5). On average, 68% [45-93%] of patients were adherent (with a threshold MPR≥0.80, n=15) over 12 months. The measure of PDC ranged from 0.65 to 0.76 over 12 months (n=6). In the only Swiss study, 42% of the 26,713 patients with T2D were adherent (PDC≥0.80) over 12 months. According to MMAS self-report questionnaires, 46% of patients [23-76%] (n=11 studies) were adherent (defined as the maximum response value for the questionnaire). Medication adherence remained suboptimal in patients with T2D. These results are in line with the WHO estimate for chronic disease patients [4].

Of the 106 studies included, 101 determinants of medication adherence were investigated. The number of studies in which the factor was significantly positively/negatively or non-significantly associated with medication adherence is reported when at least 5% of the studies examined the factor (Table 2). The determining factors of medication adherence were heterogeneous. Healthcare professionals should encourage discussion with patients about the perception and management of adverse events, self-efficacy, knowledge of the disease, and depressive symptoms that were found to be significantly associated with medication adherence.

Table 2 - Studies on determining factors associated with medication adherence in type 2 diabetes

Determining factors (reference value)	Positive association	Negative association	Non-significant association	Total
Social/economic factors				
Age (↑)	28	3	21	52
Sex (male)	12	6	30	48
Ethnicity (Caucasian)	17	1	9	27
Education level (high)	3	1	16	20
Income (high)	5	1	9	15
Marital status (married)	4	1	5	10
Employment (employee)	1	3	5	9
Place of dwelling (rural)	2	1	4	7
Healthcare team and system-related factors				
Drug costs (low)	12	-	-	12
N visits/communications with professionals (↑)	7	-	5	12
Having a health insurance	6	-	3	9
Type of health insurance (favourable)	3	-	4	7
Healthcare costs (low)	5	-	2	7
Condition-related factors				
Duration of illness (+ long)	3	1	11	15
N comorbidities (↑)	6	5	4	15
Presence of comorbidity(s)	7	3	3	13
Therapy-related factors				
N medications/doses of medication per day (high)	3	9	11	23
Type of diabetes treatment	4	6	10	20
Presence of insulin	1	3	8	12
Perception of treatment-related adverse events (↑)	-	5	1	6
Drug delivery (mail)	5	-	-	5
Patient-related factors				
Depressive status	1	7	3	11
Self-efficacy or empowerment	5	-	-	5
Knowledge of the disease (high)	4	1	-	5
Body mass index (BMI) (↑)	-	1	4	5

Impact of Medication Adherence

The second part of the literature review identified 56 studies (from the nine literature reviews and meta-analysis) examining the association between medication adherence and clinical outcomes and/or use of healthcare services or costs and/or health status/quality of life in patients with T2D (Table 3).

Table 3 - Association between better medication adherence and outcomes in type 2 diabetes

Variable	↓ Outcome	↑ Outcome	Non-significant association	Inconsistent	Total
Clinical outcomes					
Glycaemic control					
HbA1c	15	-	3	5	23
Fasting blood glucose	1	-	1	-	2
Mortality	5	-	-	-	5
Healthcare services utilisation					
Hospitalisation					
Hospitalisation history	A:1	-	A:1	-	2
Likelihood of hospitalisation	A:9/D:4	-	-	A:3/D:1	17
Duration of hospitalisation	A:2	-	A:1	A:1	4
Number of hospitalisations	A:3/D:1	-	A:1	A:1/D:1	7
Emergency room visits	8	-	1	-	9
Outpatient medical visits		3	1	1	5
Healthcare costs					
Medication costs	-	A:7/D:5	-	-	12
Medical costs (without medication costs)	A:9/D:2	A:1	A:1	D:2	15
All costs	A:9/D:2	A:3/D:1	A:4	D:1	20
Health status/quality of life					
Health status	1	-	3	1	5
Quality of Life	-	-	2	1	3

A: All-causes, D: Diabetes-related

Better adherence was associated with better glycaemic control; lower mortality, healthcare services utilisation for hospitalisations (all-cause and diabetes-related visits) and emergency room visits; but more outpatient medical visits. Mechanistically, the medication costs associated with OADs increased with adherence rates, whereas the medical costs (all-cause and diabetes-related costs) decreased. As a result, the additional costs of OADs and medical visits were offset by lower hospitalisation costs and emergency room visits. Regarding health status and quality of life, the limited number of studies and the different methods used do not allow us to draw an association with medication adherence. The high number of outpatient medical visits and the related costs associated with improved adherence may explain the important role of healthcare professionals in advising patients about the importance of medications. In conclusion, the literature review confirms the dynamic and complex nature of medication adherence and the need for individualised management [47].

Interventions in Type 2 Diabetes Patients

Collaborative patient-centred care is strongly recommended by diabetes guidelines to provide better care and facilitate patient self-management [8]. Individualised medication adherence support requires specialised skills in pharmacotherapy and therapeutic education that are not available for most patients with chronic diseases [48]. Pharmacists have a strategic role to play with the opportunity to provide services in collaboration with other healthcare professionals for optimal safety and adherence; however, they are often underutilised but can move us closer to achieving better patient outcomes in medication management in T2D [49].

Recent literature reviews have been conducted on the identification of interventions targeting medication adherence in T2D and their impact [50-54]; some of these have focused on pharmacist-led interventions [55,56]. Interventions can be characterised in four categories: screening (identifying problems with medication adherence), patient information (educating at least about the treatment and possibly the disease), medication review (optimising treatment), and coaching (individualised accompaniment of the patient's behaviour); there are also two types of interventions: 'simple' if it includes only one category or 'complex' if it includes at least two of them.

Only a limited number of T2D interventions including the participation of a pharmacist were identified in Europe compared with the number of intervention studies performed in North America or Asia. These interventions mostly lasted between 6 and 12 months and included educational and/or behavioural components [57-65]. Some interventions in these studies reported that the pharmacist always contacted the patient’s physician for approval if a medication change was made during the intervention [57-59,61,62,64,65]. Multicomponent, repeated, long-term (≥ 10 months), patient-tailored interventions (based on the patient's knowledge and experience with the disease and its treatments) appear to have a positive impact on patient outcomes, medication adherence and HbA1c levels [66].

An example of a complex intervention aimed at supporting medication adherence for chronic disease patients implemented in a community setting is the interprofessional medication adherence programme (IMAP). The programme was developed and implemented since 1995 through physician-pharmacist-nurse collaboration with various chronic disease populations, such as hypertension and HIV populations, at the Center for Primary Care and Public Health (Unisanté), University of Lausanne, Switzerland [67]. The IMAP is individualised for the patient, and the content of the interview addresses cognitive, behavioural and social aspects [68,69].

An Interprofessional Patient Support Programme: Siscare

Adapted from the IMAP, Siscare was created and has been proposed since 2011 in community pharmacies in the French-speaking part of Switzerland by Sispha (Smart and Innovative solutions for pharmacy), which is a network active involved in the development of interprofessional programmes dedicated to chronic care management [70]. The programme aims to contribute to the achievement of patients' individual therapeutic goals, to improve their general health, to promote medication adherence and patient safety, to strengthen continuity of care between the different healthcare professionals involved in the patient care pathway, and to control the evolution of overall healthcare costs induced by medication non-adherence. Siscare includes (i) semi-standardised motivational interviews conducted by a pharmacist that focus on individual patient needs; (ii) longitudinal monitoring of medication adherence in particular through EM (electronic pillboxes) and/or pill counting, patient-reported outcomes (signs and symptoms of medication problems), and clinical outcomes; and (iii) interactions between healthcare professionals to promote continuity of care (see Appendix 3 for flyer in French). Siscare focuses on the individual needs of patients to promote medication safety and adherence and can be considered a chronic care model.

Implementation science

Gap between Theory and Practice

In the past, research has largely focused on the effectiveness of the clinical interventions and not on their implementation [71], but the benefits of healthcare interventions can only be achieved if they are implemented effectively [72,73]. Currently, implementation science allows reducing the gap between the development of effective healthcare interventions and their incorporation in routine practice [74,75]. The implementation and adoption of evidence-based practices depend on behaviour changes among individuals reflected by three necessary conditions (capability, motivation, and opportunity) [76] and influenced by different factors [77]. Therefore, there is a need to use implementation to accumulate knowledge and guide interventions and to develop an attitude of behaviour change in interventions [76].

Definition of Implementation Science

Implementation is the use of strategies to adopt and integrate evidence-based interventions or changes in practice in specific contexts [78]. Implementation science examines how clinical interventions are disseminated and applied over the long term in specific contexts [79,80] and promotes the integration of research evidence into health services policies and practices to improve their quality and effectiveness [81].

Implementation success depends on what is being implemented (the intervention), where and for whom the intervention is implemented (the context), and how and by whom (implementation strategies) the intervention is implemented [82,83]. Hence, the goals of implementation science are to develop strategies to improve health services outcomes and processes to facilitate their widespread adoption; to generate ideas and generalizable knowledge about implementation processes and strategies, barriers and facilitators; and to develop, test and refine implementation theories and hypotheses [84].

Theoretical Implementation Frameworks

Recently, multiple theories, models, and frameworks have been developed to evaluate and understand the implementation of interventions [76,85-88]. These contribute to clarifying the causal mechanisms, core components or active ingredients; to explaining how and why certain results are achieved; and to developing better implementation allowing operationalisation of each concept [89].

In the context of pharmacy interventions, the Framework for the Implementation of Pharmacy Services (FISpH) was developed based on a Generic Implementation Framework (GIF) by *Moullin* et al. (2016) [90]. The GIF was first developed after conducted a literature review of existing theories, models and frameworks, and tailored to a pharmacy setting through the realisation of a qualitative study.

According to the GIF, implementation of an innovative intervention is defined as a dynamic process consisting of four stages:

- Exploration: “The innovation–decision process, whereby the end-user(s) appraise the innovation, concluding with a decision to either to accept/adopt or reject. Involves progression through awareness (of an issue, need and/or new innovation), knowledge, persuasion, opinion and decision regarding the innovation.”
- Preparation: “The course of preparing (the innovation, individuals, organisation, local environment and external system) prior to innovation use.”

- Operation: “Innovation is in use and is in the process of being integrated into routine practice through active and planned approaches.”
- Sustainability: “Process of maintaining the innovation through continued innovation use integrated as routine practice, ongoing capacity and support.”

In each stage, the success or failure of implementation of the innovative intervention is influenced by contextual factors (barriers/facilitators) that may intervene at different levels (Figure 3). For example, the implementation of an innovative pharmacy service may be compromised by its over-complexity (delivery level) and/or a lack of motivation of the pharmacist (individual) and/or poor internal pharmacy organisation (pharmacy) and/or failure to meet patient needs (local context) and/or inadequate remuneration (system).

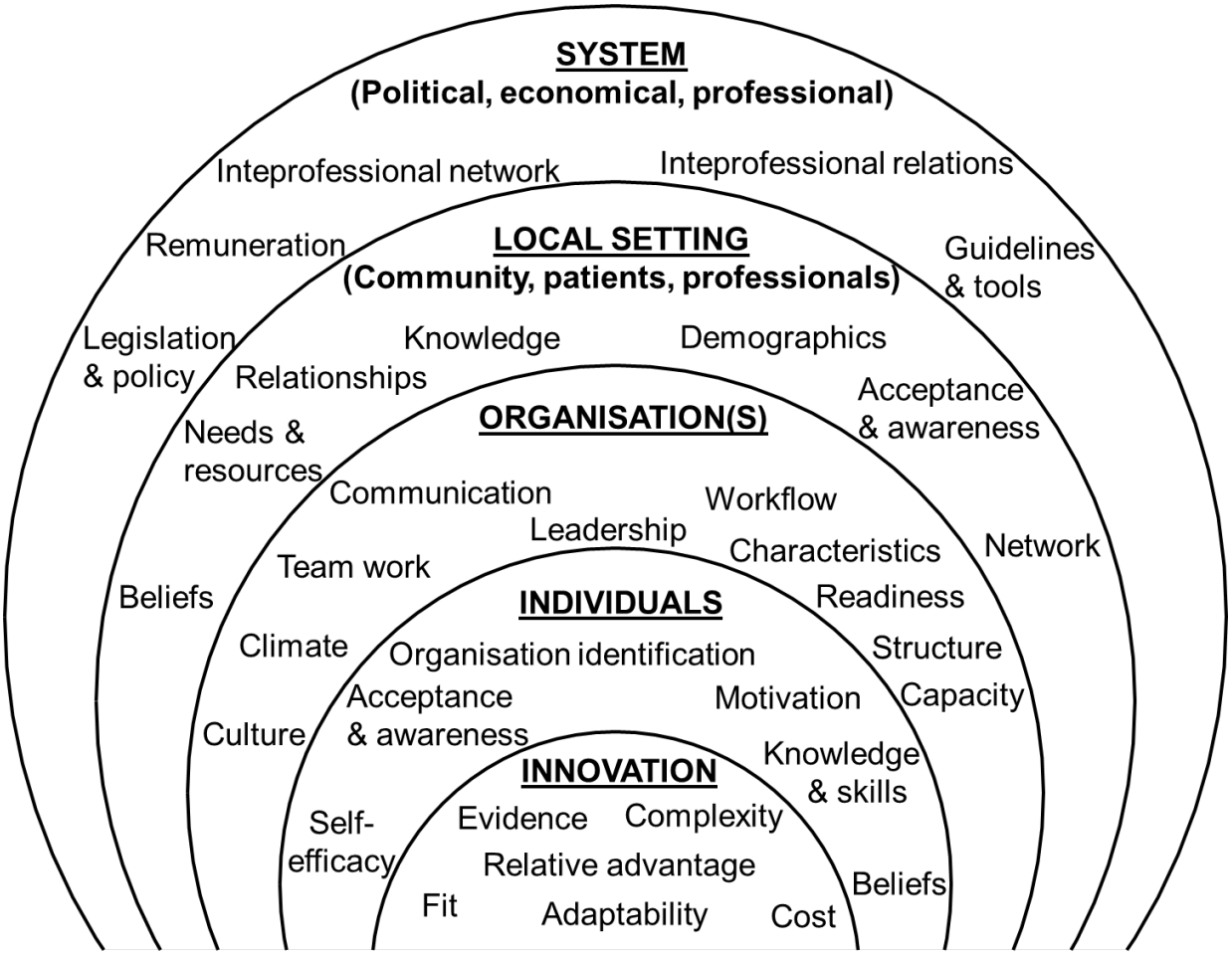

Figure 3 - Contextual domains and factors of the implementation in a pharmacy setting
Adapted from *Moullin* et al. (2016) [83]

Ongoing evaluation of the factors influencing the implementation makes it possible to act on the strategies to be adopted to overcome the main obstacles with the logic of continuous improvement of the quality of the PDCA: Plan-Do-Check-Act [91].

Hybrid designs

Efficacy, effectiveness, and implementation research should be combined to overcome their complexity and not slow the field down. The speed of moving research findings into routine adoption can be improved by considering hybrid designs, which combine elements of effectiveness and implementation research. Regarding the results of intervention, collecting implementation data such as barriers and facilitators is a great opportunity to enhance knowledge [92]. Hybrid effectiveness-implementation designs (Table 4) offer a potential solution to this problem as they promote examination of both effectiveness and implementation outcomes within a study [93].

Table 4 - Type of hybrid designs and associated research aims
Adapted from *Landes* et al. (2019) [92]

	Study design		
Research aims	Hybrid type 1	Hybrid type 2	Hybrid type 3
Primary aim	Determine the effectiveness of an intervention	Determine the effectiveness of an intervention	Determine the impact of an implementation strategy
Secondary aim	Better understanding of the context for implementation	*Can also be a co-primary aim*: Determine the feasibility and/or (potential) impact of an implementation strategy	Assess clinical outcomes associated with implementation

Objective

The FOPH decided to foster the implementation of Siscare in the French-speaking part of Switzerland for patients with T2D by funding the Siscare-DT2 project. The thesis is rooted in this research project and the objective is to evaluate the implementation and effectiveness of Siscare for patients with T2D (Siscare-DT2) in Swiss primary care.

Research questions

The thesis addressed three research questions:

- Is the implementation of Siscare-DT2 possible in primary care in the French-speaking part of Switzerland, and which strategies are appropriate for such an implementation?
- Is Siscare appropriate and effective in patients with T2D?
- How does interprofessional collaboration through Siscare-DT2 occur in primary care in the French-speaking part of Switzerland?

Research overview

Chapter 1 provides the background and rationale for the objective of the thesis. Chapter 2 presents the research protocol of Siscare-DT2 including a hybrid implementation-effectiveness design and a global view of data collected and methods used. Chapters 3 to 5 present the thesis findings focused on specific research questions:

- Chapter 3 focuses on the implementation of Siscare-DT2 in the French-speaking part of Switzerland from the pharmacy perspective, which includes an assessment of the entire implementation process and the appropriateness of the implementation strategies from this perspective.
- Chapter 4 describes the results of the effectiveness of Siscare in T2D from the patients' perspective, including medication use and adherence, clinical outcomes, quality of life and satisfaction.
- Chapter 5 evaluates the building practice of interprofessional collaboration throughout the implementation process and the appropriateness of the associated targeted strategies in Siscare-DT2.

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Chapter 2. Method

Implementation and Effectiveness of an Interprofessional Support Program for Patients with Type 2 Diabetes in Swiss Primary Care: A Study Protocol

Chapter 2 details the study protocol, which includes the mixed qualitative and quantitative methods used to evaluate the implementation and effectiveness of Siscare for patients with T2D in the French-speaking part of Switzerland. The protocol was approved by the Cantonal Ethics Committee of Research on Human Beings of the Canton of Vaud (CER-VD) [Protocol N ° 2016-00110] (see Appendix 4 for ethics approval).

This chapter is presented in the form of a paper published in *Pharmacy* (MDPI) in a special issue on "Clinical Pharmacists' Interventions in Chronic Care" in June 2020. Noura Bawab contributed to this publication in the evolution of overarching research aims, the design of the methodology, the provision of study materials, the writing of the original draft and revision at the pre-publication stages, the management and coordination of the planning and execution of research activities.

Bawab N, Moullin JC, Perraudin C, Bugnon O. Implementation and Effectiveness of an Interprofessional Support Program for Patients with Type 2 Diabetes in Swiss Primary Care: A Study Protocol. Pharmacy (Basel). 2020;8(2) ; 10.3390/pharmacy8020106.

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Article

Implementation and Effectiveness of an Interprofessional Support Program for Patients with Type 2 Diabetes in Swiss Primary Care: A Study Protocol

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Received: 19 May 2020; Accepted: 19 June 2020; Published: 21 June 2020

Abstract: This research protocol illustrates the use of implementation science to support the development, dissemination and integration in primary care of effective and sustainable collaborative pharmacy services for chronic care management. The objective is to evaluate the implementation and the effectiveness of a pharmacist-led patient support program including regular motivational interviews; medication adherence, patient-reported outcomes, and clinical outcomes monitoring; and interactions with physicians, for patients with type 2 diabetes taking at least one oral antidiabetic medication in the French-speaking part of Switzerland. This is a prospective, multi-centered, observational, cohort study using a hybrid design to assess the patient support program. The evaluation includes three levels of analysis: (1) the implementation strategies, (2) the overall implementation process, and (3) the effectiveness of the program. Qualitative and quantitative methods are used, and outcomes are assessed at each stage of the implementation process: exploration, preparation, operation, and sustainability. This research project will provide key insights into the processes of implementing patient support programs on a large scale and adapting the traditional community pharmacy practices towards the delivery of person-centered and collaborative services.

Keywords: community pharmacy; implementation science; interprofessional practice; medication adherence; patient support; type 2 diabetes

1. Introduction

Chronic diseases are a major public health issue. The prevalence of patients with chronic diseases ranges from 20 to 30% for the whole population and from 55 to 98% for the elderly (≥60 years) [1]. Chronic disease rates are increasing globally and are expected to account for 73% of all deaths in 2020 [2]. The consequences are multiple: disability, depression, distress, poor quality of life, and high resource utilization and costs [1,3]. Thus, the prevention of risk factors and chronic care management are a high priority for smarter health care.

Medication non-adherence is a preventable risk factor in reaching successful clinical outcomes for chronic diseases [4]. The World Health Organization (WHO) estimates that only half of chronic disease patients take their medication as prescribed by the physician [4]. A recent literature review shows that better adherence is associated with improved blood-glucose control and decreased health-service utilization among patients with diabetes (through reduced risk of hospitalization, emergency room visits or outpatient consultations) [5]. The Institute for Health Informatics has estimated the costs that could be avoided through more responsible use of medicines each year at $475 billion worldwide—of which, $269 billion (57%) is related to medication non-adherence [6].

Another challenge for health care systems is patient safety and their integration into the care process. Pharmacists have a responsibility to ensure that when a patient receives and uses medications, it will not cause harm. In 2017, the goal of the WHO Medication Safety Challenge was to reduce global medication errors and related harm by 50% over five years [7].

In 2012, the Swiss government recognized that pharmacists have an important role to play in acute and chronic primary care [8,9]. Their repositioning in chronic care management has become essential, as interprofessional collaboration and patient-centered care leads to increased quality of care. However, such models including community pharmacists were not widely implemented in Switzerland. The main barrier to implementation was a lack of cooperation and acceptance by service providers, because of the fear of crossing interprofessional barriers and creating financial conflicts of interest. Two expert reports, commissioned by the Swiss Confederation, recommended that the various practical models should be based on the initiative of pharmacists and physicians using a bottom–up process, obviously taking into account the other success factors [10,11]. The Swiss Federal Office of Public Health (FOPH) also expressed the desire to follow the recommendations of the expert reports by supporting the scientific evaluation of existing pilot collaborative projects including community pharmacists [9].

One of the promoted pilot projects is a chronic patient support model to optimize medication adherence and patient safety [12–14]. This program named Siscare includes three components: (a) regular motivational interviews between a patient and their pharmacist, (b) medication adherence, patient-reported outcomes, and clinical outcomes monitoring and (c) interactions with physicians. The pilot project focuses on patients with type 2 diabetes—one of the top chronic conditions contributing to mortality, morbidity and socio-economic impacts [15], and often associated with comorbidities [16]. In 2019, 7.9% of the Swiss population had type 2 diabetes [17].

At the time the evaluation was launched, the Siscare program was being delivered by only a few pharmacies with limited collaboration with physicians. However, this pilot project aimed partially to evaluate the barriers and facilitators for disseminating and implementing it as a routine interprofessional practice across the French-speaking part of Switzerland. An effective health care intervention can only lead to benefits for the patients if a sustainable implementation succeeds. Therefore, methods of implementation science are key factors to understand and accelerate innovation. Implementation science is defined as the study of methods to promote the integration of research results or evidence-based practices into health care policy and practice [18]. The implementation process is non-linear, but is generally divided into four stages: exploration, preparation, operation, and sustainability. Implementation success depends on what is being implemented (the innovation also known as the (clinical) intervention), where and for whom the innovation is implemented (the context), and how and by whom (implementation strategies) the innovation is implemented (see Table 1 for definitions) [19,20]. Moreover, the implementation and adoption of evidence-based practice depend on behavior change of the individuals [21], which can be influenced by different factors [22]. According to the Behavior Change Wheel (BCW) theory, behavior occurs as interaction between three necessary conditions: capability, motivation, and opportunity (COM-B) [21]. Therefore, there is a need to use implementation or behavior change frameworks to accumulate knowledge and guide interventions; and to develop an attitude of behavior change interventions [21].

Table 1. Definitions of the concepts in the Framework for Implementation of Services in Pharmacies (FISpH) applied to Siscare-DT2.

Concept	Definition (Adapted from Moullin et al. [20])	Application to Siscare-DT2 (Outcomes)
Implementation	The process of commencing to use and integrating innovations within a setting.	-
Innovation	Novel set of behaviors, routines, and ways of working within a setting.	Interprofessional patient support program Siscare [13] (a) regular motivational interviews between the patient and the pharmacist at least every 3 months; (b) medication adherence, patient-reported outcomes, and clinical outcomes monitoring; (c) interactions with physicians
Process of implementation	Non-linear, recursive, reiterative progression of implementation.	-
Stages of implementation	The breakdown of the complete implementation process.	-
Exploration	The innovation–decision process, whereby the end-user(s) appraise the innovation, concluding with a decision to either to accept/adopt or reject. Involves progression through awareness (of an issue, need and/or new innovation), knowledge, persuasion, opinion and decision regarding the innovation.	*Awareness*: number of pharmacies aware of the program *Adoption*: number and representativeness of volunteer pharmacies participating (registered and trained) among eligible pharmacies
Preparation	The course of preparing (the innovation, individuals, organization, local environment and external system) prior to innovation use.	*Introduction*: number of pharmacies implementing at least one implementation strategy
Operation	Innovation is in use and is in the process of being integrated into routine practice through active and planned approaches.	*Initial operation*: number and representativeness of pharmacies providing the program to at least one patient *Full operation*: number of pharmacies reaching the target number of patients (≥10 patients) Implementation outcomes—level of service provision: *Reach*: number of patients included, patient characteristics, monitoring of inclusions/refusals (documented by the pharmacists at the time of proposal and, if applicable, during the audit), stops, and retention in the program *Fidelity*: extent to which the program is delivered as defined (frequency, duration and methodology of patient-pharmacist motivational interviews) and adaptations are made by pharmacies to deliver the program (e.g., number of interviews per patient and use of electronic pillbox)

Table 1. *Cont.*

Concept	Definition (Adapted from Moullin et al. [20])	Application to Siscare-DT2 (Outcomes)
Sustainability	Process of maintaining the innovation (clinical intervention) through continued innovation use integrated as routine practice, ongoing capacity and support.	*Initial sustainability*: number of pharmacies willing to follow patients after 15 months Implementation outcomes—level of service provider: *Integration*: incorporation of Siscare into daily practice *Support*: acceptability of service
Domains	Groupings or levels of related implementation influences (and by which factors may be categorized, and strategies and evaluations targeted). Domains may vary in number and way in which they are divided.	-
Context domains	Groupings of related influences regarding the circumstances that surround the innovation to be implemented (individuals, organization, local environment, and external system).	-
Individuals	Characteristics and agency of the people involved in the innovation and/or implementation process.	Patients, pharmacists, physicians, and other health care professionals
Organization	Conditions and characteristics of the setting(s) in which the innovation is to operate.	Pharmacies and physician's offices
Local environment	Circumstances immediately surrounding the organization(s) including the community, patients and network.	Local setting including the community, patients, physicians health care professionals, and interprofessional collaboration
External system	Broad economic, political and professional milieu.	Swiss government level
Elements of implementation	Implementation impact: core considerations affecting the implementation process.	E.g., motivation, professionals' satisfaction, relations between health care professionals and patients, costs and time
Factors	Variables that may affect the implementation process—also termed facilitators and barriers or determinants of practice.	Assessed by focus groups with participating pharmacists
Strategies	Targeted efforts (method, technique or activity) designed to promote the implementation of an innovation and its integration into routine practice. Package of implementation strategies often form an implementation program.	See Section 2.6 for detailed implementation strategies and Section 2.9. for their evaluation
Evaluations	Assessment of factors, formative evaluation of strategies, process evaluation and summative evaluation of implementation and innovation outcomes.	Assessed by a mixed method (quantitative and qualitative)

This paper describes the protocol of the pilot study, promoted and funded by the FOPH, that aimed to assess the implementation process and effectiveness of the interprofessional support program for patients with type 2 diabetes (Siscare-DT2) taking at least one oral antidiabetic drug in the French-speaking part of Switzerland [23]. The French-speaking part of Switzerland is located in the western part of Switzerland and includes seven cantons. It covers 25% of the Swiss population, accounting for 2.1 million people in 2019 [24].

The study's objectives are:

(1) To evaluate the appropriateness of the implementation strategies for Siscare-DT2,
(2) To describe the implementation process of Siscare-DT2 in the French-speaking part of Switzerland, and
(3) To evaluate the effectiveness of Siscare-DT2 for patients with type 2 diabetes.

2. Materials and Methods

2.1. Design

This is a prospective, multi-centered, observational study using an implementation-effectiveness hybrid type II design [25]. The study simultaneously tests both the effectiveness of the clinical intervention and the implementation strategies [25]. The Standards for Reporting Implementation Studies (StaRI) guidelines were used in the project's execution and in the manuscript's preparation [26]. The StaRI allows implementation studies to be developed and reported transparently and accurately by encouraging researchers to describe the techniques used to promote the implementation of an intervention (implementation strategy) and the effectiveness of the intervention to be implemented across 27 items [26]. The data are collected using qualitative and quantitative methods. The study protocol was approved by the Cantonal Ethics Committee of Research on Human Beings of the Canton of Vaud [Protocol N°2016-00110].

2.2. Theoretical Implementation Framework

In this study, the Framework for Implementation of Services in Pharmacies (FISpH) was used, which was adapted for the community pharmacy setting from the Generic Implementation Framework (GIF) [19]. Moullin et al. first developed the GIF after collating the core concepts of existing implementation frameworks and models identified by a systematic review [20] such as the Consolidated Framework for Implementation Research (CFIR) [27], the Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) model [28], the Exploration, Preparation, Implementation, Sustainment (EPIS) model [29], the BCW [21] and the behavior change technique taxonomy [30]. Second, a qualitative study was conducted with 21 Australian community pharmacies to determine the pharmacy implementation process and to understand influencing factors, which led to the creation of the FISpH [31]. As such, the FISpH incorporates and tailors the aforementioned frameworks and models to community pharmacy. Thus, as the project deals with community pharmacies, the FISpH provides a solid base to be used as guidance in this hybrid study and another study used this framework in a similar context [32].

The core concepts are the process of implementation (divided into stages), the innovation to be implemented, and the multi-level context (divided into domains: individuals, organization, local setting and system) in which the implementation is to occur, which is influenced by factors, strategies, and evaluations [19]. These theoretical concepts and their operationalization to the Siscare-DT2 project are presented in Table 1.

2.3. The Intervention: Siscare Patient Support Program

2.3.1. Aims

The Siscare program aims to (1) assist patients in reaching their therapeutic goals and improving their general health, (2) support and strengthen medication adherence and patient safety, (3) strengthen

continuity of care between the different health care professionals involved in the patient care pathway, and (4) control the escalation of overall health costs induced by non-optimal use of medicines.

2.3.2. Program Description

The program includes three major components: motivational interviews; medication adherence, patient-reported outcomes, and clinical outcomes monitoring; and interactions with physicians [13,14]. First, patient-centered semi-structured individual interviews between patients and pharmacists are conducted based on the social, behavioral and cognitive approach of motivational interviewing [33]. They are short (about 15 to 20 minutes) and repeated, allowing long-term patient-reported outcomes monitoring. Second, medication adherence is monitored by an electronic pillbox with an LCD screen as a memory aid (Medical Event Monitoring System (MEMS), Aardex group) [34], which is an objective and dynamic measurement of treatment taking. Patient-reported and clinical outcomes are monitored during the patient follow up including data on patient's experiences with their treatment and management of their disease. The third component is promotion of four levels of interprofessional interactions with the physicians (see Figure S1 in Supplementary File 1 for details of the levels). The pharmacist writes a report after each interview and sends it to the referent physician of the patient (physician of the patient's choice, general practitioner or specialist, responsible for coordinating the patient's care). The report includes the following sections: (1) comments on the patient's use of the pillboxes and medication adherence graphs; (2) a summary of the interview including an overall assessment, description of omissions and medication-taking times, facilitators and barriers, behavioral skills, motivations, information given, adverse reactions, and other information relevant to patient follow-up; (3) clinical outcomes (e.g., HbA1c, blood glucose, blood pressure); and (4) a description of the patient's goals or questions for the next appointment. This approach aims to strengthen the collaborative management of the patient and allows exchange between health care professionals through information sharing of clinical data, therapeutic goals, and treatment plan.

2.3.3. Secure Web Platform

A secure web platform (Sispha SA, Ofac group, Lausanne, Switzerland) [35] was designed to guide the pharmacist intervention with a semi-standardized step-by-step process [14]. The platform combines electronic pharmaceutical and medical records saved by the pharmacist, an electronic monitoring data-uploading system, a clinical decision-making support system coupled with a safety alarm system, and an archiving material support system, including instructional material (e.g., how to conduct interviews or upload electronic monitoring data). During the interviews, the platform guides the pharmacists. The safety alarm system warns the pharmacist if recorded symptoms mentioned by the patient could be the consequence of a severe adverse reaction to a treatment to ensure patient security. The platform also enables data collection of patient-reported and clinical outcomes. At the end of each interview, the platform issues a structured report including the summary of the patient-pharmacist interview (see Section 2.3.2. Program description for details) and the medication adherence graph downloaded from the electronic pillbox intended for the physician and the patient [14].

2.4. Study Setting

Any community pharmacy member of the Sispha network can participate in the study. In 2011, a start-up (Sispha) was created aiming to facilitate the transition from the traditional role of pharmacists towards the implementation of remunerated, person-centered and collaborative pharmacy services. A small network of pharmacies has thus subscribed to the Siscare programs offered by Sispha, translating into practice the research evidence collected by the Community Pharmacy of Unisanté (Lausanne), a university development, education and research center for community pharmacy and public health.

Any community pharmacy is free to join or exit the network at any time. Member pharmacies pay an annual fee to subscribe to Sispha and have a trained staff member responsible for the program. At least one pharmacist per pharmacy receives a minimum three-day standardized training course

on how to deliver the intervention, use the platform and handle electronic monitoring (e.g., data uploading and refilling pillboxes).

2.5. Study Population and Recruitment

Recruitment happens at both the organizational (pharmacies and primary care physicians) and patient levels. First, Sispha informs and recruits their affiliated pharmacies for the project (Siscare-DT2) and, second, pharmacies and physicians recruit patients to benefit from the program. Participation by pharmacies is voluntary. The total planned duration of the project is three years including three months for pharmacy preparation and advertisement, nine months for the participant (patient) enrollment period, 15 months for the last patient included to complete follow up (as each patient is followed for 15 months for the study), and the remaining months to process and analyze the data.

2.5.1. Health Care Professionals (Other than Pharmacists)

The other health care professionals involved are the referent physicians of the included patients and any health care professional involved in the patient's care pathway. The creation of the local interprofessional network is the responsibility of the pharmacist who is in this project, the starting point to strengthen interprofessional coordination.

Firstly, prior to recruiting and including patients, pharmacists approach their local physicians and other health care professionals to build their local interprofessional networks (see Figure S1 in Supplementary File 1 for the detailed process). This process is facilitated by the use of the different tools provided by Sispha (see Table 2). When a patient is recruited, pharmacies contact the patient's physician to inform their participation in the program (unless otherwise agreed).

2.5.2. Patients

Patients are eligible if they attend a pharmacy in the Sispha network, are adults (≥18 years) diagnosed with type 2 diabetes, and take at least one oral antidiabetic medication. Patients with a diagnosis of type 1 diabetes, cognitive impairment discernable to the pharmacist or insufficient level of French to complete the questionnaires to be administered in the study are excluded. Patients may be recruited by their pharmacist or physicians and other health care professionals can inform patients about the program and refer them to the pharmacy.

Pharmacies deliver a leaflet describing the program and an information statement about the study including the patient information and consent form to the patient who can thus confirm their readiness to participate (see Supplementary File 2 for patient information and consent form). For each refusal to take part in the study, the pharmacist has to notify the reason for declining as expressed by the patient, through a document developed by the research team.

At the time of submitting the protocol, the Sispha network includes 35 pharmacies. Based on an advisory group of pharmacists with expertise in implementation, pharmacy services and community pharmacy, the research team has predicted that 20 pharmacies will participate in the study and that each will include the target number of 10 patients. This number was determined to be within the operational capacity for intervention into the ongoing workflow of all pharmacies. This leads us to a sample size of 200 patients within 20 pharmacies.

Table 2. Description of the strategies according to the different stages of the implementation process.

1. Exploration
Recognition of the project [36] by the FOPH and by other key pharmacy and health insurance stakeholders (Swiss association of pharmacists, santésuisse, curafutura)
Establishment of an interprofessional steering committee [32,36]
Information to health care professional associations (Swiss pharmacy Journal, Cantonal associations of pharmacists, mfe Swiss Association of Family Medicine, FMH Swiss Medical Association, Swiss association of diabetes, Cantonal associations of diabetes, Promotion of Integrated Patient Care Networks (PRISM), local media) [36]
Information to Sispha's pharmacies and recruitment of pharmacies [32,36]
2. Preparation
Initial training of pharmacists (study process) [36–39]
Toolkit: Siscare leaflet [36], instructional material [36,39], access to secure web-based platform (electronic patient record, clinical decision system, medication plan, adherence measurement, pharmaceutical report) [36,39]
Staff training (the Siscare program) [36,39]
Creation of local interprofessional networks by the pharmacists [36,39]
Assignment of a project manager in each pharmacy [36]
Creation of a list of eligible patients through the pharmacy database [36]
3. Operation
Information to health care professional associations [36]
Use and continuous improvement of the toolkit (based on expert opinion; see Preparation)
Information to patients (Siscare leaflet, advertisement and invitation letter) [36]
Coaching service (telephones and newsletters) and continuous training adapted to specific needs [36,39]
Continuous development of interprofessional networks [36]
Plan, Do, Check, Act (PDCA) monitoring and feedback to participants [36]
4. Sustainability
Use and validation of the toolkit (see Preparation) [36]
Continuing training of pharmacy staff [36]
Publication of findings and best practice recommendations by research team for the FOPH

2.6. Implementation Strategies

The implementation strategies available vary across the implementation stages. They are based on previous experiences that have highlighted the facilitators and barriers for transferring this type of chronic patient support programs into the daily practice of Swiss pharmacies [32,36–39]. The strategies were developed by the research team and discussed with Sispha. In addition, due to the dynamic nature of implementation process, Sispha will adapt the strategies throughout the project according to the iterative evaluation being conducted by the research team. During the study period, strategies are assessed through telephone calls and a questionnaire to pharmacies by the research team, transmitting the results to Sispha for ongoing adaptation using a Plan, Do, Check, Act (PDCA) approach [40]. The core implementation strategies are summarized across the implementation stages (Table 2).

2.6.1. The Exploration Stage

The evaluation of this pilot project has obtained the financial support of the FOPH, the Swiss Pharmacists Association (pharmaSuisse) and the health insurance stakeholders, showing political support and a favorable context for the participation of pharmacists.

Sispha has created a steering committee of stakeholders to discuss the methods and monitor the results of the study at bi-annual meetings in order to ensure continuous improvement. At each meeting, the research team is to present the study's progress and the steering committee will discuss subsequent actions. The interprofessional steering committee was created by selecting (at least) one representative from each stakeholder with interprofessional experience if possible including a family physician, an endocrinologist, two pharmacy owners from two pharmacies taking part in the study,

and one representative each from the FOPH, pharmaSuisse (Swiss association of pharmacists), a health insurance company (CSS), a national association committed to improving patient care (QualiCCare), and a member of Sispha. A diabetic patient's association was contacted but no agreement was reached on the inclusion of a patient or scientific advisor from this association and, therefore, no patient was included in the steering committee. No one had conflicts of interest with Sispha except Olivier Bugnon from the research team (as declared) and the member of Sispha leading the project in the company.

Sispha communicates with health care professional associations and local newspapers (see complete list in Table 2) to promote the program by publishing an article aimed at health care professionals and patients. Sispha also proposes the study to all registered pharmacies.

2.6.2. The Preparation Stage

Pharmacies that agree to take part in the study and adopt the Siscare concept receive a first 3 h training session one month before the beginning of the patient inclusion period. Sispha and the research team present the aim and the background of the project, the study process, all procedures (e.g., inclusion criteria and data collection) and tools.

The tools include two hundred copies of the program leaflet per pharmacy, access to the web-based module specific to the project, and the instructional material, i.e., the documents to facilitate the implementation and organization of the program delivery. Materials delivered during the training include Sispha documents (e.g., an organizational checklist, a team rationale, processes mapping, presentation slides, and standard letters to physicians and patients), documents specific to the research study such as questionnaires with coded envelopes and information and consent form for ten patients (the target number of patients to include per pharmacy), as well as a copy of the study protocol. Leaflets and instructional material are given out during the first training and are available on the web-based platform. The full list of instructional material is presented in Supplementary File 3 (Table S3).

At the first training, Sispha provides recommendations about fostering interprofessional collaborations, building capacity within the pharmacy team, and encouraging patient inclusion. First, the pharmacists are strongly encouraged to present the project to local physicians to develop their pharmacy network. Sispha encourages pharmacists to speak with physicians to reduce resistance, discuss their motivations and fears and define together how they want to collaborate. Second, each pharmacy selects one project leader or champion, who informs the entire team about the project, promotes the implementation of the program, keeps them motivated and responds in case of questions or evaluations. Third, to target patients who meet the inclusion criteria, Sispha proposes a procedure explaining how to generate a list of eligible patients with type 2 diabetes to the pharmacies. The pharmacist can then discuss this list with the physician, without selecting patients according to their a priori level of medication adherence.

2.6.3. The Operation Stage

During the operation stage, patients are informed of the program and the study via a program leaflet and advertisements. Posters and video spots are available to be distributed at the pharmacy and articles published in a patient newspaper.

To keep pharmacies motivated and focused on the objective, Sispha provides regular coaching calls to the project leader (on average about once per month during the inclusion phase, then on request). Newsletters are sent on a monthly basis to keep pharmacies up to date. The newsletters are a means to provide feedback to participants informing them about the number of inclusions of all pharmacies in real time, news, answers to questions received from pharmacies, tips, testimonials, and stories. A free hotline is also available for questions about Siscare (e.g., devices or web platform issues) or the study (e.g., instructional materials, and patient information forms) during working hours.

Sispha proposes ongoing training sessions during the study period (approximately every 6 months for the first 18 months of the project, and then at least every year thereafter) on different topics such as how to propose the program to the patient, motivational and listening techniques, patient follow-up interview, and other topics according to the implementing pharmacies' needs. A coach

and a patient-actress are present at the training sessions to enable pharmacists to practice in real-life situations. Other training, given by a physician, aims to provide pharmacists with key insights to improve physician–pharmacist collaboration. Sispha also offers its standard training about medication adherence for new subscribers.

The program costs for patients are covered by the patients' basic health insurance. There is no financial incentive for the study, as the objective is to promote long-term integration of a new practice. In parallel, an assessment of the cost of the program from a pharmacy perspective is conducted to establish the potential for a return on investment [38].

2.6.4. The Sustainability Stage

Following the 15 month operation stage of the program, every pharmacy has the possibility to continue the delivery of the Siscare program for patients with type 2 diabetes as well as for other groups of chronic patients. Sispha experts are available to provide ongoing support for all the community pharmacies and will continue to provide training.

2.7. Medical Monitoring, Adverse Reactions and Serious Events

No special medical monitoring is required for the study. However, if it proves necessary, data subjects may contact their physician.

In terms of adverse reactions or incidents, article 59 (Mandatory notification, notification system and the right to notify) of the Federal Act on Medicinal Products and Medical Devices (Therapeutic Products Act, TPA) applies [41]. This Act makes all health care professionals authorized to prescribe, dispense or use medicinal products subject to the reporting obligation. Pharmacists can report suspected adverse drug reactions using an online platform [42] or documents [43].

In accordance with Article 21 of the Ordinance on Human Research with the Exception of Clinical Trials (Human Research Ordinance, HRO), if serious events occur in participants during the research project, the research project must be interrupted [44]. A serious event is defined as any harmful event that cannot be excluded as being attributable to the collection of biological material or personal health data (requiring inpatient treatment or extension of it not planned in the protocol, permanent or severe disability or impairment, endangers life or results in death) [44]. In the case of serious events, a researcher must report them to the ethics committee within seven days, report on the link between the reported serious event and the collection of personal health data, and submit proposals for action [44].

2.8. Data Protection

Electronic data are stored on the web-based platform and their collection, use and storage shall comply with the relevant requirements of data protection legislation (see Supplementary File 2: patient information form—10. Confidentiality of data). The questionnaires and interview records will be kept at the research team's pharmacy, according to the usual recommendations for clinical research, for 10 years. The data will be coded and covered by professional secrecy. Patients are always free to answer, or not answer, questions related to this study. Once all the data have been collected, the allocation file will be locked and responsibility will be transferred to the quality research department.

2.9. Measures and Data Collection

2.9.1. Implementation Strategies

Implementation strategies used by pharmacies will be collected through telephone interviews at 5 and 12 weeks after the start of the project (quantitative evaluation was conducted by reporting the proportion of pharmacies that have implemented the strategies). The interviews will include standardized questions related to five main topics of the preparation and initial operation stages on the internal organization of the pharmacies (pharmacy team training, testing the web-based platform,

and identifying and recruiting patients) and local networking with physicians and other health care professionals.

Moreover, the satisfaction and usefulness of all the proposed strategies are to be evaluated. The influencing factors (barriers and facilitators) of the preparation and initial operation stages, including patient inclusion, are investigated through semi-structured focus groups with volunteer pharmacists, using an initial grid of questions (qualitative evaluation).

Results provided by the research team, in partnership with the Sispha team, will lead to improvement of the implementation strategies by adapting them to implementer needs (PDCA approach).

2.9.2. Overall Implementation Process Measures

The implementation process is evaluated by the indicators of progress along the different implementation stages [19]. The implementation outcomes include the level of service provision (reach and fidelity) and the level of service provider (service integration and support) [19]. The implementation impact assessed factors, strategies and evaluations affecting the implementation [19]. The outcomes assessed during the different stages are presented in Table 1.

Patient characteristics include socio-demographic variables (age, sex, level of education, professional status, participation in another support program or any diabetes association), reason(s) for inclusion and reason(s) for stopping the program, the specialty of the referent physician, and the use of the electronic pillbox. Data will be collected through the web-based platform and a questionnaire completed at baseline or during follow up.

Pharmacy characteristics include the type of pharmacy, geographical zone, type of patient-centered services offered, and quality certification (dispensing pharmacies with the aim of analyzing the quality of pharmaceutical services and continuously improving the. [45]), if they have a confidential space for patient interview with a computer, the number of pharmacists and technicians working at the pharmacy and taking part in the project, and characteristics of the project leader (age, years of experience, employment rate, function and taking part in a physician–pharmacist quality circle). Data are to be assessed by audits (for pharmacies including at least one patient) or by telephone (for other pharmacies) during the operation stage. Moreover, implementation practices (e.g., task allocation) are to be evaluated by audits and on-site observations conducted by the research team using a pre-established questionnaire (quantitative evaluation) for pharmacies including at least one patient during the operation stage.

To explore influencing factors when delivering the program and to assess pharmacists' satisfaction with the program, semi-structured focus groups with volunteer pharmacists using a grid of questions (qualitative evaluation) are conducted at the operation stage. Physician's experience and satisfaction are assessed by a short questionnaire comprising 6 closed-ended questions (and a free text field if they wanted to express themselves on a point) sent by the pharmacist to referent physicians of patients.

2.9.3. Program Effectiveness

The number and type of medications and clinical outcomes (body mass index, heart rate, systolic and diastolic blood pressure, blood sugar, glycated hemoglobin, smoking status, alcohol use, and any addiction) are collected through the web-based platform at baseline and during the study period (15 months).

Medication adherence is measured using the data from electronic pillbox for at least one oral antidiabetic medication for 15 months. The pharmacist makes the choice of medications and the number of medications to be monitored according to the patient's needs. During the 3 h training session, instructions were given on how to select the appropriate medications to be included in an electronic pillbox. A flowchart was developed based on another study [46] in order to assist pharmacists in this process by selecting at least one oral antidiabetic medication (mandatory for the study), and in the following order (if applicable and other electronic pillboxes are desired): medications with adherence problems, antihypertensive medications, antithrombotic medications, and other chronic medications.

The pharmacist remains responsible for checking the compatibility of the medications to be repackaged. The box containing the pills is available in different sizes enabling to fit the quantity and size of the pills. The pillbox is equipped with a cap containing an electronic chip that records the date and time of each opening [47]. The pharmacy team uploads the data recorded in the chip to the web-based platform at each patient visit. Medication adherence is represented by three concepts: implementation, persistence, and adherence [48,49]. Implementation is estimated by the percentage of patients who correctly take all prescribed doses of their medication on one day among all patients who are still persistent on that day. Persistence is the time between initiation and discontinuation of treatment for each patient. Discontinuation occurs when the next dose to be taken is omitted and no further dose is subsequently taken. Adherence is defined as the percentage of patients taking at least all prescribed doses of their medications correctly, among all patients initially included in the study.

General and specific quality of life is assessed using two different self-report questionnaires at baseline, 6 and 12 month follow up. General quality of life is assessed using the Short Form-12® Health Survey SF-12 (version 2, French for Switzerland), which is a 12-item questionnaire covering eight domains of health outcomes also represented by the Physical Component Summary (physical functioning, role physical, bodily pain, general health) and the Mental Component Summary (vitality, social functioning, role emotional, and mental health) [50]. Specific quality of life related to diabetes is evaluated using the Audit of Diabetes Dependent Quality of Life 19 ADDQoL (19-item version, FrCH) [51,52]. This questionnaire includes three parts: global questions, diabetes-specific questions, and questions related to 19 life domains measuring the impact of diabetes on patient quality of life (e.g., physical appearance, self-confidence, and freedom to eat). The pharmacist distributes the questionnaires to the patient who fills it in at home and sends it back to the research team with stamped addressed envelopes.

The patient's satisfaction with the program is evaluated using a self-report questionnaire (for all patients) and through qualitative interviews (for some patients) at the end of the study, i.e., 15 month follow up, or earlier if patient follow up is stopped before 15 months. The research team developed the questionnaire (see Supplementary File 4) and the interview-grid (see Supplementary File 5) based on earlier works [37,39,53]. Main topics are motivational interviews (e.g., content, frequency, and usefulness), electronic pillbox (e.g., convenience and usefulness), and interprofessional collaboration (e.g., perception and satisfaction). The questionnaire also investigates reasons for participation, the willingness to pursue the program after the study and their recommendations. The patient can also write improvements and comments. The questionnaires are distributed by the pharmacist to the patient, auto-administered at home and sent to the research team with stamped addressed envelopes. The qualitative interviews are individual and semi-structured. In order to obtain representativeness of the phenomenon and ensure heterogeneity through interviews [54], patients are selected based on primary criteria (age and gender) and secondary criteria (experience level of pharmacy according to the number of patients included $< $ or ≥ 10 patients, the number of co-treatments and the use of a weekly pillbox in addition to the electronic pillbox). Thus, the minimum sample size is 20 patients and up to data saturation.

The Siscare concept aims, among other aims, to strengthen the involvement of patients in their care and the therapeutic alliance between the pharmacist, referent physician and other caregivers. The observation of interprofessional collaboration will consider four levels of increasing interrelationships: (1) unidirectional transmission of information; (2) bidirectional exchanges of information; (3) concerted measures on objectives calling for complementary skills; (4) sharing of decisions and actions in line with a common objective (see Figure S1 in Supplementary File 1). These data are collected by questionnaires from pharmacists and referent physicians of patients included in the project.

2.10. Data Analysis

Descriptive statistics are used for quantitative data to describe participant and pharmacy characteristics, clinical outcomes (at baseline ± 3 months), quality of life score questionnaires (at

3 time points), patient satisfaction questionnaires and to report implementation results (proportion and number of pharmacies implementing strategies and number of pharmacies going through the implementation stages described in Table 1).

Additional analyses are conducted for clinical outcomes, quality of life, and medication adherence data over 15 months. For clinical outcomes and quality of life, three-level (time, patient, pharmacy) mixed-effects linear regression models are conducted to take into account that data measured on the same patient are not independent, that patients are seen by different pharmacies and that there are several patients per pharmacy. Medication adherence is assessed through implementation, persistence, and adherence (see definitions in 2.9.3. Program effectiveness). For each day, patients behavior regarding their treatment are dichotomized: in "correct", when the patient opens the electronic pillbox at least the number of times prescribed (for all medications if several monitored oral antidiabetics are under electronic pillbox), and in "incorrect", when the patient opens the electronic pillbox less than the number of times prescribed (for at least one medication if several oral antidiabetics are monitored under electronic pillbox). The implementation is represented as a function of time and modeled using the exchangeable Generalized Estimating Equations (GEEs) model, where the time is introduced using polynomials [48,49,55]. Persistence is defined using the Kaplan–Meier estimator [48,49,55]. Adherence is estimated each day of the follow up as a product between implementation and persistence (indirect estimation method) [48,49,55].

With respondents' consent, all focus groups and patient interviews are audio-recorded and transcribed, and data are subjected to formal analysis. Telephone interviews are also audio-recorded if pharmacists consent, and data are introduced into the database immediately after the call.

Microsoft Excel software (Microsoft Office Professional Plus) is used for preparing and coding all data. Descriptive statistics are conducted on Microsoft Excel, specific clinical outcomes and quality of life analysis on Stata (StataCorp, Stata Statistical Software) and medication adherence analysis on R (The R Project for Statistical Computing). MAXQDA Standard 12 (VERBI software GmBH) is used for the analysis of the qualitative data from focus groups and patient interviews. The significance level is set at $p = 0.05$.

3. Discussion

This manuscript describes the protocol of an implementation-effectiveness hybrid type II study of an interprofessional support program for patients with type 2 diabetes in primary care in the French-speaking part of Switzerland.

Using implementation science is crucial to assess the influencing factors for implementation projects and an effective innovation can fail to be implemented if strategies are not appropriate to the setting [36]. Implementation science shows that for behavioral change, strategies are required across multiple stages and levels [56–59]. In this research project, implementation strategies proposed were developed based on evidence from previous research projects [32,36,39]. Needs, barriers, and facilitators for implementation are evaluated continuously. As the information on the identified barriers is shared with Sispha, they adapt the implementation strategies and develop new ones if needed during the implementation (continuous quality improvement process). The collaboration between the research team and the purveyor, Sispha, helps to increase the adoption, implementation and sustainability of this type of support program.

An important component of this study is the provision of a multi-faceted intervention tailored to the patient's needs based on a social, behavioral, and cognitive approach. As the project takes place in a real care situation, the new involvement of the pharmacist, in collaboration with physicians, should have economic consequences that need to be estimated. It is expected that therapeutic goals would be reached at the end of the study period. The increase in better clinical outcomes (e.g., medication adherence) has been shown to increase better glycemic control, preventing complications, emergency department visits and hospitalizations [5]. Taking into account patients' experiences (patient-reported

outcomes) is also a means of strengthening their autonomy and involvement in the management of their chronic disease [60].

Several limitations in this current research project were considered when designing the study. First, our study does not include a comparison group. The analysis occurs on data over time and with before and after testing, and must take into account the fact that results may be influenced by factors other than the patient support program. Second, quality of life and patient satisfaction assessment are self-reported, and these data can be subject to bias. However, to minimize that bias, stamped addressed envelopes are delivered to the patients so that they can fill out the questionnaires at home and send them to the research team without passing through the pharmacies. Data are kept anonymous. Third, the study is proposed to pharmacies subscribed to Sispha. However, this is a selection of pharmacies that are more innovative, called the "early adopters," and may not represent the majority. Nevertheless, all pharmacies were free to subscribe to Sispha for participating in the study.

4. Conclusions

This project aims to implement the Siscare concept as a collaborative patient support program for chronic patients such as those with type 2 diabetes. The scientific evaluation observes the process in stages, which will provide insights on both the effectiveness and the identified barriers and facilitators for its implementation in primary care. In particular, the results will add new knowledge on the recommendations regarding the need to adapt the framework conditions (e.g., strategies and cost) to broaden the application of these collaborative models.

Supplementary Materials: The following is available online at http://www.mdpi.com/2226-4787/8/2/106/s1, Figure S1: Flowchart of a patient, physician and pharmacist in the study; patient information and consent Form (Supplementary File 2); Table S3: List of instructional material delivered during the first training; patient satisfaction questionnaire (Supplementary File 4); and patient interview grid (Supplementary File 5).

Author Contributions: N.B.: Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Resources, Writing—Original Draft, and Project Administration. J.C.M.: Conceptualization, Methodology and Writing—Review and Editing. C.P.: Conceptualization, Methodology, Writing—Review and Editing, Supervision, Project Administration, and Funding Acquisition. O.B.: Conceptualization, Methodology, Writing—Review and Editing, Supervision, Project Administration, and Funding Acquisition. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Swiss Federal Office of Public Health (FOPH), grant number: 15.003846, and the joint Swiss fund of quality and research RPB IV/1, grant number: 20160201, including santésuisse, Curafutura (both umbrella associations of health insurers) and pharmaSuisse (Swiss association of pharmacists) as sponsors.

Acknowledgments: The authors would like to acknowledge the funding bodies (FOPH, pharmaSuisse, santésuisse, curafutura) and all the pharmacy teams who participate in the program proposed by Sispha. The views expressed are those of the authors and not necessarily those of the funding bodies.

Conflicts of Interest: O. Bugnon is a co-founder of Sispha SA and is a member of the advisory board of Sispha SA. The other authors declare that they have no competing interests. The funders have no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results. Bi-annual meetings were organized with the FOPH (and the steering committee) to monitor the results and the study progress.

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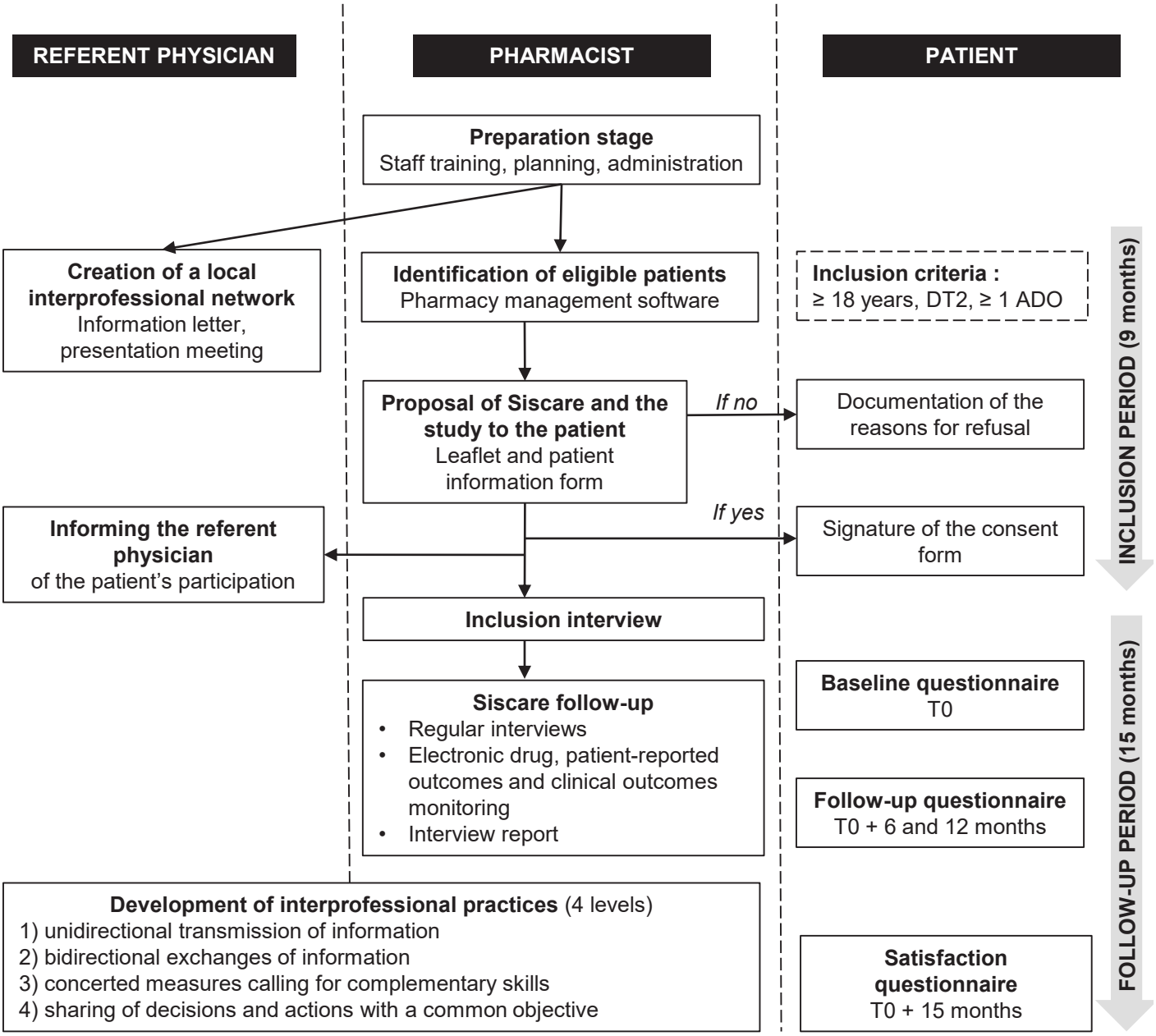
Supplementary File 1

Figure S1: Flowchart of a patient, physician and pharmacist in the study



Supplementary File 2: Patient Information and Consent Form

Patient Information

Evaluation of an interprofessional support program for patients with type 2 diabetes (pilot project Siscare-DT2) and its implementation in the French-speaking part of Switzerland.

The University Medical Policlinic (PMU) of Lausanne conducts this study in collaboration with partner physicians and pharmacists in your region.

Dear Madam, Dear Sir,

You are currently on a treatment regimen that includes at least one oral antidiabetic drug. To help you with your medication intake, your pharmacist and your physician suggest that you participate in a program called Siscare and a study to evaluate the impact of this program on your health.

Siscare allows you to benefit from personalized support, provided by your pharmacist in coordination with your physician. One of its objectives is to reinforce and optimize the safety of your treatment.

To carry out this support, personal data concerning your treatment and your health are collected by your pharmacist, then managed and stored on a secure computer platform.

This information sheet informs you about how your data are used in the study and about your rights. Please take the time to read and understand it.

1. Selecting who can participate in the study

The study is offered exclusively to adults who have been diagnosed with type 2 diabetes and are taking at least one oral antidiabetic drug.

2. Objectives and goals of the study

This study responds to a request from the Federal Office of Public Health (FOPH) to evaluate Siscare among patients with diabetes and to analyze its implementation in the French-speaking part of Switzerland.

The aim of this study is:

- To understand the process and factors associated with the implementation of the program, and
- To observe the impact of your participation in this program on your health.

3. General information about the study

The study takes place in the context of research on medication adherence for patients with chronic diseases and of national concern for quality of care.

The study begins April 1, 2016 and ends March 31, 2018 (later extended to until 30 September, 2018), with a 15-month patient follow-up. The phase during which patients may be included in the study runs from April 1, 2016 to December 31, 2016 (later extended to June 30, 2017). We plan to include at least 200 patients in the French-speaking part of Switzerland.

We are conducting this study in accordance with the requirements of Swiss legislation. In addition, we comply with all internationally recognized guidelines. The competent cantonal ethics commission has monitored and authorized the study.

4. Study procedure for participants

Your participation in this study involves following steps:

- a tailored support by your pharmacist in coordination with your physician (Siscare); and
- an evaluation of Siscare through questionnaires and, if you expressly consent, one-on-one telephone interviews between you and the principal investigator of the study mentioned below.

5. Description of Siscare

The accompaniment program includes the following steps and services:

- interviews of approximately 20 minutes, at least every three months (the theoretical frequency related to the renewal of your prescription(s), with your pharmacist in the pharmacy concerning the medication intake (including a "polymedication" interview, which is a counselling interview during which the pharmacist reviews the medications taken by the patient);

- careful monitoring of your quality of life and possible adverse effects (in accordance with the regulations set out in Article 59 of the Federal Law on Medicinal Products and Medical Devices);

- measurement of your treatment by means of an electronic pillbox system;

- sharing information with your physicians (shared treatment plan and coordinated follow-up).

The duration of participation in the support program depends on your own needs.

6. Scientific assessment

For the scientific evaluation, we ask you:

- To fill out a questionnaire that evaluates your quality of life and health status three times during the study period (at the beginning, 6 and 12 months later) and a final evaluation questionnaire (at the end of the study). These will be given to you by your pharmacist. You can then complete it at home (about 10 minutes) and return it to the address indicated using the postage-paid envelope.
- With your specific agreement, to participate in telephone interviews with the study investigators in order to find out more about your perception of the Siscare support program in which you are participating. The interview is open-ended and will be audio recorded. It will last a maximum of 30 minutes.

7. Participant rights

Your participation in this study is voluntary. No one has the right to pressure or influence you in any way. Refusing to take part will not affect your future medical care. The same principle also applies if your initial consent is revoked. You can therefore withdraw your participation at any time without giving reasons.

If you withdraw your consent, your personal data will be anonymized after it has been analyzed in accordance with Article 10 of the Human Research Ordinance, unless you expressly waive your consent at the time of withdrawal.

You may at any time ask any questions you consider necessary in connection with this study to the persons mentioned below.

8. Benefits for participants

Your participation advances knowledge to optimize coordination and quality of care.

9. Risks and constraints for participants

There are no particular risks associated with the study.

10. Confidentiality of data

The data collected by your pharmacist are information concerning your health, in particular data concerning your treatment (medication, dosage) and your illness (diagnosis, medical history), your positive or negative feelings in relation to your follow-up. Your pharmacist records these data in a secure computer platform managed by the company SISPha SA. Your pharmacist and your physician can have access to your data stored in the platform as well as technicians of the IT platform and only within the context of interventions strictly essential to the good functioning of this platform.

Use of your coded data for the study

For the purposes of this study, the data are coded. Coding means that any data that identifies you (e.g., name, date of birth, etc.) is replaced by a code, so that people who do not know this code cannot link this data to you. Within the research group of the University Medical Policlinic, the data can be consulted by authorized and clearly designated investigators, even in uncoded form. The code remains permanently within the research group of the University Medical Policlinic.

The persons within the institution of the Lausanne University Medical Policlinic authorized to access your data are:
- Noura Bawab, principal investigator, Pharmacist PhD student
- Dr. Clémence Perraudin, co-investigator
- Prof. Olivier Bugnon, Principal Investigator

Furthermore, your name may not be published in any reports or publications resulting from this study.

For how long are your data processed and stored?

Your data will be collected until the end of the study unless you revoke your consent.

The research group of the University Medical Policlinic of Lausanne will keep a copy of your coded data for legal reasons for a period of at least ten years from the end of the study.

How can you access your data?

You may at any time request in writing to know the content of the data concerning you recorded on the platform as well as that collected by the University Medical Policlinic research group. You can address your request to your pharmacist, your physician or directly to SISPha SA.

11. Fees

The services are billed to your health insurance company in accordance with the rules in force.

Your basic health insurance will cover the cost of multiple drug therapy (LAMal benefits) if you take at least four drugs at the same time over a period of at least three months.

The follow-up of your treatment by means of weekly pillbox system is also covered by your basic health insurance, as long as you take at least three different specialties in the same week.

If fewer drugs are taken, the costs will be covered by your pharmacist.

12. Remuneration of participants

There is no financial benefit to you for participating in this study.

13. Financing of the study

The study is funded by the Federal Office of Public Health (FOPH), pharmaSuisse and santésuisse.

14. Contact persons

If you have any doubts, fears or needs during or after the study, you can contact one of the following people at any time:

Concerning the study:
Mme Noura Bawab
Policlinique Médicale Universitaire,
Rue du Bugnon 44, 1011 Lausanne
Email : Noura.Bawab@hospvd.ch
Tel : 021.314.48.46

Concerning Siscare (SISPha SA):
M. Christophe Rossier
SISPha SA,
Technopôle 3, 3960 Sierre
Email : Christophe.Rossier@sispha.com
Tel : 079.216.35.62

Do not hesitate to ask for any further information you need. If you wish, you can be given the rules of the database, on simple request. We are at your entire disposal.

Written statement of consent for participation in an support program and study

- Please read this form carefully.
- Do not hesitate to ask questions if you do not understand something or if you need clarification.

Title of the study:	**Evaluation Study of the Siscare-DT2 Pilot Project**
Investigator-in-Charge:	Prof. Bugnon Olivier
	University Medical Policlinic
	Rue du Bugnon 44, 1011 Lausanne
	Tél : +41 21 314 48 42
	Olivier.Bugnon@hospvd.ch
Location of the study:	University Medical Policlinic

Siscare pharmacist

Full name:

Patient

Full name:

Date of birth:

Gender ☐ Male ☐ Female

- I declare that I have been informed orally and in writing by my pharmacist of the objectives and conduct of the study, the presumed effects, possible advantages and disadvantages.
- I certify that I have read and understood the written patient information provided to me about this study, dated .....
- I received satisfactory answers to the questions I asked about my participation in this study. I retain the written patient information sheet and receive a copy of this consent statement.
- I have been informed of the possibility of continuing my follow-up with Siscare outside of my participation in this study.
- I have been given sufficient time to make my decision.
- I also know that my personal data will be scientifically analyzed in a coded form.
- I agree that the competent specialists of the study trustee, the authorities and the Ethics Commission may consult my raw data in order to carry out examinations and checks, provided, however, that their confidentiality is strictly ensured.
- I am taking part in this study on a voluntary basis. I may, at any time and without having to provide any justification, revoke my consent to participate in this study, without suffering any inconvenience whatsoever in my subsequent medical and pharmaceutical follow-up.
- I am aware that the requirements mentioned in the information sheet to patients will have to be met for the duration of the study. The pharmacist may exclude me from the study at any time in the interest of my health.

☐ I consent to my data collected as part of Siscare being made available to my physician; I also consent to my physician providing certain medical information to enhance the coordination of my care.

☐ I consent to be called for an individual interview with the investigators.

Place, date	Patient signature

Pharmacist's certification: I certify by my signature that I have explained to this patient the nature, importance and scope of the study. I declare that I have fulfilled all obligations in connection with this study. Should I become aware, at any time during the study, of information that could affect the patient's consent to participate in the study, I undertake to inform the patient immediately.

Place, date	Pharmacist signature

Supplementary File 3

Table S3: List of instructional material delivered during the first training

Sispha material
1. Organizational checklist for the implementation at the pharmacy 2. Program leaflet 3. A team rationale (how to respond to FAQs from the team and from patients) 4. Patient inclusion diagram 5. Patient follow-up diagram 6. Procedures of patients motivational interviews: (a) first visit, (b) drafting of the interview report, (c) follow-up visit 7. Algorithm for the selection of medications to be monitored by the electronic pillbox 8. Presentation slides (a) First training (b) For physicians (c) For medical assistants (d) For pharmacy technicians 9. Collaboration with physicians (a) Information letter for physicians (b) Practical procedure for collaboration with physicians (c) Examples of letters to send to physicians (d) Information document for medical assistants (e) A rationale for physicians 10. Various tools (a) Diary for the pharmacy (b) Procedure for identifying eligible patients through a billing system (c) Example of a letter that could be sent to eligible patients (d) Histogram of patient inclusion follow-up (e) Information for patients
Research team material
1. Patient follow-up schedule 2. Participation refusal document 3. Quality of life generic questionnaire SF12 4. Quality of life specific questionnaire ADDQoL 5. Patient information and consent form 6. Study protocol 7. 10 patients files including for each: an information and consent form and 4 envelopes to be given to the patient (at T0 months, T0+6months, T0+12months, T0+15 months)

Supplementary File 4: Patient satisfaction questionnaire (translated from French)

<u>These questions are about your overall thoughts on the program</u>

What are the reasons for participating in this follow-up program?
(Multiple answers allowed)

- ☐ Because I was recently diagnosed
- ☐ Because I was starting a new treatment
- ☐ To be supported in the daily intake of my treatment
- ☐ For help in managing my illness
- ☐ Being able to discuss my illness and treatments with a healthcare professional other than my physician
- ☐ For Fear of treatment side effects
- ☐ To please my pharmacist
- ☐ To advance research
- ☐ Out of curiosity
- ☐ I don't know
- ☐ Other reasons (please specify) : ……..

How often do you think you need the help of a pharmacist for the daily intake of your medications?
(One answer allowed)

- ☐ Always
- ☐ Often
- ☐ Rarely
- ☐ Never
- ☐ I don't know

<u>These questions are about how you feel about the pharmacist interviews</u>

Were the interviews with the pharmacist useful?
(One answer allowed)

- ☐ Very useful
- ☐ Quite useful
- ☐ Rather useless
- ☐ Very useless
- ☐ I don't know

How much did the interviews with the pharmacist help you to...?

(One possible answer per line)

	A lot	Fairly	A bit	Not at all	I don't know
• … understand your treatment	☐	☐	☐	☐	☐
• … integrate the treatment into your life	☐	☐	☐	☐	☐
• … keep you motivated	☐	☐	☐	☐	☐
• … deal with difficult moments, moments of doubt	☐	☐	☐	☐	☐
• … take your medications	☐	☐	☐	☐	☐
• … manage side effects of your treatment	☐	☐	☐	☐	☐
• … react correctly in particular situations (weekends, outings, holidays, etc.)	☐	☐	☐	☐	☐
• … talk about how your feelings regarding your treatment, about your illness	☐	☐	☐	☐	☐

Other improvements noted as a result of this program (please specify):……...
……
……

During interviews with the pharmacist, how often did you have the opportunity to express any problems encountered in taking your medications?

(One answer allowed)

- ☐ Always
- ☐ Often
- ☐ Rarely
- ☐ Never
- ☐ I don't know

Did you discuss the adherence graph with your pharmacist during interviews?

(One answer allowed)

- ☐ Always
- ☐ Often
- ☐ Rarely
- ☐ Never
- ☐ I don't know

If you discussed the adherence graph during the interviews, was it useful?

(One answer allowed)

- ☐ Very useful
- ☐ Quite useful
- ☐ Rather useless
- ☐ Very useless
- ☐ I don't know

What is the reason for that?

……
……
……
……
……
……

During the follow-up, how did you feel...?

(One possible answer per line)	Always	Often	Rarely	Never	I don't know
• …monitored	☐	☐	☐	☐	☐
• …encouraged	☐	☐	☐	☐	☐
• …helped	☐	☐	☐	☐	☐

- Other pleasant or unpleasant feelings (please specify):……..
  ……

Was the duration of the interviews with the pharmacist...?
(One answer allowed)

- ☐ Too long
- ☐ Adequate
- ☐ Too short
- ☐ I don't know

Was the frequency of the interviews with the pharmacist... ?
(One answer allowed)

- ☐ Too high
- ☐ Adequate
- ☐ Not enough
- ☐ I don't know

<u>These questions are about what you think of the electronic pillbox</u>

Were the pillboxes useful?
(One answer allowed)

- ☐ Very useful
- ☐ Quite useful
- ☐ Rather useless
- ☐ Very useless
- ☐ I don't know

How easy was it to use the pillboxes in your daily life?
(One answer allowed)

- ☐ Very easy
- ☐ Quite easy
- ☐ Rather difficult
- ☐ Very difficult
- ☐ I don't know

Has the display (LCD screen) of the electronic pillbox been a useful reminder in daily life?
(One answer allowed)

- ☐ Very useful
- ☐ Quite useful
- ☐ Rather useless
- ☐ Very useless
- ☐ I don't know

To wat extent did you find the electronic pillbox cumbersome?
(One answer allowed)

- ☐ Not at all cumbersome
- ☐ Space-saving
- ☐ Rather cumbersome
- ☐ Very cumbersome
- ☐ I don't know

These questions concern the collaboration between your physician and pharmacist

How do you perceive the collaboration between your pharmacist and your physician?
(One answer allowed)

- ☐ Very present
- ☐ Relatively present
- ☐ Not very present
- ☐ Inexistent
- ☐ I don't know

Do you think the collaboration between your physician and pharmacist has improved your care management? *(One answer allowed)*

- ☐ A lot
- ☐ Fairly
- ☐ A bit
- ☐ Not at all
- ☐ I don't know

Continuation

Would you like to continue this program?
(One answer allowed)

- ☐ Yes, without a doubt
- ☐ Pretty much
- ☐ Not really
- ☐ No, I don't
- ☐ I don't know

What is the reason for that?
……
……

Recommendation

Would you recommend the program to another person with diabetes? *(One answer allowed)*

- ☐ Yes, without a doubt
- ☐ Pretty much
- ☐ Not really
- ☐ No, I don't
- ☐ I don't know

What is the reason for that?
.....
…….

Improvement

If you were in charge of this program, what would you change to improve it?

……
……
……
……

Further information

Do you have any comments (remarks, suggestions, etc.) to make about your diabetes monitoring by the pharmacist?

……
……
……
……

Supplementary File 5: Patient interview grid (telephone interviews)

Themes	Questions	Follow-up questions	Notes
Siscare	• What are the reasons for participating in this program?	• How much do you think you need a pharmacist's help with your daily medications?	
Pharmacist interviews	• How would you rate the usefulness of the interviews with the pharmacist? • What did you get out of the interviews with the pharmacist? • [If you discuss the adherence chart with the pharmacist] What do you get out of discussing adherence charts with the pharmacist?	• How would you rate the length of your visit to the pharmacist? • How would you rate the frequency of meetings with the pharmacist? • If so, how were they helpful? • If not, what improvements would you recommend? • How has the program helped you talk to your pharmacist about medication use? • How did you feel during the follow-up?	
Electronic pillboxes	• How do you rate the usefulness of these pillboxes ?	• How did you integrate the pillboxes into your daily life? • What are the advantages and disadvantages of the pillbox?	

Interprofessional collaboration	• How do you perceive the collaboration between your pharmacist and your referent physician?	• Do you think the collaboration between your physician and pharmacist has improved your care?	
Continuation/ stop	• [If patient still in program] Would you like to continue this program? • [If patient has discontinued program] Why did you stop tracking?	• Why?	
Recom-mendation	• Would you recommend the program to another person with diabetes?	• Why?	
Impro-vement	• What recommendations would you make to improve the program?	• Would you change anything in the program?	
Ending	• Is there anything else we haven't talked about that you think is important to talk about now?	-	
Questions (verificatio n)	• Can you confirm your date of birth? (DD.MM.YYYY) • Do you have a weekly pillbox at home? (Whoever prepares it) • Are you taking more than 4 oral medications over a period of at least 3 months?		..... ☐ YES ☐ NO ☐ YES ☐ NO
Acknowledgements			

Chapter 3. Implementation Results

Implementation Evaluation of an Interprofessional Programme for Supporting Patients (Siscare) with Type 2 Diabetes in a Swiss Primary Care Setting

Chapter 3 presents the results of the implementation of Siscare-DT2 and the appropriateness of the strategies from a pharmacy's perspective in a primary care setting in the French-speaking part of Switzerland.

This chapter is presented as a paper to be submitted to the journal *Research in Social and Administrative Pharmacy*. Noura Bawab contributed to this article through the conception and design of the study, the conduct of the research and investigation process, the analysis and interpretation of the data, and the writing of the manuscript.

In the appendices of the thesis manuscript, additional documents are available in French:

Implementation Evaluation of an Interprofessional Programme for Supporting Patients (Siscare) with Type 2 Diabetes in a Swiss Primary Care Setting

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Abstract

Background: In 2016, the Swiss federal government decided to back the implementation of an interprofessional patient support programme to take a position on the evolution of the pharmacist's role. The programme includes regular motivational interviews by pharmacists; medication adherence, patient-reported outcomes, and clinical outcomes monitoring; and pharmacist-physician interactions. The aim of this study is to assess from a pharmacy team's perspective the implementation of this programme for patients with type 2 diabetes taking at least one oral antidiabetic treatment, followed for 15 months, in a primary care setting of the French-speaking part of Switzerland.

Methods: This prospective, multicentre, observational, cohort study used a hybrid implementation-effectiveness design and the Framework for the Implementation of Services in Pharmacy (FISpH). Quantitative and qualitative methods assessed outcomes at each stage of the implementation process: exploration, preparation, operation, sustainability. We report a set of implementation indicators: process, outcomes and impact.

Results: An Advisory Board with 10 representatives of key national stakeholders including health authorities, physicians, pharmacists, and insurers committed to supporting the study and forty-one pharmacies were trained for the programme (*adoption*). Of these, 33 (80%) had at least one of five implementation strategies in place (*introduction*) 12 weeks after the start of the study and 27 (66%) have included at least one patient (*initial operation)*; mean inclusion per pharmacy = 8 (SD 6) patients [range: 1-29] with a total of 212 patients included across all pharmacies. Nine pharmacies (22%) met the target of 10 patients (*full operation*). We observed a common step-by-step implementation process: 1) internal organisation: coaching of staff, identification of eligible patients, 2) preparation of interprofessional practice: information and local networking with physicians; 3) relationship building with the patients. Main influencing factors identified were pharmacists' skills in motivational interviewing, support from pharmacy owners, pre-existing local interprofessional networks and profitability of the programme.

Conclusions: This implementation evaluation supports the feasibility and acceptability from the pharmacy team's perspective of the interprofessional diabetes programme. The programme's implementation on a wider scale is still fragile due to the inertia inherent in any fundamental change in practices and the economic-political uncertainties influencing the actors in primary care.

Keywords: Community pharmacy, Health Service Research, Implementation practice, Implementation science, Interprofessional collaboration, Patient Support, Type 2 diabetes, Hybrid design

Background

Chronic diseases are a major public health problem affecting 20 to 30% of the population [1] and accounting for 73% of all deaths [2]. Consequences of chronic diseases include disability, depression, distress, poor quality of life [1], and high resource utilization and costs [3]. Diabetes is one of the most common chronic diseases, affecting 9.3% of the world's population, or 463 million people, and is responsible for the deaths of 4.2 million people each year [4]. According to the World Health Organization, deaths linked to chronic diseases are preventable and actions based on latest scientific evidence and/or best practices, cost-effectiveness, affordability and public health principles should focus on chronic disease control [2,5]. In Switzerland, the government has developed a national strategy to prevent chronic diseases, delay their onset or reduce their consequences [6]. The plan includes strengthening self-management among people with chronic diseases, with for example, a chronic care model [6].

Chronic care models are needed to ensure that patients with chronic diseases receive the best-individualized care and benefit from the latest therapeutic advances. The chronic care model is an organizational approach that allows for the creation of practical, proactive, and evidence-based support for patients [7]. A recent literature review focusing on programmes related to diabetes, hypertension and cardiovascular diseases has shown benefits of implementing a chronic care model in terms of medication adherence, promotion of health behaviours, satisfaction with clinical care, and reduced medical burden [8].

An example of a chronic care model developed and implemented in the Community Pharmacy at the Centre for Primary Care and Public Health (Unisanté), University of Lausanne, Switzerland in 2004 is a patient support programme to optimize medication adherence and patient safety, and promote interprofessional collaboration [9-11]. HIV patients were first targeted and then as this activity became a routine activity it was extended to patients with chronic or acute diseases [11]. This programme, named Siscare, includes three components: (a) regular motivational interviews between a patient and their pharmacist, (b) medication adherence, patient-reported outcomes, and clinical outcomes monitoring and (c) interactions between physicians and pharmacists.

The Swiss Federal Office of Public Health decided to promote the implementation of Siscare [10-12], in primary care settings outside of Unisanté, as a strategy leading to equal access for chronic patients and socially beneficial results.

Methods

The aim of this paper is to describe the implementation results of Siscare for patients with type 2 diabetes (T2D), Siscare-DT2, in the daily practice of primary care from the pharmacy teams' perspective in the French-speaking part of Switzerland. The results on interprofessionality and the effectiveness of the intervention are detailed in other papers (to be submitted shortly).

Study design

This research is part of a larger study that used an implementation-effectiveness hybrid type II design [13] through data from a prospective, multicentre (several patient inclusion centres and one research centre), observational study combining qualitative and quantitative methods. The research protocol including the full methodology has been reported elsewhere [14]. In the present paper, the

implementation process, outcomes and impact of Siscare-DT2 is reported from the pharmacy teams' perspective. We adhered to StaRI guidelines (Standards for Reporting Implementation Studies) [15].

Theoretical implementation framework

Recently, multiple implementation frameworks of interventions in healthcare have been developed [16]. In this study, we used the Framework for the Implementation of Services in Pharmacies (FISpH) which is adapted for community pharmacy settings and based on the Generic Implementation Framework (GIF) [17,18]. Moullin et al. developed the GIF after conducting a literature review of existing frameworks models and collating the core concepts [16]. The core concepts are the intervention to be implemented; the process of implementation (divided into the four stages, based on the Exploration, Preparation, Implementation, Sustainment framework (EPIS) [19,20]); and the multi-level context (divided into domains: individuals, pharmacies, local setting and system) in which the implementation is to occur, influenced by factors (tailored for pharmacy from the Consolidated Framework for Implementation Research (CFIR) [21] and the theoretical domains framework (TDF) [22]), strategies, and evaluations. More specifically the stages of the implementation process are: (i) *exploration*: the intervention-decision process whereby the end-user(s) appraise the intervention concluding with a decision to either accept/adopt or reject; (ii) *preparation*: the course of preparing prior to intervention use; (iii): *operation*: the intervention is in use and is in the process of being integrated into routine practice through active and planned approaches; (iv) *sustainability*: the process of maintaining the intervention through continued innovation use and improvement, ongoing capacity and support [17].

Clinical intervention

Siscare is an interprofessional patient support programme including (a) regular motivational semi-structural interviews (between the patient-community pharmacist) at least every three months; (b) medication adherence monitoring by electronic pillbox (Medical Event Monitoring System MEMS, Aardex [23]) and patient-reported and clinical outcomes monitoring; (c) and feedback reports for the referent physician[1] to the pharmacist to ensure information sharing and a starting point for collaborative patient care. The programme aimed to contribute to reach patients' individual therapeutic goals and improve their general health, to support medication adherence and strengthen continuity of care between the different healthcare professionals involved in the patient care pathway.

Sispha (Ofac group, Lausanne, Switzerland) is a purveyor developing smart and innovation solutions for a network of community pharmacies wishing to implement patient-centred services [24]. Sispha designed a secure web platform for Siscare to support and structure the pharmacist intervention with a semi-standardized systematic process for the intervention to be delivered. The platform combined electronic pharmaceutical and medical information, an electronic monitoring data uploading system, a clinical-decision making support system coupled with a safety alarm system and an archiving system, and instructional material [10]. Moreover, Sispha proposes training and coaching services to help pharmacies implement and deliver patient-centred programmes.

Setting

The study population included participating pharmacies, patients with T2D, their referent physician (and any other relevant health professionals participating in the patient care pathway), and the

[1] Physician of the patient's choice, general practitioner or specialist, responsible for coordinating the patient's diabetes care.

purveyor – Sispha. Any community pharmacy in the French-speaking part of Switzerland[2] belonging to the Sispha network could take part in the study and leave the network or the study at any time. Joining Sispha involves paying an annual fee, which provides access to their web platform, training and coaching services. Eligible patients were adults (≥18 years) diagnosed with T2D, that took at least one oral antidiabetic medication. Exclusion criteria were patients with a diagnosis of type 1 diabetes, obvious cognitive impairment, or insufficient language level of French. Eligible patients were recruited either in pharmacies that were part of the Sispha network or partner general practices.

Implementation strategies

The core implementation strategies are summarized across the implementation stages in Table 1. The implementation strategies were assessed by audits of participating pharmacies after the end of the patient inclusion period and by telephone interviews at 5 and 12 weeks after the start of the study.

Table 1 - Description of the implementation strategies according to the stages of the implementation process [17]

1. Exploration
• Recognition of the project by the Swiss Federal Office of Public Health and stakeholders
• Establishment of an interprofessional steering committee
• Information to healthcare professional associations
• Recruitment of pharmacies through Sispha
2. Preparation
• Pharmacy staff training
• Toolkit: Siscare leaflet, instructional material, access to secure web-based platform
• Assignment of a project manager in each pharmacy
• Creation of a list of eligible patients through the pharmacy database
• Creation of local interprofessional networks by the pharmacists
• Information to healthcare professional associations
3. Operation
• Use and continuous improvement of the toolkit
• Information provision to patients (Siscare leaflet, advertisement and invitation letter)
• Coaching service (telephone calls and newsletters) and ongoing training adapted to specific needs
• Continuous development of interprofessional networks
• PDCA (Plan, Do, Check, Act) monitoring and feedback to participants
4. Sustainability
• Use and validation of the toolkit
• Ongoing training of pharmacy staff
• Continuous development of interprofessional networks
• Publication of findings and recommendations by the research team to the Swiss Federal Office of Public Health for improving the quality and sustainability of Siscare

Measures and data collection

We assessed the implementation process by monitoring progress indicators in the different stages [17]. The impact of implementation, also commonly described as proximal indicators of the implementation process [26] or mediators/moderators [27] in the literature, has been assessed through strategies and factors (including evaluations). The implementation outcomes were depicted at the level of service provision (how much and how well the service was being delivered) and of service provider (support provided and integration of the programme into their routine practice) in the service environment. We used qualitative and quantitative methods (see Table 2 for detailed outcomes).

[2] The French-speaking part of Switzerland is located in the western part of Switzerland and includes seven cantons. It covers 25% of the Swiss population, accounting for 2.1 million persons in 2019 [25].

Table 2 - The implementation process, impact and outcomes from a pharmacy team's perspective [17].

			STAGES			
			Exploration	**Preparation**	**Operation**	**Sustainability**
IMPLEMENTATION	**PROCESS**	**Implementation process evaluation**	*Awareness*: number of pharmacies aware of Siscare *Adoption*: number and representativeness of volunteer participating pharmacies (registered and trained)	*Introduction:* number of pharmacies implementing at least one implementation strategy (assessed during telephone interviews)	*Initial operation*: number and representativeness of pharmacies providing Siscare to at least at one patient *Full operation*: number of pharmacies reaching the target number of included patients (≥10 patients)	*Initial sustainability*: number of pharmacies willing to follow patients after 15 months and still following 10 patients during 15 months
	IMPACT	**Strategies**	Usefulness of Sispha's strategies (assessed by focus groups and telephone interviews with pharmacists during the preparation stage; by focus groups and audits in pharmacies during the operation stage)			
		Factors	Factors affecting implementation across all contextual domains/levels (assessed by focus groups) Pharmacists' satisfaction (assessed by focus groups and audits for pharmacists)			
	OUTCOMES	**Level of service provision**	*Reach*: number of patients included, general patient characteristics, monitoring of inclusions/refusals, stops, retention in the programme *Fidelity*: extent to which the programme is delivered as defined: frequency (at least every 3 months), duration (15 to 20 minutes) and methodology (motivational approach) of patient-pharmacist interviews; and adaptations made by pharmacies to deliver the programme; including • *Monitoring tools*: the use of the electronic pillbox for longitudinal measurement of medication adherence; and • *Platform use and report*: writing of a report that is sent to the patient (if desired) and the referent physician			
		Level of service provider	*Integration:* incorporation of Siscare into daily practice *(Strength of) Support:* acceptability of service by pharmacy teams (such as culture, climate, and capacity)			

Pharmacy use of the implementation strategies was assessed through telephone interviews at 5 and 12 weeks after the start of the inclusion period, indicating the proportion of pharmacies that had implemented the strategies. The interviews included standardized questions on five main topics, from the preparation and initial operation stages, on the pharmacy's internal organization and the local network with physicians and other healthcare professionals.

In addition, semi-structured focus groups with volunteer pharmacists were conducted to explore the factors influencing implementation during the preparation and operation stages of programme delivery and assessed pharmacists' satisfaction with the programme. Two semi-structured focus groups were organised during different stages: i) two sessions during the inclusion [preparation stage] period (November 2016) with a total of 17 volunteer pharmacists from 12 pharmacies, ii) two sessions during the operation phase (May 2018) with a total of 11 pharmacists from 11 pharmacies that had included at least one patient.

Sample size

At the time of submitting the protocol to the Ethics committee, 35 pharmacies were part of the Sispha network. According to the experience of the research team and Unisanté, it was expected that 20 pharmacies would accept to take part in the study. A target of 10 patients per pharmacy was set based on an advisory group of pharmacists with expertise in implementation, pharmacy services and community pharmacy. Sample size was therefore estimated to 200 patients.

Data analysis

Descriptive statistics (mean, standard deviation, minimum and maximum) were used for quantitative data: patient and pharmacy characteristics and implementation outcomes. Microsoft Excel (Microsoft Corporation, Redmond, USA) was used for preparing and coding all data and computing descriptive statistics.

With respondents' consent, all focus groups were audio-recorded, transcribed, and data were subjected to formal analysis. Telephone interviews were also audio-recorded with pharmacist's consent; data were introduced into the database immediately after the call and completed by referring to the audio recording if needed. MAXQDA Standard 12 (VERBI software GmBH) was used for the analysis of the focus groups. A list of themes was chosen (thematic analysis) from a list of factors that could influence the implementation process in each context domain [18] and according to the topic guide. For each theme, the most frequently cited influence factor is presented.

Results

Implementation process

Fig. 1 describes the indicators of progress along the implementation process.

During the exploration stage, the 47 pharmacies registered to Sispha (7% of the 662 pharmacies in the French-speaking part of Switzerland [28]) were informed by mail of the Siscare-DT2 programme (*awareness*) and 41 (87%) volunteered to take part in the Siscare-DT2 project and to train (*adoption*). The inclusion of these pharmacies in the study took place in two waves (wave 1: inclusions from April 2016 and wave 2: inclusions from January 2017).

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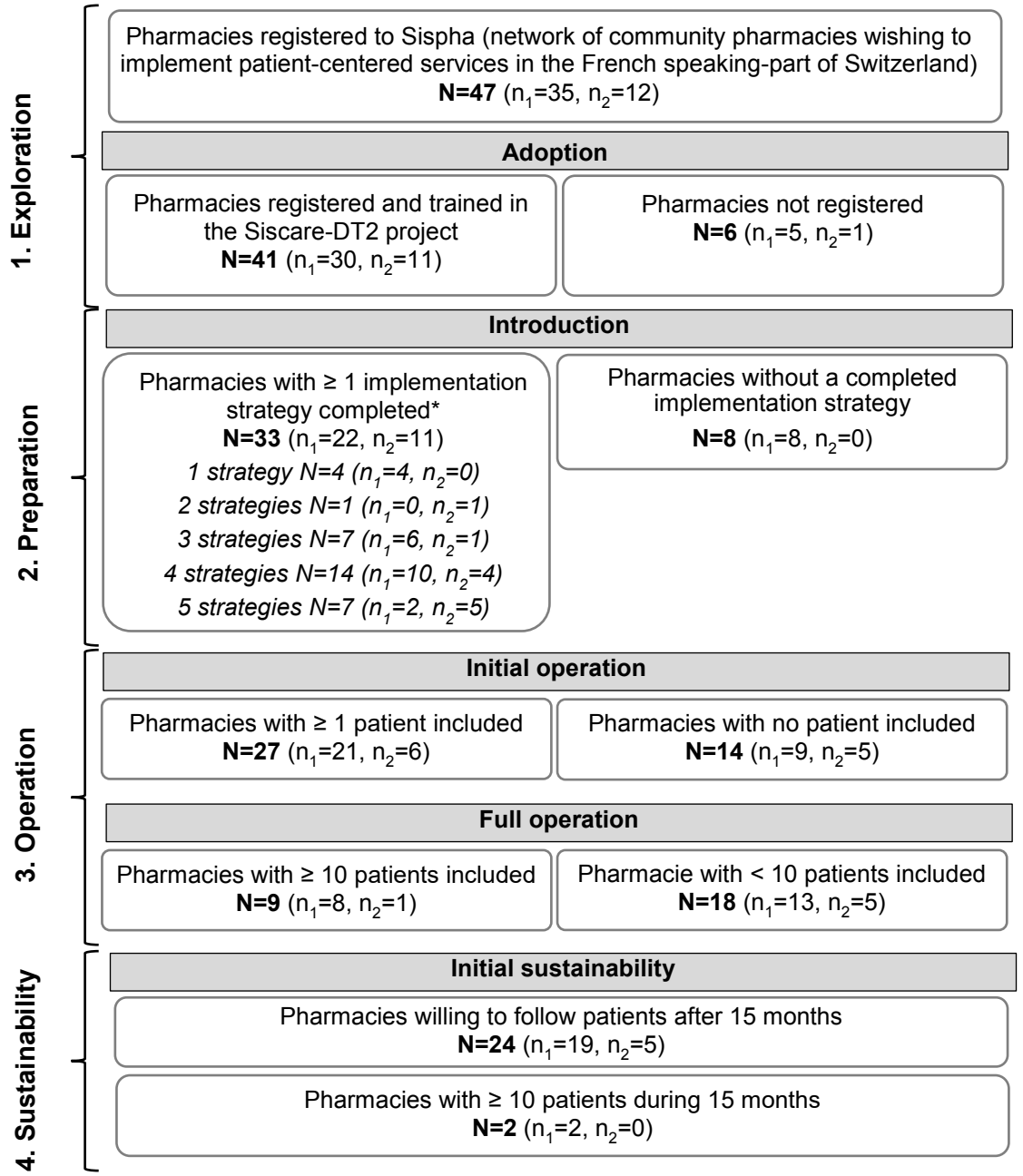
Fig. 1 - Indicators of progress of the Sicare-DT2 implementation process in the pharmacies



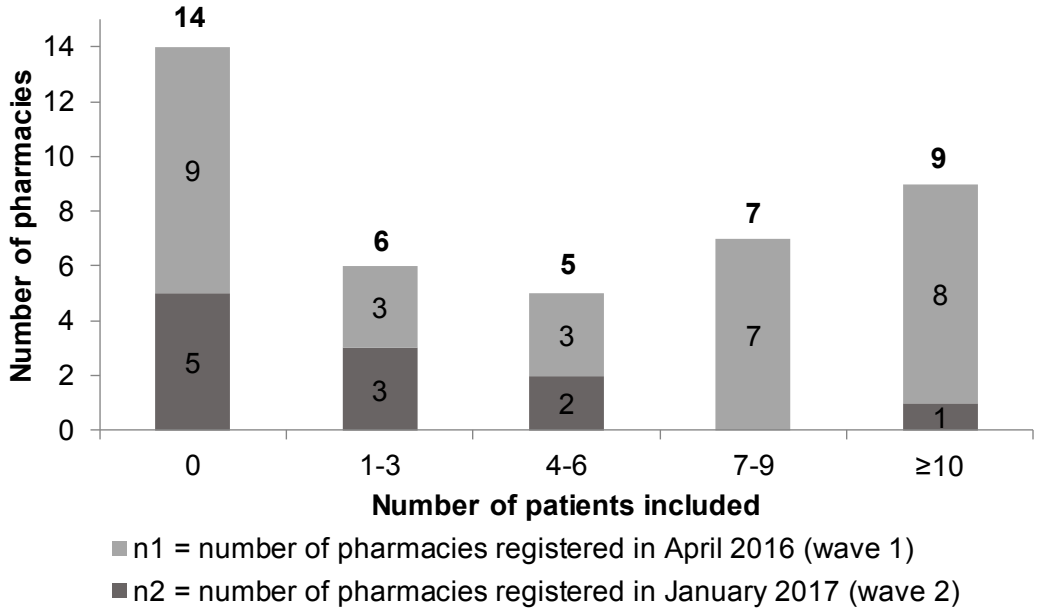
Legend: **N=** total number of pharmacies; n_1= number of pharmacies registered in April 2016 (wave 1); n_2=number of pharmacies registered in January 2017 (wave 2); *Strategies assessed were learning practice of the web-based platform, staff training, preparation of the local networking, identification of eligible patients through pharmacy database, and use of the support material (e.g. the programme leaflet).

During the preparation stage, pharmacies most often progressed through three steps before beginning to offer and deliver the programme to patients. Firstly, internal organization of the pharmacy staff occurred to inform and coach the staff on the programme and on how to identify eligible patients. Second, interprofessional collaboration was prepared by developing a network with local physicians. Twenty-one pharmacies (51%) had contacted at least one physician to inform them of the project. Finally, relationships with patients was developed by using the leaflet in a targeted way.

During the operation stage, 27 (66%) pharmacies included at least one patient in Siscare-DT2 (*initial operation*) among the 41 pharmacies (see Fig. 2 for the distribution of pharmacies according to the number of patients included). The mean number of patients included per pharmacy was 8 [SD: 6, min-max: 1-29]. Reasons reported by pharmacists who did not include any patients were lack of time and/or motivation (n=6), no eligible patients (n=2), disagreeing with the tool (electronic pillbox) (n=1) while two pharmacists withdrew from the Sispha network during the study period and the others did not specify the reason (n=3). Nine pharmacies (22%) reached the targeted number of included patients (*full operation*). Among the 26 pharmacies that included patients and responded to the on-site questionnaire (one pharmacy did not respond), 92% contacted at least one physician (n=24/26) to inform them of the project (mainly physicians from the neighbourhood and/or participants to the same interprofessional quality circle[3]). Most pharmacists organised a project presentation session for the physicians (73%, n=19/26). The programme was proposed to patients either by the pharmacist or the technician (61%, n=16/26) or only by the pharmacist (39%, n=10/26). Almost all pharmacies (96%, n=25/26) proposed the programme at the counter following a discussion with the patient, the use of the leaflet or the information document. The characteristics of volunteer pharmacies registered in the Siscare-DT2 programme (n=41) are presented according to the number of included patients in the programme (see Table 3). Pharmacists with at least one patient included were mostly located in urban and downtown areas. The characteristics of the Siscare-DT2 project manager in participant pharmacies are presented according to the inclusion of patients in the programme (see Table 4). Among pharmacies with at least one patient included, the project manager was younger, had fewer years of experience and was more often deputy than in pharmacies without patients included.

During the sustainability stage, 24 (88%) of the 27 pharmacies that included at least one patient, were willing to continue monitoring their patients after the 15 months of follow-up study (*initial sustainability*). Almost three-quarters of pharmacies (70%, n=19) reported that they continued to propose the service to patients with T2D or other diseases after the inclusion period.

Fig. 2 - Distribution of the number of trained pharmacies according to the number of patients included (n=41)



[3] Quality circles bring together five to eight physicians and pharmacists to develop collective evidenced-based guidelines to improve physician-prescribing behaviour and to put these recommendations into practice [29]

Table 3 - Characteristics of participating pharmacies (n=41)

Variable In mean and SD [min-max] or N (%)	Pharmacies with ≥1 patient *(N=27)*	Pharmacies with no patient *(N=14)*	Total *(N=41)*
Pharmacy types			
Corporate banner[a]	19 (70%)	10 (71%)	29 (71%)
Independent	8 (30%)	3 (14%)	11 (27%)
Chain	-	1 (7%)	1 (2%)
Canton			
Vaud	13 (48%)	9 (64%)	22 (54%)
Neuchâtel	4 (15%)	1 (7%)	5 (12%)
Fribourg	1 (4%)	3 (21%)	4 (10%)
Geneva	4 (15%)	0 (0%)	4 (10%)
Valais	3 (11%)	1 (7%)	4 (10%)
Bern	2 (7%)	0 (0%)	2 (5%)
Urban **location** (≥10 000 inhabitants)	15 (56%)	10 (71%)	25 (61%)
Site			
City centre	15 (56%)	6 (43%)	21 (51%)
Village	5 (19%)	2 (14%)	7 (17%)
Commercial centre	4 (15%)	2 (14%)	6 (15%)
Other (e.g. near a hospital, train station, university campus)	8 (30%)	6 (43%)	14 (34%)
Services offered[b]			
Blood pressure measurement	27 (100%)	13 (93%)	40 (98%)
Weekly pillbox	26 (96%)	13 (93%)	39 (95%)
Wound care	26 (96%)	12 (86%)	38 (93%)
Polymedication check[c]	23 (85%)	12 (86%)	35 (85%)
Colon cancer screening	22 (81%)	13 (93%)	35 (85%)
Cardio testing[d]	22 (81%)	12 (86%)	34 (83%)
Vaccination	19 (70%)	12 (86%)	31 (76%)
Allergy screening	11 (41%)	6 (43%)	17 (41%)
netCare[e]	10 (37%)	7 (50%)	17 (41%)
Smoking cessation	15 (56%)	7 (50%)	22 (54%)
Blood glucose testing	12 (44%)	3 (21%)	15 (37%)
Others	25 (93%)	9 (64%)	34 (83%)
Quality certification[b,f]	20 (74%)	11 (79%)	31 (76%)
Confidential space[b]	27 (100%)	13 (93%)	40 (98%)
Computer in the confidential space[b]	21 (78%)	11 (79%)	32 (78%)
Pharmacists working in the pharmacy[b]			
Number of pharmacists	3.3 SD 1.2 [2-6]	3.2 SD 1.1 [1-5]	3.2 SD 1.1 [1-6]
Full-time equivalent	2.7 SD 0.8 [1-5]	2.4 SD 0.9 [1-4]	2.6 SD 0.8 [1-5]
Pharmacists taking part in the project[b]			
Number of pharmacists	2.2 SD 1.2 [1-5]	1.8 SD 1.0 [1-4]	2.1 SD 1.1 [1-5]
Full-time equivalent	2.4 SD 1.7 [1-8]	1.8 SD 1.2 [1-5]	2.2 SD 1.6 [1-8]
Technicians working in the pharmacy[b]			
Number of technicians	5.1 SD 2.3 [1-10]	6.9 SD 4.6 [3-20]	5.7 SD 3.2 [1-20]
Full-time equivalent	3.9 SD 1.6 [0-8]	5.2 SD 2.5 [2-12]	4.3 SD 2.0 [0-12]
Number of technicians taking part in the project[b]			
Number of technicians	2.3 SD 2.4 [0-8]	0.6 SD 2.0 [0-7]	1.8 SD 2.4 [0-8]
Full-time equivalent	1.6 SD1.7 [0-5]	0.4 SD 1.4 [0-5]	1.2 SD 1.7 [0-5]

[a]Corporate banner brings economically independent pharmacies together vs. chain pharmacies managed by a private company
[b]Data missing for one pharmacy with no patient included
[c]Intermediate medication review [29]
[d]Gives an overview of the personal risk of heart attack and stroke [30]
[e]Service in which patients receive medical advice and support for minor illnesses and injuries, based on scientific algorithms developed by physicians and pharmacist, without an appointment at the pharmacy [31]
[f]Quality management system for dispensing pharmacies [32]

Table 4 - Characteristics of the Siscare-DT2 pharmacy project manager

Variable In mean and SD [min-max] or N (%)	Pharmacies with ≥1 patient *(N=27)*	Pharmacies with no patient[a] *(N=13)*	Total *(N=41)*
Age (years)	36.4 SD 10.2 [26-59]	42.0 SD 12.8 [28-65]	38.2 SD 11.3 [26-65]
Years of experiences	11.6 SD 10.1 [0.6-34]	18.1 SD 11.8 [2-38]	13.7 SD 11.6 [0.6-38]
Employment rate (%)	90 SD 15 [40-100]	85 SD 19 [42-100]	89 SD 16 [40-100]
Position			
Owner	2 (7%)	2 (15%)	4 (10%)
Manager or co-manager	7 (26%)	7 (54%)	14 (35%)
Deputy pharmacist	18 (67%)	4 (31%)	22 (55%)
Animation of a quality circle by the pharmacy	16 (59%)	3 (23%)	19 (48%)

[a]Data missing for one pharmacy

Implementation impact

The analysis of influencing factors in the focus groups showed that most pharmacists thought a programme such as Siscare represents a global business project necessitating a clear management strategy, and human and financial investment. Such a project needs adaptation to the local practice context, flexible project management, precise documentation of performance indicators, training and commitment of the entire team (technicians and pharmacists) and good coordination of the local network between healthcare professionals. Most pharmacies (88%, n=22/26) charged the patient follow-up to the health insurance either for all patients (n=8) or for some patients when the billing criteria were met (n=14). Three pharmacies (12%) charged nothing and offered this service free of charge. Pharmacists mostly thought this fee-for-services did not cover the total costs of patient follow-up.

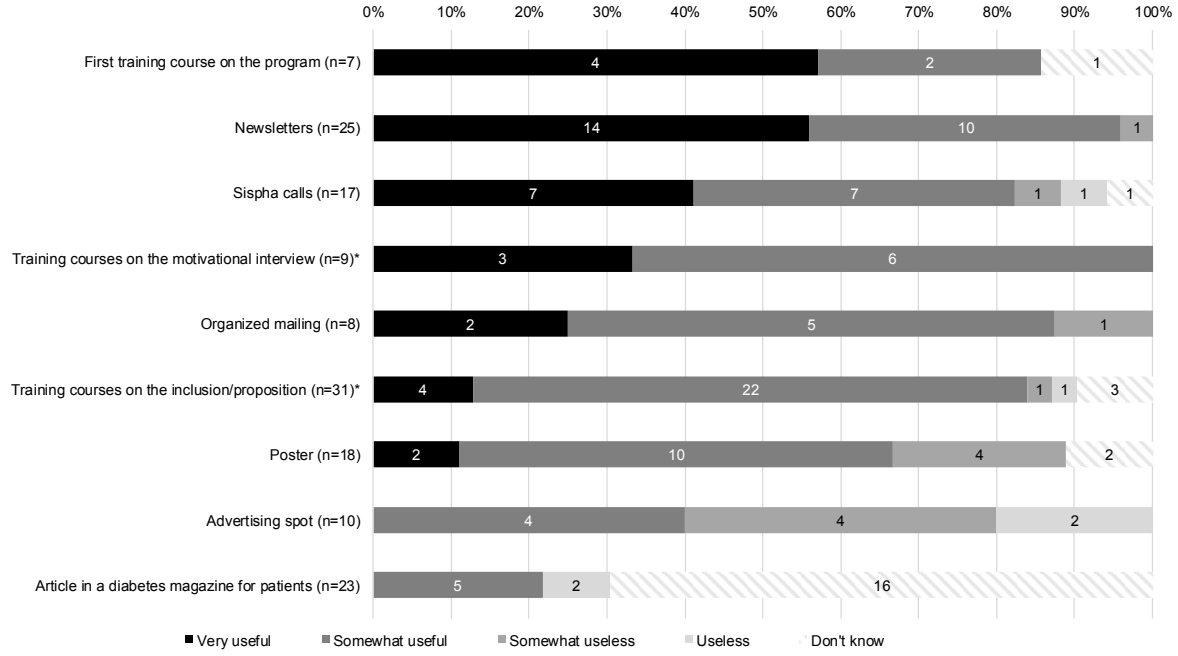
In terms of stragies, the instructional material was generally perceived as "very useful" or "somewhat useful", except information support for the pharmacy agenda. The information letter and email template to referent physicians, as well as information letter to eligible patients were considered as the most appropriate. The evaluation of all instructional materials aimed for healthcare professionals is described in Additional File 1. Pharmacists' perception of the usefulness of the different Sispha strategies is presented in Fig. 3. The results of the second focus groups sessions (n=11 pharmacists) showed that pharmacists were satisfied with their relationships with the patients in which they conduct follow up interviews. According to pharmacists, most patients were delighted to spend a special time with their pharmacist. For pharmacists, this relationship was enriched and created a privileged bond of mutual knowledge that goes beyond the conventional relationship. Pharmacists sent the reports to physicians, sometimes with questions about patient follow-up and very few of them received responses. Pharmacists believe that face-to-face meetings with physicians encourage interprofessional collaboration.

Implementation outcomes

Starting with the *reach* outcomes, 27 pharmacies included 212 patients from April 2016 to July 2017. No patients were recruited by their physicians. The anticipated inclusion period was extended by 6 months to allow this number to be reached (see Fig. 4). Only two pharmacies completed the refusal documents in real time. The average number of refusals (estimated a posteriori) was 14 per pharmacy (min 1 - max 60) and with an acceptance rate of 56%. Main reasons for refusal were the feeling by the patient that they did not need it and/or did not have medication adherence problems, lack of patient time and the perception of the pillbox as restrictive. Of the patients who began the follow-up (n=205), 120 patients (59%) were followed for at least 15 months and 77 (38%) for less than 15 months. The average

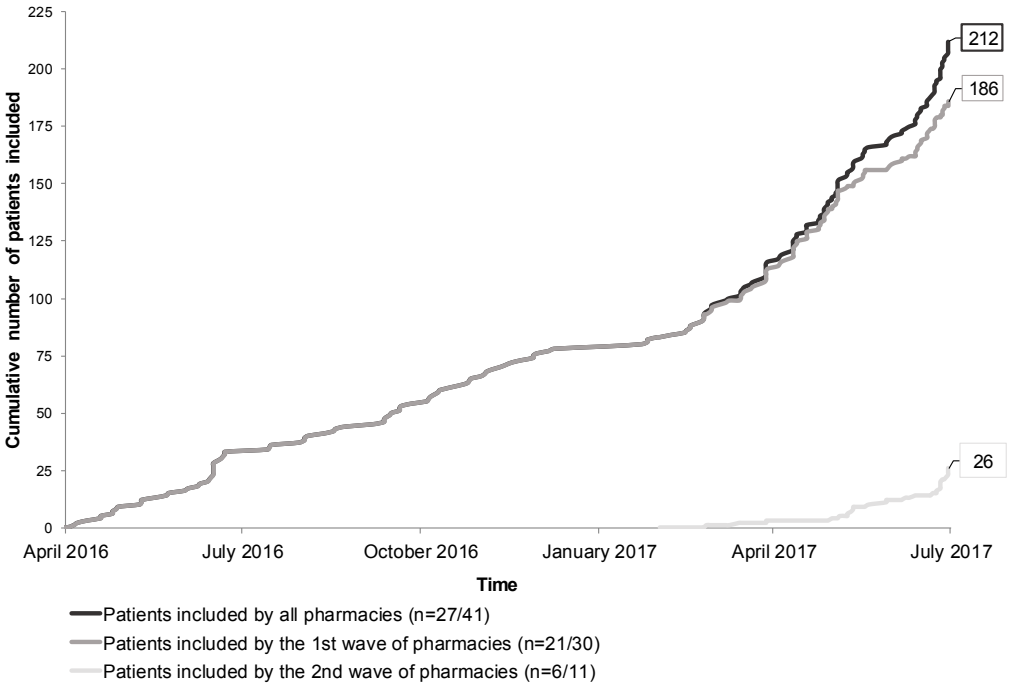
follow-up duration was 369±139 days (n=197 patients). Most common inclusion reasons were therapeutic complexity, the possibility of taking part in a study, introducing a new treatment, and medication adherence issues reported by the patient. While most common reason for stopping were that, the patient no longer wanted to continue the follow-up and refused the use of monitoring tools. The average age of patients included was 63.9 years, the majority of whom were male (n=140, 66%). At baseline, HbA1c and BMI were 7.5% (SD: 1.6) and 30.8 kg/m^2 (SD: 5.3), respectively.

Fig. 3 - Usefulness of Sispha's strategies



Legend: *Four training courses were organized on the inclusion/proposition and two on the follow-up interview. More than one pharmacist per pharmacy could assist to training courses. A pharmacist could assist to more than one training on the inclusion/proposition, opinion was given on each of the training days and then sum up

Fig. 4 - Patient inclusion monitoring



In terms of fidelity, the mean number of motivational interviews conducted by pharmacists per patient over the follow-up period of the study (15 months or less) was 4.0, SD 2.7, min 0 - max 12 (n=197 patients). Pharmacists determined the frequency of interviews according to the patient's needs (n=12/26, 46%) or by the chronic drug delivery period, i.e. every three months (n=9/26, 35%). The average duration of the inclusion interview and the follow-up interview were 42 minutes, SD 17 minutes (min 15-max 90) and 24 minutes SD 10 minutes (min 10-max 45), respectively. Most pharmacists described their interviews as spontaneous (n=17/26 pharmacists, 66%), participatory (n=25, 96%) and motivating (n=25, 96%) rather than structured, directory and without a motivational approach. More than half of the pharmacists were guided by the Sispha platform (n=14, 54%) and had a motivational approach (n=22, 85%) to the interviews. The medication adherence graph was systematically discussed during the interview for 80% of pharmacies (n=21). Of the 205 patients who had started the follow-up, 186 (91%) were monitored by the electronic pillbox and 19 (9%) did not agree to use the electronic pillbox and only use the weekly pillbox. Three quarters (n=19/26) of pharmacists sent patient-pharmacist interview reports to the referent physician of the patient (50%, n=13/26 did so systematically) and 31% (n=8/26) of pharmacies always or sometimes received responses from the physician.

Concerning the integration of the service, 77% of pharmacies (n=20/26) had defined the role of pharmacist and technician in the patient's management, mainly by oral agreement. In most cases, only the pharmacist was involved in reading and counting the electronic pillbox (77%, n=20) and preparing the electronic pillbox (70%, n=18). Pharmacists conducted all interviews and none were delegated to a technician.

According to the focus groups results, an important factor in promoting the implementation of pharmacy services is the support from pharmacy owners. Their support is essential to ensure that all staff member are committed to the adoption of a new service, that the project manager has time to devote on the implementation strategies, and that the necessary resources are available.

Discussion

This study showed that 66% of the pharmacies (n=27) provided the service to at least one patient, 22% (n=9) reached 10 or more patients and only 5% (n=2) provided the support program to at least 10 patients for 15 months.

Implementation process

The participation rate of Sispha pharmacies in the study was very high (41/47=87%) as well as the adoption rate (41/41=100%). These volunteer network pharmacies are the “early adopters” motivated by implementing professional pharmacy services, and most saw this study as an opportunity to develop them. The participating pharmacies were different from the Swiss pharmacies with a under representation of chains with 2% (1/41) vs. 31% usually (554/1806 in 2018) [33]. This limits the generalisation of the results to other regions of Switzerland where, for example, regulations allow physicians to dispense drugs in German-speaking regions [34].

Pharmacies with at least one included patient were mainly located in urban and inner city areas and had more human resources than pharmacies with no recruited patients, which could facilitate the implementation of these programmes. In addition, more pharmacies with patients included (59% vs. 23%) lead pharmacist-physician quality circles, showing that they are more comfortable interacting with physicians and are interested in improving quality and efficiency of care [29].

Surprisingly, some pharmacies voluntarily registered in the network and paying for the subscription have not implemented any strategy or/and have not included any patient. Moreover, more wave 2 pharmacies (45%) did not include any patients than wave 1 pharmacies (30%). This may be related to the fact that these pharmacies were not the first early adopters of the program and not familiar with it: if the pharmacist's does not have a value-added view of this service and even with the necessary resources and the positive decision of the chief, this pharmacist will not prioritize or offer these programs.

To reach and maintain the sustainability stage, recommendations and their adoption are needed to consolidate the spread of this coordinated approach in a greater number of regions and pathologies. For this study, the research team made recommendations to the Federal Office of Public Health at four priority levels: education, interprofesionality, communication and, technical and financial resources according to different contextual levels: federal, local, pharmacy/general practice, healthcare professionals, and patients[4].

Implementation impact

The involvement of all pharmacy staff, the knowledge of the added benefit of the service by the owner and pharmacist, and previous positive experiences in similar services facilitated the implementation of Siscare. Main barriers reported were lack of time and/or motivation, feeling unsure about communicating with physicians and lack of awareness of the profitability of the service. These factors were consistent with findings from other pharmacy implementation studies [35-39]. To address the lack of knowledge about the profitability, a study on the implementation cost and the break-event point from the pharmacy perspective was conducted. The total implementation cost in the preparation stage (i.e. before inclusion of the first patient) was estimated at 8,481 Swiss francs (CHF), half of which represented the cost of equipment [40]. The direct costs of delivering the service were estimated at 666 CHF per patient per year, including 68% of workforce time. The break-even point was estimated at 16 patients per year to cover the costs, dropping to 13 patients after the first year. These estimates were based on a theoretical number of interviews with the pharmacist: one inclusion interview and six follow-up interviews in the first year [40]. In our study, the mean number of patients included was 8 SD 6 [1-29] per pharmacy and only two pharmacies included at least 16 patients, but this indicates that the implementation is feasible.

Implementation outcomes

The patient acceptance rate was estimated to 56%. This a posteriori estimation may be underestimated, but appears consistent with other studies. A smaller study testing the ability of a physician and a nurse in the infectious diseases department of a public hospital and community pharmacies to implement a similar patient support program described an acceptance rate of 56% (17/30) [36]. Another study evaluating the implementation of a medication review with follow-up in one pharmacy described an acceptance rate of 63% (132/211) during an 18-month inclusion period [38].

Reasons expressed by patients and reported by pharmacists for declining Siscare were mainly the feeling of not needing it and/or not having medication adherence problems, and the perception that the tool was restrictive. Pharmacists may have proposed Siscare to "easy-to-include" patients without medication adherence problems. There is a need to identify patients in difficulty, e.g. refill issues, unattained therapeutic goals, etc. in order to offer these services to patients with specific needs.

[4] Personal communication: Bawab N, Rossier C, Perraudin C, Bugnon O. Evaluation du projet pilote Siscare-DT2 et de son implémentation dans l'offre de soins ambulatoires en Suisse romande. Report on the mandate of the Federal Office of Public Health. Oct 2019.

The fidelity of the intervention took into account the frequency, duration, and methodology of patient-pharmacist interviews, which were respected except for the duration. First, the frequency of pharmacist-patient interviews was mainly one every three months, which is related to the delivery condition of chronic drugs for reimbursement and consistent with the minimum frequency to ensure contact with the patient suggested during the training sessions. Second, the estimated duration of inclusion and follow-up interviews were respectively 4 and 2.5 times longer than reported in the literature [11]. The a posteriori documentation may be overestimated by adding the duration of the technical part, which could be carried out during the interview if delegated to the technician as recommend during training sessions. Indeed, the pharmacy technicians were not often involved in preparing the electronic pillbox (n=8/26 pharmacies, 30%). According to the focus groups results, this was mainly because pharmacists have not taken the time to train their technicians or do not see the point of delegating this task to them because of the small number of patients included. However, a study has shown the value of including technicians in these programs, both from a management and a success perspective [11]. Third, most pharmacists described a motivational approach and discussed the medication adherence graphs in interviews as planned.

Medication adherence tool has been adapted for 19 patients followed with weekly box. The electronic pillbox is useful to have an objective view of the dynamic behaviour of adherence but is less practical for patients with multiple medications or with already a weekly box. In our study, 32% of patients stopped Siscare for this reason. An alternative is the electronic weekly pillbox systems, which may be easier for polymedicated patients and for having an objective view of adherence [41,42]. For caregivers, the information collected will be related to all doses taken which is an asset if all pills are taken at the right time but is not appropriate if some pills in an intake are missed. An electronic weekly pillbox system is being studied for integration into the software and should be tested in future studies [43].

In addition, the effectiveness results show that the program appears to support medication adherence and clinical outcomes[5,6]. Medication adherence to oral antidiabetic drug was approximately 86% during the follow-up (n=178 patients, 84%). The baseline mean HbA1c and BMI were 7.5% and 31 kg/m^2 respectively and decreased by 0.5 (p=0.012) and 0.6 units (p=0.017) over 15 months.

Strengths and limitations

Strengths of this study include the use of knowledge from successful and unsuccessful previous experiences [10,36,37,39] and the iterative evaluations, coaching and availability of and Sispha team to assess and overcome barriers in a timely and efficient manner. Implementation science has shown that to change behaviour, strategies are needed at multiple stages and levels [44-47]. The design of this study, as well as the facilitators and barriers identified, should be considered to improve future implementation or scaling up of pharmacy services. A limitation is that pharmacists were not conscientious with the recording of data; some important data for the implementation evaluation were incomplete. We therefore tried to record missing data a posteriori, e.g. spending time for activities or reasons of refusals. Further analysis is needed to determine how to increase willingness of these pharmacies to encourage pharmacists to systematically collect this type of data. Only initial sustainability

[5] Unpublished abstract: Bawab N, Schneider MP, Locatelli I, Ballabeni P, Rossier C, Perraudin C, et al. Adherence to oral antidiabetics: a cohort study of patients participating in an interprofessional chronic patients support program in Switzerland. Oral presentation at the 23th ESPACOMP Conference, Porto, Portugal, 23 November 2019.

[6] Unpublished abstract: Bawab N, Schneider MP, Locatelli I, Ballabeni P, Rossier C, Perraudin C, et al. Implementation and effectiveness of an interprofessional support program for patients with type 2 diabetes in a Swiss primary care setting. Poster presentation at the EuroDURG Conference, Szeged, Hungary, 6 March 2020.

was assessed; full sustainability was not assessed due to the length of the study. Sispha should continuously evaluate the implementation of their program.

Conclusion

This study provides pharmacists, professional organisations and researchers with a structured and comprehensive approach to implementing pharmacy services using a theoretical framework. This implementation evaluation supports the feasibility and acceptability of the programme. However, implementing healthcare interventions remains complex and scaling up implementation is still fragile because of the inertia inherent in any fundamental change in practice and the economic-political uncertainties influencing the viability and innovative spirit of the actors in primary care. Greater use of implementation science in current practice should contribute to the successful implementation of pharmacy services.

Abbreviations

CFIR: Consolidated Framework for Implementation Research; CHF: Swiss francs; T2D: type 2 diabetes; EPIS: Exploration, Preparation, Implementation, Sustainment framework; FISpH: Framework for the Implementation of Services in Pharmacy; GIF: Generic Implementation Framework; TDF: the theoretical domains framework

Declarations

Ethics approval and consent to participate: The study protocol was approved by the Cantonal Ethics Committee of Research on Human Beings of the Canton of Vaud (Protocol N°2016-00110). Oral consent was obtained from pharmacists and written consent from patients.

Consent for publication: Not applicable.

Availability of data and materials: The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: O. Bugnon was a co-founder of Sispha SA and a member of the advisory board of Sispha SA. The other authors declare that they have no competing interests.

Funding: This work was supported by the Swiss Federal Office of Public Health (FOPH) [grant number: 15.003846] and the joint Swiss fund of quality and research RPB IV/1 [grant number: 20160201] including santesuisse, Curafutura (both associations of health insurances) and pharmaSuisse (Swiss society of pharmacists) as sponsors. No funding body was involved in the design of the study nor collection nor analysis. Bi-annual meeting was organized with the FOPH (and the steering committee) to share the results and the progress.

Authors' contributions: NB analysed and interpreted the data, and drafted the manuscript. CP assisted in interpreting the data and the preparation of the manuscript. All authors contributed to the conception and design of the study, reviewed, and approved the final manuscript for publication (except OB).

Acknowledgements: We are very grateful to the stakeholders for letting us conducting the study. We would like sincerely to thank all the pharmacies, patients and physicians for their participation. Thank you to Aurélien Georges for helping with the facilitation of the focus groups.

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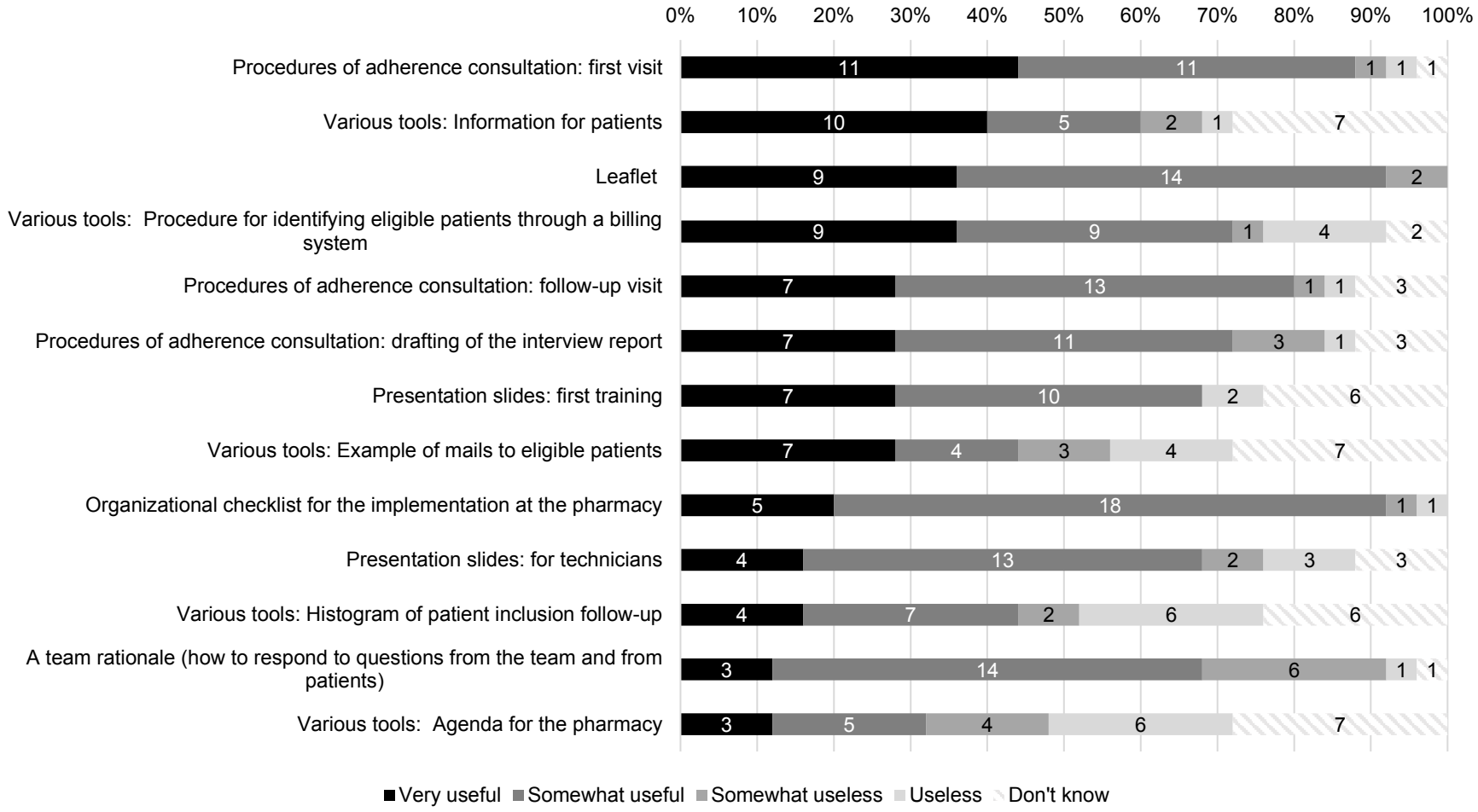
Additional material

Additional File 1 - Evaluation of instructional material by pharmacy project managers

The results presented in the table are of pharmacies that included at least one patient in the study (n=25 of 27 respondents).

The tools have been classified into procedures of adherence consultation, presentation slides, and various tools, in addition of the organizational checklist, leaflet and team rationale.



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Chapter 4. Effectiveness Results

Effectiveness of an Interprofessional Programme (Siscare) for Supporting Patients with Type 2 Diabetes

Chapter 4 describes the results of the effectiveness of Siscare in T2D from the patient's perspective, including medication use and adherence, clinical outcomes, quality of life and satisfaction.

This chapter is presented as a paper to be submitted to the journal *BMJ Open Diabetes Research & Care*. Noura Bawab contributed to this article through the conception and design of the study, the conduct of the research and investigation process, the analysis and interpretation of the data, and the writing of the manuscript.

Effectiveness of an Interprofessional Programme (Siscare) for Supporting Patients with Type 2 Diabetes

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Abstract

Aims: To assess the effectiveness of an interprofessional support programme (Siscare) that includes motivational interviews (patient-pharmacist), electronic monitoring (EM, MEMS®) of medications, patient-reported and clinical outcome monitoring, and interactions with physicians for patients with type 2 diabetes in French-speaking Switzerland.

Methods: This is a prospective, multicentre, observational cohort study using a hybrid implementation-effectiveness design. Individual daily adherence to at least one oral antidiabetic medication was measured by EM. A global adherence score was estimated by the product of the model-estimated implementation (GEE) and a non-parametric (Kaplan-Meier) estimate of persistence over time. Clinical outcomes (HbA1c, blood glucose, BMI, blood pressure, heart rate, cholesterol levels) and quality of life (QoL) were analysed over time using linear mixed-effect models.

Results: A total of 212 patients were included from 27 pharmacies: 120 (57%) patients were followed up for at least 15 months. In total, 140 (66%) patients were male, the mean age was 64 years (SD 11), and the mean number of chronic medications per patient at baseline was 5 (SD 3). Of 178 patients who used EM, 95% (95% CI: 92%-99%) were still persistent at the end of the follow-up. The percentage of persistent patients taking their medication appropriately (implementation) was stable during follow-up and was estimated to be 90% (95% CI: 87%-92%) at baseline and 88% (95% CI: 84%-91%) at month 15. At baseline, the mean HbA1c and BMI were 7.5% and 31 kg/m2, respectively, which decreased by 0.5 and 0.6 units after 15 months. QoL remained stable during follow-up.

Conclusions: The programme supports medication adherence and improves clinical outcomes, illustrating the overall preventive effect of coordinated care.

Keywords: Diabetes; Patient Support; Pharmacy services; Primary care; Medication adherence; Interprofessionality

Background

Worldwide, 9% of the adult population lives with diabetes, which affects 463 million people and causes four million deaths each year [1]. Medication is the preferred therapy to control diabetes and reduce negative clinical outcomes and mortality when dietary measures and exercise are not sufficient [2]. Despite proper diagnosis and medical care, patients rarely take their medications as prescribed and therefore do not receive optimal clinical benefits from therapy. According to a literature review, the medication adherence rate ranges from 39 to 93% [3] in patients taking diabetes medications.

Medication adherence is defined as the process by which patients take their medications as prescribed by healthcare professionals [4]. It is a dynamic and complex process characterised by the daily intake of a medication and management of a drug regimen and covers three dimensions: initiation, implementation, and persistence [5]. Medication adherence can vary over time depending on a very large number of factors, of which more than 700 have been identified [6].

Medication non-adherence leads to disease progression, poor disease management and clinical outcomes, reduced quality of life (QoL), and increased use of health resources and mortality [7]. Improved medication adherence is associated with a reduction in diabetes complications (microvascular complications, ulcers, retinopathy, acute myocardial infarction, neuropathy, or amputations) and a reduction in the number of short-term disability days [7]. Adherent patients with diabetes had 37% fewer emergency room visits and 30% fewer hospitalisations than non-adherent patients [8]. Medication non-adherence impacts healthcare systems significantly because of the wasted resources, costly and preventable adverse events and hospitalisations [9]. The total cost of diabetes decreased by 50% (from $8,867 to $4,570; US$$_{2005}$) with higher levels of medication adherence despite the increase in diabetes medication use and costs [10].

To reduce these negative outcomes, interventions from healthcare professionals are needed to support medication adherence and improve health outcomes. A recent meta-analysis of pharmacist-led interventions to improve medication adherence in adults with diabetes showed that a combined intervention strategy (including both educational and behavioural components) improved outcomes such as medication adherence and glycated haemoglobin (HbA1c) [11]. In addition, another meta-analysis examining the impact of medication adherence interventions in adults with any clinical condition identified an additive effect of longer follow-up interventions (10 months or more) [12]. Thus, the aim of this study was to assess the effectiveness of a long-term interprofessional support programme called Siscare (including community pharmacists and physicians) for patients with type 2 diabetes (T2D) in a primary care setting.

Method

Study design

This research is part of a larger study that used a hybrid implementation-effectiveness design based on data from a prospective, multicentre, and observational study [13]. This paper focuses on the effectiveness results.

Intervention

Siscare is an interprofessional patient support programme that includes the following aspects: (a) regular motivational semi-structured interviews (patient-community pharmacist) at least every three months; (b) electronic monitoring (EM) of medication adherence and feedback to the patient (MEMS® and MEMS

AS®, AARDEX Group, Switzerland) and monitoring of patient-reported and clinical outcomes; and (c) feedback reports to the referent physician (general practitioner or specialist, responsible for coordinating the patient's care) to ensure the sharing of information and provide a starting point for collaborative patient care. The programme aims to help patients reach their individual therapeutic goals to improve their general health, support medication adherence and strengthen continuity of care among the different healthcare professionals involved in the patient care pathway.

Participants and setting

Eligible patients were adults (≥18 years) diagnosed with T2D and taking at least one oral antidiabetic medication (OAD). The exclusion criteria were a diagnosis of type 1 diabetes, an obvious cognitive impairment, or an insufficient speaking level in French. Patients were recruited from community pharmacies belonging to a network implementing patient-centred services in the French-speaking part of Switzerland who volunteered to participate in the study. The sample size was estimated to be 200 patients by the advisory board. This value was calculated based on the estimated number of participating pharmacies (n=20) and the target number of patients to be recruited (10 per pharmacy).

Outcomes and measurements

Sociodemographic characteristics were collected using a self-report questionnaire at baseline. The types and numbers of medications, clinical outcomes (HbA1c, blood glucose, BMI, systolic and diastolic blood pressure, heart rate, cholesterol levels), and smoking status were documented by the pharmacist on a web-based platform at each interview during the study period (15 months). This information was obtained from measurements taken at the pharmacy, the patient (self-reported or laboratory results) and/or the physician.

Medication adherence to at least one OAD was monitored by EM for 15 months. The pharmacist was responsible for defining the number and types of medications to monitor by EM according to the patient's needs. A pillbox was equipped with a cap containing an electronic chip that records the date and time of each opening and allows the data to be uploaded to a web-based platform at each patient visit [14]. Medication adherence covered three dimensions: implementation, persistence, and adherence [5,15]. Implementation was defined as the percentage of patients who correctly took all prescribed doses of their monitored medication on one day among all patients who were still persistent on that day. Persistence defines the survival function associated with the individual time differences between the initiation and discontinuation of treatment, and persistence ended when the next dose to be taken was omitted and no further dose was subsequently taken. Unilateral discontinuation of the drug occurred when the patient discontinued the treatment on his/her own initiative, and clinically appropriate discontinuation occurred when the patient discontinued the treatment in agreement with the physician, e.g., due to adverse events or toxicity of the treatment. Any other reason for stopping the programme and/or treatment was considered censoring (e.g., patients stopped using the electronic pillbox but continued using the medication). Adherence was defined as the percentage of patients taking at least all prescribed doses of their monitored medications based on the prescribed regimen among all patients initially included in the study. At the end of the inclusion period, some patients without EM were recruited.

General and specific QoL were assessed using two self-report questionnaires at baseline and at the 6- and 12-month follow-up. The Short Form-12® Health Survey SF-12 (version 2) includes 12 items covering eight health domains and defines the Physical Component Summary (PCS) and the Mental Component Summary (MCS) [16]. The score obtained varies between 0 and 100, where 0 is the worst and 100 is the best QoL. In Switzerland, the PCS and MCS scores were 49.8 and 46.3 in a

representative sample of residents [17], while in patients with diabetes, the scores were 43.1 and 46.7, respectively [18]. The Audit of Diabetes Dependent Quality of Life 19 (ADDQoL) includes three parts: global questions, diabetes-specific questions, and questions related to 19 life domains measuring the impact of diabetes on patient QoL [19,20]. The weighted score ranges from -9 (maximum negative impact) to +3 (maximum positive impact), and the average gives an overall score for each time point. This score was estimated to be -1.6 in a cohort of Swiss diabetic patients [18].

Patient satisfaction with the programme was assessed using a self-report questionnaire at the end of the study, i.e., at the 15-month follow-up, or earlier if the patient follow-up was stopped before the end of the study. The research team developed the questionnaire based on earlier works [21-23] to cover topics on motivational interviews, EM and interprofessional collaboration in addition to reasons for participation, willingness to continue with the programme, and open comments, including space to suggest improvements. Auto-administered questionnaires were distributed to patients by the pharmacists and returned to the research team with pre-stamped envelopes. Qualitative interviews with patients were planned but were not conducted due to time constraints.

Statistical analyses

Descriptive statistics were used to describe the patients' sociodemographic and clinical characteristics at baseline (closest to time point +/- 3 months), QoL and patient satisfaction.

Medication adherence was assessed through implementation, persistence, and adherence. On each day, patients' behaviour regarding their treatment was dichotomized as "adequate" when the patient opened his/her electronic pillbox at least the prescribed number of times for each single monitored OAD; or as "inadequate" when the patient opened his/her electronic pillbox less than the number of times prescribed for at least one monitored OAD. Generalized Estimating Equation (GEE) models with an autoregressive correlation structure were adopted to estimate the population implementation trend over time; the latter entered the model using natural cubic splines. Persistence was estimated using the Kaplan-Meier survival function. Adherence was estimated empirically as the product between implementation and persistence at each follow-up time [15]. To estimate population adherence over time, GEE models were applied to observed adherence data that were weighted to correct for bias induced by censoring generated missingness [24].

Changes over time in clinical outcomes and QoL (PCS, MCS and overall ADDQoL scores) were estimated by three-level (time, patient, pharmacy) mixed-effect linear regression models. These models took into account that the data were measured repeatedly for the same patient and that patients within a pharmacy are not independent. In the analysis, the pharmacy cluster effect was negligible (no difference observed); thus, only time and patient were considered in the reported results. These analyses were performed for clinical data if at least 25% of the patients had a value at baseline. For clinical outcomes, locally weighted scatterplot smoothing (lowess smoothing) was also performed to graphically illustrate trends over time. For QoL, time was treated as an ordinal variable with three categories (baseline and 6 and 12 months), with the reference category being the baseline score. When evaluating group-level results, the proposed minimally important difference for the PCS and MCS scores was 3 points [25].

Descriptive statistics were calculated with Microsoft Excel 2016, regression and lowess analysis were performed with StataIC 16 (StataCorp, Stata Statistical Software), and medication adherence analysis

was performed with R-3.6.2 (The R Project for Statistical Computing). The statistical significance level was set at a two-sided *alpha* =0.05.

Ethical consideration

All study procedures involving human participants were performed in accordance with the ethical standards of the Cantonal Ethics Committee of Research on Human Beings of the Canton of Vaud [Protocol N°2016-00110]. Written informed consent was obtained from all patients included in the study. Data were kept in a coded form.

Results

Characteristics of the study patients

Two hundred and twelve patients were included in the study between April 2016 and June 2017 from 27 pharmacies, with a mean number of 8 (SD 6, min 1, max 29) patients per pharmacy. The baseline characteristics of the study population are shown in Table 1. The mean age of the patients was 63.9 years (min 32-max 93).

The mean number of medications per patient was 5.1 (min 1, max 19). Patients were primarily treated with an A-Class (digestive system and metabolism) medication according to the Anatomical Therapeutic Chemical (ATC) classification system, with an average of 2.1 medications per patient, followed by ATC C-class medication (cardiovascular system), with an average of 1.5 medications per patient. Most patients had one OAD (see Fig. 1), with metformin being used most common (n=137/194), followed by gliclazide (n=32/194) and the combination of metformin-sitagliptin (n=29/194).

While 72% of respondents rated their general QoL as good, very good or excellent, 68% also reported that their QoL would be better if they did not have diabetes.

Of the patients who began the follow-up, 59% (120/205) were monitored for at least 15 months, for a median of 456 days (IQR: 298-456, see Additional File 1 for details on follow-up duration). Of the 205 patients, 186 (91%) had at least one electronic pillbox, and 19 (9%) had a weekly pillbox. Eight patients (4%) had no EM data and were considered lost to follow-up (started monitoring with the pillbox but never returned to the pharmacy and/or never used the pillbox). Finally, 178 (87%) patients provided EM data.

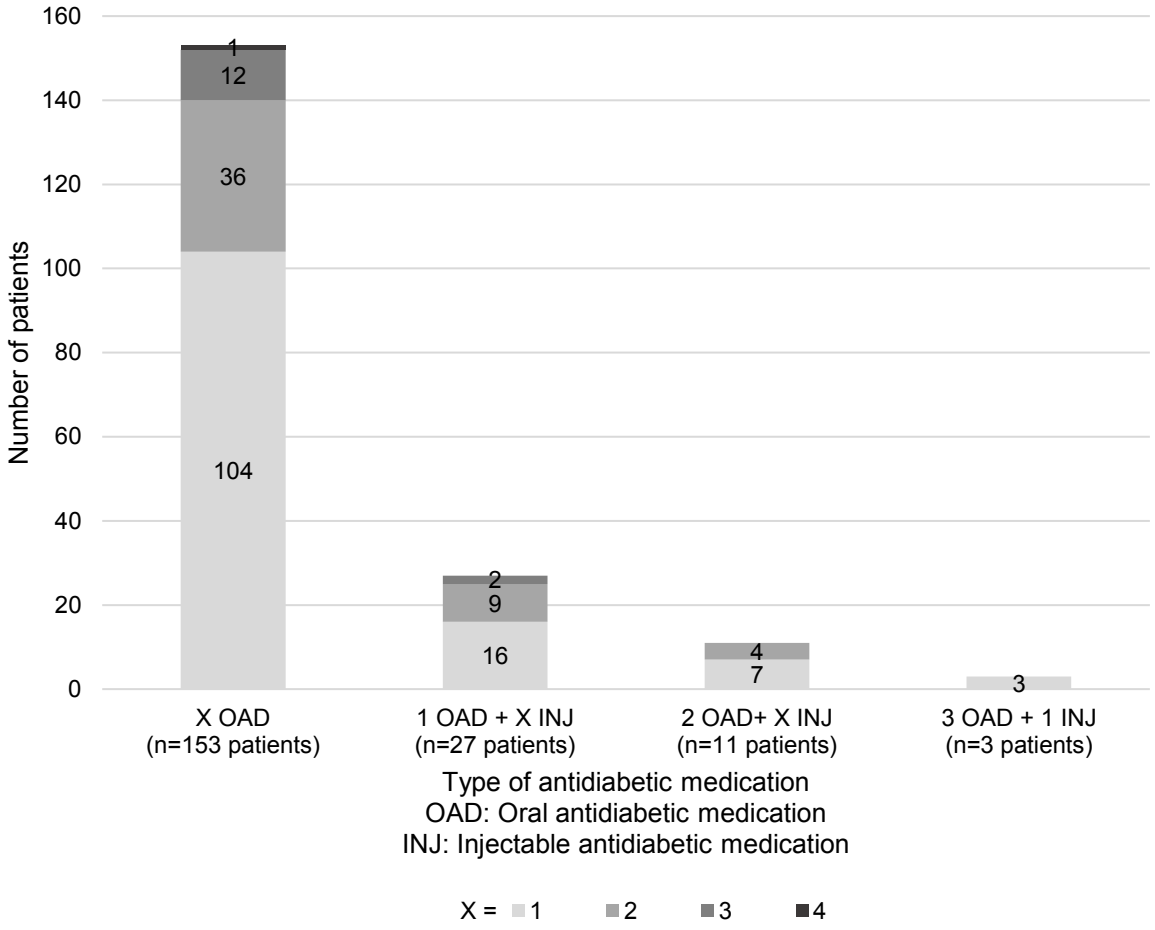
The pharmacists reported 250 inclusion reasons for 199 patients. The most common reasons were therapeutic complexity (n=70/199 patients, 35% of patients), participation in a study (n=39, 20%), introduction of a new treatment (n=28, 14%), medication adherence issues exposed by the patient (n=27, 14%), failure to achieve therapeutic objectives (n=22, 11%), suspicion of non-adherence by the healthcare professional (n=15, 8%), and treatment intensification (n=13, 7%). Among the patients who stopped the follow-up before 15 months (n=77), the pharmacists reported 86 reasons for 62 patients: no longer wanted to continue with the follow-up (n=25/62, 40% of patients), refused to use EM (n=20, 32%), achieved their therapeutic objectives (n=8, 13%), changed pharmacies or moved (n=7, 11%), and stopped treatment (n=7, 11%).

Table 1 - Baseline characteristics of the study patients

Characteristics *(n=number of collected data)*	**Values in N (%) or mean (SD)**
Sociodemographic characteristics	
Age, years *(n=212)*	63.9 (11.3)
<65 years	99 (47%)
65-74 years	80 (38%)
≥75 years	33 (15%)
Women *(n=212)*	72 (34%)
Education level *(n=156)*	
Primary	68 (44%)
Secondary	57 (36%)
Tertiary	28 (18%)
Other	3 (2%)
Employment status *(n=159)*	
Retired	85 (54%)
Employee	43 (27%)
Independent or family business	7 (4%)
Looking for a job	8 (5%)
Inability to work	8 (5%)
Other	8 (5%)
Participation in another support programme or diabetic patient association *(n=157)*	10 (6%)
Smoking status *(n=99)*	
Non-smoker	74 (75%)
Current smoker	24 (25%)
Medication	
Total number of medications per patient *(n=194)*	5.1 (3.3)
Number of antidiabetic medications per patient *(n=194)*	104 (54%)
1	52 (27%)
2	28 (14%)
3	10 (5%)
4	
Type of antidiabetic medication *(n=194)*	
Oral medication only	153 (79%)
Oral and injectable medication	41 (21%)
Clinical characteristics	
HbA1c, % *(n=82)*	7.5 (1.6)
HbA1c categories	
≤ 7.0%	41 (50%)
]7.0-8.0] %	22 (27%)
]8.0-9.0] %	9 (11%)
>9.0%	10 (12%)
Blood glucose, mmol/L *(n=90)*	8.2 (3.2)
BMI, kg/m^2 *(n=76)*	30.8 (5.3)
Systolic blood pressure, mmHg *(n=99)*	136 (16)
Diastolic blood pressure, mmHg *(n=74)*	83 (9)
Heart rate, bpm *(n=49)*	76 (12)
Cholesterol	
Total, mmol/L *(n=18)*	5.0 (1.2)
LDL-C *(n=21)*	3.0 (1.1)
HDL-C *(n=17)*	1.3 (0.6)
Triglycerides *(n=18)*	2.3 (1.5)
Quality of life	
General: SF-12	
PCS score *(n=156)*	46.34 (8.72)
MCS score *(n=157)*	45.61 (10.51)
Diabetes-specific overall ADDQol score *(n=162)*	-1.59 (1.83)

ADDQol: Audit of Diabetes-Dependent Quality of Life; BMI: body mass index; BP: blood pressure; HbA1c: glycated haemoglobin; HDL-C: HDL cholesterol; LDL-C: LDL cholesterol; MCS: Mental Component Summary; PCS: Physical Component Summary; SF-12: 12-Item Short Form Health Survey.

Fig. 1 - Patients stratified by type and number of antidiabetic medications at baseline (n=194 patients)



Number of patients is presented on the vertical axis according to the antidiabetic treatment regimen: oral antidiabetics alone or with injectable antidiabetic medications.

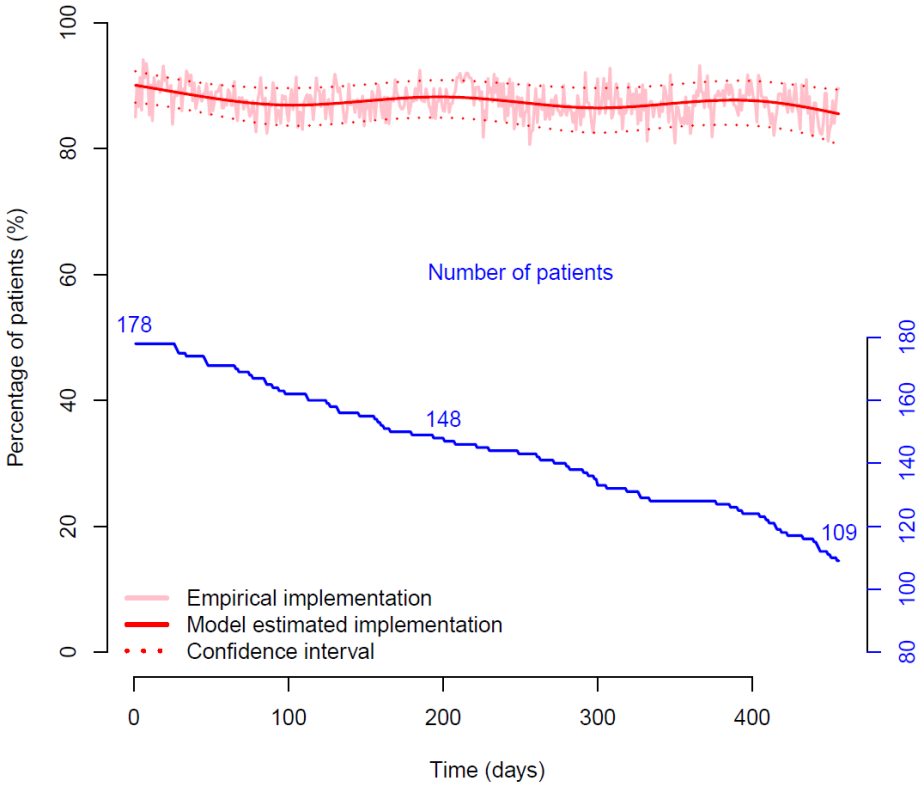
Medication trends

Of the patients with complete data at 15 months, 28/117 (24%) had a change (addition or withdrawal) in OAD, including 14 patients (12%) with an addition of one or two OADs. The mean number of OADs per day was constant over the study period (see Additional File 2 for the evolution of the average number of medications over time).

Medication adherence

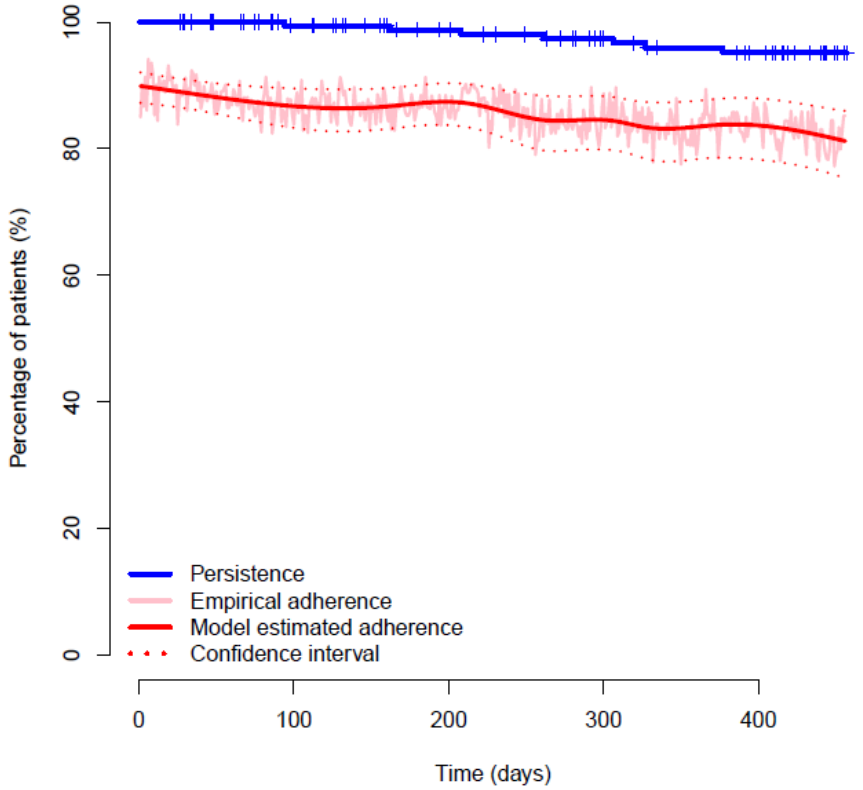
The mean monitoring time was 372 days (SD 137, min 26 - max 456). Implementation was globally stable with low and constant variability over time (see Fig. 3). The implementation rate was estimated at 90.1% (95% CI 87.3-92.3) at the beginning of monitoring, 86.9% (95% CI 83.6-89.6) at day 100 and 87.6% (95% CI 83.6-90.7) at day 400 (GEE model). Seven patients discontinued their OAD, including six for an appropriate clinical reason and one on his/her own initiative (see Fig. 2 for Kaplan-Meier persistence and adherence estimates). The persistence rate at the end of follow-up (percentage of subjects who did not stop their treatment) was 95.2% (95% CI 91.7% - 98.7%).

Fig. 3 - Implementation results with the Generalized Estimating Equation exchangeable model (auto-regressive)



The pink curve represents the proportion of patients with the correct number of daily pillbox opening(s) among patients still under observation over time (implementation); red curves represent the model-estimated implementation rate with 95% confidence interval; and the blue curve represents the number of patients over time.

Fig. 2 - Persistence and medication adherence results



The pink curve represents the proportion of patients with the correct number of daily pillbox opening(s) among all patients over time (empirical adherence); red curves represents model-estimated adherence with 95% confidence interval; the blue curve represents the number of patients still under treatment using the Kaplan-Meier survival estimate (persistence); the vertical blue bars represent the censored patients; and the jumps represent discontinuation.

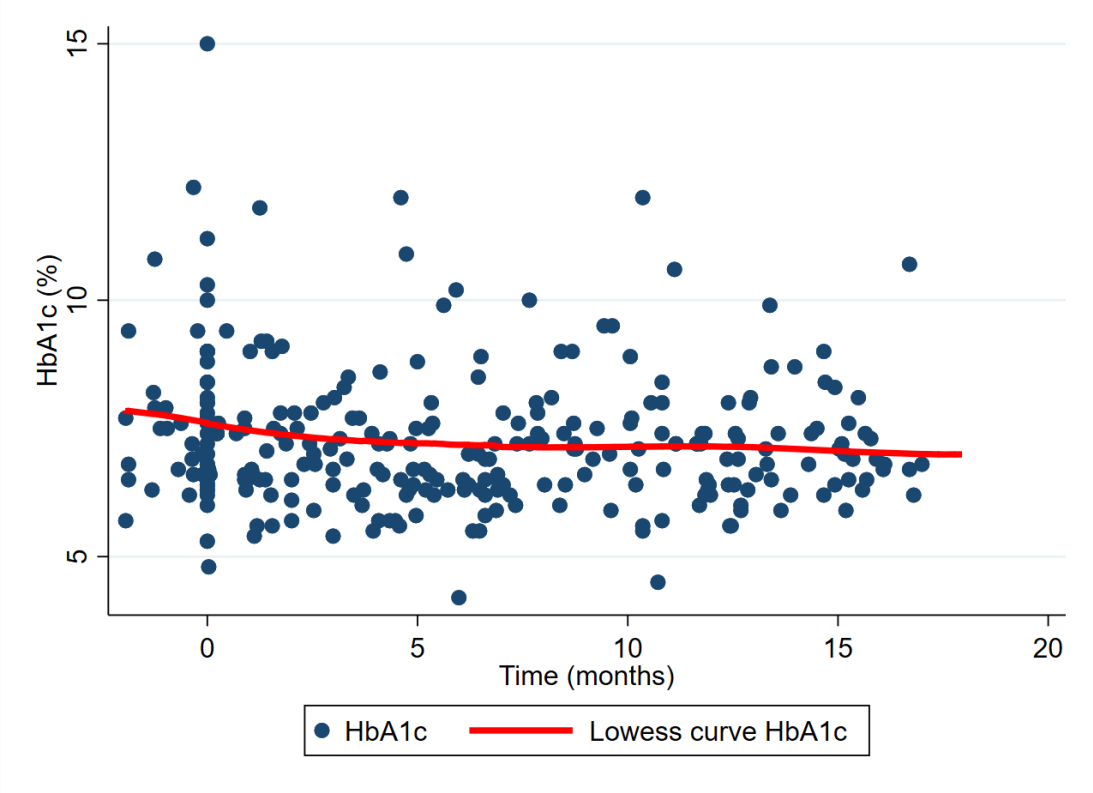
Clinical outcomes

The mean HbA1c decreased by an average of 0.032 units per month (95% CI -0.056 to -0.007, P=0.012, see Fig. 4), which represents a decrease of 0.473 units over the 15-month monitored period. Without considering the extreme value documented for one patient at the beginning of follow-up (HbA1c=15%), the effect of time remained significant, corresponding to a mean decrease of 0.022 units per month (95% CI -0.039 to -0.006, P=0.008, n=292 observations and 118 patients) and thus a cumulative decrease of 0.336 units over 15 months.

BMI significantly decreased by 0.043 units per month (95% CI -0.077 to -0.008, P=0.017, see Additional File 3) or 0.641 units over 15 months. After removing the highest BMI value (BMI = 54 kg/m2), the decrease was 0.042 units per month (95% CI -0.076 to -0.007, P=0.018, n= 226 observations for 84 patients) and 0.622 units over 15 months.

Regarding the other clinical data (blood glucose, blood pressure and heart rate), the results did not change significantly over time (see Additional File 3 and Additional File 4).

Fig. 4 - Distribution of patient HBA1c over time (*n= 289 observations for 118 patients)* and lowess non-parametric regression



The red line represents local weighted scatterplot smoothing (lowess), which is a set of simple regressions applied to subsets of data.

Quality of life

The number of questionnaires completed at baseline and at 6 and 12 months was 163, 103, and 69, respectively.

According to the regression model, the mean PCS score at 6 months was 0.34 units higher than at baseline (95% CI -0.85 to -1.52, P=0.577). Between baseline and 12 months, there was a decrease of 1.64 units (95% CI: -3.02 to -0.25, P=0.020). The estimated mean decrease between 6 and 12 months was 2.00 units (95% CI: -3.43 to -0.51, P=0.008). The mixed regression model showed that the mean

MCS score increased significantly by 0.17 units per month (95% CI 0.01 to 0.32, P=0.032). Detailed PCS and MCS values and each dimension of the SF-12 at baseline and 6 and 12 months are presented in the Online Appendix (Additional File 5).

The mean overall ADDQoL score decreased over the short term but increased over the long term without significance (-0.060 units at 6 months, 95% CI -0.287 to 0.166, P=0.602 and 0.004 units at 12 months, 95% CI -0.261 to 0.269, P=0.978; see Additional File 6 and Additional File 7 for the weighted impact scores and responses, respectively, for the 19 domains at each time point).

Patient satisfaction

Sixty-eight patients (33%) responded to the patient satisfaction questionnaire. Thirty-five (51%) respondents joined the study to help research efforts, 21 (31%) enrolled for support in their daily treatment, 16 (25%) participated to please their pharmacist, and six (9%) joined because they had to start a new treatment.

Most patients (96%, n=65) reported that the length and frequency of the interviews were adequate, rated the interviews as somewhat to very helpful (79%, n=54) and felt that the interviews allowed them to express problems they encountered while taking their medications (78%, n=53). A minority of patients (19%, n=13) felt they were being controlled (see Additional File 8 for detailed patients' opinions about the interviews). Fifty-seven patients (84%) found the EM pillbox easy to use, useful and space saving. For 74% of patients (n=50), the collaboration between their pharmacist and referent physician was considered to be relatively present to very present, and 30 (44%) patients declared that the collaboration improved their management. Finally, 24% of patients (n=16) definitely wanted to continue the programme, 22% (n=15) were most likely going to continue, 25% (n=17) preferred to stop, and 19% (n=13) reported that they no longer wanted to continue at all. Three-quarters of the patients (75%, n=51) would recommend this programme to another person with diabetes.

Discussion

This study assessed the 15-month effectiveness of Siscare for patients with T2D in a primary care setting in Switzerland. The results show stable and high medication adherence over time. The only other Swiss study based on health insurance data for patients with diabetes taking OADs showed a medication adherence rate of 42% (percentage of days covered, PDC≥80%) over 12 months (n=26,713 patients) [26], which is in contrast with the very high medication adherence rate in the study. No recommendations to pharmacists were made regarding which patients should be included (e.g., medication adherence level) outside the specified inclusion criteria. According to the focus group results[1], pharmacists mostly selected patients based on the likelihood that they would accept the programme. However, the study population was comparable to that of two other studies conducted in Switzerland [26,27]. Moreover, the age categories and education levels of the patients corresponded to the Swiss epidemiological data, as the prevalence of the disease increases beyond the age of 55 years and people with a low education level were twice as likely to have diabetes as those with a higher education level (8% versus 4%) [28]. The higher proportion of men taking part in the study also reflects the reality that 5% of men versus 3% of women had diabetes in 2017 [28]. Data on the representativeness of the patients allow us to reduce potential selection bias in the study population. Hence, the very high level of medication adherence does not seem to be influenced by the patient characteristics but rather by the novelty of the electronic pillbox, especially during the first few months.

The baseline HbA1c averaged 7.5% and decreased by 0.3-0.5 units after 15 months, while the effect of adding an OAD on HbA1c ranged from 0.5 to 1.0% after 3 to 6 months in the literature [29]. In addition, a subanalysis of our data conducted among patients with a baseline HbA1c ≥ 7.5% showed a significant decrease in HbA1c of 0.082 units per month (95% CI -0.147 to -0.018, P=0.012, n=99 observations and 33 patients) and a cumulative decrease of 1.2 units over 15 months. As other studies have shown, patients with higher HbA1c levels at baseline are likely to benefit more from interventions [30-32]. Particular efforts should be made by community pharmacists to screen for such patients.

Most included patients had regular contact with their pharmacist during the study, at least every 12 weeks, while the frequency of physician visits was unknown. Regular meetings with healthcare professionals are essential to allow patients to play a more active role in the management of their disease [33]. Medication use partly relies on the patients' trust in healthcare professionals. The key to improving the quality of chronic patient care seems to be dependent on patient-tailored monitoring to achieve therapeutic objectives and maintain stability over time. In addition, a large majority of patients with T2D have comorbidities such as hypertension and dyslipidaemia and are prescribed more medications, mainly cardiovascular medications [34]. This may lead to a complex treatment plan, more adverse events and medication adherence issues, particularly for conditions that are mostly asymptomatic, such as diabetes, dyslipidaemia, and hypertension [35].

Twenty patients stopped the programme due to failure to use the EM, notably when the patients were using a weekly pillbox for other medications. An electronic weekly pillbox system may seem easier for patients taking multiple medications [36], but we still lack data on the best device to satisfy patients, healthcare professionals and researchers. Research is still needed on the appropriate device that should be integrated into the patients' daily lives.

Regarding the satisfaction questionnaire, 75% of the responders would recommend the programme to another person with diabetes. The response rate of the patients to the satisfaction questionnaire was rather low (33%) and probably included those who were the most satisfied. The results on whether to continue the programme were mixed, suggesting that patients were satisfied with the service and that its duration was sufficient. More research on the duration of such programmes is needed.

The results of this study suggest that there is a major need for healthcare professionals to support chronic patients by tailoring interventions to their needs. Newly diagnosed patients have a greater demand for knowledge than patients who have been living with diabetes for several years but still need support to improve the management of their disease [37]. Pharmacists should also focus on patients with obvious medication adherence issues and high HbA1c values.

The strength of this hybrid implementation-effectiveness study design lies in the electronic and longitudinal monitoring of medication adherence and patient-reported outcomes in a real-world setting over a long and representative period. Moreover, the implementation evaluation allowed us to monitor and collect data regarding the feasibility and acceptability of the programme by community pharmacists[1] and build interprofessional collaborations through Siscare[2]. However, this study has limitations that need to be considered for future research. First, the study does not include a control group; therefore, we

[1] Publication in submission: Bawab N, Moullin JC, Bugnon O, and Perraudin C, et al. Implementation Evaluation of an Interprofessional Programme for Supporting Patients (Siscare) with Type 2 Diabetes in a Swiss Primary Care Setting.

[2] Publication in submission: Bawab N, Moullin JC, Jotterand S, Rossier C, Schneider MP, Bugnon O, and Perraudin C. Building Interprofessional Collaborative Practices through a Support Programme for Patients with Type 2 Diabetes in Primary Care

cannot reach a conclusion on the direct cause of the decrease in HbA1c. This design was chosen because this intervention had already shown effectiveness in HIV patients, which supports its applicability to this new study population [21,22]. Randomisation in routine care is quite difficult to implement, but other designs should be carefully considered in future research [38]. Second, patient self-reported QoL and satisfaction data may be subject to bias, but the use of stamped addressed envelopes, the recommendation to fill in the questionnaire outside of the pharmacy, and the fact that the research team was different from the field intervention team limited this bias. With regard to clinical outcomes, no decrease in blood glucose levels was observed, which could be related to the different sources of these outcomes (e.g., self-reported without ensuring good clinical practice). As food consumption influenced the result, the lack of measurement standardisation led to a greater heterogeneity among these values than among HbA1c. Access to a common database or platform should improve the quality of care by providing physicians with a continuously updated treatment plan and the pharmacist with access to the clinical data. Third, the real-world setting was chosen because of the hybrid effectiveness-implementation design of the study; this fact certainly contributed to the large amount of missing data. Nevertheless, the amount of missing data for HbA1c was consistent with that in another study (61% missing vs 60% in our study at baseline) [39]. Finally, we cannot exclude that other factors, such as dietary and lifestyle habits, contributed to the decrease in HbA1c. We also assume that this programme itself has an impact not only on medication adherence but also on other daily behaviours, such as food and exercise, that the pharmacist may have discussed with the patient in a more structured way than typical for usual care. This needs further investigation.

Conclusions

Medication adherence was consistently high and stable during the 15-month intervention, and the HbA1c values improved, with no major changes in diabetes treatment or involvement of other support mechanisms. Pharmacists should tailor such support programmes to patients with medication adherence problems and/or those who have not achieved their therapeutic goals to improve the quality of care and prevent negative outcomes. Particular attention should be paid to patient screening.

Abbreviations

ADDQoL: Audit of Diabetes Dependent Quality of Life; BMI: Body Mass Index; EM: Electronic Monitoring; HbA1c: Glycated haemoglobin; IQR: Interquartile Range; Lowess: local weighted scatterplot smoothing; MCS: Mental Component Summary; OAD: oral antidiabetic medication; INJ: injectable antidiabetic medication; PCS: Physical Component Summary; PDC: Percentage of Day Covered; QoL: Quality of Life; T2D: type 2 diabetes.

Declarations

Acknowledgements: The authors would like to sincerely acknowledge the funding bodies (Swiss Federal Office of Public Health, PharmaSuisse, Santésuisse, Curafutura) and all pharmacy teams, patients and physicians who participated in the programme and the study. The views expressed are those of the authors and not necessarily those of the funding bodies.

Funding: This work was supported by the Swiss Federal Office of Public Health (FOPH) [grant number: 15.003846] and the joint Swiss fund of quality and research RPB IV/1 [grant number: 20160201], including Santésuisse, Curafutura (both umbrella associations of Swiss health insurers) and PharmaSuisse (Swiss association of pharmacists) as sponsors. No funding body was involved in the design of the study, data collection or analysis. Bi-annual meetings were organised with the FOPH (and the steering committee) to monitor the results and the study progress.

Conflict of interest: O. Bugnon was a co-founder of Sispha SA and is a member of the advisory board of Sispha SA. The other authors declare that they have no competing interests.

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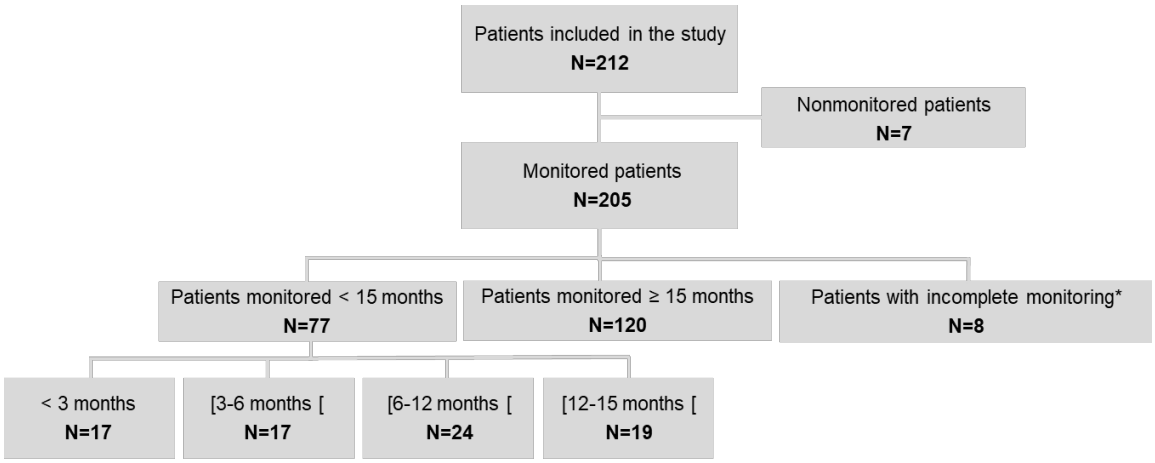
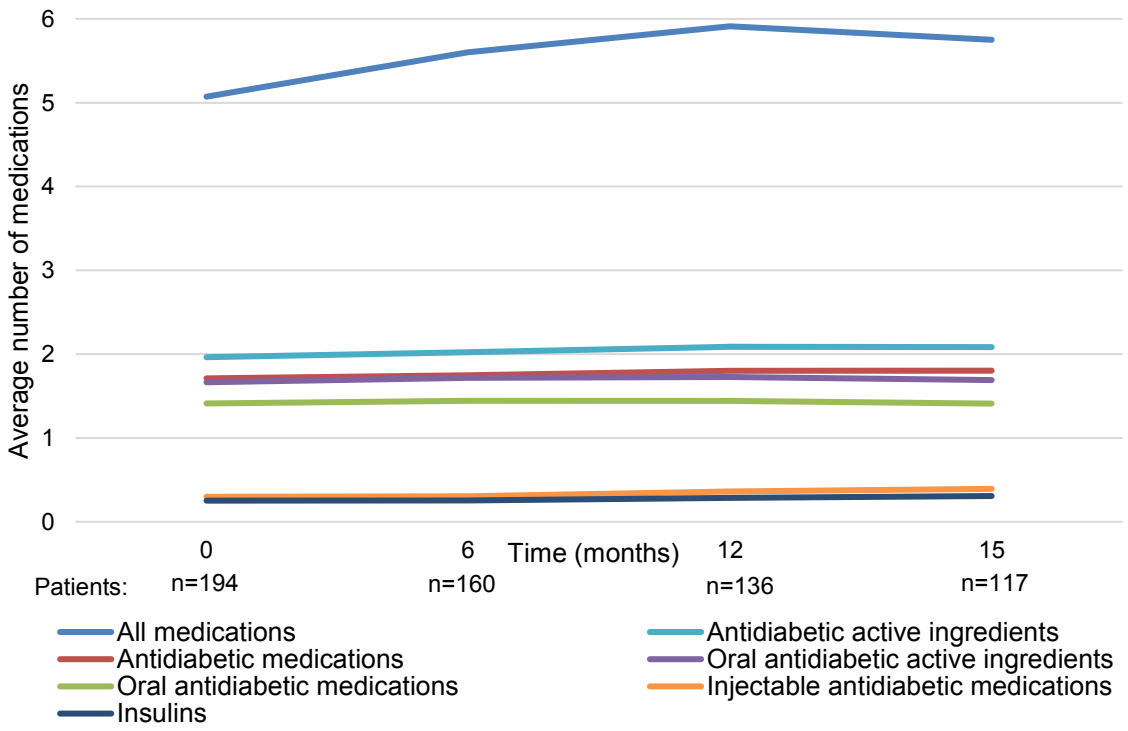
Additional material

Additional File 1 - Number of patients followed according to duration of the study



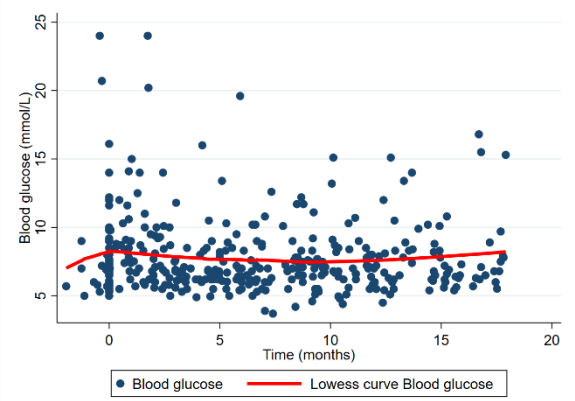
*Patients with incomplete monitoring are those who started follow-up and received electronic pillboxes but never returned to the pharmacy and/or had never used the device (no opening data).

Additional File 2 - Evolution in the average number of medications over time for all patients present at each time point

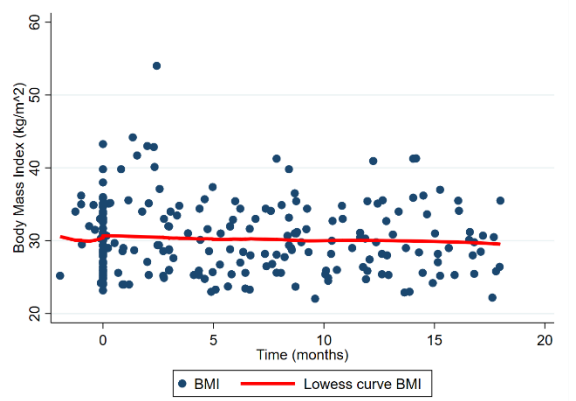


Additional File 3 - Distribution of patient clinical outcomes over time (blood glucose, body mass index, systolic and diastolic blood pressure, and heart rate - lowess non-parametric regression)

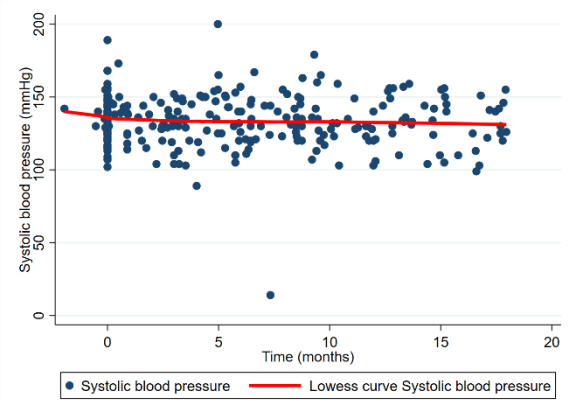
Blood glucose



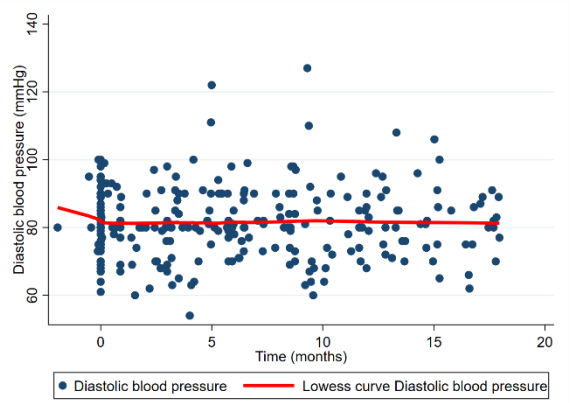
Body mass index



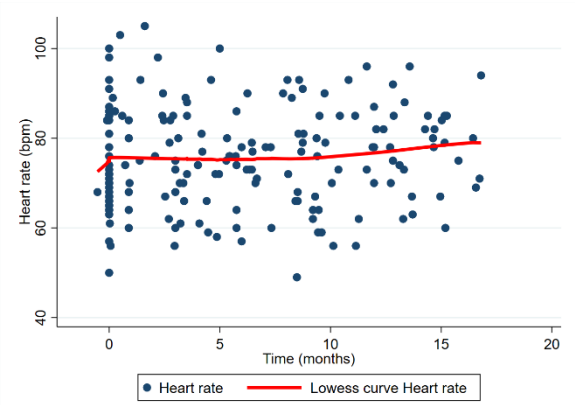
Systolic blood pressure



Diastolic blood pressure



Heart rate

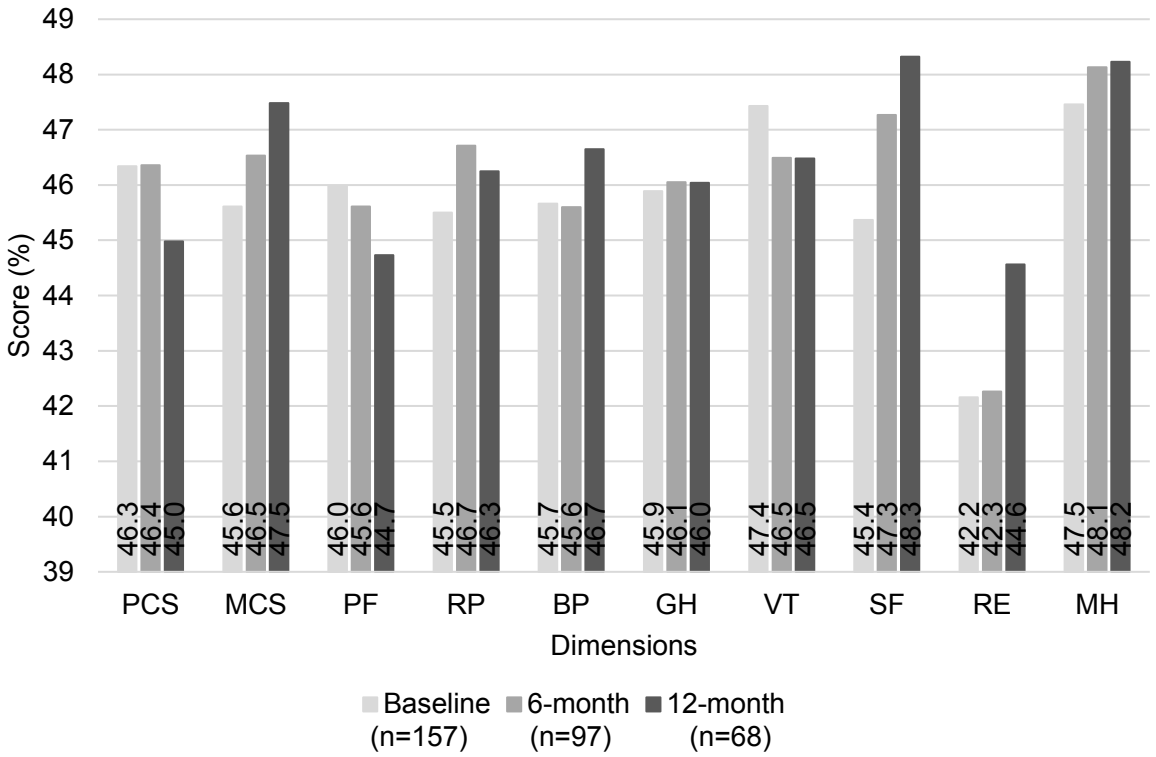


Additional File 4 - Results of the mixed-effect linear regression models for the clinical outcomes: blood glucose, systolic and diastolic blood pressure, and heart rate

Variable	Change in unit/month	Lower CI	Upper CI	P value	Observa-tions	Patients
Blood glucose (all data), mmol/L	-0.028	-0.085	0.029	0.340	378	124
Blood glucose (excluding the 5 highest observations), mmol/L	0.005	-0.043	0.053	0.838	373	122
Systolic blood pressure (all data), mmHg	-0.088	-0.435	0.259	0.620	262	90
Systolic blood pressure (excluding the lowest observation), mmHg	0.000	-0.358	0.360	0.997	261	90
Diastolic blood pressure (all data), mmHg	0.188	-0.074	0.450	0.160	258	87
Diastolic blood (pressure excluding the 2 highest observations), mmHg	0.132	-0.104	0.367	0.274	256	87
Heart rate (all data), bpm	0.099	-0.125	0.324	0.385	184	58

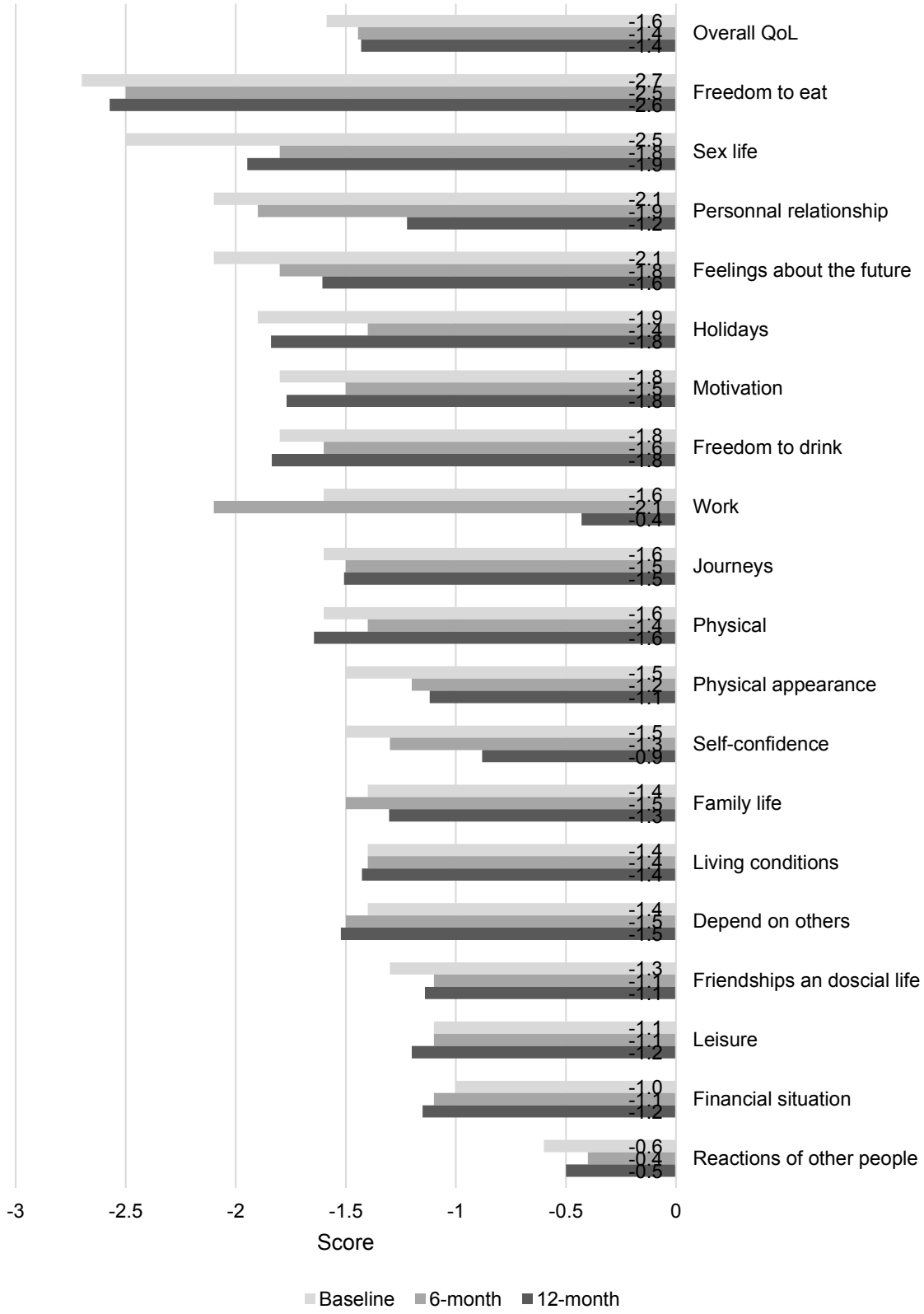
CI: 95% Confidence Interval

Additional File 5 - SF-12 scores for Physical Component Summary (PCS), Mental Component Summary (MCS), and the eight dimensions at baseline, 6 and 12 months

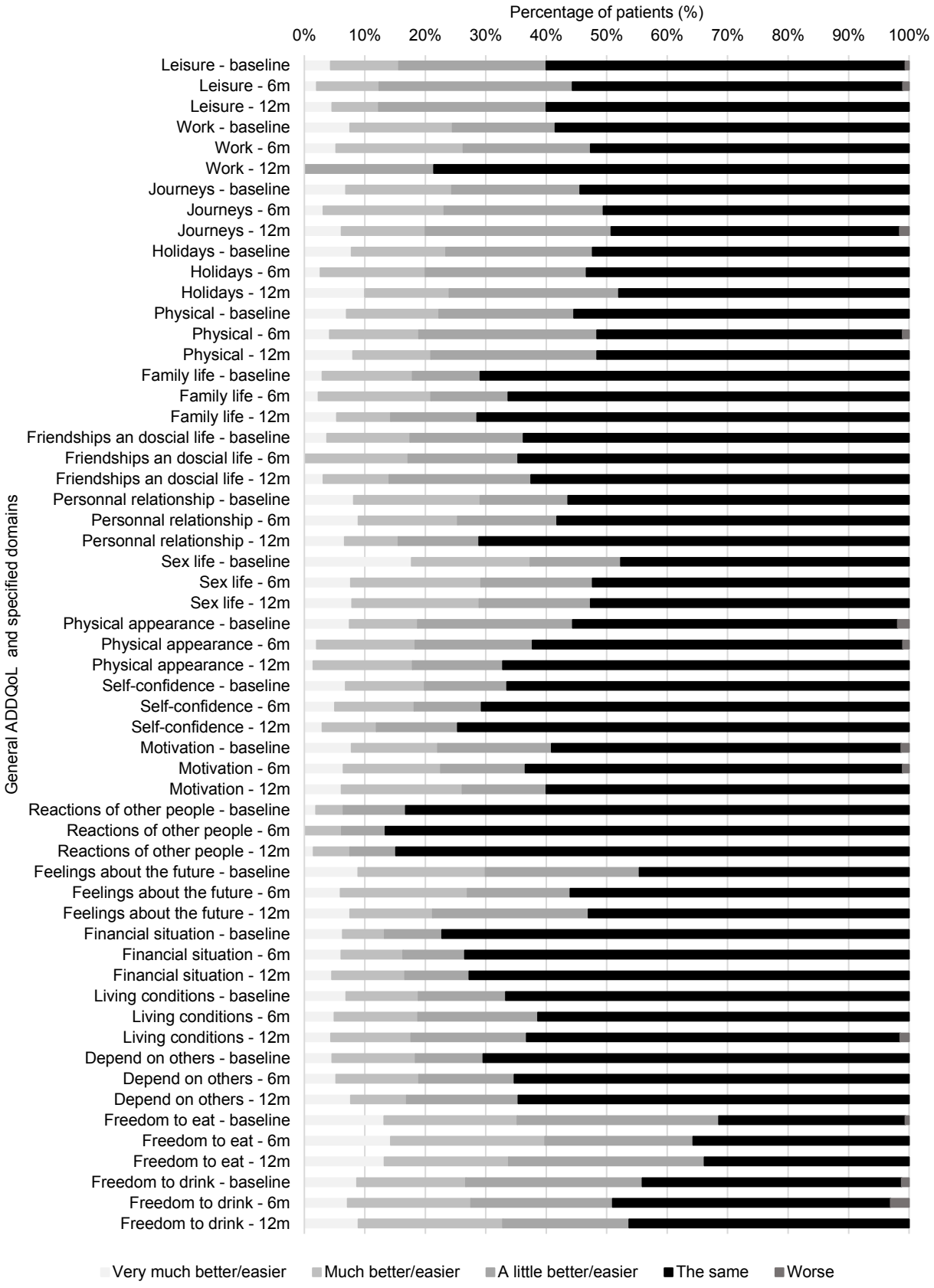


BP, bodily pain; GH, general health; MH, mental health; PF, physical functioning; RE, role-emotional; RP, role-physical; SF, social functioning; VT, vitality.

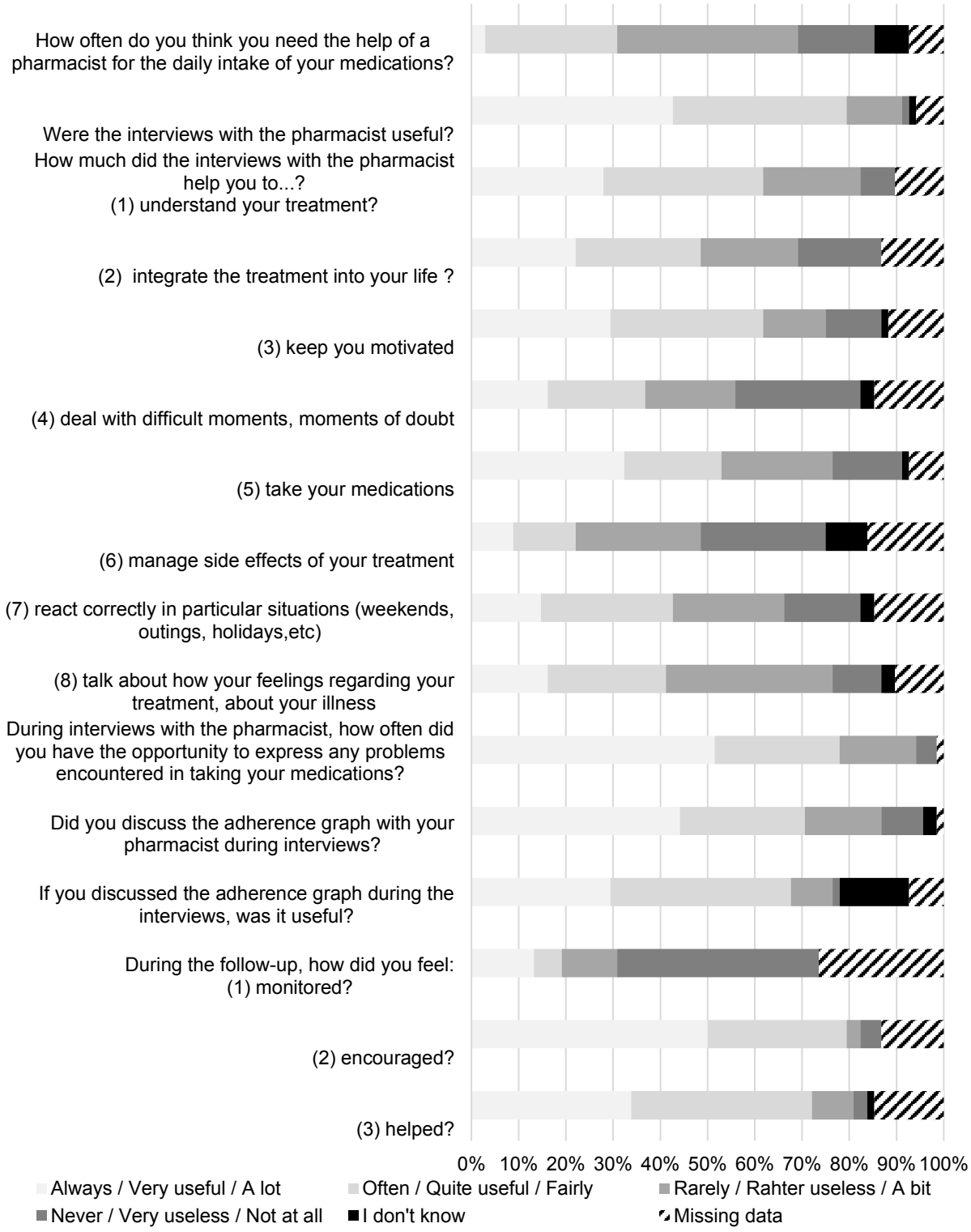
Additional File 6 - ADDQoL weighted impact score: overall and specific domains



Additional File 7 - Percentage of patients according to responses for general ADDQol and specified domains at baseline, 6 (6m) and 12 (12m) months



Additional File 8 - Patients' opinions about the interviews (n=66 patients)



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Chapter 5. Interprofessionality Results

Building Interprofessional Collaborative Practices through a Support Programme for Patients with Type 2 Diabetes in Primary Care

Chapter 5 evaluates the building of interprofessional collaborative practices throughout the implementation process and the appropriateness of the associated targeted strategies in Siscare-DT2.

This chapter is presented as a paper to be submitted to the Journal *Journal of Interprofessional Care*. Noura Bawab contributed to this article through the conception and design of the study, the conduct of the research and investigation process, the analysis and interpretation of the data, and the writing of the manuscript.

Building Interprofessional Collaborative Practices through a Support Programme for Patients with Type 2 Diabetes in Primary Care

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Abstract

Aim: The aim of this study was to assess the building of interprofessional collaborative practices throughout the implementation process of a patient support programme (Siscare) in primary care for patients with type 2 diabetes. The programme included (i) regular patient-pharmacist motivational-based interviews, (ii) medication adherence, patient-reported, and clinical outcome monitoring; and (iii) interactions between the referent physician and pharmacist.

Methods: This investigation was a prospective, multicentre, observational, mixed-methods cohort study. Quantitative (questionnaires and audits) and qualitative (focus groups) data were collected to assess progress indicators of interprofessional collaboration at each stage of the implementation process: exploration, preparation, operation, and sustainability. Interprofessionality was operationalized through four progressive levels of interrelationship practices between the healthcare professionals. In addition, the usefulness of the implementation strategies, influencing factors, healthcare professionals' and patients' satisfaction, and fidelity of the interprofessional collaboration components of Siscare were evaluated.

Results: The exploration stage included recognition of the project by stakeholders, the creation of an interprofessional steering committee, the provision of information to healthcare professional associations and the adoption of the programme by 41 pharmacies. During the preparation stage, 24 pharmacies contacted 366 physicians, and 19 pharmacies presented the programme at 43 meetings attended by 115 physicians. During the operation stage, 27 pharmacies included 212 patients; however, no physician referred a patient to a pharmacy or prescribed Siscare. Collaboration primarily occurred through the unidirectional transmission of information from the pharmacist to the physician (level 1: 70% of pharmacists transmitted interview reports to physicians), bidirectional exchange of information sometimes occurred (level 2: 42% received physician responses), and concerted measures of treatment objectives took place occasionally (level 3). Regarding sustainability, 29 (88%) of the 33 physicians surveyed were in favour of this type of collaboration, and 23 (70%) were willing to prescribe the programme to other eligible patients. Previous participation in interprofessional quality circles fostered collaboration, and appropriate pre- and post-graduate education, financial incentives and material resources were needed to promote the collaboration.

Conclusions: Despite multiple implementation strategies, interprofessional collaborative practices remained infrequent, but the patient support programme was well received by the pharmacists, patients and the physicians. Effective implementation strategies need to be further explored.

Background

Chronic diseases are a major public health issue and are estimated to affect 57% of the world's population in 2020 [1]. In Switzerland, there are approximately 2.2 million patients with chronic diseases [2], of whom almost a quarter suffer from diabetes [3]. The consequences of these diseases are manifold [4-6], and delaying their effects is essential if more people are to remain healthy and maintain their quality of life despite illness. People with chronic diseases can be supported by need-based health promotion programmes to reduce the risk of further illness, avoid complications, and reduce the need for more intensive care [7].

Collaboration between healthcare professionals such as physicians, pharmacists, nurses, and their teams, as well as patient-centred care, have been shown to improve the quality of care [8-12]. *Interprofessionality* can be defined as the collaboration between distinct professions that manifests itself in various forms of increasing interrelationship practices [13]. Responsible use of medications is a major aspect of patient care in which several health professionals can play an important role. The process includes prescription by the physician based on the diagnosis, appropriate and tailored dispensation by pharmacists, taking the medication for the prescribed duration according to the intake instructions by the patients (e.g., adherence), and possible assistance with in-home administration by nurses. A study that aimed to describe the accuracy of clinicians' estimates of patient adherence to HIV antiretroviral drugs showed that clinicians tend to overestimate medication adherence and inadequately detect poor adherence and may therefore miss important opportunities to intervene to improve drug self-management [14]. Medication adherence is a dynamic process that fluctuates over the course of life events. Physicians may also be influenced by the so-called "toothbrush effect", with patients taking medication more regularly before a medical appointment (similar to a visit to the dentist) [15]. Pharmacists can play a key role in identifying patients who are not adhering to their treatment, particularly when therapeutic goals are not met, in order to support patients before intensifying therapy or undergoing additional examinations [15]. Supporting chronic patients through programmes requires a long-term collaborative commitment that takes into account the specific context and needs of each patient.

The benefits of healthcare interventions can only be achieved if they are implemented effectively [16,17]. In the past, research has largely focused solely on the effectiveness of clinical interventions and not on their implementation in the delivery setting [18]. Implementation science has been developed to reduce the gap between the development of effective healthcare interventions and their incorporation into routine practice [19,20]. The objective of this study was to assess the building of interprofessional collaborative practices throughout the implementation process of a support programme (Siscare) for patients with type 2 diabetes (T2D), Siscare-DT2, in primary care in the French-speaking part of Switzerland [21].

Methods

Study design and theoretical framework

This research is part of a larger prospective, multicentre, and observational study that used a hybrid implementation-effectiveness design and the Framework for the Implementation of Services in Pharmacy (FISpH) [22]. The research protocol, including the full methodology, has been presented elsewhere [21].

Intervention

The intervention, called Siscare, is an interprofessional patient support programme that includes (i) regular motivational semi-structured interviews (patient-community pharmacist), at least every three months; (ii) electronic monitoring of medication adherence by electronic pillbox (MEMS® and MEMS AS®, AARDEX Group, Switzerland), patient-reported and clinical outcomes; and (iii) interactions between the referent physician and pharmacist to promote the continuity of care [21]. The referent physician of the patient is a general practitioner or a specialist, who is usually responsible for coordinating the patient's diabetes care. The interaction between the healthcare professionals begins with the transmission of a report from the pharmacist to the physician after each interview, including a description of medication adherence, barriers and facilitators, adverse reactions, clinical outcomes and patient engagement. The programme aims to contribute to reaching individual patient therapeutic goals and improving patient general health, to support medication adherence, and to strengthen the continuity of care between the different healthcare professionals involved in the patient care pathway. Siscare is offered by Sispha SA, a purveyor that has been developing smart and innovation solutions for a network of community pharmacies, since 2011 [23], based on adaptations of the interprofessional medication adherence programme (IMAP) that was developed and implemented with various chronic populations, such as hypertension and HIV patients, through a physician-pharmacist-nurse collaboration at the Center for Primary Care and Public Health (Unisanté), University of Lausanne, Switzerland, starting in 1995 [24,25].

Participants and setting

Participants in the study were pharmacists, patients and their referent physicians. Any community pharmacy in the French-speaking part of Switzerland could join the Sispha network and take part in the study, or leave the network or study at any time. The French-speaking part is located in the Western part of Switzerland, comprises seven of the 26 cantons and represents 25% of the Swiss population, or 2.1 million people in 2019 [26]. Patients were eligible if they came to a network pharmacy or a partner general practice, were adults (≥18 years) diagnosed with T2D, and took at least one oral antidiabetic medication. Exclusion criteria were a diagnosis of type 1 diabetes, an obvious cognitive impairment, and an insufficient ability to speak French for completing the questionnaires.

Recruitment was done at three levels: (1) Sispha promoted the study to all pharmacies in the network and recruited the volunteer participants; (2) the recruited pharmacists promoted Siscare to physicians in their neighbourhood or acquaintances to create local interprofessional networks and to promote the inclusion of patients in the medical practices; and (3) the recruited pharmacists identified their eligible patients via the pharmacy database, without selecting patients based on their *a priori* level of medication adherence, and informed the referent physician of the inclusion of a patient.

Implementation strategies

Targeted efforts designed to promote the implementation of the intervention, its integration into routine practice and particularly the building of collaborative practices were developed (see Table 1). These implementation strategies were divided across the four stages of the implementation process [22]: exploration (appraisal of the service to either accept or reject it), preparation (preparation of the staff and setting and getting the system ready for delivery), operation (the process followed to integrate and use a service within a setting), and sustainability (integration and continuation of service delivery).

Measures

Measures were evaluated across the different stages of the implementation process [22]: indicators of interprofessional collaborative practices and operationalization across four levels (see Table 2); usefulness of the implementation strategies; influencing factors, and healthcare professionals' and patients' satisfaction with collaborative practices; and fidelity to the use of the interview report sent by the pharmacist to the physician, and adaptations if any.

Data collection

Data were collected using both qualitative and quantitative methods. The qualitative methods included two semi-structured focus groups conducted with volunteer pharmacists to explore their motivation, facilitators and barriers related to topics such as the inclusion of patients, the delivery of the intervention, and interprofessional collaboration. Two sessions were held during the inclusion period (preparation stage - November 2016), with a total of 17 pharmacists from 12 pharmacies, and two sessions during the delivery of Siscare-DT2 (operation stage - May 2018), with 11 pharmacists from 11 pharmacies who had included at least one patient. Quantitative methods included monitoring of data uploaded on the web-based platform used by pharmacists to deliver Siscare-DT2, questionnaire (through telephone calls) and on-site audit for pharmacies, and a questionnaire submitted to physicians and patients. The questionnaire for physicians evaluated their experience and satisfaction with Siscare and consisted of six questions (see Additional File 1), while the patient questionnaire addressed perceptions and satisfaction with interprofessional collaboration with two questions. Both questionnaires were on a four-point scale. All evaluation materials were developed by the research team.

Data analysis

With participants' consent, all telephone interviews and focus groups were audio-recorded. Focus groups were transcribed, and data were formally analysed with MAXQDA Standard 12 (VERBI software GmBH). Descriptive statistics were calculated with Microsoft Excel software (Microsoft Office Professional Plus).

Ethical consideration

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Cantonal Ethics Committee of Research on Human Beings of the Canton of Vaud [Protocol N°2016-00110]. Informed consent was obtained from all individual participants included in the study. Pharmacists provided oral consent, and patients provided written consent. Data were coded.

Table 1 - Implementation strategies to build interprofessional collaborative practices in Siscare-DT2

Target	Stages of the implementation process			
	1. Exploration	**2. Preparation**	**3. Operation**	**4. Sustainability**
Stakeholders	• Recognition of the project by stakeholders • Establishment of an interprofessional steering committee	• Bi-annual meetings between Sispha, the research team and the steering committee to present the study's progress and discuss subsequent actions		• Recommendations to the Swiss Federal Office of Public Health
Pharmacy team (including pharmacist and technician)	• Recruitment of pharmacies	• Toolkit: Siscare leaflet, communication material, access to secure web-based platform • Staff training • Creation of a list of eligible patients through the pharmacy database	• Use and continuous improvement of the toolkit • Ongoing staff training adapted to pharmacies' specific needs	
Physicians and pharmacists	• Information through professional associations	• Set up of local interprofessional networks by the pharmacists	• Continuous development of interprofessional networks	
Research team	• Implementation-effectiveness research protocol	• Data collection • PDCA (Plan, Do, Check, Act) monitoring and feedback to participants • Publication of findings and recommendations		

Table 2 - The four progression levels of building interprofessional practices

Levels of collaboration	Measured outcomes	Observed findings in Siscare-DT2
1 - Unidirectional transmission of information Pharmacist → Physician	• The pharmacist promotes Siscare to physicians and their assistants in the neighbourhood/acquaintances. • The pharmacist informs the referent physician after having included a patient in Siscare, sends the patient's treatment plan and the interview report to the referent physician, and gives a copy to the patient.	• 89% (n=24/27) of pharmacists contacted physicians to inform them of the project, 73% presented the project to them in person, and 30% (n=8/27) of pharmacists had occasional contact with medical assistants. • 70% (n=19/27) of pharmacists sent a report to the physician.
2 -Bidirectional exchange of information Pharmacist ↔ Physician	• The physician shares the clinical outcomes and therapeutic objectives with the pharmacist.	• 42% (n=8/19) of pharmacists have always or sometimes received answers from the physician regarding the interview report.
3 - Concerted measures of treatment objectives, calling for complementary skills between Pharmacist ‹ › Physician	• The physician refers the patients to the pharmacy or prescribes Siscare. • The physician approves, and if necessary adapts, the treatment plan in consultation with the pharmacist; and discusses solutions to address medication nonadherence, management of side effects, unreached therapeutic goals or other issues in accordance with the patient.	• No physician referred an eligible patient to a pharmacy or prescribed Siscare. • 52% (n=17/33) of pharmacists had occasional discussions with physicians about patients' monitoring.
4 - Sharing of decisions and actions in line with a common therapeutic objective Pharmacist ◄ ► Physician	• The physician and the pharmacist together discuss specific objectives and field of actions with the aim of defining and sharing joint responsibilities between all healthcare providers by integrating the patient to adapt his care according to medication non-adherence, side effects, unreached therapeutic goals or other issues.	• No concertation between physician, pharmacist, and patient.

3. Results

The exploration stage

The Federal Office of Public Health and health insurance stakeholders supported the project, and an interprofessional steering committee of ten members was established (see Fig. 1). Communication of the project began with the official announcement of the Federal Office of Public Health, and then various associations agreed to publish a specific announcement, mainly healthcare professional associations and patient journals. The Federal Office of Public Health's official support was perceived by pharmacists as facilitating the communication and collaboration with patients and physicians and supporting their credibility.

The preparation stage

Pharmacists, who contacted physicians to inform them on the project, mainly selected local physicians, referent physicians of their eligible patients, participants in the same interprofessional quality circle[1] or the largest prescribers of antidiabetics to their patients. Several methods were used to initiate the first contact: mail (n=13), telephone (n=8), face-to-face (n=13), e-mail (n=6), and fax (n=3). Pharmacists either met the physicians personally, (n=14), or presented the project at a quality circle meeting (n=7). Two pharmacies invited 200 physicians by mail to an information meeting to present the project, but no physician came.

In the first round of focus groups, pharmacists reported that collaboration was almost non-existent, as the response rate of physicians to information or invitation to a meeting was quite low (see Fig. 1). The relationship appeared to be one-sided, which was demotivating for pharmacists.

The usefulness of communication material to promote collaboration with the physician were mostly perceived as "*very useful*" or "*somewhat useful*" by the pharmacists, with the exception of the information support for physician's assistants, because it was underused (see Fig. 2).

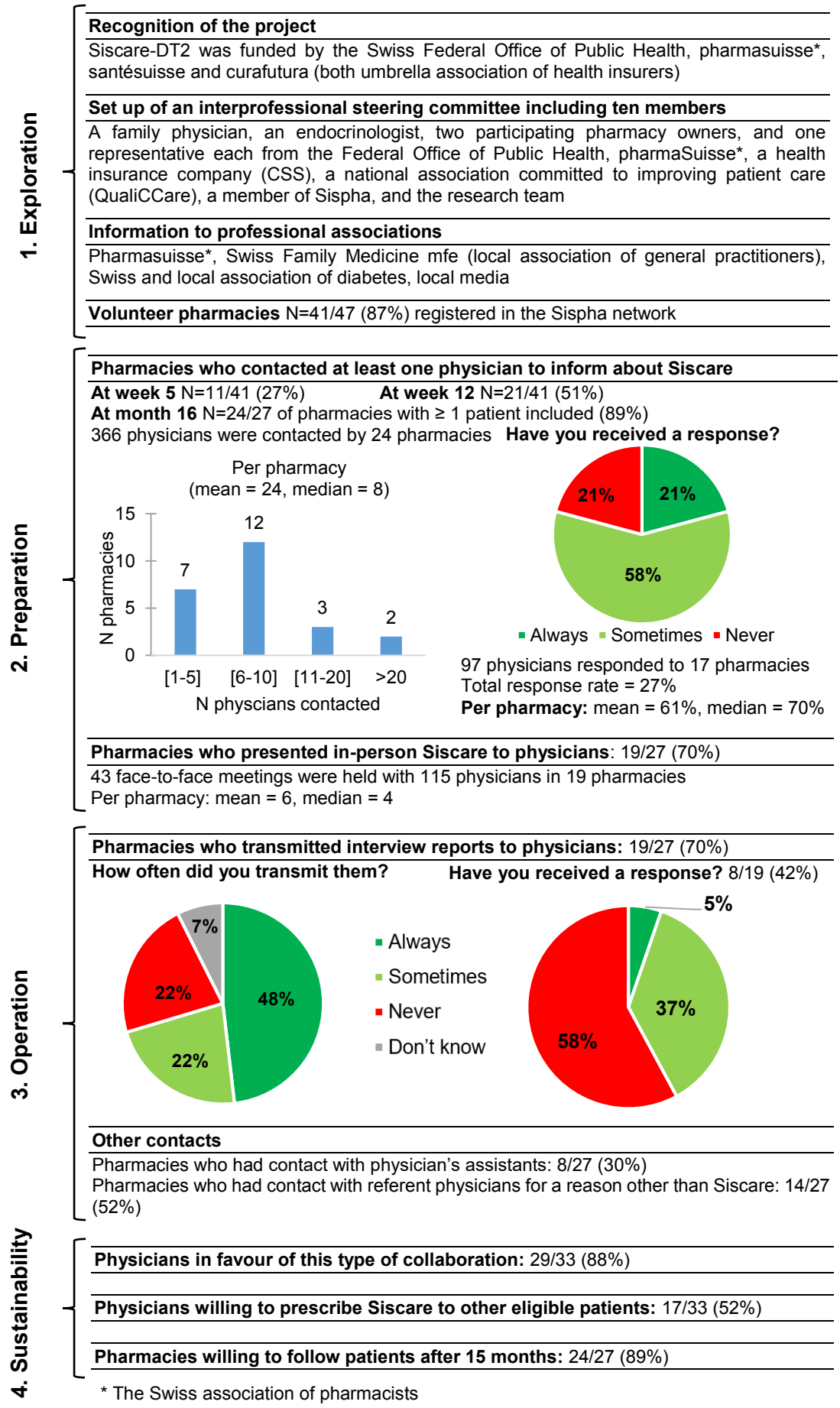
The operation stage

A total of 212 patients were included by 27 pharmacies. Referent physicians were a general practitioner for 77% (141/184) of patients, a diabetologist or endocrinologist for 18% (34/184) and another specialist for 5% (9/184) (e.g., infectious disease specialist or cardiologist). Overall, 89 physicians (71%) followed one patient, 23 (18%) two patients, 5 (4%) three patients, 6 (5%) four patients, and 2 (2%) five patients.

Collaboration primarily occurred through the unidirectional transmission of information from the pharmacist to the physician (level 1: 70% (19/27 of pharmacists transmitted interview reports to physicians); bidirectional exchange of information sometimes occurred (level 2: 42% received physician responses), and concerted measures of treatment objectives took place occasionally (level 3) (see Table 2).

[1] Quality circles bring together five to eight physicians and pharmacists to develop collective evidence-based guidelines to improve physician-prescribing behaviour and to put these recommendations into practice [27]

Fig. 1 - Outcomes of interprofessional collaborative practices throughout the implementation process of Siscare-DT2



* The Swiss association of pharmacists

The methods used to send the interview reports included: fax (n=10), mail (n=8), and e-mail (n=6). Sixteen pharmacies used the automatic template of the web-based platform, and three pharmacies developed their own shorter template. Several strategies were used by pharmacists to encourage physician response, e.g., follow-up questions at the end of the report, and notification call before sending the report. In some cases, reports were sent only when a problem was encountered (e.g., medication adherence, adverse reaction, failure to achieve therapeutic objective). Half of the physicians (55%, n=18/33 respondents to the final questionnaire) discussed the programme with their patients during the medical visit, and 67% of physicians (22/33) found the report useful.

In the second round of focus groups, pharmacists reported being demotivated by the lack of response after sending reports to the physician. In addition, pharmacists felt that they could not easily contribute to further patient management because there were already multiple healthcare professionals involved, such as a general practitioner, a diabetologist and a nurse specialized in diabetes. Pharmacists initially doubted their added value in the management of the patient's care, but after several trainings and after having initiated Siscare, this feeling faded. Interprofessional collaboration was deemed satisfactory for only two pharmacists who favoured a pre-existing relationship and the organisation of a face-to-face meeting before the inclusion of patients. Few pharmacists had any contact with physician's assistants.

The sustainability stage

Among physicians who responded to the final questionnaire, 67% (n=22/33) perceived the programme as beneficial for their patients in terms of medication adherence and/or medication management. Regarding willingness to prescribe Siscare, 52% (17/33) of physicians said they strongly or fairly agree, while 36% said they strongly or somewhat disagree (n=6) or totally disagree (n=6).

Among the 68 patients who responded to the satisfaction questionnaire, 74% (n=50), considered the collaboration between their pharmacist and referent physician to be relatively present to very present, and 44% (n=30) stated that it improved their management. A clinical vignette of a patient included in Siscare-DT2 is described in Fig. 3. In the focus groups, pharmacists declared that the remuneration system for the programme and the lack of interactions on the web-based platform with physicians were obstacles to the sustainability of interprofessional collaborative practices through Siscare.

Fig. 2 - Evaluation of pharmacists' perception on the usefulness of the communication material to promote collaboration (n=25 pharmacies)

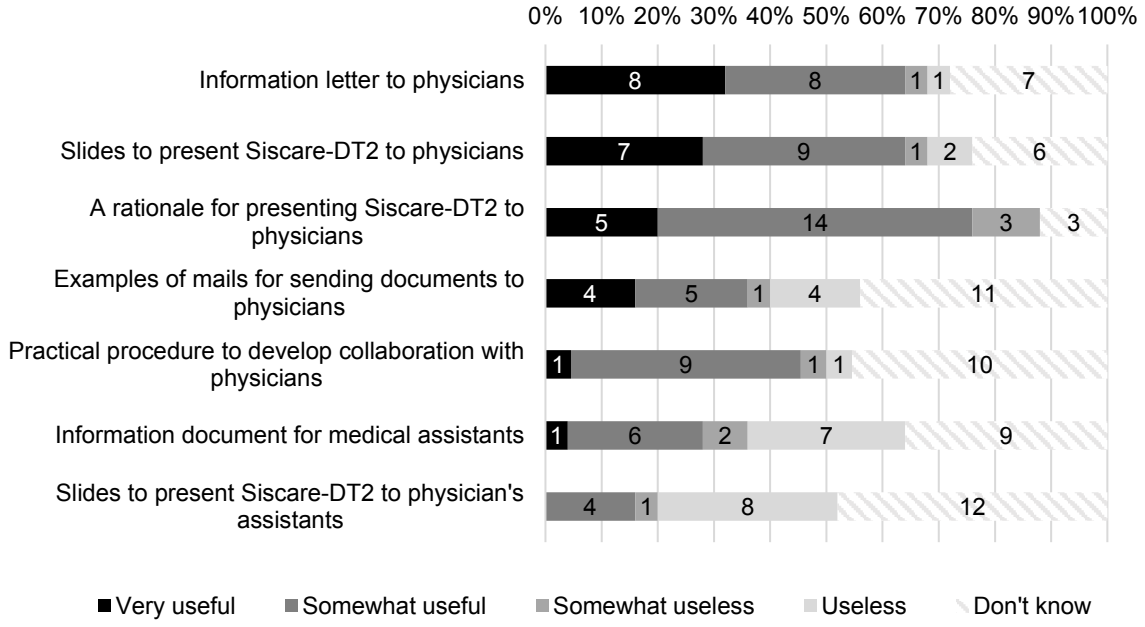


Fig. 3 - Clinical vignette of a patient included in Siscare-DT2

- 73 year-old retired man with a high level of education
- Type 2 diabetes diagnosis > 10 years, hypertension, already had a heart attack
- Motivated to be adherent, supported by his social network, fears having to switch to insulin and is concerned about the duration of his treatment and its effects, especially on his kidneys, willingness to reduce the number of medications
- A referent physician (general practitioner), regular patient of a network pharmacy
- Reason for Siscare inclusion: to obtain support in the daily management of his treatment/illness from a professional other than his referent physician, curious about how interprofessional collaboration could contribute to his care.
- Treatment plan at inclusion:

Id	Drugs	Indication	Regimen	Monitoring
D1	Acetylsalicylic acid tablet 100 mg	Myocardial infarction	1-0-0	Electronic monitoring (electronic pillbox)
D2	Clopidogrel 75 mg		1-0-0	
D3	Candesartan/Hydrochlorothiazide tablet 16/12.5 mg	Hypertension	1-0-0	
D4	Vildagliptine/Metformin tablet 50/500 mg (> 4 years)	Type 2 diabetes	1-0-1	

- Evolution of clinical outcomes, medication adherence (see Additional File 2 for adherence graphs) and clinical decisions

	Baseline	6-months	12-months	18-months	22-months	24-months
HbA1c	7.1%	6.5%	7.0%	7.0%	-	-
Adherence to OAD°	72%	80% D1 discontinued by physician	99% Routine reinforcement	97%	34% Trips abroad and jet lag make it difficult to take 3 tablets /day	100%
Clinical decisions*	Siscare initiated by pharmacist in agreement with patient and physician before intensifying diabetes treatment	D4 switched to metformin 500 mg twice daily	Metformin 500 mg was increased to three times daily	-	Diet recommend-dations by the pharmacist	Switch to metformin 850 mg twice daily to reduce the number of tablets
BMI	26.9 kg/m^2	-	-	-	-	25.1 kg/m^2
Siscare content	• 9 pharmacist-patient interviews • Reports were sent to the referent physician after each interview and followed by a telephone call when a medical visit was deemed necessary and action was required.					
Added value	• The **patient** perceived a real benefit from the electronic pillboxes, and the interviews helped building new habits. He did not feel controlled, but encouraged and supported. The patient was reassured about his treatment, he paid attention to his diet, and concerns faded away. Siscare has allowed him, through better adherence, to lighten the treatment and reduce the risk of side effects. He appreciated the availability of the pharmacy team to talk about his concerns and he felt that the collaboration greatly improved his care. To improve the programme, the patient suggested organizing a joint meeting with his referent physician and his pharmacist. • The **pharmacist** felt the relationship with the patient and the physician was improved. Discussing therapeutic goals with the physician and exploring the patient's feelings allowed the pharmacist to propose a sound course of actions and to adjust her intervention. These therapeutic relationships are perceived as a reward for the pharmacist by creating a special bond of mutual knowledge that goes beyond the conventional relationship. • The **physician** found it crucial that pharmacists and physicians be trained in therapeutic patient education and share the same relational approach so that the patient could benefit fully from interprofessional collaborations.					

° Clopidogrel and antihypertensive medications were taken regularly in the morning
* Pharmacist, physician and patient agreements

Discussion

Despite multiple implementation strategies, collaboration primarily occurred solely through the unidirectional transmission of information (level 1); bidirectional exchange of information occurred sometimes (level 2), and concerted measures of treatment objectives took place occasionally (level 3). Pharmacists expressed frustration because physicians did not often respond to the interview reports. No physician prescribed Siscare, but no objections were identified, and seventeen physicians (51%) declared they were willing to prescribe Siscare to other eligible patients.

To increase adoption of Siscare by pharmacists and physicians, more communication and exchange is needed so that healthcare professionals are aware of the existence and benefits of these collaborative practices [28]. This has already begun with the inclusion of Siscare in the Swiss catalogue of models of good interprofessional practice [29]. Siscare is an original patient support programme with the intervention of the community pharmacist as a trigger factor. The inclusion of physicians early in the development of patient-centred interprofessional services, including defining the roles and responsibilities, is paramount to fostering higher levels of collaboration [30,31].

The participating pharmacists did not feel sufficiently trained and doubted their credibility and added value in the management of T2D patients. There is a need for joint pre- and post-graduate education of healthcare professionals to face this barrier. Today, the number of universities offering both lectures and practical courses to healthcare students such as pharmacists, nurses, physicians, dentists, and physiotherapists is increasing [32-34], but the amount of time devoted to this education in formal pharmacy curricula remains low [35,36]. There is a need to allocate increased resources to initial and continuing interprofessional education [37]. In Switzerland, the Swiss InterProfessional Education Course (SwissIPE) association was founded in 2018 to promote interprofessional collaboration and leadership in integrated ambulatory care and nursing homes with health insurance and other ambulatory care facilities; it offers training in interprofessional teamwork and joint leadership [38].

The interprofessional collaboration through Siscare focused on the collaboration between the pharmacist and the referent physician. Nevertheless, this bilateral collaboration should then be integrated into the patient's overall care path by integrating the other healthcare professionals involved. T2D patients often have other chronic diseases requiring the involvement of other specialists. Medication nonadherence is a topic rarely discussed in medical visits and is often underestimated by physicians, mostly due to the limited time spent on this issue during training [39,40]. Thanks to their pharmacological knowledge, pharmacists should play a key role in identifying patients at risk of suboptimal medication use, even if the different healthcare expertise, e.g., specialized nurses, in supporting adherence can complement each other [12,41]. Therefore, it is essential to open a discussion with all healthcare professionals involved in patient management and to define their scope of action adapted to the local and interpersonal context [13,30]. The Swiss interprofessional platform has elaborated a set of 21 criteria concerning the development and implementation of interprofessional projects, which can improve the success of such projects when used from the outset [31].

Appropriate financial resources are a key element in the sustainability of interprofessional collaboration in patient support programmes [30]. In Switzerland, physician tariff headings include fees for the coordination of care in the absence of the patient (e.g., review of patient’s file, obtaining information from third parties, discussions with therapists and caregivers), but are limited to a maximum of 60 minutes every three months for patients who need it [42]. However, for pharmacists, there is a reimbursable fee for Siscare that pays for work at the pharmacy but does not include collaboration fees [43].

Consequently, the Swiss billing system does not encourage interprofessional collaboration because there is no specific funding to pay for coordination between healthcare professionals, but only a few isolated tariff headings. The Federal Office of Public Health and the Swiss association of pharmacists (pharmasuisse) are currently discussing the development of a new system of performance-based pharmacy remuneration for 2021, including individual remuneration based on the degree of effective care and allowing for adequate pricing [44].

The lack of interactions of the web-based platform with physicians appeared to be an obstacle to the sustainability of interprofessional collaborative practices through Siscare. Material resources must be developed to facilitate information exchange and collaboration between professionals [30]. Sispha's web-based platform has been interconnected to the billing management system of the pharmacy, simultaneously allowing access to clinical information (guidelines and decision aids) and generating an automated treatment plan and an interview report written by the pharmacist. The information collected by each healthcare provider should be systematically shared through a joint and effective electronic medical record to improve collaboration and patient follow-up. To this end, incentives should facilitate the development of IT solutions that allow a secured exchange of data, also including the patient. In Switzerland, a strategy defined by the Federal Council to ensure and improve the quality of care is the increased use of e-health, including the introduction and active promotion of an electronic patient record [45]. This record includes data and documents important for further treatment and follow-up, made available to other healthcare professionals, according to patient's consent [46], while its organisational, technical and safety aspects are regulated by a new law that came into force in 2017 [47]. An association called CARA was constituted by five cantons as a joint force to establish a single e-health platform for healthcare providers and the population of Western Switzerland [48]. In addition, a cooperative society of pharmacists, Ofac, has bought Sispha SA and intends to integrate Siscare care into its e-health platform Abilis, which will cover all Switzerland.

No physician had referred a patient to a pharmacy. Yet, physicians and pharmacists should complement each other in identifying patients who would benefit most from Siscare. Pharmacists can identify patients by considering medication adherence issues, side effects, polypharmacy, and aging through the pharmacy software, discussing with the patient at the counter or in a counselling room, and when providing pharmacy services such as medication reviews [41,49]. In parallel, physicians can be more attentive during events that may influence medication adherence, e.g., new diagnosis or treatment, therapeutic goals not reached. Because Siscare is a generic approach, the recruitment pool can also be broadened by including other patients who would benefit from Siscare, notably patients who have other chronic diseases (e.g., cardiovascular disorders, hypertension, HIV, oral oncology, transplant or multiple sclerosis) or require critical short-term treatment (e.g. patients with hepatitis C) [50,51].

There are several limitations to this study. First, interprofessional collaboration outcomes were mainly analysed in pharmacies that included at least one patient. They were the most innovative. Our results do not represent pharmacies that are less responsive to such programmes. Second, the results were collected through questionnaires, audits or focus groups with volunteers at a point in time, and not along a continuum. Therefore, some information may have been missed, and interprofessional collaboration underestimated.

Conclusions

Siscare is an innovative patient support programme that promotes interprofessional collaborative practices, with the intervention of the community pharmacist as a trigger factor. The pharmacist monitors and informs the referent physician about the medication adherence of the patient, while the physician retains leadership of the treatment. Nevertheless, despite multiple implementation strategies, interprofessional collaboration remained infrequent in this study; however, Siscare was well received by the pharmacists, patients and physicians. A promising start to the collaboration occurred in pharmacies, but active participation of the physicians is still lacking. Effective implementation strategies need to be further explored.

Abbreviations

FISpH: Framework for the Implementation of Services in Pharmacy; T2D: type 2 diabetes.

Declarations

Acknowledgements: The authors would like to sincerely acknowledge the funding bodies (FOPH, pharmaSuisse, santésuisse, curafutura) and all the pharmacy teams, patients and physicians who participated in the program. The views expressed are those of the authors and not necessarily those of the funding bodies.

Funding: This work was supported by the Swiss Federal Office of Public Health (FOPH) [grant number: 15.003846] and the joint Swiss fund of quality and research RPB IV/1 [grant number: 20160201] including santésuisse, Curafutura (both umbrella associations of Swiss health insurers) and pharmaSuisse (Swiss association of pharmacists) as sponsors. No funding body was involved in the design of the study, data collection or analysis. Bi-annual meetings were organized with the FOPH (and the steering committee) to monitor the results and the study progress.

Conflict of interest: S. Jotterand, C. Rossier, and O. Bugnon are co-founders and shareholders of Sispha SA and members of the advisory board of Sispha SA. The other authors declare that they have no competing interests.

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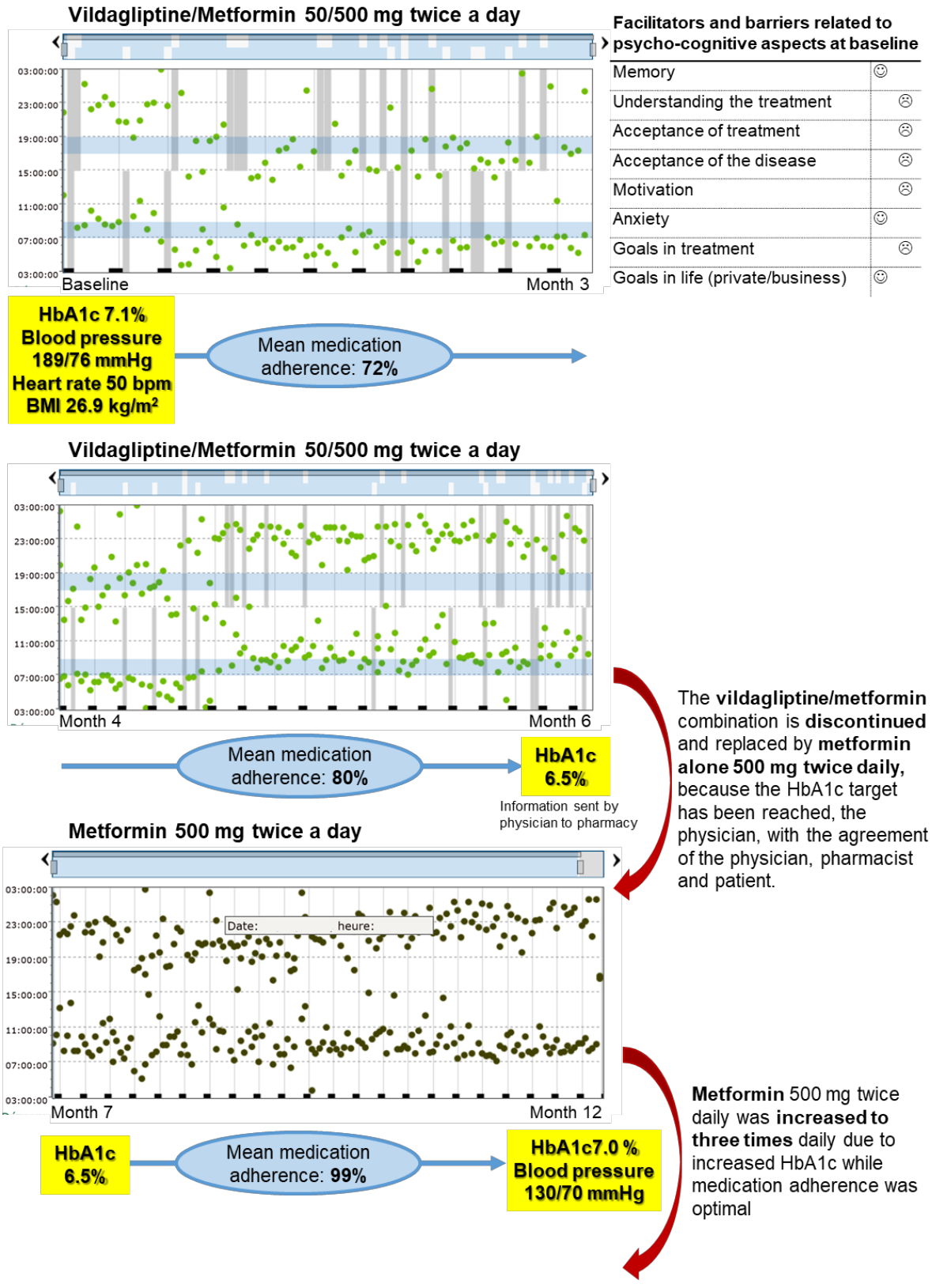
Additional Material

Additional File 1 - Physician questionnaire on the evaluation of the interprofessionality in Siscare-DT2

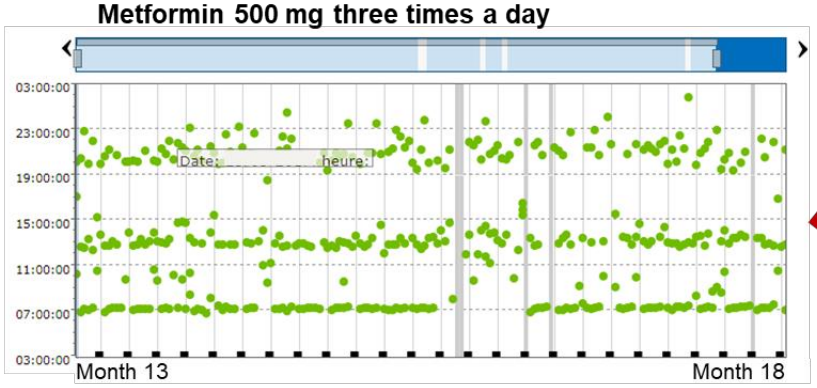
Questions	Absolutely	Rather	A little	Not at all	I don't know
1. In general, are you in favour of a programme that supports a patient's treatment?	☐	☐	☐	☐	☐
2. More specifically, concerning the case of your patient, do you think that it has been beneficial to him/her in terms of adherence and/or management?	☐	☐	☐	☐	☐
3. Also in the case of your patient, was the interview report you received from his pharmacist helpful?	☐	☐	☐	☐	☐
4. Was your patient's participation in this programme discussed during any of your consultations?	☐	☐	☐	☐	☐
5. Would you recommend this type of programme to other patients who might be eligible for it?	☐	☐	☐	☐	☐
6. In general, do you support this type of collaboration with the pharmacist?	☐	☐	☐	☐	☐
7. Any comment:					

Additional File 2 - Illustration of the daily openings of the electronic pillbox containing the oral antidiabetic medication, the evolution of the clinical outcomes and treatment over 24 months of a patient included in Siscare-DT2.

Each dot represents a pillbox opening: days on the x-axis and hours on the y-axis.



Metformin 500 mg three times a day



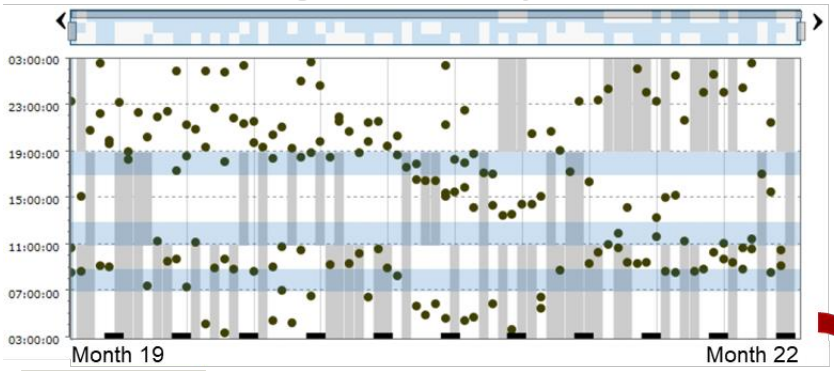
Metformin 500 mg twice daily was **increased to three times** daily due to increased HbA1c while medication adherence was optimal

HbA1c 7.0%
Blood pressure 130/70 mmHg

Mean medication adherence: **97%**

HbA1c 7.0%
Blood pressure 120/70 mmHg

Metformin 500mg three times a day

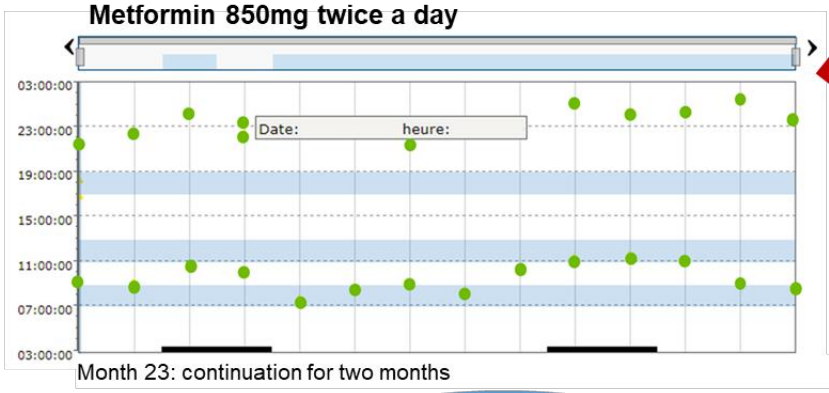


HbA1c 7.0%
Blood pressure 120/70 mmHg

Mean medication adherence: **34%**

As it was **difficult** to manage **three intakes** per day due to **foreign travel,** treatment was switched from metformin 500 mg to **metformin 850 mg twice daily**, which simplifies, especially when travelling. In accordance with the patient, the pharmacist suggested this change to the physician, which was approved by all.
The pharmacist also recommended that the patient make an appointment with the physician for a blood test.

Metformin 850mg twice a day



Mean medication adherence: **100%**

BMI 25.1 kg/m²

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Chapter 6. General Discussion

Implementation science has become more important and popular for putting effective patient support programmes in place. This thesis presents original research using both implementation science and clinical research with quantitative and qualitative methods (presented in chapter 2) to analyse the implementation and effectiveness of Siscare-DT2 in Swiss primary care.

The thesis showed that the implementation of Siscare-DT2 in community pharmacies is feasible and acceptable (chapter 3). The implementation process, outcomes and impact were described and assessed in 41 “early adopters” (i.e., community pharmacies belonging to a network). An orderly three-step implementation process was observed: internal organisation, the creation of interprofessional practices with physicians, and the development of the relationship with patients. The study findings indicate that operational success in the implementation of Siscare-DT2 in pharmacies implies a global corporate project involving a clear project management strategy; human and financial investments; precise documentation of performance indicators; commitment of the entire staff team; and good coordination within the local healthcare provider network. The implementation of the programme on a wider scale is still tentative due to the inertia inherent in any fundamental change in practices and the economic-political uncertainties influencing the actors in primary care.

Moreover, research on the effectiveness suggested that Siscare supports medication adherence and improves the clinical outcomes of patients with T2D (chapter 4). The monitoring of 212 patients included in Siscare-DT2 showed a stable and high level of adherence to OAD over a 15-month monitoring period, which is higher than what is described in the literature for this population. The percentage of patients persistently and appropriately taking their medication was estimated at 90% at baseline and 88% at 15 months. Linear mixed-effect models showed that the average HbA1c level decreased from 0.3 to 0.5 units (%) after 15 months, while the effect of adding an OAD on HbA1c levels ranged from 0.5 to 1.0 units (%) after 3 to 6 months according to the literature [94]. The observed decrease was even higher in patients with a baseline HbA1c level ≥ 7.5% (cumulative decrease of 1.2 units over 15 months), thus indicating the importance screening patients before inclusion. The participants’ quality of life remained stable during the study, and 75% (n=51/68) of the patients who responded to the satisfaction questionnaire reported that they would recommend Siscare to another person with diabetes. These results illustrate the overall effectiveness of a patient support programme carried by pharmacists in agreement with physicians. Siscare should be prescribed to patients who could benefit from close and motivational monitoring of their medication, similar to the referral of a patient to a dietician or to a programme for physical activity.

Finally, Siscare represents a promising start for interprofessional collaboration (chapter 5). The study focussed on the building of interprofessional collaborative practices throughout the implementation process of Siscare-DT2. The interprofessionality has been operationalised through four progressive levels of interrelationship practices between the pharmacist and the referent physician of the patient. Despite multiple implementation strategies, collaboration primarily occurred solely through the unidirectional transmission of information from the pharmacist to the physician (level 1); bidirectional exchange of information sometimes occurred (level 2); and concerted measures of treatment objectives took place occasionally (level 3). No physician has referred a patient to a pharmacy or prescribed Siscare, and their level of active participation in Siscare-DT2 was low. However, Siscare-DT2 has been

well received by the patients and physicians: 88% (n=29/33) of physicians who responded to the final questionnaire were in favour of this type of collaboration. Previous participation in interprofessional quality circles fosters collaboration, and appropriate pre- and post-graduate education, financial incentives and material resources are needed to promote collaboration. This aspect needs to be further explored.

The next section discusses the findings of this research and relates them with each other to highlight recommendations for the sustainable implementation of Siscare in the contexts of patients with chronic diseases, the quality of the healthcare system and research.

Recommendations

The success or failure of the implementation of an innovative intervention is influenced by contextual factors (barriers/facilitators) intervening at different levels according to *Moullin* et al. (2016). These recommendations target different levels of actions from a micro- to a macrolevel: innovation, individuals (pharmacists, physicians), organisations (pharmacies, general practices), local setting (community, patients, local healthcare professionals), and the system (political, economic, professional) [83]. These recommendations are presented through five themes: communication, interprofessionality, material resources, education, and financial resources.

Communication

Chronic patients should be more informed about Siscare in pharmacies. Only 6% of patients with T2D included in Siscare-DT2 took part in another form of support (e.g., a dietician) or were part of a patient association, whereas in the Swiss diabetes cohort of the canton of Vaud CoDiab-Vd 2017, 12% of participants were members of a diabetes association [95]. This difference shows that the population still has too little access to resources that can help the patient manage diabetes and its related aspects. Moreover, in a sample of Swiss patients with diabetes on health insurance, adherence to OAD was low: only 42% of patients were considered to be adherent (PDC ≥80%) over 12 months (n=26,713 patients) [45], while in Siscare-DT2, 88% of patients were adherent after 15 months. These findings show that there is still room for improvement with respect to adherence. Patients with chronic diseases may not be aware that their pharmacist can play a key role in their care, likely due to the current changing role of community pharmacies in the healthcare system and the availability of new professional pharmacy services (e.g., health promotion and advice, vaccination) [96]. The abovementioned factors and the generally favourable opinion of patients on this new type of patient support programme suggest that communication to the general public and other healthcare providers about professional pharmacy services should be improved so that patients with chronic diseases can experience these services and recognize the skills and competencies of healthcare providers.

Locally, various stakeholders can enhance this information and communication, including health insurance companies, patient associations, Sispha, physicians, pharmacists, or other caregivers. On a larger scale, the FOPH can officially disseminate the results of SIScare-DT2 and these perspectives to politicians, partners and the general public, as its support is perceived as facilitating communication and collaboration (with physicians and patients) and enhancing their credibility. Health professional associations (e.g., local (SVPh) and national (pharmaSuisse) pharmacy or medical (SVM) societies) should also relay the FOPH's communication to their members and the public, and health insurance associations (e.g., Curafutura, Santésuisse, umbrella associations of Swiss health insurers) can encourage their policyholders to benefit from this type of programme.

Interprofessionality

Siscare promoted interprofessional collaboration between pharmacists and referent physicians of patients and their teams. Although collaboration primarily occurred solely through the unidirectional transmission of information from the pharmacist to the physician, the participating physicians who responded to the final questionnaire evaluated interprofessional collaboration positively. Moreover, the findings regarding effectiveness, the positive opinion of patients and their high level of satisfaction with the interprofessional collaboration in Sicare-DT2 should encourage professionals to promote this type

of collaboration. The observed success factors of interprofessional collaboration in Siscare-DT2 are consistent with previous reports or studies: patient-centred approaches involving all stakeholders, appropriate remuneration and legislation, interprofessional education, known and recognised complementary skills, and access to medical records [23,97-99].

We observed the almost absence of interprofessionality with mainly only unidirectional interprofessional collaboration. We are aware that professional practice changes are difficult to implement and take time for sustainability. However, it is possible that some adjustments in the implementation strategies could have led to better results. For example, the project was solely presented to physicians by the pharmacists and not the research team. Including the research team in this collaboration at the start of such a project could have increased the collaboration and help pharmacists to be in touch with physicians but this decision was made on purpose in order to initiate and/or foster the local network between healthcare professionals on a long-term basis as in a real life context. The physicians could have been contacted by the research team after the first contact with the pharmacist. The research team could have presented the project and included the doctors in the focus group. The pharmacist and the physician should discuss around a table to define their needs and recruit together the patients to be monitored according to the tasks/responsibilities they would have defined together.

The findings of Siscare-DT2 led to the integration of Siscare into the directory of good interprofessional practices of the FOPH as part of the promotional programme “Interprofessionality in Healthcare” to more widely disseminate knowledge on practice [100]. There are two types of criteria for selecting good practice models: qualification and evaluation criteria [101]. The qualification criteria imply that the model supports the objectives of the promotional programme, the involvement of at least two groups of healthcare professionals from the outset with interests and needs of patients at the heart of the project, allowing transferability to another context. The evaluation criteria include a global approach (as opposed to an isolated approach); high potential input; a model that is already operational and integrated in another context; a model that was developed with knowledge-based, innovative and promising and national coverage including rural and urban areas. To help with the development and evaluation of interprofessional projects, the Swiss Interprofessional Platform has also elaborated a set of 21 criteria improving the success of such projects when used from the outset [102]. These criteria are divided into three categories: (i) prerequisite criteria, including interprofessional aspects (which overlap with FOPH's evaluation criteria and are related to the relevance of the primary ambulatory care project) and sustainability; (ii) methodological criteria, including the context studied, the evaluation of the project and its implementation; and (iii) interprofessional criteria, including the skills and responsibilities of professionals, communication between them, interprofessional training and applicability, and the impact of the project in other contexts. Using these criteria from the outset will help to increase collaboration between healthcare providers.

Healthcare professionals should meet to collaboratively build the optimal process of interaction and communication and precisely define the roles and responsibilities of each participant [99,102]. Professional organisations can increase contacts between healthcare professionals to promote knowledge of each provider’s skills through the organisation of national (e.g., symposium, round tables) or local events (e.g., quality circles, forums, meetings, job shadowing). In this sense, Siscare-DT2 has already been presented in a workshop in October 2019 during a joint event for physicians and pharmacists of the canton of Vaud, Switzerland [103]. At the local level, further pilot projects testing

novel forms of interprofessional collaboration (e.g., by including physician assistants and nurses of medical-social centres) should be supported.

Material resources

Today, the Sispha web-based platform corresponds to an electronic patient data management system and a clinical information system (guidelines and decision aids). It allows the pharmacist to conduct patient interviews, establish a medication plan and edit the interview reports for patients and physicians. The platform is currently connected with the pharmacy management system of the primary dispensary (Tactil by pharmactic, a company of the Ofac group, which is a cooperative society of pharmacists) [104]. In the future, the platform should be interconnected with other primary care systems within the framework of an electronic patient record to facilitate information exchanges between healthcare providers. In line with this objective, the Ofac group company, which bought Sispha, intends to integrate the web platform into its Abilis e-health platform, allowing information exchanges with other primary care systems across all of Switzerland [105].

The federal government must develop appropriate incentives to facilitate the development of and access to information technology solutions leading to these facilitated exchanges, including access for the patient. In Switzerland, the electronic patient record is being introduced, and a law was drafted in 2017 to define its organisational, technical and safety aspects [106]. However, many questions remain about what kind of information should be shared (treatment, medical and/or personal data?), by whom (all or designed healthcare providers and patients?), with what levels of access and visibility (name of prescribers or pharmacies and other actors?). Additionally, there are questions about how it could be done in practice. The electronic patient record is having a hard time getting established because there are many points to consider. Much remains to be done to actively promote the use of appropriate e-health in the coming years [107].

Education

The findings of Siscare-DT2 showed that the implementation strategies proposed by Sispha, such as training sessions (on project management, motivational communication, and interprofessional teamwork) and on-site coaching, were suitable for pharmacies as long as the change of practices is considered a team/company project and not an individual project. Moreover, after each training session, participating pharmacies were motivated and tended to include more patients than non-participating pharmacies. In this sense, it is essential that healthcare professionals and their teams, such as pharmacists, have confidence in their own skills, are trained and believe in their ability to lead and coordinate this type of service.

Appropriate pre- and post-graduate education is crucial for enabling healthcare professionals to develop skills in interprofessional collaborative practices. For pre-graduate education, tertiary education institutions (universities and colleges) should support the integration of collaborative models (such as Siscare) into the initial education of future healthcare professionals, including project management and implementation change. The number of universities offering educational courses between healthcare students of different disciplines is increasing [108-110]. In Switzerland, an Interprofessional Simulation Centre (CiS) was initiated in 2013 for the joint development of an interprofessional skills training programme in pre-university training [111]. The CIS aims to share educational tools that are very similar to acute complex situations (using dummies or simulated patients) with clinical skills specific to the

various health professions. Above all, the CIS aims to provide the skills needed for collaborative practice in the professional field by training healthcare students. The time devoted to this teaching in formal pharmacy programmes remains low and should be increased [112,113].

Postgraduate education on interprofessional practices for all healthcare professionals in primary care remains rare in Switzerland. Since 2018, the Swiss InterProfessional Education Course (SwissIPE) has promoted interprofessional collaboration and leadership in integrated ambulatory care, nursing homes, health insurance and other ambulatory care facilities [114]. The courses address the challenges facing the Swiss health system by providing participants with basic knowledge on how to collaborate in an integrated system of care and on the functioning of a team and its supervision; by enabling them to initiate, develop, evaluate and support a quality, equitable and sustainable interprofessional project; and by leading a team of professionals from different educational backgrounds who are working to meet the needs of the patient. Political and economic systems must encourage pharmacies, general practices, and other health centres to train all their employees to work in interprofessional teams.

Financial resources

From the community pharmacist's perspective, the lack of awareness of the profitability of Siscare had been declared in the focus groups as an important barrier to the implementation of the service. Some financial measures for professional pharmacy services are crucial for the business owner to overcome this barrier [115,116]. For this purpose, a study was conducted by colleagues from the Community Pharmacy Research Team of Unisanté in parallel with Siscare-DT2 [117]. The study aimed to estimate the implementation costs and the break-even point of Siscare for patients with chronic diseases in Switzerland. A 3-step approach was used: (i) microcosting analysis: the identification of implementation activities, the quantification and valuation of required resources with the implementation costs (including service support and direct delivery costs) analysed according to the implementation stages; (ii) break-even analysis, i.e., the minimum number of patients to be included and monitored so that the revenue generated covers at least the total cost of implementation; and (iii) univariate sensitivity analyses to assess the impact of parameter variation. The total implementation costs in the preparation stage (i.e., before inclusion of the first patient) were estimated at 8,481 Swiss francs (CHF), half of which represented costs of equipment. The direct costs of delivering the service were estimated at 666 CHF per patient per year, including 68% of workforce time. The break-even point analysis considered the current national reimbursement system model. In Switzerland, the pharmacist can charge a total of 1,195 CHF per patient per year, including a fee-for-service plus the sale of pillboxes if the patient is simultaneously prescribed at least three chronic medications (e.g., resulting in three EM). With a fourth chronic medication or more, the pharmacist can charge an additional polymedication check (medication review) fee (48.60 CHF every six months). With these assumptions, the break-even point was estimated at 16 patients per year to cover the costs, decreasing to 13 patients after the first year. These estimates were based on a theoretical number of interviews with the pharmacist: one inclusion interview and six follow-up interviews in the first year. In Siscare-DT2, the mean number of patients included was 8 (SD 6, range: 1-29) per pharmacy, and only two pharmacies included at least 16 patients, but this indicates that the implementation is feasible.

Appropriate financial resources are also a key element in the sustainability of interprofessional collaboration in patient support programmes [99]. The Swiss billing system does not encourage interprofessional collaboration because there is no specific funding to pay for coordination between healthcare professionals but only a few isolated tariff headings. Consequently, the FOPH and the Swiss

association of pharmacists (pharmasuisse) are currently discussing the development of a new system of performance-based pharmacy remuneration for 2021 or 2022, including individual remuneration based on the degree of effective care and allowing for adequate pricing [118].

From the healthcare insurers' perspective, information on the cost-effectiveness of Siscare is crucial to the sustainability of the service. Such a study was not conducted in this thesis because the healthcare insurance data could not be collected in Siscare-DT2. The literature review conducted within this thesis showed that better adherence was associated with better glycaemic control (HbA1c) and lower mortality, with generally decreased healthcare services utilisation for hospitalisations (all-cause and diabetes-related) and emergency room visits but with a higher number of outpatient medical visits, which may explain the important role of healthcare professionals in advising patients about the importance of medication. Overall, the additional costs of OADs and medical visits were offset by lower hospitalisation costs and emergency room visits. Based on these findings, it seems reasonable to state that participation in Siscare of patients with chronic diseases is clinically favourable (it prevents diabetes-related complication and reduces hospitalisations and emergency room visits) and economically favourable from the insurer's point of view. Moreover, the annual cost of the programme for the insurer was estimated at 1,195 CHF per patient for the insurer [117]. In Switzerland, the risk of hospitalisation for an adherent patient is 7% lower each year than for a non-adherent patient [45], and the average cost of a day of hospitalisation is estimated to be 2,245 CHF in 2018 [119]. From the insurer's point of view, the cost of the programme, as well as the potential additional cost of medication and outpatient medical visits, should be offset by a reduction in hospitalisations and emergency room visits, which are particularly costly. These key assumptions suggest the cost-effectiveness of Siscare and indicate that it should be integrated into new insurance models, which would facilitate patient access.

Finally, the FOPH, the Swiss National Science Foundation (SNSF), and other possible funders should financially support hybrid implementation-effectiveness research protocols to promote scientific evaluations of interprofessional patient support programmes with the participation of all stakeholders.

Methodological Reflections

Strengths

This thesis is innovative. It uses implementation science and clinical research with both quantitative and qualitative methods. The operationalisation of the implementation concepts in pharmacy practice research, the development of evaluation tools (e.g., interview guides, questionnaires for patients and professionals), and the tailored implementation strategies provide guidance for future research as well as the implementation or scaling up of professional pharmacy services in other contexts. This study used FISpH as a theoretical framework developed for community pharmacies in 2016, which was also used in other studies in Australia [120], Spain [121], Belgium [122], and Switzerland [123,124] and has been shown to be relevant.

This work has placed the patient with type 2 diabetes at the centre of concerns. The questionnaire of patient satisfaction showed that patients were satisfied of the programme. Moreover, three quarters of the patients would recommend the programme to another person with diabetes. Assessing satisfaction of patients is crucial because it is an indicator of quality of care [125]. Face-to-face or phone interviews with participants who drop-out of the study could have increase our knowledge about patient satisfaction and how to better adapt the intervention but due to time constraints, we were unable to conduct these interviews. Nevertheless, this intervention is easily adaptable to the patient's needs regarding the motivational approach (individual approach), the frequency of visits (which can be modulated over time), and the tools used to assist in medication intake. These research findings are not limited to type 2 diabetes and apply to all other diseases on a short or long period of time.

Another strength of this research is that views and opinions were gathered from different perspectives: pharmacies, patients, and physicians. Moreover, the FOPH, the Swiss associations of health insurers (Santésuisse and Curafutura), and the Swiss pharmacists' association (pharmaSuisse) were indirectly involved through their financial support, and biannual meetings were held with the steering committee to monitor the results and the study progress. Including all stakeholders has also been demonstrated to be crucial in previous studies [126,127].

As shown by the literature review carried out within this thesis, there are very few studies that have collected electronic longitudinal data on medication adherence of patients with T2D in a real-world setting over a long and representative period of time. The evaluation of clinical outcomes over a long period (15 months) and measurement of medication adherence using an electronic pillbox allowed us to conduct an accurate longitudinal analysis of the behaviour of patients participating in the support programme.

Limitations

No recommendations to pharmacists were made regarding which patients should be included (e.g., medication adherence level) outside the specified inclusion criteria: adult, with T2D, and taking an OAD. According to the focus group results, pharmacists mostly selected patients based on the likelihood that they would accept the programme. The possible selection of patients for inclusion by pharmacists could explained the number of drop-outs - by including patients who do not have an high need for this kind of support and consequently the high medication adherence observed. However, the study population was comparable to that of two other studies conducted in Switzerland [45,95].

This potential selection bias may affect positively and negatively the results of the implementation and the effectiveness. In terms of implementation, the pharmacy team could offer the programme to patients known to be less reluctant, with good contact, or acquaintances, instead of systematically offering the programme to all patients coming to the pharmacy with type 2 diabetes. In terms of effectiveness, selecting patients with poor baseline adherence or glycaemic control would have increase the beneficial results of the intervention. With regard to the aspect of interprofessional collaboration, pharmacists could also have selected patients for whom the referring doctor was already known to the pharmacy and with whom exchanges were favourable. Aware of these facts, it was intended to leave the pharmacist free to include patients, as this was a real life study.

Caution must be exercised in interpreting the results of this cohort study. This type of study makes it possible to observe the evolution of the outcomes , but it is not possible to state with certainty that the changes observed herein are solely linked to the intervention alone. A randomised control trial would have made it possible to conclude with certainty if the intervention had an effect or not by comparing two random groups of patients. However, setting up a randomized trial or monitoring a cohort of control patients did not seem feasible from the point of view of the budgetary framework and inclusion by pharmacies. There remains a difficulty to include pharmacies that could be randomised in a control group, and the fact of intervening to implement could bring more results than in the control group. Moreover, randomisation in routine care is quite difficult to implement [128], but other designs should be carefully considered in future research [129]. The presence of a control group would also probably lead to an increase in missing data unless more standardisation occurs from the design of the study thus reducing the aspect of implementation in care practices. With regard to clinical outcomes, no decrease in blood glucose levels was observed, which could be related to the different sources of these outcomes (e.g., self-reported without ensuring good clinical practice). As food consumption influenced the result, the lack of measurement standardisation led to a greater heterogeneity among these values than among HbA1c. Considering the amount of missing data, these were consistent for HbA1c at baseline when compared to another study using a randomised control trial design [60]: 61% missing vs 60% in our study. The creation of a sub-group of Sispha pharmacies that are already trained to deliver Siscare but who would have to forego Siscare-DT2 would lead to frustration and demoralisation. A before/after design with patients serving as their own controls for three months before the intervention with the use of the electronic pillbox to determine initial medication adherence was considered but later abandoned. The measurement system itself may favourably influence the adherence rate in the short term (usually less than three months) and would have compromised the results [130].

The fidelity of the intervention, i.e., the extent to which the programme is delivered as defined, was been assessed for the frequency (at least every 3 months) and duration (15 to 20 minutes) of patient-pharmacist interviews, the use of EM tool (pillbox), and the platform use and interview report (the generation of a report through the web-based platform and transmitted to the referent physician). The results showed that the intervention was delivered with fidelity with respect to these components, except that interviews were longer than expected. Assessing the fidelity of an intervention is essential after having described the core components [126]. Variations in the execution of the intervention may impact its effectiveness. Core components are those considered key for the intervention to be effective, while secondary elements can then be adapted (to the person or context) without impacting the effectiveness of the intervention (such as the time of the interview). In this thesis, fidelity was operationalised based on the research team expertise and assessed through an audit at the pharmacy using standardised questions but only at one time point during the operation stage. It would have been interesting to test

the fidelity of the intervention at several time points and from the patient perspective to verify the validity of the response process. No specific tool was used to assess fidelity, and very few tools were available when designing the study. Currently, as implementation science evolves, different tools have been developed to assess fidelity, but empirical research is still needed to test their validity [131]. Also regarding the fidelity in terms of interviews, most pharmacists described a motivational approach and discussed the medication adherence graphs in interviews as planned. However, the evaluation of the fidelity content occurred through questionnaires. Observations of some interviews would have increase the reliability of the fidelity intervention. Filming interviews in order to assess the motivational aspect and receive feedback on the content would have increase implementation of such interventions but is time consuming.

The clinical values have been documented by the pharmacist in the platform, but their origin can be diverse. For instance, blood glucose could have been measured directly at the pharmacy, measured by the physician during a medical consultation, or self-measured and reported by the patient. It was expected that clinical values were received from the physician. Standardisation of the assessment could have improved the quality of data reporting by asking the patients to bring their latest laboratory report for the interview at the pharmacy. Access to a common database could also have reduced the amount of missing data by providing a continuously updated treatment plan and access to clinical data and other information relevant to patient care.

Various considerations need to be taken into account when assessing medication adherence. First, the use of multiple measures increases the validity of the measurement, but we could not reconcile the EM data with the pill count data due to inconsistency of the reported measures of pill count by pharmacies. Nevertheless, previous studies have shown that the difference between reconciled and unreconciled EM measures was minimal [132,133]. Second, because of problems with extracting data from the database of the pillbox openings, the data for each patient were reviewed and validated with the pharmacist if there were any inconsistencies, which is time consuming and not feasible for studies involving even more patients. Nevertheless, the benefits of EM outweigh these limitations. Third, we did not conduct further analysis to determine whether the influencing factors identified in the literature review and available in Siscare-DT2 impacted adherence. Further investigation would lead to complete scientific literature because EM adherence data are rare.

The method of literature review, which involved selecting articles from recent literature reviews, may have led to the omission of recently published studies, especially those that focus on EM. In addition, the quality and the risk of bias were not assessed given the quantity of articles and the time available. Only one person carried out the screening, but the studies were discussed with two other investigators. However, the 2020 update (addition of three literature reviews and 10 articles) was performed by two different investigators (double-checking).

Future Research Directions

Meeting the needs of patients is paramount. Patient support programmes must be developed with patients (and healthcare professionals) and for them. The components of programmes must be adapted to the patient's needs. The specific reasons for satisfactory and dissatisfactory patients could be collected and analysed through a qualitative study. This would allow a better understanding of patients' needs and expectations, as well as identify the strengths and weaknesses of patient support programmes in order to adapt, optimise and support its dissemination.

It is also important that the patient needs, preferences and perspectives are taken into account when choosing the method of measuring adherence. As the use of the electronic pillbox was the most commonly cited reason for refusal and stopping the programme in patients taking multiple medications, research should focus on expanding the range of measurement tools. This is also an opportunity to move towards tools that assess all medications in order to have an overview of all medications and to link this adherence to clinical or other outcomes. In addition, the appropriate duration of support should be determined. At Unisanté, the extent to which the duration of IMAP impacts long-term adherence and whether it meets the needs of patients with T2D and renal failure are currently being researched [67].

Given the current health situation (i.e., the COVID-19 pandemic) and the recommendations to reduce interactions between individuals, alternatives should be considered to continue the provision of high-quality care. The patient-pharmacist interview could be done online with the integration of a smartphone application linked to the electronic patient record [134]. With the COVID-19 pandemic, data sharing is accelerating, leading to the opportunity for pharmacists to develop an intervention in this sense. This also raises many questions, such as ethics and feasibility in pharmacy.

Implementation and related research must be covered for all patients in the French-speaking part of Switzerland, as well as throughout other parts of Switzerland and in other countries. Taking into account the context is essential for success; future studies are needed to confirm and/or improve the delineation of the implementation process and exposed influences in other contexts. Framework, barriers and facilitators have been studied extensively; there is a need to focus on the evaluation of tools and strategies. Implementation strategies need to be reported appropriately, with a clear description (as would a clinical intervention) of each strategy and the context [135,136]. In addition, linking the strategies to outcomes will facilitate future replication, comparison and evaluation across studies [137,138]. Different study designs may be needed to assess the effects of components of implementation programmes and individual implementation strategies.

Documentation of the implementation activities and resources used by pharmacists to implement and deliver the service should be strengthened to deepen this type of analysis, which is essential to increase the value of the service. The cost of implementation and the break-even point were conducted from a pharmacist's point of view, taking into account the actual tariff heading (RBP IV) [117]. These analyses should determine the new optimal tariff heading that will come into effect in the coming years [139].

The implementation, dissemination and sustainability of interprofessional collaboration are crucial for future sustainable health systems. Pharmacists play an ideal position in primary care to trigger it and provide a gateway to easy access in a world of rising healthcare costs, an ageing population, patients with special needs and a growing shortage of healthcare professionals.

Conclusions

This thesis used an innovative methodology of implementation science and clinical research (chapter 2) to evaluate an interprofessional patient support programme (Siscare) for patients with T2D (Siscare-DT2) in Swiss primary care with quantitative and qualitative data. The results contributed to increasing knowledge in the implementation and dissemination of Siscare in the management of patients with chronic diseases and the promotion of interprofessional collaboration with the intervention of the community pharmacist as a trigger factor in Switzerland. Only a few studies have collected electronic and longitudinal data on adherence, clinical, and patient-reported outcomes for T2D in a real-world setting over a long and representative period of time.

The implementation of Siscare-DT2 is feasible and acceptable from a pharmacy point of view (chapter 3). The operational success of programmes such as Siscare represents a corporate project involving a clear management strategy, human and financial investments, precise performance indicator documentation, commitment of the entire pharmacy team, and good coordination of the local network (physicians-pharmacists-caregivers).

Siscare supports medication adherence and improves clinical outcomes in patients with T2D (chapter 4). Adherence to OAD was maintained at a high level, and HbA1c levels improved over the course of the programme, without major changes in diabetes treatment or involvement of other supports and with stable quality of life. These results illustrate the overall effectiveness of a personalised and coordinated support of patients carried by pharmacists in agreement with physicians.

Siscare-DT2 has been shown to be a starting point for collaboration between healthcare professionals (chapter 5). Collaboration has mainly taken the form of unidirectional transmission of information from pharmacist to physician (level 1); bidirectional exchange of information occurred sometimes (level 2), and concerted measures of treatment objectives took place occasionally (level 3). No physician prescribed Siscare, but Siscare-DT2 has been well received by patients and physicians without any objections.

The implementation of Siscare on a larger scale is still fragile because of the inertia inherent in any fundamental change in practice that requires time, perseverance, and changes in mentality but also because of the economic and political uncertainties influencing primary healthcare providers. The results of the thesis led to recommendations on five themes: communication, interprofessionality, material resources, education, and financial resources. Future research should be conducted to ensure the viability of these results and to consolidate the dissemination of this type of patient support programme.

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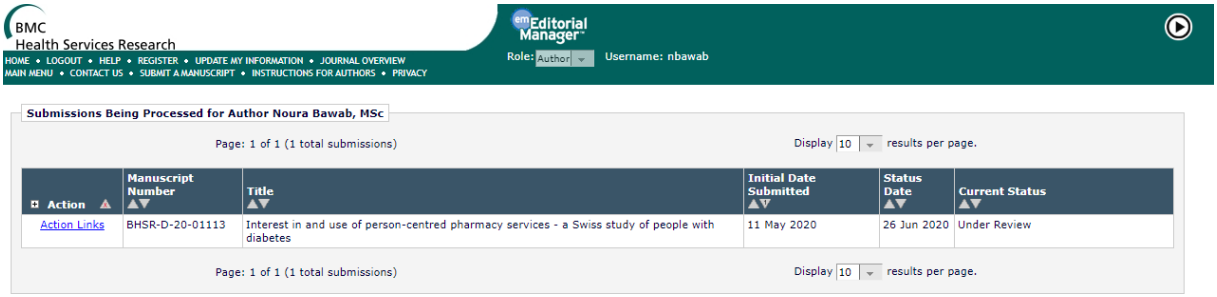
Appendices

Appendix 1 - Article on Pharmacy Services

Interest in and Use of Person-centred Pharmacy Services - a Swiss Sudy of People with Diabetes

Alongside this thesis and in partnership with another research team from the Center for Primary Care and Public Health (Unisanté), University of Lausanne, a study was undertaken to evaluate the interest in and use of pharmacy services among a population-based cohort of patients with diabetes in the canton of Vaud (CoDiab-Vd) in Switzerland. The full article follows this page, including additional material, and is in review in *BMC Health Services Research since May 19, 2020*. Noura Bawab contributed to this article through formal analysis, manuscript writing, and data presentation.



Interest in and Use of Person-centred Pharmacy Services - a Swiss Study of People with Diabetes

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Abstract

Background*:* Diabetes is one of the most important chronic diseases and affects 9% of the world's population. To support these people in the day-to-day management of their treatments, pharmacies can offer professional pharmacy services. These are defined as one or more actions organized or provided in a pharmacy to optimize the process of care, with the goal of improving health outcomes and the value of healthcare. Such services have to be tailored to the needs and interests of patients. This study aimed to evaluate interest in and use of pharmacy services among people with diabetes in the canton of Vaud, Switzerland.

Methods: This cross-sectional study analysed self-reported data from 790 people with diabetes included in the CoDiab-VD cohort. Questions focused on sociodemographic and economic characteristics, diabetes and its management, and interest in and use of pharmacy services related to (1) medication intake and adherence and (2) diabetes and general health. Descriptive analyses were first conducted. Logistic regression analyses were then performed for pharmacy services that were of interest to ≥50% of respondents.

Results: The mean age of participants was 66 years, and the sample included more males (59%) than females. The pharmacy services that interested the most respondents were individual consultation, pill boxes or weekly pill boxes, treatment plans, checks of all medications, first medical opinions from pharmacists and counselling on devices. Factors significantly associated with interest in pharmacy services were being older, having a lower self-efficacy score, taking more than three medications and having a positive opinion about pharmacists.

Conclusions: This study provides key information on interest in and use of pharmacy services among patients with diabetes in Switzerland; it should help pharmacists individualize their services for patients.

Keywords: Diabetes, Patient Support, Pharmacy services, Primary care, Switzerland

Introduction

Diabetes is one of the most important chronic diseases and contributes to mortality, morbidity and socio-economic impacts [1]. Worldwide, it affects 9.3% of the population, equal to approximately 463 million people [2]. According to the International Diabetes Federation, the number of people with diabetes will continue to increase over the next decades [3]. To support these people in the daily management of their treatments, pharmacies can offer professional pharmacy services tailored to the needs and interests of patients.

Moullin et al. defined a professional pharmacy service as “an action or set of actions undertaken in or organised by a pharmacy, delivered by a pharmacist or other health practitioner, who applies their specialised health knowledge personally or via an intermediary, with a patient or client, population or other health professional, to optimise the process of care, with the aim to improve health outcomes and the value of healthcare” [4].

To our knowledge, little data are available on interest in pharmacy services among people with diabetes. This study aimed to assess interest in and use of pharmacy services among people with diabetes included in the CoDiab-VD cohort who responded to the 2017 annual questionnaire, which included a thematic module about pharmacy services [5].

Methods

Study design

Data from a cross-sectional survey conducted in the fall of 2017 as part of the CoDiad-VD cohort were used [5]. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were used in the project’s execution and in the manuscript’s preparation [6].

Setting and participants

In Switzerland, community pharmacies can provide pharmacy services, some of which are remunerated and covered for patients by basic health insurance according to the tariff headings [7]. These pharmacy services include pharmacists' basic cognitive services (e.g., medication delivery, counselling services, prescription/dosage/drug-drug interaction checks, and checks of patient records), medication intake support (directly observed therapy, fractioned delivery or provision of a pill box filled with medication for one or more weeks), or individual consultation with the pharmacist [7]. In 2016, the Swiss Federal Council was invited to explore the various possibilities for repositioning pharmacists in primary care. The council stated that community pharmacists have an important role to play and that shifting from traditional medication delivery and counselling towards the provision of patient-centred and interprofessional pharmacy services was essential [8].

In 2011-12 and 2017, people with diabetes were recruited into the CoDiab-VD cohort. Participation in the CoDiab-VD cohort was offered to individuals visiting a participating pharmacy with a diabetes-related prescription. At the time of recruitment, non-institutionalised adults (≥18 years old) who had been diagnosed with diabetes for at least 12 months and were living in the canton of Vaud (French-speaking part of Switzerland) were eligible. Women with gestational diabetes and individuals with cognitive impairment or without sufficient French language skills to complete the questionnaire were excluded [5,9]. In 2017, the questionnaire was sent by mail to the participants recruited in 2011-12 and were distributed in-person in community pharmacies during the 2017 recruitment period.

Participants who were recruited in 2011-12 and 2017 were very similar at the time of recruitment in terms of their sociodemographic characteristics, health status and behaviours and self-reported diabetes status [10]. In 2017, the total number of respondents was 790, including 276 individuals included in the CoDiab-VD cohort who were recruited in 2011-12 and 514 newly recruited participants.

Study questionnaire and data collection

Participants completed a self-administered paper questionnaire that included questions on different aspects of diabetes and diabetes care, questions on their own characteristics, and a thematic module about pharmacy services (see Additional File 1). The participants completed the questionnaire at home and sent it back by mail to the investigators. Participants were free to not answer certain questions.

Measurements

For the purpose of this study, data collected on the participants' interest in and use of pharmacy services offered by community pharmacies were used (*very interested, a little interested* or *not interested* and *already used* or *never used*). Two types of pharmacy services were studied: (1) patient support in the management of their medication intake and adherence (individual consultation with the pharmacist, SMS or email reminders for medication intake, a smartphone application, (electronic) pill boxes or weekly pill boxes, and treatment plans for all medications); (2) patient support in the management of their diabetes and general health (screening for chronic conditions, monitoring of blood levels or pressure, influenza immunisation, counselling on the use of devices, support to quit smoking or lose weight, first medical opinions from pharmacists about health status, and checks of all medications). Moreover, the participants' interest in and use of consultation with their reference physicians were investigated.

We also used data collected on participants' sociodemographic and economic characteristics, including age, sex, education (*primary* - completion of compulsory school or less, *secondary* - vocational training or high school, or *tertiary* - university or technical college); financial hardship affecting participants' ability to pay household bills during the last 12 months [11]; health status, including perceived health status (first question of the SF-12 questionnaire) [12] and body mass index (kg/m^2); health behaviours, including physical activity (using questions from the Swiss Health Survey) [13], smoking status and alcohol consumption (using the AUDIT-C questionnaire) [14]; type of diabetes (*type 1, type 2, other* or *unknown*); medication management, including the frequency of pharmacy visits (*≥1 time per week, 2-3 times per month, 1 time per month,* or *<1 time per month*), the number of medications per day (*1-3, 4-6, 7-9, ≥10 medications*) and the mode of administration of antidiabetic medication (*with* or *without insulin or other injectable drugs*); diabetes self-management, including participation in diabetes education courses; and self-efficacy according to the Stanford Diabetes Self-efficacy scale [15]. Participants' opinions (*agree*, *disagree*) about their medications and pharmacists were also investigated. Participants' opinions about their medications were investigated with three questions (derived from the Adherence Estimator, a three-item proximal screener for the likelihood of non-adherence to prescription medications) [16] on the importance of prescribed medications, the fear of the harmfulness of prescribed medications, and the burden of non-reimbursed medications. A composite variable for opinion about medications was constructed: respondents with positive opinions in response to the three questions about their medications (*agree*, *disagree*, and *disagree*, respectively) were considered to have a positive opinion. Participants' opinions about pharmacists were also investigated with three questions that assessed participants' perceptions of pharmacists as experts on medications, health professionals and simply shopkeepers. A composite variable for opinion about pharmacists was constructed: respondents

with positive opinions in response to the three questions related to pharmacists (*agree*, *agree*, and *disagree*, respectively) were considered to have a positive opinion. The original questions in French and their English translations are available in the Additional File 1.

Statistical analyses

First, descriptive analyses were conducted to describe participants' characteristics, diabetes status (medications and management), opinions about medications and pharmacists, and interest in and use of both types of pharmacy services. Then, multivariate logistic regression analyses were performed to examine which factors were associated with interest in both types of pharmacy services, targeting items that interested at least 50% of the respondents. The following covariates were considered based on their a priori likelihood of influencing interest in pharmacy services: age, sex, education, financial hardship, antidiabetic medication including injections, participation in diabetes education courses, Stanford Diabetes Self-efficacy score, number of medications taken per day (1-3, 4-6, and ≥7 medications per day, with the latter category divided between 7-9 and ≥10), positive opinion about medications, and positive opinion about pharmacists. Odds ratios, predicted probabilities and their 95% confidence intervals were estimated. Moreover, the predicted probabilities of being interested in pharmacy services were plotted according to the number of medications taken per day and the age of the participants, which are patient characteristics known by pharmacists; sex was not present in the graphics because of the absence of a difference in levels of interest between females and males. All other covariates in the logistic regression models were held constant. Logistic regression models were assessed for influential observations and tested their calibration using the Hosmer-Lemeshow goodness-of-fit test. All statistical analyses were performed using Stata 16.0 for Windows (Stata Corporation, College Station, TX, USA, stata.com). P-values <0.05 were considered statistically significant.

Results

Table 1 details the demographic characteristics, health status and health behaviours of participants. The mean age of the 790 participants was 66.0 years (range: 18 to 92 years), and the majority of participants were men (59%). Less than 16% of the participants reported a primary education level, and 32% reported having difficulty paying bills during the past 12 months. Over a quarter of the participants were considered physically inactive, and 80% were overweight or obese.

Most participants (72%) reported having type 2 diabetes, and more than half of participants (57%) received antidiabetic treatment including insulin or another injectable. Most respondents (71%) took more than three medications per day. Details of the frequency of pharmacy visits, diabetes self-management, and participants' opinions about medications and pharmacists are presented in Table 2.

The proportions of participants who were interested in different pharmacy services and who declared having previously used them are presented in Fig. 1. Pharmacy services that generated the greatest interest were also those that were the most used: individual consultation, pill boxes, treatment plans, checks of all medications, first medical opinions and counselling on devices. In addition, 85% of the respondents were interested in receiving practical information about their medications during a medical consultation with their physician, and 59% declared that they already benefited from this service.

The results of logistic regression analyses of the pharmacy services that interested at least 50% of the participants are presented in Table 3; the predicted probabilities are available in the Additional File 2.

Table 1 - Participants' characteristics (sociodemographic characteristics, health status and health behaviours)

Variable	N total	% (N) or mean (SD)
Sociodemographic and economic characteristics		
Age	790	66.0 (12.5)
Sex	790	
Female		40.9% (323)
Male		59.1% (467)
Education	745	
Primary		15.8% (118)
Secondary		53.2% (396)
Tertiary		31.0% (231)
Financial hardship[a]	768	
Yes		32.4% (249)
No		67.6% (519)
Health status		
Perceived health status[b]	779	
Excellent		1.8% (14)
Very good		12.8% (100)
Good		62.8% (489)
Fair		19.9% (155)
Poor		2.7% (21)
BMI (kg/m^2)	758	
Underweight (< 15.5)		0.7% (5)
Normal (18.5-24.9)		19.7% (149)
Overweight (25-29.9)		38.0% (288)
Obese (≥ 30)		41.7% (316)
Health behaviours		
Physical activity[c]	766	
Active		53.7% (411)
Partly active		17.5% (134)
Inactive		28.9% (221)
Smoking status	766	
Non-smoker		39.0% (299)
Former smoker		42.2% (323)
Current smoker		18.8% (144)
Alcohol consumption	752	
Not risky or not excessive		58.0% (462)
Risky or excessive[d]		42.0% (313)

BMI, Body mass index
[a] Difficulty paying bills in the last 12 months
[b] First question of the Short Form Health Survey -12 (SF-12)
[c] Swiss Health Survey: active: ≥ 150 minutes of moderate physical activity or ≥ two intense activities per week; partly active: 30 to 149 minutes of moderate physical activity or one intense activity per week; inactive: < 30 minutes of moderate physical activity and < one intense activity per week
[d] Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) score ≥ 4 for men and 3 for women

Table 2 - Medication management, diabetes self-management, and participants' opinions about their medications and pharmacists

Variable	Total N	%[a] (N) or mean (SD; min-max)
Medication management		
Type of diabetes	790	
Type 1		11.4% (90)
Type 2		72.0% (569)
Other or unknown		16.6% (131)
Frequency of pharmacy visits	747	
≥1 time per week		6.7% (50)
2-3 times per month		30.1% (225)
1 time per month		35.3% (264)
<1 time per month		27.8% (208)
Number of medications per day	773	
1-3 medications		29.4% (227)
4-6 medications		41.9% (324)
7-9 medications		19.7% (152)
≥10 medications		9.1% (70)
Antidiabetic medication	788	
Excluding insulin or other injectables		43.0% (339)
Including insulin or other injectables		57.0% (445)
Diabetes self-management		
Participation in one or more diabetes education courses	771	
Yes		35.4% (273)
No		64.6% (498)
Stanford Diabetes Self-efficacy overall score[b]	755	7.5 (1.8; 2.1-10.0)
Participants' opinions about their medications		
"Medications that are prescribed to me are important"	768	
Disagree		4.2% (32)
Agree		95.8% (736)
"I fear that prescribed medication are more harmful than beneficial"	757	
Disagree		86.4% (654)
Agree		13.6% (103)
"Non-reimbursed medications are burdensome for me"	760	
Disagree		27.9% (212)
Agree		72.1% (548)
Positive opinion about medications on all 3 items[c]	770	
Yes		23.6% (182)
No		76.4% (588)
Participants' opinions about pharmacists		
"Pharmacists are experts in medications, side effects and medication interactions"	741	
Disagree		6.3% (47)
Agree		93.7% (694)
"Pharmacists are health professionals, just like physicians or nurses"	734	
Disagree		15.7% (115)
Agree		84.3% (619)
"Pharmacists are just shopkeepers who sell products in pharmacy"	722	
Disagree		85.9% (620)
Agree		14.1% (102)
Positive opinion about pharmacists on all 3 items[d]	764	
Yes		65.5% (500)
No		34.6% (264)

[a] Due to rounding, the sum of the percentages is not always equal to 100%.
[b] The Stanford Diabetes Self-efficacy overall score ranges from 0 to 10, with a higher score indicating a higher level of self-efficacy.
[c] Composite variable for opinion about medication: respondents answering *agree*, *disagree*, and *disagree* to the three items, in that order, were considered to have a positive opinion.
[d] Composite variable for opinion about pharmacists: respondents answering *agree*, *agree*, and *disagree* to the three items, in that order, were considered to have a positive opinion.

Fig. 1 - Pharmacy services interest and utilisation: medication intake and adherence (top), diabetes and general health (bottom)

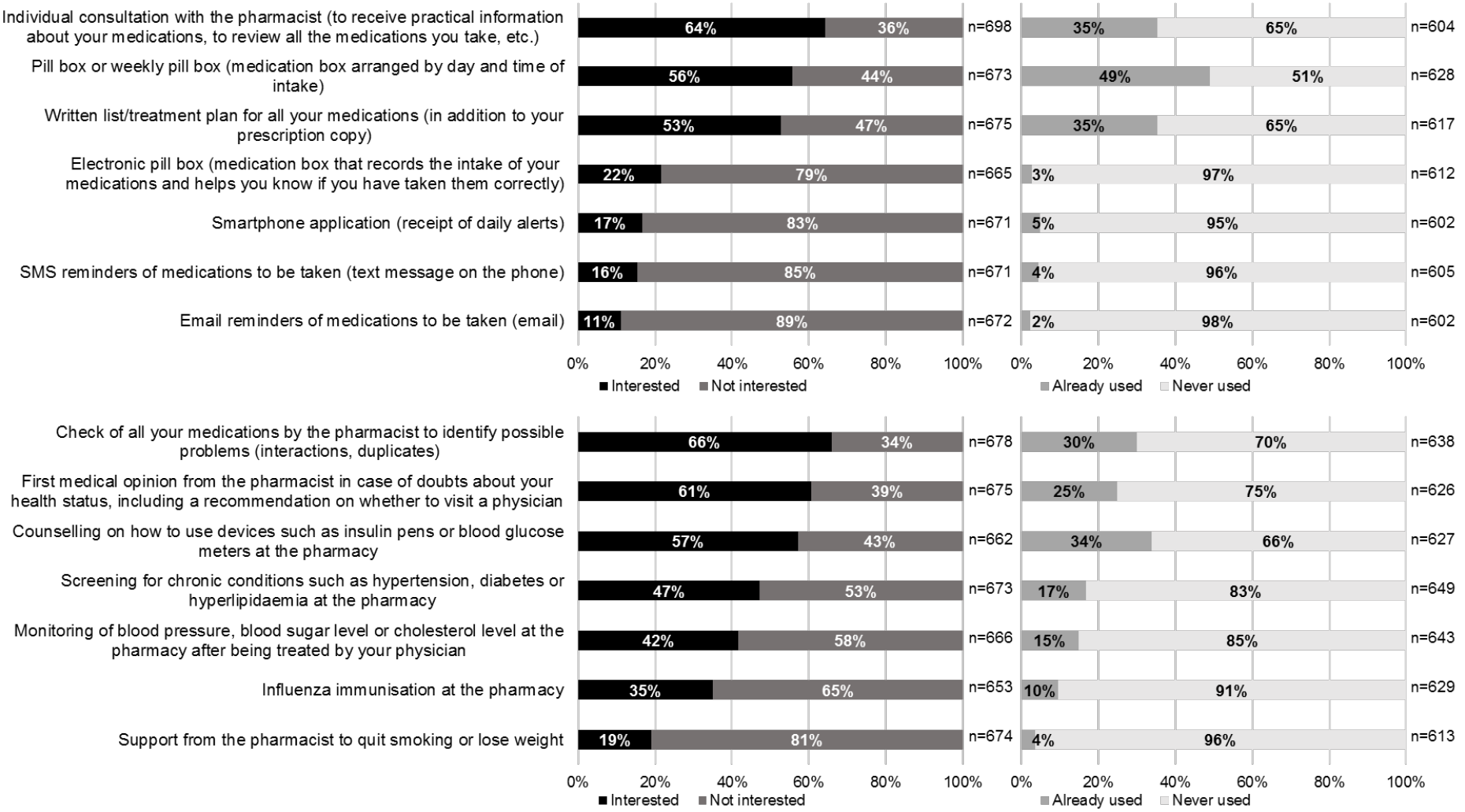

Table 3 - Logistic regression analyses of the pharmacy services that interested ≥50% of the participants

		Medication intake and adherence						Diabetes and general health					
		Consultation with pharmacist (n=625)		Pill box or weekly pill box (n=608)		List of all medications/treatment plan (n=606)		Check of all medications (n=610)		First medical opinion (n=608)		Counselling on how to use devices (n=596)	
		OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	<65 years	1.00		1.00		1.00		1.00		1.00		1.00	
	65-74 years	2.03 (1.35 to 3.04)	**<0.01**	1.26 (0.84 to 1.88)	0.26	1.26 (0.84 to 1.89)	0.26	0.93 (0.62 to 1.42)	0.75	0.82 (0.55 to 1.22)	0.33	1.36 (0.91 to 2.03)	0.14
	≥75 years	3.28 (1.95 to 5.52)	**<0.01**	2.05 (1.24 to 3.37)	**0.01**	1.41 (0.87 to 2.30)	0.16	0.69 (0.42 to 1.12)	0.13	0.51 (0.32 to 0.82)	**0.01**	1.01 (0.63 to 1.61)	0.97
Sex	Female	1.00		1.00		1.00		1.00		1.00		1.00	
	Male	1.10 (0.76 to 1.59)	0.60	0.90 (0.63 to 1.30)	0.58	1.22 (0.85 to 1.75)	0.29	0.84 (0.58 to 1.22)	0.35	0.69 (0.48 to 1.00)	0.05	0.69 (0.48 to 1.00)	0.05
Education	Primary	1.00		1.00		1.00		1.00		1.00		1.00	
	Secondary	0.93 (0.54 to 1.59)	0.79	0.79 (0.46 to 1.34)	0.38	1.16 (0.69 to 1.96)	0.58	1.65 (0.98 to 2.78)	0.06	1.08 (0.64 to 1.82)	0.77	1.22 (0.72 to 2.08)	0.45
	Tertiary	0.76 (0.43 to 1.34)	0.34	0.91 (0.51 to 1.62)	0.75	1.14 (0.65 to 2.02)	0.65	1.95 (1.10 to 3.46)	**0.02**	1.33 (0.76 to 2.35)	0.32	0.99 (0.56 to 1.75)	0.98
Financial hardship	No	1.00		1.00		1.00		1.00		1.00		1.00	
	Yes	1.38 (0.93 to 2.06)	0.11	1.21 (0.82 to 1.79)	0.34	1.21 (0.82 to 1.79)	0.33	1.11 (0.74 to 1.66)	0.61	1.37 (0.92 to 2.03)	0.12	1.13 (0.77 to 1.67)	0.53
Treatment including injections	No	1.00		1.00		1.00		1.00		1.00		1.00	
	Yes	1.02 (0.71 to 1.48)	0.91	1.12 (0.78 to 1.61)	0.53	1.09 (0.76 to 1.57)	0.63	0.79 (0.55 to 1.15)	0.22	1.05 (0.74 to 1.51)	0.77	1.25 (0.88 to 1.78)	0.22
Participation in diabetes education course	No	1.00		1.00		1.00		1.00		1.00		1.00	
	Yes	1.03 (0.71 to 1.51)	0.87	0.85 (0.59 to 1.23)	0.38	0.74 (0.51 to 1.08)	0.12	1.24 (0.85 to 1.83)	0.27	1.04 (0.72 to 1.51)	0.82	0.80 (0.55 to 1.15)	0.23
Stanford Diabetes Self-efficacy	Overall score	0.94 (0.85 to 1.04)	0.23	0.88 (0.79 to 0.97)	**0.01**	0.88 (0.79 to 0.97)	**0.01**	0.90 (0.81 to 1.00)	0.06	0.87 (0.79 to 0.97)	**0.01**	0.90 (0.81 to 0.99)	**0.03**
Number of medications taken	1 to 3	1.00		1.00		1.00		1.00		1.00		1.00	
	4 to 6	1.51 (1.00 to 2.26)	**0.05**	2.10 (1.40 to 3.15)	**<0.01**	1.84 (1.23 to 2.77)	**<0.01**	1.29 (0.85 to 1.94)	0.23	0.94 (0.62 to 1.41)	0.75	1.14 (0.76 to 1.71)	0.52
	≥7	2.06 (1.27 to 3.35)	**<0.01**	3.47 (2.16 to 5.57)	**<0.01**	3.84 (2.39 to 6.18)	**<0.01**	2.11 (1.28 to 3.48)	**<0.01**	1.20 (0.74 to 1.93)	0.46	1.28 (0.80 to 2.05)	0.30
Positive opinion about medication	Less positive	1.00		1.00		1.00		1.00		1.00		1.00	
	Positive +++	0.95 (0.62 to 1.46)	0.83	0.92 (0.61 to 1.40)	0.71	0.74 (0.48 to 1.12)	0.16	0.90 (0.59 to 1.39)	0.64	1.23 (0.81 to 1.88)	0.33	0.84 (0.55 to 1.27)	0.41
Positive opinion about pharmacists	Less positive	1.00		1.00		1.00		1.00		1.00		1.00	
	Positive +++	1.69 (1.17 to 2.45)	**0.01**	1.32 (0.91 to 1.91)	0.15	1.21 (0.84 to 1.76)	0.30	1.58 (1.09 to 2.28)	**0.02**	1.51 (1.05 to 2.17)	**0.03**	1.46 (1.02 to 2.10)	**0.04**

Significant p-values (<0.05) in bold

Higher age, tertiary education, lower self-efficacy score, taking more than three medications, and a positive opinion about pharmacists were all significantly associated with interest in certain pharmacy services. A lower self-efficacy score was significantly associated with greater interest in pill boxes, treatment plans, first medical opinions, and counselling on device use. Taking more than three medications was associated with greater interest in individual consultation with the pharmacist, pill boxes, and treatment plans, while only taking ≥7 medications was associated with interest in checks of all medications. Participants who reported a positive opinion about pharmacists were more interested in individual consultation with the pharmacist, checks of all medications, first medical opinions, and counselling on device use. Gender, financial hardship, diabetes treatment including injections, participation in diabetes education courses, and a positive opinion about medication were not significantly associated with interest in any of the pharmacy services investigated.

Based on the logistic regression models, predicted probabilities of being interested in pharmacy services were computed according to number of medications taken and age, with all other covariates held constant; the results are presented in the Additional File 3. The older participants were and the more medications they took, the more they were interested in services related to medication intake and adherence. For services related to diabetes and general health, the trends were less clear; a higher number of medications taken was associated with higher probabilities of interest, while older age was associated with lower probabilities of interest in those services.

Discussion

This study describes interest in and use of pharmacy services among Swiss patients with diabetes in the CoDiab-VD cohort. The pharmacy services that interested the most respondents were individual consultation, pill boxes or weekly pill boxes, treatment plans, checks of all medications, first medical opinions from pharmacists and counselling on devices. According to the participants, the most valuable pharmacy services related to medication intake and adherence as well as diabetes and general health were mainly personal and patient-specific, which highlights the need to individualise and target specific services based on patients' personal needs. Furthermore, first medical opinions and checks of all medications were the two services with the greatest differences between interest and use levels, indicating an opportunity to develop these services to meet patients' needs.

Factors positively associated with interest in pharmacy services were higher age, higher education level, taking four or more medications and a positive opinion about pharmacists, while the self-efficacy score was negatively associated with interest in pharmacy services. Participants' opinions about their medications mainly showed that their prescribed medications are important to them and that they do fear of harm from the medications but rather are concerned about reimbursement for their medications. This finding probably reflects a general concern about medications, their prices and their reimbursement rather than a specific concern related to antidiabetic medications, as these medications are all reimbursed in the Swiss health system; the finding also shows the need to propose pharmacy services that are reimbursed.

Pharmacists are very accessible health care professionals, as most of the respondents visited a pharmacy at least once a month. This accessibility combined with the positive opinion about pharmacists suggests that pharmacists could actively participate in quality improvement initiatives targeting the care of patients with chronic conditions.

Multivariate analyses showed that the most notable factors related to interest in pharmacy services were being older, having a lower self-efficacy score, taking more than three medications and having a positive opinion about pharmacists. Lower Stanford self-efficacy scores mean that participants are less confident about being able to overcome barriers and accomplish tasks. Lower self-efficacy scores in this study were related to higher interest in pharmacy services, which may have been related to patients' beliefs about the need for pharmacy services. When patients perceive the need for and benefits of pharmacy services, they are more interested in them [17]. In contrast, patients who believe they do not need pharmacy services [18-20] and who are satisfied with their current medication [18] logically have a lower interest in, or use of, pharmacy services. Taking more than three medications per day was associated with greater interest in certain pharmacy services, confirming that taking more medications is associated with a greater number of drug-related problems, which is a measure of the potential value of (interest in and use of) pharmacy services from patients' points of view [21,22]. Moreover, having a positive opinion about pharmacists can indicate an appreciated personal relation with the pharmacist based on good communication [20]. Seeing the pharmacist as a trusted and accessible expert in his or her area of expertise is also associated with increased interest in the use of pharmacy services [19]. In Switzerland, this association has been identified by the national government, which financially supports the scientific evaluation of the implementation of an interprofessional and tailored support programme (safety and medication adherence) for people with type 2 diabetes [8,23].

The main strength of this study was that the survey included people with diabetes spread throughout a Swiss region who were recruited from community pharmacies. This approach should have allowed the inclusion of participants who were more representative of the population of patients with diabetes than if the recruitment had been carried out in a specialised medical or hospital setting.

In the interpretation of the results, the following limitations need to be considered. Data were based exclusively on self-reports, which involves the probable over- or under-representation of certain phenomena. Without access to other data, however, the use of this type of data is considered appropriate [24]. The recruitment method allowed us to limit selection bias; the limited selection bias was also supported by the fact that the characteristics of the participants in this cohort were comparable to those of people with diabetes in other Swiss studies in terms of age, sex, smoking status, body mass index, and total number of medications taken [25-28].

In conclusion, the results of this study provide a better understanding of the people who are most interested in pharmacy services to support the assessment of their needs and the development of tailored, appropriate solutions. These results should also motivate pharmacists to explain the importance of pharmacy services so that people can perceive their benefits. Since pharmacies are often visited by patients with chronic conditions, more effort should be made to involve pharmacists in health promotion or prevention initiatives such as flu vaccination and weight loss or smoking cessation programmes.

Declarations

Ethics approval and consent to participate: The CoDiab-VD cohort study protocol was approved by the Cantonal Ethics Committee of Research on Human Beings of the Canton of Vaud (CER-VD, protocol numbers 151/11 and PB_2017_00232). This study is registered with ClinicalTrials.gov, identifier NCT01902043. Written informed consent was obtained from all participants, and data were kept confidential.

Consent for publication: Not applicable.

Availability of data and materials: The metadata from the CoDiab-VD datasets supporting the conclusions of this article are available in a public repository (CoDiab-VD: Cohort of Patients with Diabetes in the Canton of Vaud (Switzerland)), doi:10.16909/dataset/18. Data are available upon request to be made via the repository.

Competing interests: None declared.

Funding: This work was supported by the Department of Public Health of the canton of Vaud ('Programme cantonal Diabète'). The funding source was not involved in the study design, the collection, analysis and interpretation of data; the writing of the article, or the decision to submit the article for publication.

Authors' contributions: **Noura Bawab**: Formal analysis, Writing – Original Draft, Visualization **Emilie Zuercher**: Conceptualization, Formal analysis, Investigation, Data Curation, Writing – Review & Editing, Visualization. **Tania Carron**: Investigation, Writing – Review & Editing. **Léonie Chinet**: Conceptualization, Writing – Review & Editing. **Olivier Bugnon**: Conceptualization, Writing – Review & Editing, Funding acquisition. **Jérôme Berger**: Conceptualization, Methodology, Writing – Review & Editing, Supervision. **Isabelle Peytremann-Bridevaux**: Conceptualization, Writing – Review & Editing, Supervision Project administration, Funding acquisition. All authors have approved the final article.

Acknowledgements: We would like to thank all pharmacies and patients with diabetes who participated in the study. We would also like to thank Paul Thoueille for translating the questionnaire, Talitha Orlandi for her review, and Patrick Taffé for statistical advice.

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Additional material

Additional File 1 - Participant questionnaire items in French and their translations into English

French (original)	English (translation)
Sociodemographic and economic characteristics	
Laquelle des propositions suivantes décrit le mieux la formation la plus élevée que vous avez terminée ? - Aucune scolarité achevée - Scolarité obligatoire - Apprentissage (CFC), formation/école professionnelle achevée - Maturité (baccalauréat), maturité professionnelle, école normale, école de commerce, école de culture générale - Ecole technique et/ou professionnelle supérieure, maîtrise fédérale ou professionnelle - Niveau universitaire (y compris Hautes Ecoles Spécialisées (HES), Ecole polytechnique, Beaux Arts, etc.) - Autre	Which of the following best describes the highest training you have completed? - No schooling completed - Compulsory education - Initial vocational training (Federal Certificate of Capacity) or professional training or school completed - General or professional baccalaureate, teacher training school, or upper secondary specialised school - Technical and/or higher vocational school or Federal Diploma of Higher Education and Advanced Federal Diploma of Higher Education - University level (including specialised high schools, polytechnic schools, fine arts schools, etc.) - Other
Durant les 12 derniers mois, avez-vous eu de la peine à payer les factures de votre ménage (impôts, assurances, téléphone, électricité, carte de crédit, etc.) ? Oui ou non	During the last 12 months, have you had trouble paying your household bills (taxes, insurance, telephone, electricity, credit cards, etc.)? Yes or No
Health status	
Quel est votre poids actuel ? (en kg)	What is your current weight? (in kg)
Quelle est votre taille actuelle (hauteur) ? (en cm)	What is your current height? (in cm)
Health behaviours	
Mettez une croix dans la case qui vous décrit le mieux - Je fume actuellement - J'ai fumé mais je ne fume plus actuellement - Je n'ai jamais fumé	Check the box that best describes you: - I am a smoker - I used to smoked but I no longer smoke - I have never smoked
Pendant vos loisirs, avez-vous au moins une fois par semaine une activité physique qui vous fasse transpirer ? (par exemple : course à pied, vélo, marche rapide…) Oui ou non Si oui, en moyenne, combien de jours par semaine ?	In your spare time, do you engage at least once a week in a physical activity that makes you sweat? (e.g., running, cycling, brisk walking...) Yes or No If yes, how many days per week on average?
Les questions suivantes ne concernent plus seulement les activités physiques qui vous font transpirer, mais également d'autres formes de mouvements moins intensifs.	The following questions no longer only concern physical activities that make you sweat but also other forms of less intensive activity.
Si vous pensez à des activités physiques au cours desquelles vous êtes au moins un peu essoufflé(e), comme la marche rapide, les excursions à pied, la danse, le jardinage ou différents sports: combien de jours par semaine pratiquez-vous de telles activités physiques ? - Jours par semaine *(de 1 à 7 jours)* - Jamais - Je ne sais pas	Thinking about physical activities in which you are at least a little out of breath, such as brisk walking, hiking, dancing, gardening or various sports, how many days per week do you do such physical activities? - Days per week (1 to 7 days) - Never - I don't know
Quelle est en moyenne la durée de ces activités physiques pendant ces jours ? - Heures et minutes par jour - Je ne sais pas	What is the average duration of such physical activity on these days? - Hours and minutes per day - I don't know

Medication management	
Savez-vous de quel type de diabète vous êtes atteint(e) ? - Type 1 - Type 2 - Autre - Je ne sais pas	Do you know what type of diabetes you have? - Type 1 - Type 2 - Other - I don't know
A quelle fréquence vous rendez-vous en pharmacie pour aller chercher vos médicaments ? - Une fois par semaine ou plus souvent - 2-3 fois par mois - Une fois par mois - Moins d'une fois par mois	How often do you go to the pharmacy to get your medication? - Once a week or more often - 2-3 times a month - Once a month - Less than once a month
Combien de médicaments différents prenez vous par jour ? *(si vous prenez plusieurs fois le même médicament, comptez-le une seule fois)* - 1 à 3 médicaments par jour - 4 à 6 médicaments par jour - 7 à 9 médicaments par jour - 10 médicaments par jour ou plus - Je ne prends aucun médicament - Je ne sais pas	How many different medications do you take per day? *(if you are taking the same medication several times per day, count it only once)* - 1 to 3 medications per day - 4 to 6 medications per day - 7 to 9 medications per day - 10 or more medications per day - I don't take any medication - I don't know
Actuellement, vous êtes traité(e) pour le diabète par… ? *(plusieurs réponses possibles)* - Des comprimés (antidiabétiques oraux) - De l'insuline - Une injection autre que de l'insuline (par exemple : Victoza, Byetta, Bydureon) - Aucun des traitements mentionnés - Je ne sais pas	Currently, you are being treated for diabetes with...? (*multiple answers allowed*) - Tablets (oral antidiabetic medication) - Insulin - An injection other than insulin (e.g., Victoza, Byetta, Bydureon) - None of the treatments mentioned - I don't know
Diabetes self-management	
Depuis le diagnostic de votre diabète, avez-vous participé à un ou des cours pour patients sur la gestion de votre diabète (séances individuelles ou en groupe) ? *(plusieurs réponses possibles)* - Oui, j'ai participé dans l'année qui a suivi mon diagnostic - Oui, j'ai participé plus d'une année après mon diagnostic - Oui, j'ai participé à la suite d'une hospitalisation - Oui, j'ai participé à la suite d'une complication de mon diabète (sans hospitalisation) - Oui, j'ai participé à un cours spécifique sur la gestion de l'insuline lors de l'introduction du traitement par insuline - Non, je n'ai jamais participé à un cours sur la gestion de mon diabète - Je ne sais pas	Since you were diagnosed with diabetes, have you attended any diabetes education courses (either one-on-one or group sessions)? (*multiple answers allowed*) - Yes, I attended in the year following my diagnosis - Yes, I attended more than a year after my diagnosis - Yes, I attended following a hospitalisation - Yes, I attended following a diabetes-related complication (without hospitalisation) - Yes, I attended a specific course on the management of insulin use when an insulin therapy was introduced - No, I have never attended any diabetes education course - I don't know
People's opinions about their medications and pharmacists	
Option de réponses - Pas du tout d'accord - Plutôt pas d'accord - Plutôt d'accord - Tout à fait d'accord - Sans avis *(première question uniquement)*	Response options - Strongly disagree - Somewhat disagree - Somewhat agree - Strongly agree - No opinion (*first question only)*
Veuillez indiquer votre degré d'accord ou de désaccord avec les affirmations ci-dessous à propos du rôle des pharmaciens : - Les pharmaciens sont des professionnels de santé, au même titre que les médecins et les infirmiers(ères) - Les pharmaciens sont des experts en médicaments, effets secondaires et interactions médicamenteuses - Les pharmaciens sont juste des commerçants qui vendent des produits en pharmacie	Please indicate your level of agreement or disagreement with the following statements about the role of pharmacists: - Pharmacists are health professionals, just like physicians and nurses - Pharmacists are experts in medications, side effects and medication interactions -Pharmacists are just shopkeepers who sell products in pharmacies

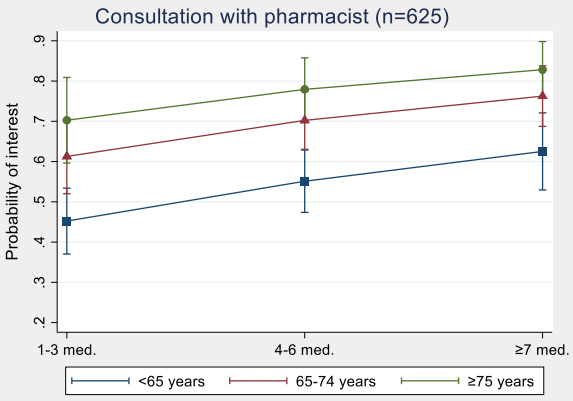
Pharmacy services	
Option de réponses	Response options
Intérêt personnel : Non, ça ne m'intéresse pas Oui, ça m'intéresse un peu Oui, ça m'intéresse beaucoup Déjà utilisé ? Oui, déjà utilisé Non, jamais utilisé	Personal interest: No, I'm not interested Yes, I'm a little interested Yes, I'm very interested Already used? Yes, already used No, never used
Etes-vous intéressé(e) par les aides suivantes pour vous soutenir dans la prise de vos médicaments, et les avez-vous déjà utilisées ? - Entretien individuel avec le pharmacien (pour recevoir des informations pratiques sur vos médicaments, faire un bilan de tous les médicaments que vous prenez, etc.) - Consultation spécifique chez votre médecin (pour recevoir des informations pratiques sur vos médicaments, faire un bilan de tous les médicaments que vous prenez, etc.) - Rappels des médicaments à prendre par SMS (message texte sur le téléphone) - Rappels des médicaments à prendre par email (message électronique, courriel) - Application sur smartphone (réception d'alertes journalières) - Pilulier ou semainier (boîte à médicaments, rangés par jours et heures de prise) - Pilulier électronique (boîte à médicaments qui enregistre la prise de vos médicaments et vous aide à savoir si vous les avez bien pris) - Liste écrite / plan de traitement de tous vos médicaments (en dehors de l'ordonnance)	Are you interested in the following aids to support you in taking your medication, and have you ever used them? - Individual consultation with the pharmacist (to receive practical information about your medications, to review all the medications you take, etc.) - Specific consultation with your physician (to receive practical information about your medications, to review all the medications you take, etc.) - SMS reminders of medications to be taken (text message on the phone) - Email reminders of medications to be taken (email) - Smartphone application (receipt of daily alerts) - Pill box or weekly pill box (medication box arranged by day and time of intake) - Electronic pill box (medication box that records the intake of your medications and helps you know if you have taken them correctly) - Written list or treatment plan for all your medications (in addition to your prescription copy)
Etes-vous intéressé(e) par les services suivants proposés en pharmacie, et les avez-vous déjà utilisés ? - Tests en pharmacie pour détecter les maladies chroniques telles que l'hypertension, le diabète ou un niveau de cholestérol trop élevé (dépistage) - Surveillance en pharmacie de votre pression/tension artérielle, taux de sucre dans le sang, ou taux de cholestérol, après avoir reçu un traitement de votre médecin - Vaccination contre la grippe en pharmacie - Conseils en pharmacie sur la manière d'utiliser des appareils, tels que les stylos injecteurs d'insuline ou les lecteurs de glycémie - Aide par le pharmacien pour arrêter de fumer ou contrôler votre poids - Premier avis de la part du pharmacien en cas de doute sur votre état de santé, incluant la recommandation de consulter ou non un médecin - Contrôle de tous vos médicaments par le pharmacien afin de détecter d'éventuels problèmes (interactions, doublons)	Are you interested in the following pharmacy services and have you ever used them? - Screening for chronic conditions such as hypertension, diabetes or hyperlipidaemia at the pharmacy - Monitoring of blood pressure, blood sugar level or cholesterol level in pharmacy after being treated by your physician - Influenza immunisation at the pharmacy - Counselling on how to use devices such as insulin pens or blood glucose meters at the pharmacy - Support from the pharmacist to quit smoking or lose weight - First medical opinion from the pharmacist in case of doubts about your health status, including a recommendation on whether to visit a physician - Check of all your medications by the pharmacist to identify possible problems (interactions, duplicates)

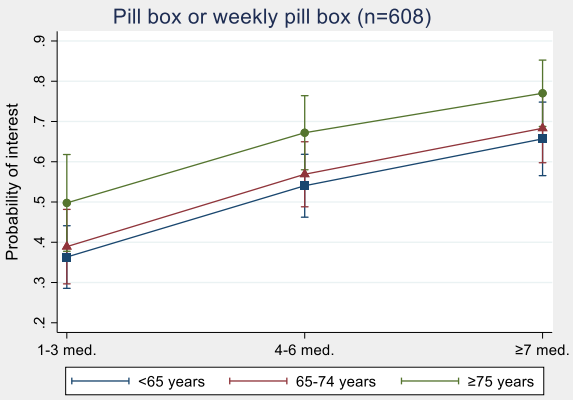
Additional File 2 - Predicted probabilities obtained from logistic regression analyses of the pharmacy services that interested ≥50% of the participants and their 95% confidence intervals

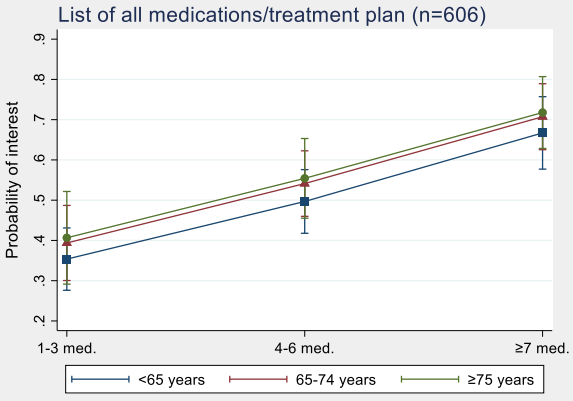
		Medication intake and adherence						Diabetes and general health					
		Consultation with pharmacist (n=625)		Pill box or weekly pill box (n=608)		List of all medications/ treatment plan (n=606)		Check of all medications (n=610)		First medical opinion (n=608)		Counselling on how to use devices (n=596)	
		Predicted probability	(95% CI)	Predicted probability	(95% CI)	Predicted probability	(95% CI)	Predicted probability	(95% CI)	Predicted probability	(95% CI)	Predicted probability	(95% CI)
Age	<65 years	0.54	[0.47 to 0.60]	0.50	[0.44 to 0.57]	0.49	[0.43 to 0.56]	0.69	[0.63 to 0.75]	0.66	[0.60 to 0.72]	0.55	[0.49 to 0.61]
	65-74 years	0.69	[0.63 to 0.75]	0.56	[0.49 to 0.62]	0.55	[0.48 to 0.61]	0.68	[0.61 to 0.74]	0.61	[0.55 to 0.68]	0.62	[0.56 to 0.69]
	≥75 years	0.78	[0.71 to 0.85]	0.66	[0.58 to 0.74]	0.57	[0.49 to 0.66]	0.61	[0.52 to 0.69]	0.50	[0.42 to 0.59]	0.55	[0.47 to 0.64]
Sex	Female	0.63	[0.57 to 0.69]	0.57	[0.51 to 0.63]	0.50	[0.44 to 0.57]	0.69	[0.63 to 0.75]	0.66	[0.60 to 0.72]	0.63	[0.56 to 0.69]
	Male	0.65	[0.61 to 0.70]	0.55	[0.50 to 0.60]	0.55	[0.50 to 0.59]	0.65	[0.61 to 0.70]	0.58	[0.53 to 0.63]	0.54	[0.49 to 0.59]
Education	Primary	0.67	[0.58 to 0.77]	0.59	[0.49 to 0.69]	0.50	[0.40 to 0.61]	0.56	[0.45 to 0.67]	0.58	[0.47 to 0.69]	0.55	[0.44 to 0.67]
	Secondary	0.66	[0.61 to 0.71]	0.54	[0.49 to 0.59]	0.54	[0.48 to 0.59]	0.67	[0.62 to 0.72]	0.60	[0.54 to 0.65]	0.60	[0.54 to 0.65]
	Tertiary	0.61	[0.55 to 0.68]	0.57	[0.50 to 0.64]	0.53	[0.47 to 0.60]	0.70	[0.64 to 0.77]	0.64	[0.58 to 0.71]	0.55	[0.48 to 0.62]
Financial hardship	No	0.62	[0.58 to 0.67]	0.54	[0.49 to 0.59]	0.52	[0.47 to 0.56]	0.66	[0.61 to 0.71]	0.59	[0.54 to 0.64]	0.57	[0.52 to 0.61]
	Yes	0.69	[0.63 to 0.75]	0.58	[0.52 to 0.65]	0.56	[0.49 to 0.63]	0.68	[0.62 to 0.75]	0.66	[0.59 to 0.73]	0.59	[0.52 to 0.67]
Treatment including injections	No	0.64	[0.58 to 0.70]	0.54	[0.48 to 0.60]	0.52	[0.46 to 0.58]	0.70	[0.64 to 0.75]	0.60	[0.54 to 0.66]	0.55	[0.48 to 0.61]
	Yes	0.65	[0.60 to 0.69]	0.57	[0.52 to 0.62]	0.54	[0.49 to 0.59]	0.65	[0.60 to 0.70]	0.62	[0.56 to 0.67]	0.60	[0.55 to 0.65]
Participation in diabetes education course	No	0.64	[0.60 to 0.69]	0.57	[0.52 to 0.62]	0.55	[0.51 to 0.60]	0.65	[0.60 to 0.70]	0.61	[0.56 to 0.65]	0.59	[0.55 to 0.64]
	Yes	0.65	[0.59 to 0.71]	0.53	[0.47 to 0.60]	0.49	[0.42 to 0.55]	0.70	[0.64 to 0.76]	0.62	[0.55 to 0.68]	0.54	[0.47 to 0.61]
Number of medications taken	1 to 3	0.56	[0.49 to 0.64]	0.40	[0.33 to 0.47]	0.38	[0.31 to 0.45]	0.60	[0.53 to 0.67]	0.61	[0.53 to 0.68]	0.55	[0.47 to 0.62]
	4 to 6	0.65	[0.60 to 0.71]	0.58	[0.52 to 0.64]	0.53	[0.46 to 0.59]	0.66	[0.60 to 0.71]	0.59	[0.53 to 0.65]	0.58	[0.52 to 0.64]
	≥7	0.72	[0.65 to 0.79]	0.69	[0.62 to 0.76]	0.69	[0.62 to 0.76]	0.75	[0.69 to 0.82]	0.65	[0.57 to 0.72]	0.60	[0.53 to 0.68]
Positive opinion about medication	Less positive	0.65	[0.61 to 0.69]	0.56	[0.52 to 0.60]	0.55	[0.50 to 0.59]	0.67	[0.63 to 0.71]	0.60	[0.55 to 0.64]	0.59	[0.54 to 0.63]
	Positive +++	0.64	[0.56 to 0.71]	0.54	[0.46 to 0.62]	0.48	[0.40 to 0.56]	0.65	[0.57 to 0.73]	0.64	[0.57 to 0.72]	0.54	[0.46 to 0.63]
Positive opinion about pharmacists	Less positive	0.57	[0.50 to 0.64]	0.51	[0.45 to 0.58]	0.50	[0.43 to 0.57]	0.60	[0.53 to 0.67]	0.55	[0.48 to 0.62]	0.52	[0.45 to 0.59]
	Positive +++	0.68	[0.64 to 0.72]	0.58	[0.53 to 0.62]	0.54	[0.50 to 0.59]	0.70	[0.66 to 0.74]	0.64	[0.59 to 0.69]	0.60	[0.56 to 0.65]

Additional File 3 - Predicted probabilities of interest in pharmacy services according to number of medications (1-3, 4-6 or ≥7 medications) and age (<65, 65-74, ≥75 years) with all other covariates held constant in the logistic regression models

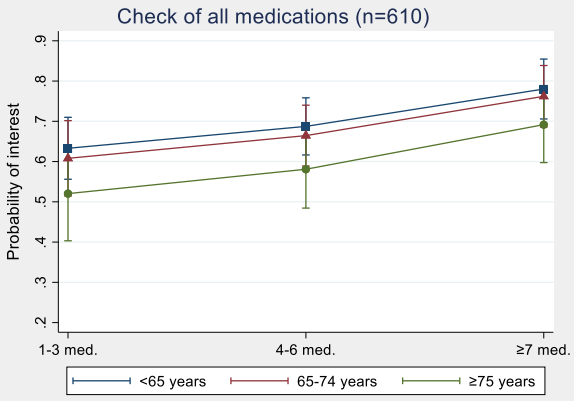
Medication intake and adherence

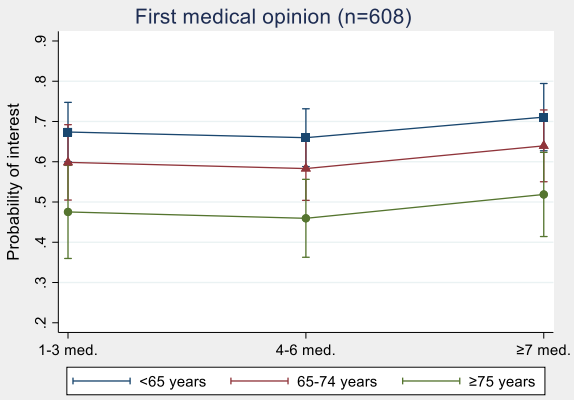


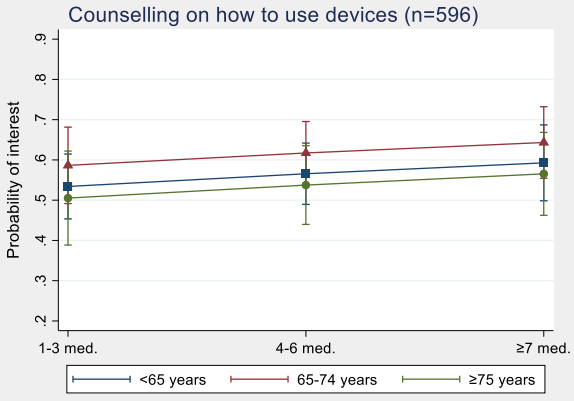




Diabetes and general health







Appendix 2 - Literature Review

As part of this thesis, a systematic literature review on medication adherence in patients with T2D was conducted in 2016 and updated in 2020 to synthesise current knowledge (i) on OAD adherence including methods, prevalence, and determinants and (ii) on associations between medication adherence and clinical outcomes, healthcare services utilisation and costs, and health status/quality of life. The literature review was entirely conducted by Noura Bawab and is in preparation for submission in a peer-reviewed journal. The complete methodology and detailed results of the literature review are available in French as two following articles:

- Literature Review (Part I): Methods of Measurement, Prevalence and Determinants of Medication Adherence in Patients with Type 2 Diabetes;
- Literature Review (Part II): Association between Medication Adherence and Clinical Outcomes, Healthcare Utilisation/Costs, and Health status/Quality of Life in Patients with Type 2 Diabetes.

Unisanté | Centre universitaire de médecine générale et santé publique Lausanne, Suisse

Revue de littérature (partie I) : méthodes de mesure, prévalence et déterminants de l'adhésion thérapeutique chez les patients diabétiques de type 2

Siscare-DT2

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INTRODUCTION

1. Le diabète

Le diabète est une maladie caractérisée par une glycémie (= taux de glucose sanguin) trop élevée dont la cause est une anomalie de sécrétion d'insuline (absence ou insuffisance), un défaut d'action de l'insuline (dit couramment « résistance à l'insuline ») ou une combinaison de ces deux facteurs [1].

Le nombre de personnes diagnostiquées est en constante augmentation, en particulier chez les enfants et les adolescents [1]. En 2015, le nombre de personnes adultes atteintes de diabète est estimé à 415 millions dans le monde (et 59.8 millions en Europe). Selon l'estimation de l'*Atlas du Diabète*, ce chiffre atteindrait 642 millions en 2040. En Suisse, la prévalence du diabète chez les adultes (âgés de 20 à 79 ans) est estimée à 7.7% (480'700 cas de diabète) en 2015 [2].

Il existe quatre types de diabète différents :

1) Diabète de type 1 : causé par un défaut de production de l'insuline par les cellules bêta des îlots de Langerhans du pancréas (5 à 10% des cas de diabète) ;
2) Diabète de type 2 : induit par une résistance à l'insuline et/ou une carence en sécrétion d'insuline (environ 90% des cas de diabète) ;
3) Diabète gestationnel : trouble de la tolérance glucidique pendant la grossesse (2 à 5 % des grossesses) qui disparaît généralement après l'accouchement ;
4) Autre type de diabète : lié à une pathologie ou à une autre cause (chirurgie, traitement médicamenteux, malnutrition, infection,… ; 1 à 2 % des cas de diabète) [1].

Le diabète peut provoquer des complications telles que des maladies oculaires, cardiovasculaires, rénales ou du système nerveux et des complications lors de la grossesse, altérer l'hygiène bucco-dentaire, ou provoquer des problèmes vasculaires et infectieux au niveau des pieds ('le syndrome du pied du diabétique'). Ces complications sont d'autant plus sévères si la prise en charge n'est pas optimale. Une meilleure gestion du diabète, en contrôlant le mieux possible la glycémie, la pression artérielle et le taux de cholestérol, permet d'éviter ou de retarder l'apparition de ces complications [2].

Les conséquences du diabète ont un impact non négligeable sur les coûts de la santé. Selon la Fédération Internationale du Diabète, 5 à 20% des coûts totaux de santé seraient dédiés au diabète au niveau mondial et 9% en Europe [2].

Le traitement du patient diabétique de type 2 repose en première ligne sur les mesures hygiéno-diététiques de base associées à la prise de médicaments par voie orale. Les antidiabétiques oraux (ADO) sont classés en deux catégories. Les antidiabétiques dit « insulinotropes » stimulent la sécrétion d'insuline comme les sulfonylurées (glibenclamide, glimépiride, gliclazide, glibornuride, glipizide), les glinides (répaglinide, natéglinide, meglitidines) et les inhibiteurs de la dipeptidyl peptidase-4 (sitagliptine, vidalgliptine, saxagliptine, linagliptine, alogliptine). Les médicaments « non insulinotropes » diminuent la résistance à l'insuline comme les biguanides (metformine) ou les glitazones (rosiglitazone, pioglitazone, troglitazone), retardent l'absorption intestinale des glucides comme les inhibiteurs des alpha-glucosidases (acarbose) ou diminuent la réabsorption rénale du glucose comme les inhibiteurs du co-transporteur sodium-glucose de type 2 SGLT-2 (dapagliflozine, canagliflozine, empagliflozine). Les incrétinomimétiques ou agonistes du

Glucagon-like peptide 1 (exénatide, liraglutide), l'insuline ainsi que l'analogue de l'amyline (la pramlintide) sont des traitements administrés par injection [3,4].

Les patients diabétiques de type 2 sont souvent polymorbides (p.ex. obésité, dyslipidémie, hypertension) et polymédiqués [3]. La prise de médicaments au quotidien peut s'avérer difficile chez de nombreux patients. Une approche interprofessionnelle est primordiale dans le soutien et l'accompagnement de ces patients, notamment en matière d'adhésion thérapeutique [1].

2. L'adhésion thérapeutique

a) Définition

L'adhésion thérapeutique est un processus complexe qui caractérise la prise et la gestion d'un traitement au quotidien par un patient [1]. Le patient est « adhérent » s'il prend son traitement tel qu'il lui a été prescrit, en termes de durée et de prise. L'adhésion est un processus dynamique et complexe qui se décompose en trois dimensions (cf. Figure 1) [5]:

- **l'initiation :** qui débute le processus thérapeutique et correspond au moment où le patient prend la première prise du traitement prescrit ;
- **l'implémentation :** qui caractérise la qualité d'exécution du traitement par le patient, de son initiation jusqu'à la dernière dose, par rapport au schéma posologique prescrit ;
- **la persistance** : qui caractérise la durée de prises du traitement, de son initiation jusqu'à son interruption [6]. La discontinuation marque la fin de la thérapie, quand la prochaine dose à prendre est omise et qu'aucune dose n'est prise par la suite.

Le soutien et l'accompagnement de l'adhésion thérapeutique reposent sur une approche multidimensionnelle impliquant à la fois la politique et l'organisation du système de santé, les acteurs de soins, les patients et leur réseau social (cf. Figure 1) [5]. Les formes de non-adhésion ainsi que leurs déterminants sont multiples et n'ont pas le même impact sur l'état de santé du patient (cf. Figure 2).

Figure 1: Processus d'adhésion thérapeutique (« *Adherence to medications* ») et de gestion de l'adhésion (« *Management of adherence* ») [5]

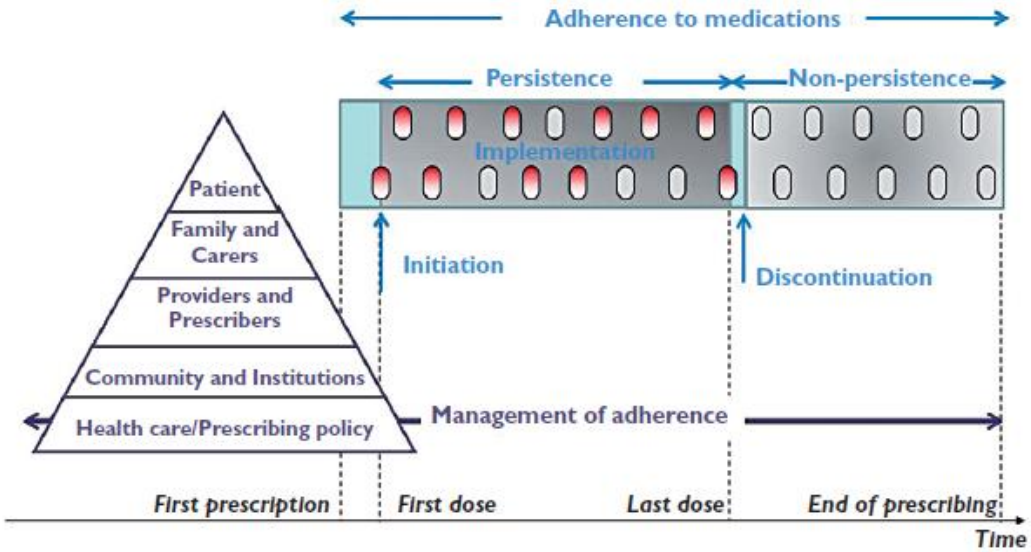


Figure 2: Les différentes formes de la non-adhésion thérapeutique [5]

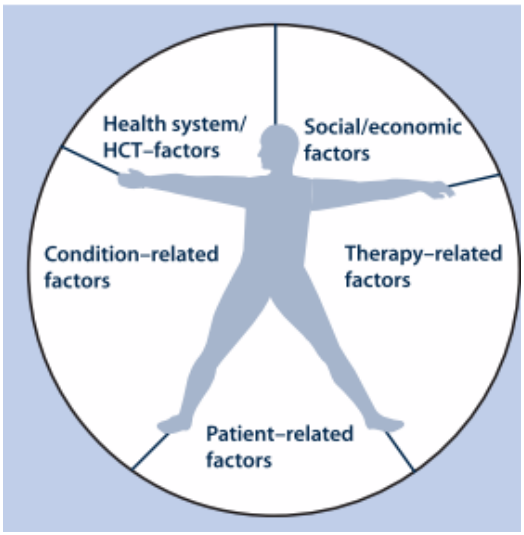
Temps →

Phase	Initiation	Implémentation	Persistance
Non-adhésion	le patient ne commence pas le traitement	le patient reporte la prise du traitement, omet de prendre son traitement ou prend des doses supplémentaires	le patient arrête son traitement
Mesure	Variable binaire (Oui/Non)	Historique de dosage	Durée de prise jusqu'à l'arrêt

b) Les déterminants de l'adhésion thérapeutique

L'Organisation Mondiale de la Santé (OMS) estime que 50% des patients chroniques n'adhèrent pas à leurs traitements [1]. L'adhésion thérapeutique peut varier dans le temps en fonction de très nombreux facteurs, recensés à plus de 700 [7]. Ces facteurs peuvent être regroupés en cinq dimensions, qui interagissent entre elles (cf. Figure 3).

Figure 3: Les déterminants de l'adhésion thérapeutique et des exemples [1]



Dimensions	Exemples
Facteurs liés au patient	sa personnalité, ses attitudes et croyances, sa motivation
Facteurs liés à la maladie	handicap, comorbidités, durée
Facteurs liés au traitement	nombre de prise journalière / comprimés, durée, effets indésirables
Facteurs sociaux et économiques	statut professionnel, niveau d'éducation, soutien des proches
Facteurs liés au système de santé et à l'équipe soignante	accessibilité, relation patient-médecin, formation des soignants

c) Méthodes de mesure de l'adhésion thérapeutique

Il n'y a pas de « gold standard » pour mesurer l'adhésion thérapeutique, chaque mesure fournissant une approximation des différents aspects de la prise de médicaments [8]. Contrairement aux méthodes directes, qui mesurent l'ingestion du médicament (p.ex. via des marqueurs biochimiques ou pharmacologiques comme l'hémoglobine glyquée chez les patients diabétiques qui est aussi un indicateur des états d'hyperglycémie des 3 derniers mois précédant la mesure [3]), les mesures indirectes sont des mesures proxys de l'adhésion thérapeutique. Le chapitre suivant présente les mesures indirectes les plus utilisées.

i. Les mesures d'auto-évaluation

Les questionnaires auto-administrés, journal de bord ou interviews permettent de faire une photo de l'adhésion thérapeutique dans une population donnée. Les deux questionnaires les plus utilisés, et validés en plusieurs langues sont le : Morisky Medication Adherence Scale (MMAS) et le Medication Adherence Report Scale (MARS).

Le MMAS est un questionnaire qui se décline en quatre ou huit questions binaires (Oui/Non) [9] (cf. Annexe 1). Il permet de caractériser le comportement global du patient face à sa prise de médicaments. Un score peut être calculé en sommant par exemple les réponses (p.ex. *« Vous arrive-t-il parfois d'oublier de prendre vos comprimés* ? *»* avec Oui=1 et Non=0). Dans ce cas, les scores les plus faibles indiquent une meilleure adhésion et un score ≥1 indique au moins un problème d'adhésion. Le score permet de classer les patients, généralement en trois catégories : « adhésion faible », « adhésion moyenne », « adhésion élevée », et d'estimer la proportion de patients considérés comme « adhérents » en fonction d'un niveau seuil défini (pas de consensus).

Contrairement au MMAS, le MARS se mesure généralement pour chaque médicament pris par le patient [10,11] (cf.Annexe 2). Le questionnaire se décline en cinq ou dix questions. Les items du MARS peuvent refléter la non-adhésion non intentionnelle (p.ex. *« I forget to take my glucose-lowering drugs »)*, ou les différentes formes d'une non-adhésion intentionnelle (p.ex. « *I alter the dose of my glucose-lowering drugs* »). Les répondants indiquent la fréquence de chaque item dans les trois derniers mois via une échelle de Likert en cinq points (1 : « toujours » à 5 : « jamais »). Le score peut donc aller de cinq à vingt-cinq, les scores les plus élevés suggérant une meilleure adhésion.

ii. Les outils électroniques

Les outils électroniques (p.ex. semainier, blister ou pilulier équipés de puces électroniques) permettent une mesure longitudinale de la fréquence et de l'agenda des prises de médicaments. A chaque ouverture, la date et l'heure sont enregistrées et peuvent être téléchargées via un logiciel.

iii. Les données de renouvellement d'ordonnances et remboursement

Les données disponibles dans les pharmacies ou caisses d'assurance permettent d'estimer un taux d'adhésion en comptant le nombre de jours pendant lesquels le patient est/n'est pas approvisionné en médicaments. Les trois principales mesures tirées de ces données sont le *Medication Possession Ratio* (MPR), le *Percentage of Days Covered* (PDC) et le *Continuous Measure of Medication Gaps* (CMG).

Le MPR correspond au nombre total de jours pour lesquels le médicament a été dispensé à un patient divisé par le nombre de jours durant lesquels le patient aurait dû prendre le médicament[8]. Il se calcule selon les formules suivantes [12] :

$$(1) MPR = \frac{total\ Rx\ days\ of\ supply}{last\ Rx\ date - first\ Rx\ date + last\ Rx\ days\ of\ supply}$$

$$(2) MPR = \frac{total\ Rx\ days\ of\ supply}{Fixed\ interval\ (365\ days\ e.g.)}$$

Le dénominateur se différencie par

(1) : le nombre de jours d'observations variables en fonction des dates de renouvellement
(2) : un intervalle fixe pour la durée d'observation

Selon la formule choisie, le MPR peut dépasser la valeur de 1 (surestimation). Dans ce cas, il est difficile d'interprété la « surestimation ». Il est recommandé de tronquer le MPR à 1 pour les valeurs supérieures. De plus, lorsqu' un patient prend au moins 2 médicaments simultanément, le numérateur (la somme des jours d'approvisionnement de tous les médicaments) est divisé par le nombre de médicaments pris pendant cette période. Il n'y a pas de consensus pour définir un seuil « acceptable » d'adhésion, le plus communément utilisé est 80%.

Le PDC représente le nombre de jours d'approvisionnement en médicaments depuis la première prescription et pour une période donnée [8]. Il se calcule selon la formule suivante [12] :

$$PDC = \frac{total\ days\ all\ drug(s)\ available}{days\ in\ follow-up\ period\ (365\ days\ e.g.)}$$

On remarque que le PDC ne peut dépasser la valeur de 1. De plus, il prend en compte l'adhésion par jour pour l'ensemble des médicaments d'un patient, et évite de compter deux fois les jours de « couverture » médicamenteuse, car une journée n'est comptée que si tous les médicaments sont disponibles ce jour-là. Il n'y a pas de consensus pour définir un seuil « acceptable » d'adhésion, le plus communément utilisé est 80%.

Le CMG (ou « taux de non-couverture » en français) représente le nombre de jours pendant lesquels le patient n'avait pas de médicaments disponibles divisé par le nombre de jours pendant lesquels il aurait dû en avoir. Contrairement aux deux précédentes mesures, un taux plus proche de 0 indique donc une meilleure adhésion [13]. La moyenne de la valeur du CMG fournit une valeur générale de non-adhésion basée sur l'absence de médicaments : 0 reflète une adhésion complète et 1 reflète une non-adhésion complète. Il se calcule selon la formule suivante [14] :

$$CMG = \frac{total\ days\ of\ treatment\ gaps}{total\ days\ to\ next\ fill\ or\ end\ of\ observation\ period\ (e.g. 365\ days\ )}$$

On remarque que le CMG peut être calculé uniquement pour les patients ayant reçu au moins deux remplissages [13]. Le seuil « acceptable » d'adhésion est généralement fixé à 20%.

iv. Le comptage

Lors d'un renouvellement, le comptage du nombre de comprimés restant, par exemple dans un semainier, permet d'estimer la prise de médicaments du patient. Un taux d'adhésion peut être calculé : nombre d'unités de médicaments distribuées multiplié par le dosage, divisé par le nombre de comprimés qui auraient dû être consommés selon le dosage et le nombre de jours dans la période analysée (donner en % de valeur) [8].

v. Les résultats cliniques

La mesure des résultats cliniques spécifiques à une maladie peut constituer une manière d'estimer l'atteinte des objectifs thérapeutiques selon les bonnes pratiques (p.ex. tension artérielle ou taux de cholestérol) [8].

En conclusion, chaque outil a des avantages et inconvénients et leur utilisation dépendra essentiellement de leur disponibilité, leur coût, leur performance (spécificité/sensibilité) et des biais potentiels dans le contexte clinique spécifique (sur/sous-estimation, biais positif de prise, etc.) [8]. Les questionnaires auto-administrés permettent d'évaluer le comportement général du patient face à sa prise de médicaments à un temps précis (étude transversale) mais ne fournissent pas d'informations sur l'adhésion thérapeutique dans le temps. Les données de renouvellement et remboursement ne reflètent pas les variations dans l'agenda de prises journalières. Les piluliers électroniques permettent une analyse de l'agenda de prise des médicaments mais peuvent avoir une influence positive sur l'adhésion pendant les premiers mois d'utilisation. Toutes ces méthodes de mesure apparaissent donc comme complémentaires et leur usage combiné permet d'augmenter la validité et la fiabilité des données collectées [8]. L'estimation de la prévalence de l'adhésion thérapeutique est ainsi influencée par la méthode de mesures appliquée. Toute synthèse des résultats d'une revue de littérature sur le sujet de l'adhésion thérapeutique doit par conséquent décrire très précisément le contexte clinique et la méthode de mesures utilisée.

MÉTHODOLOGIE DE LA REVUE DE LITTERATURE

1. Objectifs

Les objectifs de la présente revue de littérature sont les suivants :

i) Evaluation des méthodes de mesures de l'adhésion thérapeutique aux antidiabétiques oraux (ADO)
ii) Evaluation de la prévalence « naturelle » (sans intervention spécifique de soutien aux patients) chez les patients diabétiques de type 2
iii) Identification des déterminants de l'adhésion thérapeutique aux ADO et caractérisation de leurs influences.

2. Stratégie de recherche

Une recherche de littérature a été entreprise dans PubMed et Embase en combinant des termes MESH/Emtree avec des mots-clés : « type 2 diabetes », « medication adherence», « clinical impact », « economical impact » (cf. Annexe 3 décrivant les algorithmes complets).

3. Sélection des revues de littérature et méta-analyses

Critères d'inclusion :

- Revue systématique de littérature ou méta-analyse qui évalue les déterminants, l'impact clinique et/ou économique de l'adhésion thérapeutique ;
- Résultats reportés au moins pour les patients diabétiques de type 2 ;
- Prise d'ADO (avec ou sans traitement injectable) ;
- Article de langue française ou anglaise ;
- Publication entre le 01.01.2004 et le 29.06.2020.

Critères d'exclusion :

- Patients diabétiques de type 1 uniquement ;
- Revue de littérature narrative ;

La sélection des articles a été effectuée par lecture du titre, de l'abstract, puis du texte complet.

4. Sélection des études au sein des revues de littérature et méta-analyses

Critère d'inclusion supplémentaire:

- Patients majeurs (âge ≥ 18 ans).

Critères d'exclusion :

- Parution de l'étude avant 2004 ;
- « Résultat clinique » comme valeur d'adhésion, p.ex. l'hémoglobine glyquée.

5. Extraction des données des études sélectionnées

Les données extraites de ces études étaient :

- la référence
- le pays où l'étude a eu lieu
- la source des données étudiées
- le type d'étude
- le nombre de patients
- les caractéristiques des patients (type de diabète, âge, type d'ADO)
- la méthode de mesure de l'adhésion thérapeutique
- la période d'observation de l'adhésion thérapeutique
- la valeur de l'adhésion mesurée
- les facteurs influençant l'adhésion.

RESULTATS

1. Sélection des articles

a) Sélection des revues

La recherche dans les bases de données nous a permis d'identifier 630 revues de littérature et méta-analyses auxquelles 3 revues de littérature ont été rajoutées à la suite d'une recherche manuelle (cf.). Après le processus de sélection, 9 revues de littératures ont été incluses dans l'analyse. Aucune méta-analyse n'a été incluse (une seule traitait des taux d'adhésion thérapeutique mais sans décrire d'impact clinique ou économique.

b) Sélection des études

Au sein des 9 revues de littérature et après retrait des doublons, 192 études (dont une étude ajoutée manuellement) ont été retenues. Après application des critères de sélection, 106 études ont été incluses dans ce rapport (cf.).

2. Description générale des études

Les études incluses ont été publiées entre 2004 et 2016, 68% (n=72) d'entre elles ont été réalisées aux Etats-Unis et 14% (n=15) en Europe, principalement aux Pays-Bas. Seulement 1 étude a été menée en Suisse [15]. Les études ont été conduites le plus souvent de manière rétrospective (55%, n=58) ou transversale (33%, n=35), mais plus rarement selon une démarche prospective (12%, n=13).

3. Type de population étudiée

Le nombre de participants au sein des études variait de 20 à plus d'un million, les données d'assurance permettant d'analyser des grandes cohortes de patients. La moyenne et la médiane du nombre de participants était de 50'136 et 1'815, respectivement (n=106). La majorité des études (34%, n=36) comptaient 101 à 1000 patients. L'âge moyen des populations étudiées variait de 37 à 75 ans, la moyenne étant de 59 ans (n=66). Pour 89% (n=94) des études, les patients étaient diabétiques de type 2 et pour 3% (n=3) elles concernaient des patients diabétiques de type 1 ou 2. Pour 8% (n=9) des études, le type de diabète n'était pas spécifié.

L'adhésion thérapeutique mesurée concernait les ADO seuls dans 64% (n=68) des études, les ADO ainsi que les formes injectables dans 24% (n=25) des études alors que les médicaments observés n'étaient pas spécifiés dans 12% des études (n=13). Parmi l'ensemble des études, 18 % (n=19) s'intéressaient à des initiations de traitements, chez des patients nouvellement diagnostiqués. Cependant, le type de patients (patient naïf ou diabétique de longue date) n'était pas spécifié pour 52% (n=55) des études.

4. Méthodes de mesure de l'adhésion thérapeutique

Le Tableau 1 présente les méthodes de mesure de l'adhésion thérapeutique en fonction de la durée de suivi (une même étude pouvant utiliser plusieurs méthodes). Parmi les 106 études, 118 mesures d'adhésion ont été reportées. Les principales méthodes utilisées étaient l'analyse des données de renouvellement d'ordonnances et remboursement (64%, n=75) et les auto-évaluations par questionnaire (34%, n=40).

Parmi les études traitant des données de renouvellement d'ordonnances et de remboursement, la méthode de calcul du MPR sur 12 mois a été le plus souvent utilisée.

Figure 4: Flow chart de sélection des études, adapté de PRISMA [16,17]

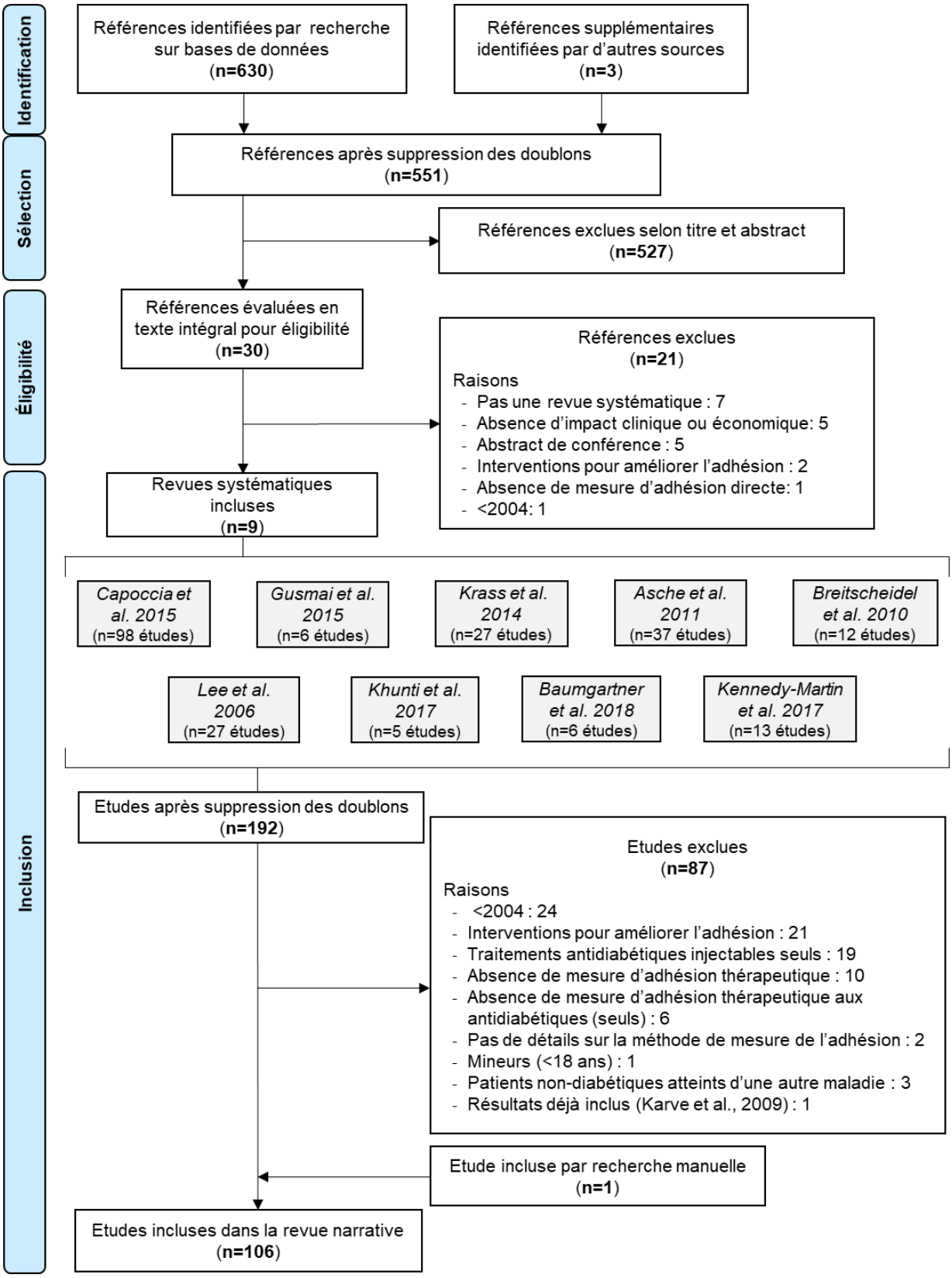


Tableau 1: Méthodes de mesure de l'adhésion thérapeutique utilisées en fonction de la durée de suivi (n=122, plusieurs méthodes possibles par étude)

	Durée de suivi				
Source de données	**< 6 mois** (n=4)	**6-9 mois** (n=5)	**12 mois** (n=46)	**>12 mois** (n=22)	**n/s** (n=1)
Données de renouvellement/ remboursement (n=75)	**n=1** Initiation: 1 [18]	**n=5** MPR : 3 [19-21] PDC : 2 [22,23]	**n=46** MPR: 24 [24-47] PDC: 9 [15,44,48-54] CMG: 2 [44,55] Autres: 11 [39-42,44,56-61]	**n=22** MPR: 13 [62-74] PDC : 4 [75-78] CMG : 2 [79,80] Autres: 3 [71,81,82]	**n=1** MPR : 1 [83]
Comptage (n=2)	**n=2** [84,85]	-	-	-	-
Pilulier électronique (n=1)	**n=1** [86]	-	-	-	-
Auto-évaluations (n=40)[1]	**n=40** Morisky Medication Adherence Scale (MMAS)[2] : 21 [43,87-106] Medication Adherence Report Scale (MARS)[3]: 4 [107-110] Autre échelle : 15 [85,99,110-122]				

[1] Pas de durée de suivi pour ces études transversales ; [2] à 4 questions (n=17) ou 8 questions (n=4)
[3] à 5 questions (n=3) ou 10 questions (n=1); MPR: Medication Possession Ratio, PDC: Proportion of Days Covered, CMG: Continuous Measure of Medication Gaps, n/s: non spécifié

5. Prévalence de l'adhésion thérapeutique

La méthodologie et présentation des résultats des études sont assez variables, ainsi une étude peut calculer un score 'moyen' de l'adhésion thérapeutique en fonction de la méthode de mesure et/ou rapporter la proportion de patients considérés comme 'adhérents' ou 'non adhérents' selon un niveau seuil défini. De plus, certaines études rapportent des résultats d'adhésion en fonction de différents sous-groupes dans l'étude (p.ex. type d'établissement consultées, type de traitement ADO, etc.), sans information sur la prévalence pour la cohorte entière. Ce constat rend difficile la synthèse des résultats des études. Ce chapitre synthétise les résultats disponibles dans les études concernant la prévalence de l'adhésion thérapeutique dans la cohorte entière de patients étudiée (si cela était pertinent, une moyenne parmi les sous-groupes étudiés était calculée), en fonction de la mesure utilisée.

a) Les mesures d'auto-évaluation

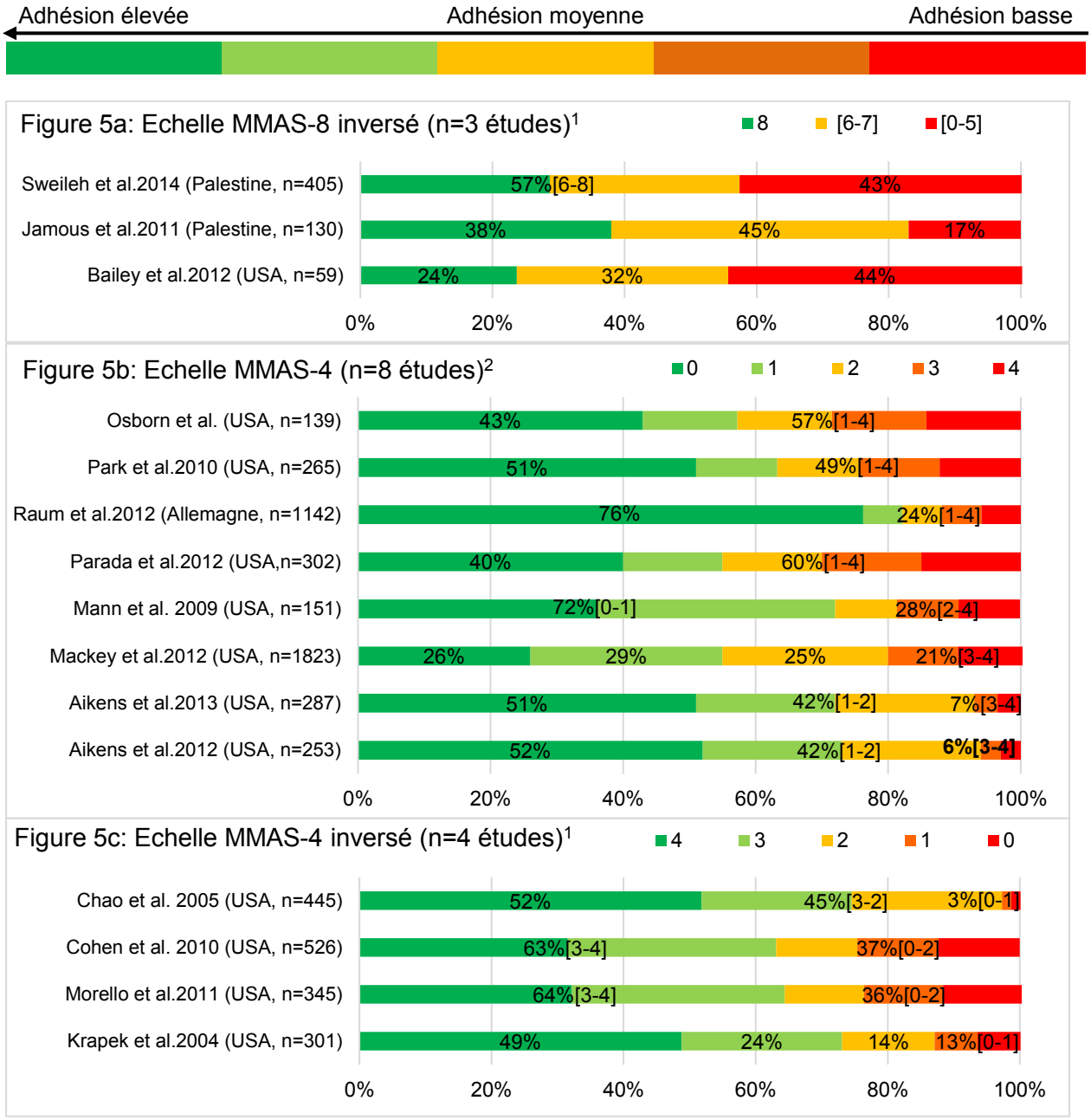
Ce chapitre se focalise sur les deux échelles validées les plus utilisées dans la littérature : le score de Morisky (MMAS) et le MARS, les autres échelles utilisées n'étant pas validées ou peu étudiées.

Sur les 21 études qui utilisaient l'échelle de Morisky (MMAS), 13 permettaient de répartir les répondant selon leur score. La Figure 5 représente la répartition des répondants (Adhésion élevée/moyenne/basse) en fonction du score. Le manque de consensus sur le niveau seuil à utiliser pour caractériser les patients « adhérents/non adhérents » rend difficile l'estimation d'une prévalence moyenne de l'adhésion parmi les études. Néanmoins, en prenant comme niveau seuil, la valeur maximale (i.e. MMAS8-inversé=8, MMAS4=0, MMAS4-inversé=4) : 46% [23%-76%] (n=11) des patients avaient un score « élevé » d'adhésion (4 études ne permettent pas de connaître le % de patients avec un score « élevé »

dû à un regroupement de classes). Ce score maximal correspond à aucun problème d'adhésion identifié (Cf. Annexe 1).

Deux études utilisaient le score MARS pour estimer la proportion de patients « adhérents ». Les différents niveaux seuil rend néanmoins les résultats non comparables. Au Pays-Bas, 50% des patients étaient « adhérents », avec un score égal à 25 (score maximum) pour tous les médicaments pris par le patient (n=20 patients) [107]. En Iran, 87% des patients étaient « adhérents » mais avec un niveau seuil beaucoup moins exigeant (score plus élevé que la moitié du score total) [110].

Figure 5 : Répartition des répondants en fonction de leur score de *Morisky Medication Adherence Scale* (n=15 études)



[1] Un score plus élevé indique une meilleure adhésion ; [2] Un score plus bas indique une meilleure adhésion

b) Données de renouvellement et remboursement

L'hétérogénéité des mesures de l'adhésion thérapeutique via les données de renouvellement et remboursement suggère d'être prudent quant à la volonté de synthétiser la prévalence de l'adhésion thérapeutique dans la littérature. A titre d'illustration, l'étude américaine de Karve et al. 2008 [44] compare les différentes méthodes d'estimation du taux d'adhésion thérapeutique chez les patients diabétiques de type 2 (n=4 943) : le taux d'adhésion variait de 0.75 à 0.91 selon la mesure choisie. Ce chapitre se focalise principalement sur les résultats des trois méthodes les plus utilisées : le MPR, le PDC et le CMG.

Avant toute chose, nous rappelons que les estimations de l'adhésion aux antidiabétiques oraux via les données de renouvellement et remboursement peuvent être exprimées de deux façons :

- le taux moyen d'adhésion au niveau du patient (p.ex. MPR moyen dans la population)
- le pourcentage de patients « adhérents », c'est-à-dire avec un taux supérieur ou égal à un niveau seuil défini. Il n'y a pas de niveau seuil consensuel reconnu en ce qui concerne la prise d'ADO pour les patients diabétiques de type 2, mais pour le MPR et le PDC, ce niveau seuil est souvent de 80%.

Parmi les études utilisant le MPR comme méthode de mesure, 68% des patients étaient adhérents (i.e. MPR ≥ 80%) (n=15) à 12 mois, et le MPR moyen était estimé à 70% (n=8) (cf. Annexe 4). Les autres études ne permettaient pas d'évaluer un des deux résultats.

Les études mesurant le PDC montraient un taux d'adhésion moyen semblable : 70% à 12 mois (n=7) (Cf. Annexe 5), mais avec une proportion de patients plus faible : 59% de patients adhérents (n=7). Une seule étude était menée en Suisse à partir des données d'assurance du groupe Helsana (n=26 713 patients) [15]. Après un an, seulement 42% de la population avait un PDC ≥80%, et le PDC moyen était de 67.9(26.9) %.

Les quatre études utilisant la mesure du CMG montrait des résultats assez comparables : à 12 mois le nombre moyen de jours sans médicaments disponibles sur le nombre total de jours durant lesquels le patient aurait dû en avoir était de 25% (n=1) (cf, Annexe 6).

Intéressons-nous maintenant à l'évolution de la prévalence de l'adhésion thérapeutique au fil du temps. Concernant la phase d'initiation, une seule étude liait les données électroniques de santé aux données de la pharmacie pour évaluer la proportion de patients qui initiaient le traitement aux Etats-Unis [18]. Sur 1132 patients, seulement 85% des patients allaient réellement chercher leur traitement d'ADO ou injectables à la pharmacie dans les 30 jours suivant la prescription. Le Tableau 2 présente les résultats de la prévalence de l'adhésion thérapeutique en fonction de la mesure et durée de suivi des études. Il montre une diminution tendancielle de l'adhésion thérapeutique dans le temps.

Tableau 2 : Prévalence de l'adhésion thérapeutique en fonction de la durée de suivi

	6-9 mois	12 mois	> 12 mois
MPR moyen	**0.86** [0.83-0.89](n=2)	**0.70** [0.56-0.82*] (n=6)	**0.62** [0.48-0.78] (n=5)
PDC moyen	-	**0.72** [0.65-0.76] (n=6)	**0.74** (n=1)
CMG moyen		**0.25**[1] (n=1)	
% patients avec MPR ≥ 0.80	-	**68%** [45-93%] (n=15)	**53%** [29-60%] (n=5)
% patients avec PDC ≥ 0.80	**65%** (n=1)	**59%** [38-82%] (n=7)	**47%** [9-73%] (n=3)
% patients avec CMG ≤ 0.20		**75%**[2] (n=1)	**66%** (n=2)

* La moyenne a été calculée en excluant l'étude pour laquelle le MPR n'est pas tronqué à 1.00.
[1] Le CMG représente le nombre de jours pendant lesquels le patient n'avait pas de médicaments disponible divisé par le nombre de jours pendant lesquels il devait en avoir. Un taux plus proche de 0 indique une meilleure adhésion
[2] CMG <0.20.

c) Comptage

Les deux études qui mesuraient l'adhésion thérapeutique par comptage utilisaient comme niveau seuil une prise de médicaments supérieure à 90% et inférieur à 105% sur la période. Les résultats étaient très différents, avec 17% de patients adhérents à un mois au Mexique (n=238) [84] et 62% de patients adhérents à 3 mois en Iran (n=248) [85].

d) Outils électroniques

La seule étude, évaluant l'adhésion thérapeutique par le biais de piluliers électroniques, rapportait un taux d'adhésion de 99.1% sur un suivi de 2 mois[86]. Ce résultat peut probablement s'expliquer par l'observation d'un effet positif des piluliers électroniques sur l'adhésion des patients sachant que leur comportement est mesuré. Selon la littérature, cet effet devrait s'estomper après quelques mois.

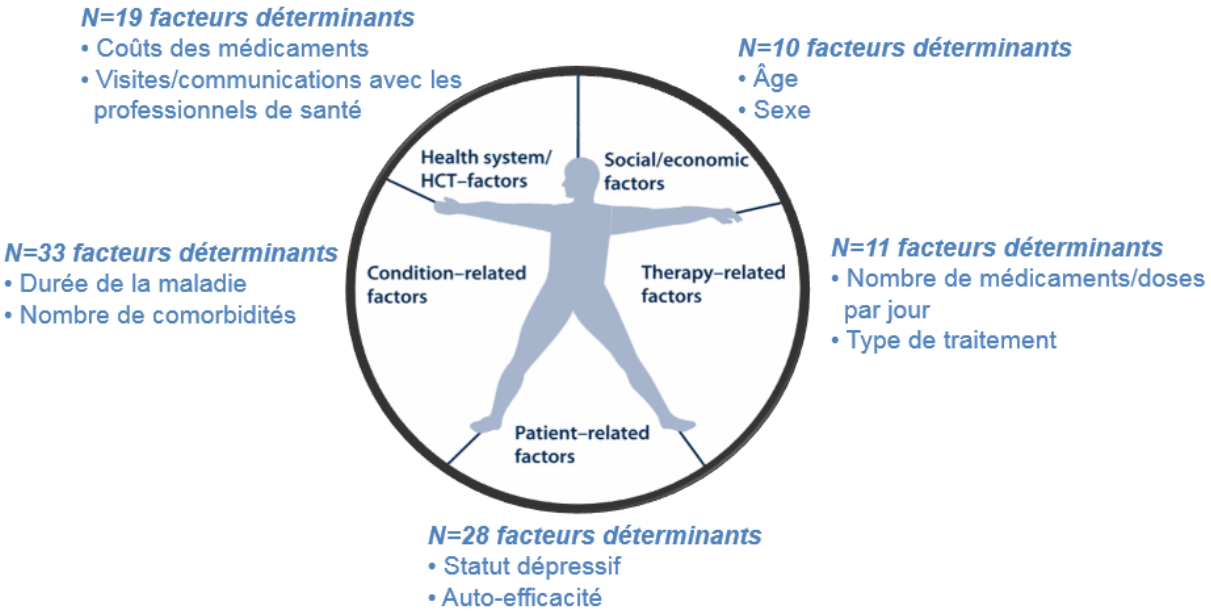
En conclusion, la revue de littérature montre que l'adhésion thérapeutique reste sous-optimale chez les patients diabétiques de type 2. Selon les études transversales par auto-évaluations, environ 50% des patients diabétiques de type 2 se déclarent « adhérents ». Cette photo correspond à l'estimation de l'OMS pour les patients chroniques. Peu d'études se sont intéressées à la phase d'initiation, mais l'unique étude observait que 15% des patients ne commenceraient jamais leur traitement. Enfin, les études transversales tendent à montrer une diminution de l'adhésion au fil du temps.

Concernant les méthodes identifiées dans la littérature, les données de renouvellement majoritairement utilisées permettent d'analyser l'adhésion thérapeutique pour des grandes cohortes de patients diabétiques de type 2. Néanmoins, elles ne permettent pas d'évaluer la réelle ingestion des médicaments et sa qualité par rapport à la prescription. Aucune étude ne mesurait l'adhésion thérapeutique par piluliers électroniques sur un suivi de plus de deux mois. Ce type d'outil permet néanmoins une mesure plus fine de l'adhésion thérapeutique.

6. Les facteurs déterminants de l'adhésion thérapeutique

Les facteurs déterminants de l'adhésion thérapeutique chez les patients diabétiques de type 2, étudiés dans la littérature, ont été classés selon les 5 catégories de la classification de l'OMS [1]: a) facteurs sociaux et économiques; b) facteurs liés au système de santé et à l'équipe soignante; c) facteurs liés à la maladie; d) facteurs liés au traitement; et e) facteurs liés au patient (cf. Figure 3). Parmi les 106 études, 101 déterminants ont été étudiés. La Figure 6 présente le nombre de facteurs déterminants étudiés dans chacune de ces dimensions, les deux facteurs les plus étudiés dans chacune d'elle servent d'illustrations.

Figure 6: Répartition des facteurs déterminants (n=101) de l'adhésion thérapeutique étudiés en fonction des 5 dimensions définies par l'OMS [1]



Le Tableau 3 présente les facteurs déterminants de l'adhésion thérapeutique étudiés par au moins 5 % des études sélectionnées (i.e. n=5 études) en fonction de la classification de l'OMS [1]. Les valeurs présentées sont le nombre d'études pour lesquelles le facteur déterminant était associé de façon significative positivement/négativement, ou non significative à l'adhésion thérapeutique chez les patients diabétiques.

Tableau 3: Facteurs déterminants associés à l'adhésion thérapeutique chez les patients diabétiques

Facteur déterminant (valeur de référence)	Association significative positive avec l'adhésion	Association significative négative avec l'adhésion	Association non significative avec l'adhésion	Total
A) FACTEURS SOCIAUX ET ECONOMIQUES				
Âge (↑)	28 [23,24,27,31,37,40-43,50,52,53,59,61,63,66,71,73,75,77,83,86,87,94,95,105,112,121]	3 [49,64,110]	21 [15,31,32,34,36,47,68,82,85,88,89,93,102-104,106,108,111,114,120]	**52**
Sexe (mâle)	12 [15,23,41,42,49,50,52,53,63,64,75,77]	6 [27,43,61,73,83,94]	30 [24,31,32,34,36,37,40,47,59,63,68,71,82,85,86,88,93,95,102-106,108,111,112,120,121]	**48**
Ethnie (caucasienne)	17 [23,32,41,50,56,64,65,71,77,82,116,121]	1 [34]	9 [36,43,88,89,93,94,103,104,112]	**27**
Niveau d'éducation (élevé)	3 [50,85,103]	1 [25]	16 [36,43,47,82,89,93,95,102,104,106,108,110-112,120]	**20**
Revenu (élevé)	5 [61,77,116,121,122]	1 [102]	9 [43,45,50,82,88,89,93,102,104]	**15**
Statut marital (marié)	4 [64,95,106,120]	1 [111]	5 [32,43,47,102]	**10**
Emploi (employé)	1 [76]	3 [61,95,121]	5 [36,43,75,76,111]	**9**
Lieu d'habitation (rural)	2 [64,65]	1 [45]	4 [83,102,120]	**7**
B) FACTEURS LIÉS AU SYSTEME DE SANTE ET A L'ÉQUIPE SOIGNANTE				
Coûts des médicaments (faible)	12 [18,25,29,35,49,50,70,75,91,104,116,118]	-	-	**12**
Visites/communications avec les professionnels (+ fréquentes)	7 [32,45,67,73,75,79]	-	5 [36,82,94,95,120]	**12**
Avoir une assurance-maladie	6 [50,61,66,116,119]	-	3 [36,94]	**9**
Type d'assurance-maladie (favorable)	3 [15,102,119]	-	4 [31,40,93,102]	**7**
Coûts des soins de santé (faible)	5 [57,64,66,116,120]	-	2 [57,83]	**7**
C) FACTEURS LIÉS À LA MALADIE				
Durée de la maladie (+ longue)	3 [43,45,105]	1 [68]	11 [86,94,95,102,103,106,108,110,112,121]	**15**
N comorbidités (↑)	6 [24,52,59,61,87,104]	5 [23,64,66]	4 [83,102]	**15**
Présence de comorbidité(s)	7 [42,53,61,64,73,77,105]	3 [32,106,112]	3 [37,47,88]	**13**

N= Nombre

Tableau 3 (suite): Facteurs déterminants associés à l'adhésion thérapeutique chez les patients diabétiques

Facteur déterminant (valeur de référence)	Association significative positive sur l'adhésion	Association significative négative sur l'adhésion	Association non significative sur l'adhésion	Total
D) FACTEURS LIÉS AU TRAITEMENT				
N médicaments/doses de médicaments par jour (élevé)	3 [39,59,62,95]	9 [31,32,39,63,73,86,103,106,120]	11 [31,77,94,102,104,105,112,114,122]	**23**
Type de traitement antidiabétique	4 [41,71]	6 [85,107,108,120]	10 [27,36,40,43,62,83,103,106,112,121]	**20**
Présence d'insuline	1 [61]	3 [21,37,68]	8 [43,88,102,103,106,114,121]	**12**
Perception des effets indésirables liés au traitement (↑)	-	5 [19,99,113,120,122]	1 [105]	**6**
Délivrance des médicaments (voie postale)	5 [26,32,50,51,75]	-	-	**5**
E) FACTEURS LIÉS AU PATIENT				
Statut dépressif	1 [47]	7 [32,49,55,93-95,99]	3 [40,87,88]	**11**
Auto-efficacité ou empowerment	5 [90,98,99,102]	-	-	**5**
Connaissance de la maladie (élevée)	4 [103,106,120]	1 [68]	-	**5**
IMC (↑)	-	1 [86]	4 [43,85,95,112]	**5**

N= Nombre, IMC = Indice de Masse Corporelle

L'interprétation de ces résultats doit rester très prudente au vu de l'hétérogénéité des études en termes de population, type d'étude, mesure de l'adhésion, nombre de variables testées dans le modèle, etc. Néanmoins, l'objectif était d'avoir un aperçu des facteurs déterminants étudiés dans la littérature, ainsi que la tendance des résultats quant à leur association avec l'adhésion thérapeutique chez les patients diabétiques de type 2.

Les facteurs sociaux et économiques sont les plus étudiés dans la littérature. Les facteurs du sexe, du niveau d'éducation – lié au revenu –, de l'emploi et du lieu d'habitation semblent avoir un effet non significatif sur l'adhésion thérapeutique ; tandis qu'une augmentation de l'âge serait associée de façon non significative (n=21/52 études) ou de façon positive (n=28/52 études) à l'adhésion. L'ethnie semble jouer un rôle dans l'adhésion, ce qui corrobore l'état des connaissances pour d'autres pathologies. Les caucasiens semblaient avoir une meilleure adhésion par rapport aux Africains ou Afro-américains et aux Hispaniques.

Parmi les facteurs liés au système de santé et à l'équipe soignante, les résultats tendent à supporter le lien entre la prise en charge des dépenses de santé et l'adhésion thérapeutique. Premièrement, toutes les études évaluant les coûts des médicaments (n=12) montrent une association positive avec l'adhésion thérapeutique : un coût moindre de médicaments a un impact positif sur l'adhésion ; ainsi que des coûts moindres de soins de santé pour 5/7 études. Parmi celles-ci, une étude, menée au Japon sur 66 patients, mesurait l'adhésion avant et après une augmentation de la franchise de 20 à 30%. Les résultats étaient néanmoins influencés par la présence de complications : une baisse significative de l'adhésion était constaté uniquement chez les patients sans complication [57]. Les résultats concernant le lien entre assurance-maladie (adhésion et type de contrat) et adhésion thérapeutique sont toutefois moins clairs. Enfin, les résultats des 12 études évaluant l'impact de la fréquence des contacts avec les professionnels de santé ne permettent pas de conclure.

Concernant les facteurs liés à la maladie, l'adhésion thérapeutique ne semble pas liée à la durée de la maladie chez les patients diabétiques : 11/15 études montrent une association non significative. Les résultats pour les comorbidités (présence, nombre) sont contradictoires, et ne permettent pas de conclure. Ceci est probablement dû à un effet différent en fonction du type de comorbidité présentée et du nombre. Deux études concluent un impact négatif sur l'adhésion à partir de 3 comorbidités [119] chez une population de non-vétérans , ou à partir de 5 comorbidités [15] pour une population suisse de patients diabétiques de type 2. Enfin, une étude évaluait l'influence de 12 comorbidités sur l'adhésion thérapeutique [49]. Parmi celles-ci, 8 comorbidités (trouble de l'acidité gastrique, anxiété, épilepsie, fibrose kystique, glaucome, hyperlipidémie, maladie vasculaire périphérique ou coronarienne, syndrome de l'intestin irritable) avaient un impact négatif sur l'adhésion et 4 n'étaient pas significativement associées à celle-ci. De plus, dans une autre étude, 4/5 complications (amputations/ulcères, infarctus du myocarde, neuropathie et événements rénaux) étaient associés à une baisse de l'adhésion chez une population américaine suivie sur une durée de 2 ans pour l'apparition de complications [75].

Concernant les facteurs liés au traitement, le nombre de médicaments/doses par jour ne semble pas être associé de façon significatif à l'adhésion thérapeutique (n=11/23) ou influencer négativement celle-ci (n=8/21). Pour les types de traitement antidiabétique, la prise de metformine semble diminuer l'adhésion (n=5/6). Ce résultat pourrait être lié à ses effets indésirables gastro-intestinaux relativement fréquents [123]. Cependant les études ne permettent pourtant pas de conclure si l'association est liée à la substance elle-

même ou au fait de son large usage, notamment en première ligne de traitement. La présence d'insuline en plus d'un traitement antidiabétique par voie orale avait un impact négatif sur l'adhésion aux ADO pour 3 études [21,37,68]. Il semble également qu'une perception plus importante d'effets indésirables serait associée à une diminution de l'adhésion thérapeutique.

Les facteurs liés au patient sont moins étudiés dans la littérature. En prenant en compte le nombre limité d'études, les facteurs liés au patient (p.ex. auto-efficacité[1], empowerment, degré de connaissances de la maladie, absence d'un statut dépressif) sont des facteurs associées positivement à l'adhésion thérapeutique des patients diabétiques (n=5 études). Ces résultats soulignent l'importance d'un accompagnement sur le long terme des patients par les professionnels de la santé.

CONCLUSION

En conclusion, beaucoup d'études ont été identifiées par l'approche structurée appliquée. De manière générale, elles confirment le caractère dynamique et complexe de l'adhésion thérapeutique. La comparaison des études est rendue difficile par leur hétérogénéité (population, contexte, type d'études, mesure de l'adhésion, définition ou non d'un seuil d'adhésion jugée comme adéquate, durée de suivi) et le risque de biais. L'étude menée en Suisse, en accord avec la littérature internationale, démontre que l'adhésion thérapeutique n'est pas satisfaisante pour une grande partie des patients diabétique de type 2. Les résultats concernant les nombreux déterminants de l'adhésion thérapeutique sont également hétérogènes. Ils permettront néanmoins d'enrichir la discussion concernant les résultats en cours de récolte dans le cadre du programme SISCare-DT2. Aucune étude ne mesurait l'adhésion thérapeutique par piluliers électroniques sur un suivi de plus de 2 mois. Ce type d'outil de mesure, considéré comme cher dans de nombreux pays, permet néanmoins une mesure longitudinale plus fine de l'adhésion thérapeutique. Là aussi les mesures collectées par le programme SISCare-DT2 devraient permettre l'acquisition de nouvelles connaissances bienvenues.

Les facteurs associés de façon assez claire à l'adhésion thérapeutique – comme la perception des effets indésirables et leur gestion, l'auto-efficacité, les connaissances de la maladie et le statut dépressif, représentent des éléments à considérer attentivement dans les interventions menées au cours du programme SISCare-DT2. Le pharmacien devrait notamment favoriser la discussion avec le patient au sujet de l'existence ou non d'effets indésirables, des connaissances sur la pathologie et du niveau de compétences du patient vis-à-vis de la prise en charge de sa maladie. Le pharmacien devrait également favoriser la coordination des soins en cas de signes de dépression.

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[1] les croyances des individus quant à leurs capacités à réaliser des performances particulières (Source : Rondier, M.
A. Bandura. « Auto-efficacité. Le sentiment d'efficacité personnelle » 2009)

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ANNEXES

Annexe 1 : Questionnaire original de Morisky à 8 questions - MMAS (version anglaise)

Morisky 8-Item Medication Adherence Questionnaire

Question	Patient Answer (Yes/No)	Score Y=1; N=0
Do you sometimes forget to take your medicine?		
People sometimes miss taking their medicines for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your medicine?		
Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?		
When you travel or leave home, do you sometimes forget to bring along your medicine?		
Did you take all your medicines yesterday?		
When you feel like your symptoms are under control, do you sometimes stop taking your medicine?		
Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?		
How often do you have difficulty remembering to take all your medicine? __ A. Never/rarely __ B. Once in a while __ C. Sometimes __ D. Usually __ E. All the time		A = 0; B-E = 1
	Total score	

Scores: >2 = low adherence
1 or 2 = medium adherence
0 = high adherence

Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care.* 1986;24:67-74.

Annexe 2 : Questionnaire original du Medication Adherence Report Scale à 10 questions (version anglaise)

MARS questionnaire

	Question	Answer
1	Do you ever forget to take your medication?	Yes / No
2	Are you careless at times about taking your medication?	Yes / No
3	When you feel better, do you sometimes stop taking your medication?	Yes / No
4	Sometimes if you feel worse when you take the medication, do you stop taking it?	Yes / No
5	I take my medication only when I am sick	Yes / No
6	It is unnatural for my mind and body to be controlled by medication	Yes / No
7	My thoughts are clearer on medication	Yes / No
8	By staying on medication, I can prevent getting sick.	Yes / No
9	I feel weird, like a 'zombie' on medication	Yes / No
10	Medication makes me feel tired and sluggish	Yes / No

Annexe 3 : Algorithmes appliqués à la recherche de littérature effectuée

Pubmed

("Diabetes Mellitus, Type 2"[Mesh] OR (Diabetes[tiab] AND (type II[tiab] OR type 2[tiab] OR "non insulin dependent"[tiab]))) AND ("Medication Adherence"[Mesh] OR ((Medication*[tiab] OR Patient[tiab] OR Therap*[tiab] OR treatment*[tiab]) AND (adherence[tiab] OR compliance[tiab]))) AND ("Health Care Costs"[Mesh] OR "Models, Economic"[Mesh] OR "Outcome Assessment (Health Care)"[Mesh] OR ((impact*[tiab] OR aspect*[tiab] OR model*[tiab] OR cost[tiab] OR costs[tiab] OR assessment*[tiab]) AND (clinical[tiab] OR econom*[tiab] OR outcome*[tiab] OR medication*[tiab] OR medical[tiab] OR treatment*[tiab])) OR "impact study"[tiab]) AND (("2004/01/01"[Date - Publication] : "3000"[Date - Publication]) AND ("french"[Language] OR "english"[Language]) AND ("meta analysis"[Publication Type] OR "review"[Publication Type] OR "systematic"[Filter]))

Embase

(('non insulin dependent diabetes mellitus'/exp OR ('non insulin dependent diabetes mellitus' OR (diabetes AND (type NEAR/1 2))):ab,ti) AND ('medication compliance'/exp OR ((medication OR patient OR therapy OR treatment) NEAR/5 (adherence OR compliance)):ab,ti) AND ('economic aspect'/exp OR 'treatment outcome'/exp OR ((impact* OR aspect* OR model* OR cost OR costs OR assessment*) NEAR/5 (clinical OR econom* OR outcome* OR medication* OR medical OR treatment*)):ab,ti OR 'impact study':ab,ti)) AND (([systematic review]/lim OR [meta analysis]/lim OR [review]/lim) AND ([english]/lim OR [109]/lim) AND [2004-2017]/py)

Annexe 4 : Prévalence de l'adhésion thérapeutique dans les études utilisant le MPR

Références	Durée de suivi	MPR moyen	% de patients adhérents (MPR≥0.80)
Florez et al. 2010 (USA, n=360, ADO, naïfs)	6 mois	0.89(0.34)	-
Lafata et al. 2009 (USA, n=5 070, ADO)	6 mois	0.83(0.25)	-
Lawrence et al. 2006 (USA, n=1 668, ADO)	9 mois	0.73[1]	
Briesacher et al. 2008 (USA, n=105 225, ADO, naïfs)	12 mois	-	65.4%
Cheng et al. 2015 (Taiwan, n=129 792, ADO, insuline possible)	12 mois	-	58.8% [1]
Colombi et al. 2008 (USA, n=2 052, ADO, insuline possible)	12 mois	-	74%
Haupt et al. 2009 (Suède, n=221 566, ADO)	12 mois	1.07 ± 0.30*	89.8%
Hepke et al. 2004 (USA, n=57 687, ADO et/ou insuline)	12 mois	-	45.6%
Hertz et al. 2005 (USA, n=6 090, naïf ADO et/ou insuline)	12 mois	-	53.8%
Hunt et al. 2009 (USA, n=4 585, ADO)	12 mois	0.82(0.30)	69%
Kocarmik et al. 2012 (USA, n=280 603, ADO)	12 mois	-	70.7%
Kogut et al. 2004 (USA, n=1 067, ADO)	12 mois	-	77%
Kreyenbuhl et al. 2010 (USA, n=22 014, ADO, insuline possible)*	12 mois	-	45%
Lau et al. 2004 (USA, n=900, ADO)	12 mois	-	71.2%
Sokol et al. 2005 (USA, n=3 260, ADO et/ou insuline)	12 mois	-	55.2%
Van Dijk et al. 2007 (Pays-Bas, n=2 428, ADO)	12 mois	-	93.1%
Voorham et al. 2011 (Pays-Bas, n=2 945, ADO)	12 mois	-	80.5%
White et al. 2004 (USA, n=67 029, ADO)	12 mois	0.78(0.26)	68% (MPR > 0.75)
Cohen et al. 2010 (USA, n=526, ADO)	12 mois	-	33.3% (MPR ≥ 0.65)
Shenolikar et al. 2008 (USA, n=3 137, ADO, naïfs)	12 mois	0.56	-
Shenolikar et al. 2006 (USA, n= 1073, ADO, naïfs)	12 mois	0.59(0.32)	-
Karve et al. 2008 (USA, n=4 943, ADO)	12 mois	0.76(0.28)	-
O'Shea et al. 2013 (Irlande, n=21 280, ADO, naïfs)	12 mois	0.67	-
Gentil et al. 2015 (Canada, n=301, ADO)	12 mois	-	74.40%
Hansen et al 2010 (USA, n=108 592, ADO)	24 mois	-	58.8%
Hong et al. 2014 (Corée, n=23 034, ADO, naïfs)	24 mois	0.78[1]	59.5%[1]
Hong and Kang 2011 (Corée, n=40 082, ADO, naïfs)	24 mois	-	29.40%
Jha et al. 2012 (USA, n=135 639, ADO)	24 mois	-	60%
Yu et al. 2010 (USA, n=4 708, ADO)	26 mois	0.48(0.39)	-
Balkrishnan et al. 2007 (USA, n=1 705, ADO, naïfs)	30 mois	0.49[1]	-
Balkrishnan et al. 2004 (USA, n=3 483, ADO, naïfs)	36 mois	0.58[1]	-
Egede et al. 2012 (USA, n=740 195, ADO et/ou insuline)	60 mois	0.78	57.7%
Cheng et al. 2013 (Taiwan, n=11 580, ADO, naïfs)	84 mois	-	-
Wong et al. 2011 (Chine, n=26 782, ADO)	n/s	-	89.6%

*exclusion pour le calcul de la moyenne car MPR non tronquée à 1.00.
[1] estimation pour la cohorte entière à partir des résultats stratifiés en groupes
n/s = non spécifié

Annexe 5 : Prévalence de l'adhésion thérapeutique dans les études utilisant le PDC

Références	Durée de suivi	PDC moyen	% de patients adhérents (PDC≥0.80)
Yang et al. 2009 (USA, n=1 101 533, ADO)	9 mois	-	64.9%
Bryson et al.2013 (USA, n=444 418, ADO)	12 mois	-	70.6%
Zhang et al. 2011 (USA, n=22 546, ADO)	12 mois	-	41.6%
Gu et al. 2010 (USA, n=12 881, ADO et/ou insuline)	12 mois	0.76	82%[1]
Huber et al. 2016 (Suisse, n=26 713, ADO)	12 mois	0.68(0.27)	42.4%
Karve et al. 2008 (USA, n=4 943, ADO)	12 mois	0.75(0.27)	-
Sharma et al. 2012 (USA,n= 407 555, ADO et/ou insuline)	12 mois	0.73(0.27)	
Hagen et al. 2014 (USA, n=4 978, ADO)	12 mois	0.73	57%
Ho et al. 2006 (USA, n=11 532, ADO)	12 mois	-	79.7%
Lo-Ciganic et al. 2015 (USA, n=33 130, ADO)	12 mois	0.65	38%
Gibson et al. 2010 (USA, n=55 356, ADO)	18 mois	-	72.7%
Zhu et al. 2015 (USA, n=24 067, ADO)	24 mois	-	9.4%
Stuart et al. 2015 (USA, n=894, ADO	24 mois	0.74	58.2%

[1] estimation pour la cohorte entière à partir des résultats stratifiés en groupes

Annexe 6 : Prévalence de l'adhésion thérapeutique dans les études utilisant le CMG

Références	Durée de suivi	CMG moyen[1]	% patients adhérents (CMG≤0.20)
Karve et al. 2008 (USA, n=4 943, ADO)	12 mois	0.25(0.27)	-
Katon et al. 2009 (USA, n=1 155, ADO, + insuline possible)	12 mois	-	75.3% (CMG<0.20)
Ratanawongsa et al. 2013 (USA, n=7 303, ADO, + insuline possible)	20 mois	-	75%
Pladevall et al. 2004 (USA, n=308, ADO)	36 mois	0.22(0.19)	57%

[1] le CMG se lit à l'inverse des autres mesures : 0 indique une meilleure adhésion

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Revue de littérature (partie II) : association entre adhésion thérapeutique et outcomes cliniques, utilisation/coûts des services de soins, et état de santé/qualité de vie chez les patients diabétiques de type 2

SISCare-DT2

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INTRODUCTION

La première partie de la revue de littérature traitait des méthodes de mesure, de la prévalence et des déterminants de l'adhésion thérapeutique chez les patients diabétiques de type 2. Cette deuxième partie traite de l'association entre l'adhésion thérapeutique et les outcomes cliniques, l'utilisation et les coûts des services de soins et l'état de santé/la qualité de vie.

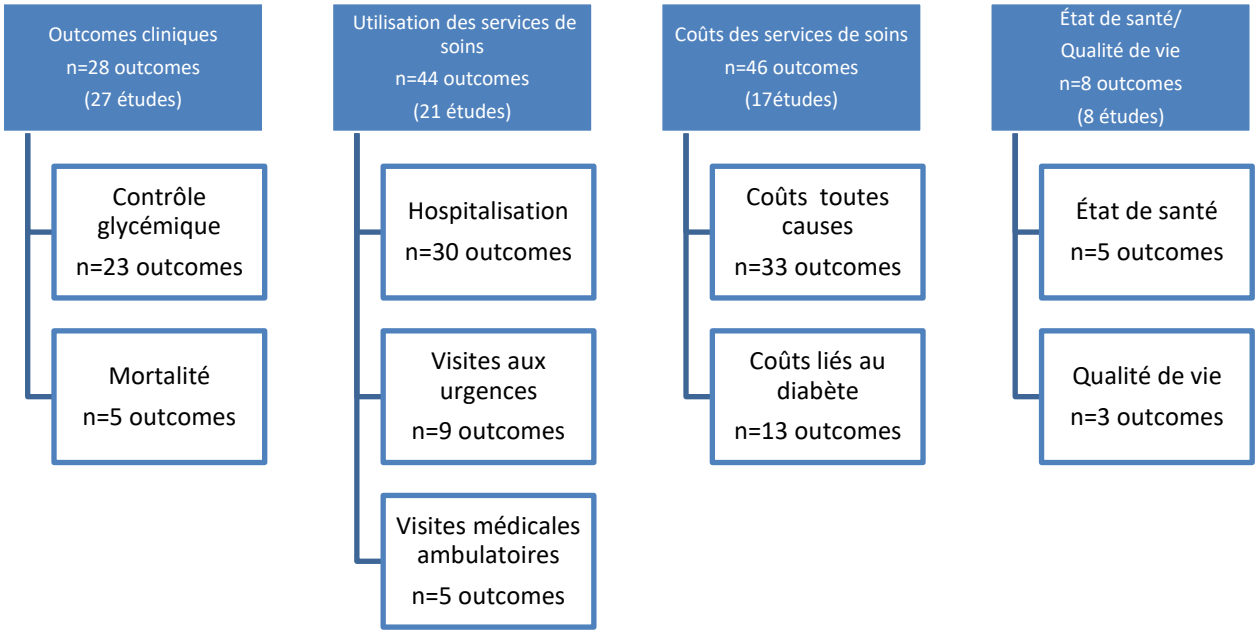
METHODOLOGIE

La méthode de sélection des articles suit celle de la partie I de la revue de littérature (cf. partie I, Méthodologie de la revue de littérature).

RESULTATS

Parmi les 106 études sélectionnées selon le processus de la Figure 4 : Flow chart de sélections des études, adapté de Prisma (cf. Partie I de la revue de littérature), 56 observaient l'association entre adhésion thérapeutique et outcomes cliniques et/ou utilisation des services de soins et/ou coûts des services de soins et/ou de l'état de santé/qualité de vie. La Figure 1 présente la répartition des études en fonction de l'outcome étudié.

Figure 1: Type et nombre d'outcomes étudiés dans l'association avec l'adhésion thérapeutique (n=56 études, plusieurs outcomes par étude sont possibles)



1. Association entre adhésion thérapeutique et outcomes cliniques

Parmi les 27 études qui ont étudié l'association entre l'adhésion thérapeutique et les outcomes cliniques, 23 considéraient le contrôle glycémique comme outcome (hémoglobine glyquée - HbA1c- ou glycémie) et cinq la mortalité.

a) Contrôle glycémique

Parmi les 23 études, 21 caractérisaient le contrôle glycémique via l'HbA1c et deux via la glycémie à jeun.

Contrairement à la glycémie à jeun, qui est une mesure instantanée, le taux d'HbA1c permet de rendre compte de la glycémie moyenne sur une longue période (environ deux à trois mois) [1]. Le diagnostic du diabète peut être confirmé quand le taux d'HbA1c ou la glycémie à jeun dépasse la valeur de 6.5% ou 126mg/dl respectivement [1]. L'objectif cible de l'HbA1c chez un patient diabétique peut varier dans une plage de valeurs de 6 à 8%, dépendant de différents facteurs liés au patient [2]. Certains facteurs, autres que la glycémie et la durée de vie des globules rouges, peuvent influencer le taux d'HbA1c tels qu'une anémie hémolytique, ou un saignement chronique ou aigu.

Les analyses statistiques pour évaluer l'association entre l'adhésion et le contrôle glycémique différaient d'une étude à l'autre :

- comparaison de la moyenne de l'HbA1c/glycémie entre le groupe de patients considérés comme « adhérents » versus « non-adhérents », définis par un seuil d'adhésion (cf. Partie I) ;
- comparaison de la proportion de patients considérés comme « adhérents » selon un seuil d'HbA1c /glycémie défini (e.g. HbA1c>7% ou ≤7%) ;
- test d'association entre l'adhésion et le taux HbA1c/glycémie via des modèles de régression.

Les résultats de ces études ont été classés en trois catégories : association (statistiquement) significative, association (statistiquement) non significative, résultats contradictoires. Quand l'association est significative : une meilleure adhésion peut être associée soit à une diminution, soit à une augmentation du taux d'HbA1c. Les résultats sont classés comme contradictoires lorsqu'une étude présente des résultats différents selon le sexe des patients [3], la méthode de mesure de l'adhésion [4,5] ou le moment de mesure du taux de l'HbA1c (à baseline ou après la période de suivi de l'adhésion) [6].

i. Hémoglobine glyquée

Parmi les résultats des études s'intéressant à l'HbA1c (n=23 résultats pour 21 études, cf. Tableau 1), la majorité (n=15/23 [65%] résultats, 14 études) suggérait qu'une meilleure adhésion était significativement associée à une diminution de l'HbA1c. Cinq résultats (n=5/23 [23%] résultats, 4 études) étaient contradictoires.

Tableau 1: Résultat de l'association entre une augmentation de l'adhésion et une variation du taux d'HbA1c en fonction des méthodes de mesure de l'adhésion et de la durée de suivi (n=23 résultats pour 21 études)

	Durée de suivi				
Source de données	**<6 mois** (n=3)	**6-9 mois** (n=1)	**12 mois** (n=6)	**>12 mois** (n=2)	**Total (n=12)**
Données de renouvellement / remboursement (n=10)	n=1 Contradictoire : 1 [6]	n=1 ↓ HbA1c: 1 [7]	n=6 ↓ HbA1c: 4 [8-11] Association NS :1 [12] Contradictoire : 1 [4]	n=2 ↓ HbA1c: 1 [13] Association NS : 1 [14]	n=10 : ↓ HbA1c: 6 Association NS :2 Contradictoire : 2
Comptage (n=1)	n=1 ↓ HbA1c:1 [15]	-	-	-	n=1 ↓ HbA1c:1
Piluliers électroniques (n=1)	n=1 Contradictoire : 1 [5]	-	-	-	n=1 Contradictoire : 1
Auto-évaluations (n=11)	n=11 ↓ HbA1c 8 [15-22] Association NS : 1 [23] Contradictoire : 2 [3,4]				

Légende : ↓ HbA1c = une augmentation de l'adhésion est associée significativement à une diminution de l'HbA1c ; NS=Non significative

1. *Méthode de mesure de l'adhésion au moyen des données de renouvellement ou de remboursement (n=10 résultats pour 10 études)*

En distinguant les études par méthode d'évaluation de l'adhésion (cf. Partie I) : 6/10 (60%) des études utilisant des données de renouvellement ou de remboursement (cf. Annexe 1) concluaient que l'adhésion était associée à un meilleur contrôle glycémique (c'est-à-dire à une diminution de l'HbA1c), contre deux études démontrant une association non significative et deux des résultats contradictoires.

Focalisons-nous sur les études avec un suivi ≥ 12 mois. Cinq études trouvaient qu'une augmentation de l'adhésion était significativement associée à une diminution de l'HbA1C, parmi un groupe de patients naïfs initiant un ADO. Sur 12 mois, une augmentation de 10% de l'adhésion était associée à une diminution de 0.1% de l'HbA1c ($p<0.001$) pour Rozenfeld et al 2008 (n=249 patients) [10] et une augmentation de 25% de l'adhésion était associée à une diminution de 0.06% de l'HbA1c (p non spécifié) pour Adams et al. 2008 (n=1'806 patients) [8]. Penning-van Beest et al. 2008 (n=2'012 patients) [9] montrait un risque accru de 18% de non-atteinte de la valeur cible (HbA1c<7%) pour les patients « non persistants » par rapport aux patients « persistants » (persistance évaluée sur 248 jours en moyenne). Enfin, sur une durée de 36 mois [13] : une augmentation de 10% du score du CMG (= adhésion moins bonne) était associée à une augmentation de 0.14% de l'HbA1c (n=308 patients).

2. *Méthode de mesure de l'adhésion par comptage (n=1 résultat pour 1 étude)*

Une étude (n=248 patients) [15] mesurait l'adhésion par comptage (et par questionnaire auto-évalué) (cf. Annexe 2). La moyenne de l'HbA1c était significativement plus faible dans le groupe de patients « adhérents » versus « non-adhérents » (7.2% *vs* 7.9%, $p<0.05$). Cependant, l'indicateur de mesure de l'adhésion, ainsi que le seuil de classification utilisé n'étaient pas précisés.

3. Méthode de mesure de l'adhésion par piluliers électroniques (n=1 résultat pour 1 étude)

Une étude (n=60 patients) [5] suivait l'adhésion des patients via des piluliers électroniques sur une durée de deux mois (cf. Annexe 2). Deux types d'indicateurs de mesure de l'adhésion étaient étudiés: (1) le pourcentage de jours durant lesquels la dose était prise comme prescrite, et (2) le pourcentage de doses prises comme prescrites. Les résultats étaient contradictoires selon l'indicateur de mesure utilisé : si la dose prescrite, prise sur 96.4% des jours, était inversement corrélée avec les taux d'HbA1c, le pourcentage de doses prises comme prescrites n'était pas corrélé de manière significative avec l'HbA1c.

4. Méthode de mesure de l'adhésion par auto-évaluation (n=11 résultats pour 11 études)

Parmi les études qui évaluaient l'adhésion par auto-évaluation (cf. Annexe 3), 8/11 (72%) concluaient qu'une meilleure adhésion était significativement associée à des taux d'HbA1c plus faibles. Une étude montrait une association non significative et deux études présentaient des résultats contradictoires.

Parmi les études montrant une association significative entre augmentation de l'adhésion et diminution de l'HbA1c (n=8), trois études utilisaient le questionnaire validé de Morisky à quatre ou huit questions (cf. Partie I, MMAS-4, MMAS-8) et rapportaient les résultats suivants:

- une augmentation de 1 point (=adhésion moins bonne) sur l'échelle de score de l'adhésion de 4 points (MMAS-4) était associée à une augmentation de 0.16% de la valeur l'HbA1c mesurée six mois plus tard (n=287 patients) [16] ;
- un score ≥3 sur 4 (=bonne adhésion) était associé à un taux d'HbA1c inférieur de 10% comparé aux patients avec un score inférieur à 3 (n=301 patients) [19] ;
- des scores plus élevés d'adhésion étaient significativement corrélés avec des taux d'HbA1c plus faibles : le score médian MMAS-8 était significativement plus élevé dans le groupe de patients avec une HbA1c≤6.5% par rapport au groupe de patients avec une HbA1c>6.5% (8.0 *vs* 5.7, p<0.001) (n=505 patients) [17].

Les cinq autres études utilisaient d'autres questionnaires validés [18,20] ou des questionnaires non validés [15,21,22]. Parmi celles-ci, trois démontraient un taux d'HbA1c plus faible dans le groupe de patients « adhérents » comparé au groupe de patients « non-adhérents » (n=248 [15]; n=976 [20] et n=766 [21] patients). Dans une autre étude menée par Alvarez et al. 2008 [18] (n=1'709 patients), la proportion de patients considérés comme « adhérents » était supérieure dans le groupe avec une HbA1c<6.5% par rapport à celle dans le groupe avec une HbA1c≥6.5%. Enfin, Tiv et al. 2012 [22] (n=3'637 patients) rapportait qu'une faible adhésion était associée à un taux d'HbA1c>8%.

ii. Glycémie à jeun

Deux études étudiaient l'association entre l'adhésion (mesurée par auto-évaluation) et la glycémie à jeun (cf. Annexe 4). L'étude utilisant un questionnaire évaluant les comportements de non-adhésion involontaire (n=114 patients) rapportait une différence non significative de la moyenne de la glycémie entre le groupe de patients « adhérents » (score=0/4) versus « non-adhérents » (score≥1/4) [24]. La deuxième étude (n=120 patients) comparait la proportion de patients « adhérents » (score=4/4) et « non-adhérents » (score≤3/4) en fonction de l'atteinte de l'objectif cible de glycémie (entre 70 et 130 mg/dL) ou non (<70 ou >130 mg/dL). Parmi les patients qui avaient atteint l'objectif cible de glycémie, 91.7% était « adhérents » *vs* 8.1% « non-adhérents » (p=0.025) [25].

b) Mortalité

Les cinq études qui évaluaient l'association entre l'adhésion et la mortalité avaient les mêms conclusion : une meilleure adhésion était associée à un risque diminué de mortalité. L'étude menée en Suisse sur 12 mois de suivi, à l'aide de données de remboursement (n=26'713 patients) rapportait une réduction de 10% du risque de mortalité toutes causes parmi les patients « adhérents » (PDC≥80%) par rapport aux patients « non adhérents » (PDC<80%) (RR=0.90, IC_{95} 0.82-0.99, p<0.05) [26]. Une autre étude menée aux États-Unis [27] sur une population d'anciens combattants (n=629'563 patients) âgés en moyenne de 65±11 ans, mesurait l'adhésion par MPR. Plus de 22% de la cohorte était décédée durant la période de suivi de 5 ans, avec une proportion huit fois plus élevée chez les patients du quintile inférieur de MPR (0-49.3%) que chez les patients du quintile le plus élevé (94.2-100.0%).

c) Discussion/Conclusion

En conclusion, la majorité (n=16/23, 70%) des études rapportait une association significative entre une meilleure adhésion thérapeutique et un meilleur contrôle glycémique (HbA1c/glycémie). Une augmentation de 10% et de 25% de l'adhésion était associée à une diminution de l'HbA1c de 0.1% (n=2 études) [10,13] et de 0.06% respectivement (n=1 étude) [8]. Une association entre l'augmentation de l'adhésion et la diminution de l'HbA1c est observée plus fréquemment dans les études qui évaluaient l'adhésion via des mesures subjectives (c'est-à-dire via des questionnaires auto-évalués) (8/11,73%) *versus* des mesures objectives (7/12, 58%). Les résultats des études dépendent des méthodes utilisées pour mesurer l'adhésion. De plus, le seuil de l'HbA1c choisi pour réaliser des analyses statistiques peut varier de 6.5 à 8% en fonction de l'étude. Il faut donc rester prudent quant à l'interprétation de ces résultats. Cependant, ces études tendent à montrer qu'une meilleure adhésion est associée à un meilleur contrôle glycémique.

Les études analysant l'association entre l'adhésion thérapeutique et la mortalité (n=2) avaient les mêmes conclusions : une meilleure adhésion semble être liée à un taux de mortalité plus faible.

2. Association entre adhésion thérapeutique et utilisation des services de soins

Parmi les 21 études (44 résultats) évaluant l'association entre l'adhésion et l'utilisation des services de soins, 20 (95%) mesuraient l'adhésion au moyen des données de renouvellement d'ordonnances ou de remboursement et une étude (5%) utilisait un questionnaire d'auto-évaluation (MMAS-4) [28]. Les caractéristiques des études sont détaillées en annexes (cf. Annexe 5, Annexe 6, Annexe 7, Annexe 8).

Les outcomes étudiés étaient variables: association entre adhésion et hospitalisation (n=30 résultat, 21 études) [11,26,28-46], visites aux urgences (n=9 résultats, 8 études) [29,32,33,37,40,41,44,46] et visites médicales ambulatoires (n=5 résultats,5 études) [29,30,32,40,43].

a) Hospitalisation

Les résultats sont présentés en deux parties : ceux en lien avec les hospitalisations toutes causes et ceux en lien avec les hospitalisations uniquement liées au diabète (et à des causes cardiovasculaires pour une étude [36]). Si une étude ne spécifiait pas la cause d'hospitalisation, celle-ci était classée dans les résultats « hospitalisation toutes causes ».

Comme pour le chapitre sur le contrôle glycémique, les résultats étaient classés ensuite en trois catégories en fonction de la significativité de l'association entre adhésion et hospitalisation : association

significative, non significative ou résultats contradictoires. Quand l'association est significative : une meilleure adhésion peut être associée à une diminution de l'hospitalisation ou dans le cas contraire : une meilleure adhésion peut être associée à une augmentation de l'hospitalisation.

De plus, nous avons distingués 4 outcomes d'hospitalisation : le fait d'avoir eu un antécédant d'hospitalisation (avant la période de suivi de l'adhésion), la probabilité d'hospitalisation, la durée d'hospitalisation et le nombre d'hospitalisation (pendant ou après la période de suivi de l'adhésion [32]).

Le Tableau 2 présente les résultats de l'association entre adhésion et hospitalisation en fonction de la cause d'hospitalisation (toutes causes ou liée au diabète) et de la significativité de l'association (significative : ↑ ou ↓ outcome ; non significative ou contradictoire).

Tableau 2: Nombre d'études évaluant l'association entre une augmentation de l'adhésion et l'hospitalisation en fonction de la cause d'hospitalisation (n=30 résultats pour 21 études)

Causes d'hospitalisations	Association	Types d'hospitalisation			
		Antécédent d'hospitalisation	Probabilité d'hospitalisation	Durée d'hospitalisation	Nombre d'hospitalisation
Toutes causes (n=23)	↑ outcome (n=0)	-	-	-	-
	↓ outcome (n=15)	1[26]	9[11,26,30,37,38,43-46]	2[40,46]	3[29,30,40]
	Non significative (n=3)	1[35]	-	1[28]	1[32]
	Contradictoire (n=5)	-	3[31,34,39]	1[39]	1[33]
Liées au diabète (n=7)	↑ outcome (n=0)	-	-	-	-
	↓ outcome (n=5)	-	4[36,38,42,43]	-	1 [41]
	Non significative (n=0)	-	-	-	-
	Contradictoire (n=2)	-	1[34]	-	1[33]

i. Hospitalisation toutes causes

1. Statistiques descriptives

Sur 6 mois, la proabilité d'hospitalisation dans une cohorte de patients diabétiques de type 2 (n=302 patients) était égal à 4% (n=1 étude) [28]. Ce pourcentage se situait entre 8% et 37% pour une durée de suivi de 12 mois (n=7 études) [26,31,33-35,37,39] et entre 55 et 64% pour une durée de 30 mois (n=2 études) [29,30]. Pour une étude menée sur 12 mois [40], le nombre moyen d'hospitalisation était de 1.13 ± 3.86 pour une durée moyenne de 1.06 ± 4.68 jours.

2. Association entre adhésion et hospitalisation toutes causes (n=23 résultats)

2.1. Résultats des études avec association significative : ↓ hospitalisation (n=15 résultats)

Parmi les résultats des études regardant l'association entre adhésion et hospitalisation toutes causes (cf. Annexe 5), 12 concluaient à une association significative entre une augmentation de l'adhésion et une diminution de l'outcome d'hospitalisation pour tous les types d'hospitalisations.

2.1.1. Antécédent d'hospitalisation (n=1 résultat)

L'étude suisse (n=26'713 patients) menée sur 12 mois démontrait que les patients « non-adhérents » (PDC<80%) étaient plus hospitalisés pendant l'année qui précèdait le suivi de l'adhésion comparés aux patients « adhérents » (PDC≥80%) : 10.9% *vs* 7.7% (p≤0.01) [26].

2.1.2. Probabilité d'hospitalisation (n=9 résultats)

Des neuf études, quatre menées sur un suivi de 12 mois rapportaient les résultats suivants :

- une augmentation du MPR de 10% était associée à une diminution relative de la probabilité d'hospitalisation de 6.8% (n=4'710 patients) [30] à 6.9% (n=3'137 patients) [37] ;
- une probabilité d'hospitalisation de 55% pour un 1≤MPR≤19% *vs* 30% pour un 80≤MPR≤100% (n=3'260 patients) [38] ;
- une réduction relative de la probabilité d'hospitalisation de 7% chez les patients « adhérents » (PDC≥80%) *vs* « non-adhérents » (PDC<80%), (n=26'713 patients, Suisse) [26].

2.1.3.Durée d'hospitalisation (n=2 résultats)

Pour une étude menée sur 12 mois (n=67'029 patients) [40], la durée d'hospitalisation était plus élevée pour les patients avec un MPR≤75% par rapport aux autres (75%≤MPR≤95% et MPR>95%, p<0.001) chez des patients souffrant de diabète de type 2 uniquement et pour une cohorte de patients souffrant de diabète et de pathologies cardiovasculaires.

2.1.4.Nombre d'hospitalisations (n=3 résultats)

- Une augmentation de 10% du MPR était associée à une diminution relative de 8% et de 6.6% du nombre d'hospitalisation pour une durée de suivi de 12 mois (n=4'710 patients) [30] et de 30 mois (n=1'705 patients) [29] respectivement.
- Sur 12 mois, les patients avec un MPR>95% avaient un nombre moyen d'hospitalisations plus faible par rapport aux autres patients (75%<MPR≤95% et MPR≤75%, p<0.001) pour une cohorte de patients diabétiques de type 2 avec ou sans maladies cardiovasculaires (n=67'029 patients) [40].

2.2. Résultats des études avec association non significative (n=3 résultats)

Pour deux études menées sur 12 (n=22'014 patients) [35] et 18 (n=55'356 patients) [32] mois et une étude transversale (n=302 patients) [28], les résultats de l'association entre adhésion et hospitalisation étaient non significatifs.

2.3. Résultat des études avec association contradictoire (n=4 résultats)

Pour quatre études, les résultats étaient contradictoires : ils différaient selon l'âge des patients (n=2'052 patients, 12 mois de suivi) [31], la méthode de mesure de l'adhésion (n=4'943 patients, 12 mois de suivi) [34], la méthode de classification des patients comme « adhérents » / « non-adhérents » (n=57'687 patients, 12 mois de suivi) [33] ou le type d'ADO : anciens *vs* nouveaux principes actifs (n=7'441 patients, 84 mois de suivi) [39].

ii. Hospitalisation liée au diabète

1. Statistiques descriptives

Le pourcentage d'hospitalisation (liée au diabète ou à des maladies cardiovasculaires), dans deux populations de patients diabétiques de type 2, était de 6% (n=4'943)[34] et 7% (n=900)[36] sur une durée de 12 mois.

2. Association entre adhésion et hospitalisation liée au diabète (n=7 résultats)

2.1. Résultats des études avec association significative (n=4 résultats)

Parmi les sept études qui analysaient l'association entre adhésion et hospitalisation liée au diabète (cf. Annexe 6), quatre menées sur 12 mois rapportaient une baisse de la probabilité d'hospitalisation chez les patients « adhérents ».

- Pour une étude (n=900 patients) [36], les patients « non-adhérents » (MPR<80%) étaient 2.5 fois plus susceptibles d'être hospitalisés (en lien avec le diabète ou des causes cardiovasculaires) par rapport aux patients « adhérents » (MPR≥80%, p≤0.01).
- Pour un autre étude (n=3'260 patients) [38] rapportait une probabilité d'hospitalisation plus faible pour les patients « adhérents » (MPR≥80%) *vs* « non-adhérents » (MPR<80%, p<0.05). La probabilité d'hospitalisation, augmentait au fur et à mesure que l'adhésion diminuait et, cette probabilité était la plus élevée et égale à 30% pour le groupe de patients avec un MPR le plus faible (1%≤MPR≤19%) *vs* 13% pour le groupe « adhérents » (MPR≥80%).

2.2. Résultats des études avec association contradictoire (n=2 résultats)

Les deux autres études menées sur 12 mois rapportaient des résultats contradictoires selon la méthode de mesure de l'adhésion (n=4'943 patients) [34] ou la classification de patients considérés comme « adhérents » / « non-adhérents » (n=57'687 patients) [33].

b) Visites aux urgences

1. Statistiques descriptives

Le pourcentage de patients ayant eu au moins une visite aux urgences sur 12 mois durant la période de suivi de l'adhésion était de 17% [33] et de 40% [37] selon les études. White et al. 2004 et Gibson et al. 2010 rapportaient un nombre de visites aux urgences de 0.34±0.98 (sur 12 mois) [40] et de 0.64±1.71 (sur 24 mois) [32] respectivement.

2. Association entre adhésion et visites aux urgences (n=9 résultats)

2.1. Résultats des études avec association significative (n=8 résultats)

Parmi les neuf résultats (8 études) ayant évalué les visites aux urgences comme outcome (cf. Annexe 7), huit démontraient une association significative entre des niveaux d'adhésion plus élevés et une diminution des visites aux urgences toutes causes (n=7) ou liées au diabète ou problèmes cardio- ou cérébraux-vasculaires (n=1).

- Deux études concluaient que chaque augmentation du MPR de 10% était associée à une diminution relative des visites aux urgences de 5.1% (n=3'137 patients) sur 12 mois[37] et de 3.6% (n=1'705 patients) [29] sur 30 mois.
- Deux autres études démontraient que les patients « adhérents » (MPR ou PDC≥80%) avaient une diminution relative des visites aux urgences de 12% (n=57'687 patients) [33] à 20% (n=55'356 patients) [32] par rapport aux patients « non-adhérents » (MPR ou PDC<80%) sur 12 et 18 mois respectivement.
- Pour une autre étude menée sur 12 mois, le nombre de visites aux urgences était plus faible pour les patients « adhérents »(MPR>95%) par rapport aux patients « non-adhérents » (75%<MPR≤95% et MPR≤75%, p<0.001) (n=67'029 patients) [40].

2.2. Résultat de l'étude avec association contradictoire (n=1 résultat)

Une seule étude menée sur 12 mois évaluait le nombre de visites aux urgences uniquement liées au diabète : les résultats étaient contradictoires selon la méthode de classification des patients considérés comme « adhérents » / « non-adhérents » (n=57'687 patients) [33].

c) Visites médicales ambulatoires

1. Statistiques descriptives

Le nombre moyen de visites médicales ambulatoires était évalué entre 5 et 6 (en fonction de l'absence ou de la présence de trouble schizophrénique respectivement) sur 12 mois (n=22'014 patients) [35] et à 12±9.25 sur 2 ans (n=55'356 patients) [32].

2. *Association entre adhésion et visites médicales ambulatoires (n=5 résultats)*

2.1. *Résultats des études avec association significative (n=3 résultats)*

Parmi les cinq études évaluant les visites médicales ambulatoires toutes causes (cf. Annexe 8) , trois concluaient qu'une meilleure adhésion était associée à un nombre de visites médicales ambulatoires plus élevé.

- Une étude (n=22'014 patients), a démontré qu'un nombre plus élevé de visites médicales ou psychiatriques ambulatoires au cours de l'année précédant le suivi de l'adhésion (12 mois) était associé à une probabilité moins élevée de non-adhésion (OR=0.996, p<0.0001) [35].
- L'autre étude (n=55'356 patients), menée sur 18 mois démontrait que les patients ayant une adhésion élevée (PDC≥80%) avaient une augmentation relative du nombre de visites chez le médecin de 67% par rapport aux patients « non-adhérents » (PDC<80%) [32].

2.2. *Résultat de l'étude avec association non significative (n=1 résultat)*

Une étude menée sur 30 mois montrait une association non significative (n=1'705 patients) [29].

2.3. *Résultat de l'étude avec association contradictoire (n=1 résultat)*

Une étude menée sur 12 mois présentait des résultats contradictoires selon si les patients diabétiques de type 2 avaient ou non des maladies cardiovasculaires (n=67'029 patients) [40].

d) Discussion/Conclusion

Pour l'ensemble des outcomes de l'utilisation des services de soins (hospitalisations, visites aux urgences et visites médicales ambulatoires), plus de la moitié des résultats (n=28/44 [64%] résultats) des 21 études démontraient qu'une meilleure adhésion était associée à une diminution de l'utilisation des services de soins (n=20/30 [67%] résultats pour l'hospitalisation ; n=8/9 [89%] résultats pour les visites aux urgences et n=0/5 [0%] résultats pour les visites médicales ambulatoires). Trois études concernant les visites médicales ambulatoires démontraient une tendance inverse, mais une interprétation différente peut toutefois être faite : un suivi médical ambulatoire plus fréquent semble améliorer l'adhésion thérapeutique des patients diabétiques (n=3/5 [60%] résultats). Cinq études présentaient des résultats contradictoires (n=9/30 [30%] résultats) au sein desquelles une meilleure adhésion était toutefois associée à une diminution de l'utilisation des services de soins pour une sous-population étudiée : les patients âgés de plus de 65 ans [31], les patients sous anciens ADO : metformine et sulfonylurées [39], les patients diabétiques de type 2 atteints de maladies cardiovasculaires [40], ceux avec MPR≥1%[33], et selon certaines méthodes de mesure de l'adhésion utilisées [34].

En conclusion, ces études tendent à démontrer qu'une meilleure adhésion est associée à une diminution de l'utilisation des services de soins en ce qui concernent l'hospitalisation (toutes causes ou liée au diabète) et les visites aux urgences. Un nombre plus élevé de visites médicales ambulatoires semblent être associé à une meilleure adhésion, ce qui pourrait être expliqué par le rôle important des professionnels de santé dans le conseil aux patients sur l'importance du traitement médicamenteux.

3. Association entre adhésion thérapeutique et coûts des services de soins

Les études qui évaluaient l'association entre l'adhésion et les coûts des services de soins au moyen de données de renouvellement d'ordonnances ou de remboursement se déroulaient principalement aux Etats-Unis (n=13/17 études pour 40/47 résultats).

Généralement, les coûts évalués étaient ceux couverts par les assurances maladies, sans prise en compte des coûts financés directement par les patients (p.ex. quotes-parts ou franchises).

Nous avons distingué les études en fonction des outcomes de coût évalués : les coûts des médicaments, les coûts médicaux et les coûts totaux. Les coûts des médicaments comprenaient les coûts de toutes les ordonnances ambulatoires délivrées par des pharmacies d'officine. Les coûts médicaux comprenaient les coûts des consultations médicales (généralistes et spécialistes), services ambulatoires d'urgence, hospitalisation et soins dans les maisons de repos ; les services de soins à domicile n'étaient généralement pas inclus. Les coûts totaux représentent la somme des coûts médicaux et des coûts des médicaments.

Comme pour le chapitre sur l'utilisation des services de soins, les résultats sont présentés en en fonction du type de coût : les coûts toutes causes et les coûts uniquement liés au diabète. Les coûts toutes causes étaient les coûts des médicaments, médicaux ou totaux associés à n'importe quel problème de santé. Les coûts liés au diabète étaient les coûts associés uniquement au traitement de cette maladie. Si une étude ne spécifiait pas le type de coûts, celle-ci était classée dans la partie « coûts toutes causes ».

Comme pour les deux chapitres précédents, les résultats étaient classés en trois catégories en fonction de la significativité de l'association entre adhésion et les coûts : significative, non significative ou résultats contradictoires. Quand l'association est significative : une meilleure adhésion peut être associée à une diminution des coûts ou dans le cas contraire : une meilleure adhésion peut être associée à une augmentation des coûts.

Le Tableau 3 présente les résultats de l'association entre adhésion et coûts en fonction du type de coûts (toutes causes ou liés au diabète) et de la significativité de l'association (significative : ↑ ou ↓ des coûts ; non significative ou contradictoire).

Tableau 3: Résultats de l'association entre une augmentation de l'adhésion et les coûts en fonction du type de coût et de l'outcome chez les patients diabétiques de type 2 (n=47 résultats pour 17 études)

Type de coûts	Association	Outcome des coûts		
		Coûts des médicaments	Coûts médicaux	Coûts totaux
Toutes causes (n=34)	↓ coûts (n=18)	-	9 [29,33,38,40,47-49] (uniquement coûts hospitaliers [46,50])	9 [38,40,43,46,47,50-53]
	↑ coûts (n=11)	7 [29,33,38,40,47,48,50]	1 (uniquement coûts ambulatoires[50])	3 [29,33,41]
	Non significative (n=5)	-	1[34]	4 [30,37,48,49]
	Contradictoire (n=0)	-	-	-
Liés au diabète (n=13)	↓ coûts (n=4)	-	2 [38,41]	2[38,52]
	↑ coûts (n=6)	5 [33,38,41,46,48]	-	1[33]
	Non significative (n=0)	-	-	-
	Contradictoire (n=3)	-	2[33,34]	1[51]

a) Coûts toutes causes

i. Coûts des médicaments

1. Statistiques descriptives

Pour trois études [38,40,50], les coûts annuels des médicaments totaux variaient de 970$ à 2'510$. Une autre étude, menée par Balkrishnan et al. 2007, rapportait un coût de médicaments totaux entre 29'029$ et 29'171$ en fonction de l'ADO sur une durée de 30 mois [29].

2. Association entre adhésion et coûts des médicaments (n=7 résultats)

Tous les résultats (n=7) des sept études concluaient une association significative entre une augmentation de l'adhésion et une augmentation des coûts des médicaments totaux.

- Trois études menées sur 12 mois (n=3'260 [38], n=57'687[33] et n=67'029[40] patients) rapportaient que lorsque le niveau d'adhésion augmentait les coûts des médicaments totaux augmentaient.
- Pour une étude menée sur 30 mois (n=1'705 patients), une augmentation du MPR de 10% était associée à une augmentation relative des coûts des médicaments totaux de 12.7% [29].
- Pour une autre étude menée sur 30 mois (n=740'195 patients), le groupe de patients « non-adhérents » (MPR<80%) avait des coûts des médicaments totaux plus faibles de 37% par rapport au groupe de patients « adhérents » (MPR≥80%) [50].

ii. Coûts médicaux

1. Statistiques descriptives

Pour trois études [34,38,40], les coûts médicaux annuels variaient de 4'090$ (pour des patients diabétiques de type 2 sans maladies cardiovasculaires) à 29'108$ (pour des patients diabétiques de type 2 avec maladies cardiovasculaires). Balkrishnan et al. 2007 rapportait un coût maximal de 15'000$ et de 16'063$ en fonction de l'ADO sur une durée de 30 mois [29]. Pour une étude ayant distingué les coûts médicaux hospitaliers et ambulatoires, ceux-ci variaient (en fonction du taux d'adhésion) de 9'581$ à 15'337$ et de 3'220$ à 3'835$ respectivement [50].

2. *Association entre adhésion et coûts médicaux (n=11 résultats)*

2.1. *Résultats des études avec association significative : ↓ coûts (n=9 résultats)*

Parmi les onze résultats des onze études regardant l'association entre adhésion et coûts médicaux toutes causes (cf. Annexe 9), neuf concluaient à une association significative entre une augmentation de l'adhésion et une diminution des coûts.

- Sur une période de suivi de 12 mois, trois études (n=3'260[38], n=57'687 [33] et n=67'029 patients[40]) rapportaient que les coûts médicaux diminuaient avec des niveaux plus élevés d'adhésion. Pour une d'entre elles [33], la diminution des coûts en fonction de l'adhésion concernait des valeurs de MPR≥40%, car les coûts augmentaient lentement jusqu'à un MPR de 20 à 39% (effet seuil).
- Sur une période de suivi de 30 mois, une augmentation du MPR de 10% était associée à une diminution relative des coûts de 2.1% (n=1'705 patients) [29].
- Sur une durée de suivi de 30 mois, l'étude sur les coûts hospitaliers (n=740'195 patients) observait des coûts plus élevés de 41% dans le groupe de patients « non-adhérents » (MPR<80%) par rapport au groupe de patients « adhérents » (MPR≥80%) [50].

2.2. *Résultat de l'étude avec association significative : ↑ coûts (n=1 résultat)*

Pour l'étude qui étudiait les coûts ambulatoires (coûts médicaux et visites aux urgences, hors hospitalisation) sur 30 mois (n=740'195 patients), le groupe de patients « non-adhérents » (MPR<80%) avait des coûts plus faibles de 7% par rapport au groupe de patients « adhérents » (MPR≥80%) [50].

2.3. *Résultat de l'étude avec association non significative (n=1 résultat)*

Pour une étude menée sur 12 mois, l'association entre adhésion (mesurée grâce aux données et de remboursements d'ordonnance) et coûts était non significative (n=4'943 patients) [34].

iii. Coûts totaux

1. *Statistiques descriptives*

Pour sept études [30,37,38,40,51-53], les coûts totaux toutes causes sur 12 mois se situaient entre 5'215$ et 30'816$ pour une population de patients diabétiques de type 2. Balkrishnan et al. 2007 rapportait un coût maximal de 45'233$ sur une durée de 30 mois [29].

2. *Association entre adhésion et coûts totaux (n=16 résultats)*

2.1. *Résultats des études avec association significative : ↓ coûts (n=9 résultats)*

Parmi les 16 résultats des 16 études regardant l'association entre adhésion et coûts totaux (cf. Annexe 9), neuf concluaient à une association significative entre une augmentation de l'adhésion et une diminution des coûts totaux toutes causes.

- Sur une période de suivi de 12 mois (n=1'073 patients), une réduction relative des coûts de 2% était associée à une augmentation du MPR de 10% (p<0.001) chez des patients naïfs [52].
- Pour deux autres études menées sur 12 mois (n=3'260 [38] et n=67'029 patients [40]), les coûts totaux diminuaient avec des niveaux plus élevés d'adhésion. Parmi ces deux études, une présentait des coûts nettement plus importants pour des patients diabétiques de type 2 souffrant de maladies cardiovasculaires comparés à des patients diabétiques sans maladies

cardiovasculaires, quelle que soit la valeur du MPR (p.ex. coût annuel avec et sans maladies cardiovasculaires pour un MPR>95% : 29'815$ *vs* 5'706$) [40].

- Sur une période de suivi de 24 mois, une réduction annuelle de 846$ des coûts totaux était observée chez les patients « adhérents » (MPR≥80%) *vs* « non-adhérents » (MPR<80%) (n=108'592 patients) [51].
- Sur une durée de suivi de 30 mois, le passage d'un MPR<80% à un MPR≥80% entrainait des économies potentielles de 994 millions de dollars par année, chez une population d'anciens combattants (n=740'195 patients) [50].
- Sur une période de suivi de 36 mois (n=3'483 patients), les patients qui commençaient une thiazolidinedione avaient une meilleure adhésion (MPR plus élevé de 13%) comparés aux patients qui commençaient un autre ADO (sulfonylurée ou metformine) et les patients sous thizaolidinedione avaient 16.1% moins de coûts annuels que les patients sous un autre ADO (p<0.01) [53].

2.2. Résultats des études avec association significative : ↑ coûts (n=3 résultats)

Pour trois études, il y avait une association significative entre une augmentation de l'adhésion et une augmentation des coûts totaux toutes causes.

- Sur une période de suivi de 12 mois (n=57'687 patients), les patients avec un MPR>40% présentaient des coûts plus élevés que les patients avec un MPR≤40% [33].
- Sur une durée de 30 mois (n=1'705 patients), une augmentation du MPR de 10% était associée à une augmentation relative des coûts de 2.6% [29].

2.3. Résultats des études avec association non significative (n=4 résultats)

Les quatre études, dont deux étaient menées sur 12 mois sur des patients naïfs (n=3'137 [37] et n=4'710 patients [30]), montraient que les résultats de l'association entre adhésion et coûts totaux toutes causes étaient non significatifs.

b) Coûts liés au diabète

i. Coûts des médicaments

1. Statistiques descriptives

Pour une étude [38], le coût annuel des médicaments liés au diabète variait de 55$ à 763$ par patient en fonction du taux d'adhésion.

2. Association entre adhésion et coûts des médicaments liés au diabète (n=5 résultats)

Les résultats (n=5) des cinq études (n=3'260 [38] et n=57'687[33] patients) regardant l'association entre adhésion et coûts des médicaments liés au diabète (sur 12 mois) rapportaient une association significative : lorsque le niveau d'adhésion augmentait, les coûts des médicaments liés au diabète augmentaient.

ii. Coûts médicaux

1. Statistiques descriptives

Pour deux études [34,38], les coûts médicaux annuels étaient de 667$[34] à 8'812$[38].

2. Association entre adhésion et coûts médicaux liés au diabète (n=4 résultats)

2.1. Résultats de l'étude avec association significative : ↓ coûts (n=2 résultats)

Sokol et al. 2005 démontrait que sur une durée de suivi de 12 mois (n=3'260 patients)[38], les coûts médicaux liés au diabète diminuaient avec des niveaux plus élevés d'adhésion (p<0.0001).

2.2. Résultats de l'étude avec association contradictoire (n=2 résultats)

Deux études menées sur 12 mois présentaient des résultats contradictoires : une en fonction de la méthode de mesure (n=4'943 patients) [34] et une autre étude (n=57'687 patients) [33] constatait que les coûts médicaux liés au diabète augmentaient lentement jusqu'à une valeur du MPR de 20 à 39%, à partir duquel il y avait une diminution constante des coûts (effet seuil).

iii. Coûts totaux

1. Statistiques descriptives

Pour trois études [38,51,52], les coûts annuels totaux liés au diabète variaient de 1'440$ à 8'867$.

2. Association entre adhésion et coûts totaux liés au diabète (n=4 résultats)

2.1. Résultats des études avec association significative : ↓ coûts (n=2 résultats)

Parmi les quatre résultats des quatre études regardant l'association entre adhésion et coûts totaux liés au diabète (cf. Annexe 10), deux concluaient à une association significative entre une augmentation de l'adhésion et une diminution des coûts totaux liés au diabète.

- Une augmentation du MPR de 10% était associée à une diminution relative des coûts totaux liés au diabète de 4% durant la deuxième année de suivi après l'initiation de l'ADO chez des patients naïfs (n=1'073 patients) [52].
- Une autre étude menée sur 12 mois (n=3'260 patients) rapportait que les coûts totaux liés au diabète diminuaient avec des niveaux plus élevés d'adhésion malgré l'augmentation des coûts des médicaments liés au diabète (coûts 80%≤MPR≥100% *vs* 1%≤MPR≥19% : 4'570$ *vs* 8'867$) [38]

2.2. Résultat de l'étude avec association significative : ↑ coûts (n=1 résultat)

Hepke et al.2004 met en évidence qu'un taux d'adhésion élevé (mesurée par MPR) était associé à des coûts totaux liés au diabète plus élevés pour une durée de suivi sur 12 mois (n=57'687 patients) [33].

2.3. Résultat de l'étude avec association contradictoire (n=1 résultat)

Pour une étude menée sur 24 mois (n=108'592 patients) [51], les patients « adhérents » (MPR≥80%) avaient des coûts totaux liés au diabète inférieurs aux patients « non-adhérents » (MPR<80%) pour la population sous sulfonylurées et pioglitazones (p<0.05) mais pas pour les patients sous metformine.

c) Discussion/Conclusion

Concernant les coûts des médicaments (toutes causes et liés au diabète) : toutes les études démontraient qu'une augmentation de l'adhésion était associée à une augmentation des coûts des médicaments ce qui est attendu (n=7/7 [100%] pour les coûts toutes causes et n=5/5, 100% pour les coûts liés au diabète).

Concernant les coûts médicaux (toutes causes et liés au diabète) : plus de la moitié (n=11/15, 73%) démontraient qu'une meilleure adhésion était associée à une diminution des coûts médicaux (n=9/11 [82%] pour les coûts toutes causes et n=2/4 [50%] pour les coûts liés au diabète), un résultat (n=1/15,

7%) démontrait qu'une meilleure adhésion était associée à une augmentation des coûts médicaux (n=1/11 [9%] pour les coûts ambulatoires toutes causes). Ce résultat peut être mis en lien avec celui du chapitre précédent et le rôle des professionnels de santé dans la prise en charge de l'adhésion thérapeutique des patients : le suivi rapproché du médecin (plus grand nombre de visites médicales) était associé à une meilleure adhésion, ce qui est évidemment associée à un coût médical plus élevé.

Concernant les coûts totaux (toutes causes et liés au diabète) : plus de la moitié des résultats (n=11/20, 55%) démontraient qu'une meilleure adhésion était associée à une diminution des coûts totaux (n=9/16 [56%] pour les coûts toutes causes et n=2/4 [50%] pour les coûts liés au diabète), et quatre résultats (n=4/20, 20%) démontraient qu'une meilleure adhésion était associée à une augmentation des coûts totaux (n=3/16 [19%] pour les coûts toutes causes et n=1/4 [25%] pour les coûts liés au diabète).

En conclusion, ces études tendent à démontrer qu'une meilleure adhésion est associée à une diminution des coûts de soins de santé pour les coûts totaux et médicaux. Le surcoût mécanique lié à une meilleure adhésion pour le poste des médicaments, voire pour celui des consultations ambulatoires, serait alors compensé par une diminution des coûts pour les autres postes (urgences et hospitalisations). De plus, des coûts totaux, médicaux et des médicaments plus élevés ont été observés chez des patients diabétiques de type 2 avec maladies cardiovasculaires *vs* sans maladies cardiovasculaires[40] ; ce résultat confirme l'importance de la prise en charge de ces patients multimorbides.

4. Association entre adhésion thérapeutique et état de santé/qualité de vie

Parmi les huit résultats des huit études transversales évaluant l'association entre l'adhésion et l'état de santé/qualité de vie, 5/8 études (63%) évaluaient l'adhésion au moyen de questionnaires d'auto-évaluation (MMAS-4, MMAS-8 ou une autre méthode d'auto-évaluation), 2/8 (25%) au moyen des données de renouvellement d'ordonnances ou de remboursement (MPR) et 1/8 (13%) par comptage. Les caractéristiques des études sont détaillées en annexe (cf. Annexe 11 et Annexe 12).

Selon l'OMS, la définition d'un « bon état de santé » est « un état de complet bien-être physique, mental et social, et ne consiste pas seulement en une absence de maladie ou d'infirmité » (1948) [54]. L'état de santé d'une population ou d'un groupe de personnes malades peut s'exprimer en termes quantitatifs (espérance de vie, nombre d'années de vie gagnées ou perdues, etc.) ou qualitatifs (vécu subjectif ; état fonctionnel, état global de santé, etc.).

Le concept de qualité de vie liée à l'état de santé en médecine est né plus tard. Il n'existe pas de définition consensuelle car c'est un concept abstrait, complexe et multidimensionnel [55]. L'OMS donne la définition suivante : « C'est la perception qu'a un individu de sa place dans l'existence, dans le contexte de la culture et du système de valeurs dans lesquels il vit en relation avec ses objectifs, ses attentes, ses normes et ses inquiétudes. Il s'agit d'un large champ conceptuel, influencé de manière complexe par la santé physique du sujet, son état psychologique, son niveau d'indépendance, ses relations sociales ainsi que sa relation aux éléments essentiels de son environnement » (1994) [56].

Il existe deux types d'instruments de mesure de la qualité de vie liée à l'état de santé :

- Génériques : instruments qui peuvent être utilisés et comparés chez des patients présentant des maladies ou conditions différentes mais qui sont peu sensibles aux changements et peu spécifiques (p.ex. : Short Form Health Survey à 12 items SF-12 ou à 36 items SF-36, World Health Organization Quality of Life WHOQOL) ;

- Spécifiques : instruments spécifiquement développés pour une maladie ou une condition de santé, plus sensibles et plus spécifiques mais qui ne permettent pas de comparaison entre des patients avec des maladies ou conditions différentes (p.ex. : Audit of Diabetets Dependent Quality of Life ADDQol = mesure individualisée de l'impact du diabète sur la qualité de vie)

Selon la recherche bibliographique menée, cinq études évaluaient l'état de santé et trois études évaluaient la qualité de vie liée à l'état de santé.

Comme pour les trois chapitres précédents, les résultats ont été classés en trois catégories en fonction de la significativité de l'association entre l'augmentation de l'adhésion thérapeutique et l'état de santé/qualité de vie liée à l'état de santé : association significative (↑ ou ↓ de l'outcome), non significative ou résultats contradictoires.

Le Tableau 4 présente les résultats de l'association entre une augmentation de l'adhésion thérapeutique et l'état de santé ou la qualité de vie liée à l'état de santé en fonction de la significativité de l'association (significative : ↓ ou ↑ de l'outcome ; non significative ou contradictoire).

Tableau 4: Résultats de l'association entre une augmentation de l'adhésion thérapeutique et l'état de santé/qualité de vie liée à l'état de santé (n=8 résultats pour 8 études)

Association	Etat de santé	Qualité de vie liée à l'état de santé
↓ outcome (n=0)	-	-
↑ outcome (n=1)	1[57]	-
Non significative (n=5)	3[3,58,59]	2[21,60]
Contradictoire (n=2)	1[28]	1[61]

a) Etat de santé

Les cinq études évaluaient l'état de santé par une question générale sur l'état de santé perçu par le patient (p.ex. « *Comment décrivez-vous votre état de santé général ? Faible, moins bon, bon, très bon, excellen*t » [3]). L'échelle de réponses variait en fonction des études (cf. Annexe 11).

1. Résultats des études avec association significative (n=1 résultat)

Parmi les cinq résultats des cinq études évaluant l'association entre adhésion thérapeutique et état de santé, une étude (n=59 patients) [57] démontrait qu'un plus mauvais état de santé (score 1/4 de l'échelle) était associé à une non-adhésion (score 0≤MMAS-8≤6).

2. Résultats des études avec association non significative (n=3 résultats)

Pour trois études, l'association entre adhésion et état de santé était non significative (n=265 [58], n=1'141 [3] et n=2'194 [59] patients).

3. Résultat de l'étude avec association contradictoire (n=1 résultat)

Pour la population entière d'une étude réalisée aux États-Unis (n=302 patients) [28], l'association entre adhésion et état de santé était non significative mais pour la sous-population latino-américaine à prédominance espagnole (patients nés à l'étranger, n=238), il y avait une association significative entre une augmentation de l'adhésion et une diminution de l'état de santé. Pour chaque augmentation de score l'état de santé auto-évalué (échelle de 1=faible à 5=excellent), la probabilité de non-adhésion (score MMAS-4≥1) augmentait d'un facteur 1.6 (OR=1.6, p=0.03).

b) Qualité de vie liée à l'état de santé

Les trois études évaluaient la qualité de vie par des instruments de mesure génériques : SF-12, SF-36 ou WHOQOL à 100 items (cf. Annexe 12).

1. Résultats des études avec association non significative (n=2 résultats)

Pour deux études, l'association entre l'adhésion et la qualité de vie liée à l'état de santé étaient non significative (n=238 [60], adhésion évaluée par comptage sur un mois ; et n= 766 [21] patients, adhésion auto-évaluée par questionnaire).

2. Résultat de l'étude avec association contradictoire (n=1 résultat)

Pour une étude (n=360 patients) [61], un score élevé de la composante mentale du SF-36 était associée significativement $p<0.05$) à une meilleure adhésion (MPR mesuré sur six mois). Cependant aucun renseignement concernant la composante physique du SF-36 n'était donné.

c) Discussion/Conclusion

Seule une étude (13%) démontrait qu'une meilleure adhésion était associée à un meilleur état de santé. Cinq études (63%) ne démontraient aucune association significative. Deux études (25%) démontraient une association contradictoire en fonction de la sous-population étudiée[28] ou de la composante (mentale) du questionnaire étudiée [61].

Le nombre limité d'études (n=8) et la diversité des méthodes d'évaluation de l'état de santé ou de la qualité de vie liée à l'état de santé (questionnaire général ou très spécifique, multidimensionnel), rend la comparaison compliquée. Ces différents paramètres ne nous permettent pas de conclure à propos d'une éventuelle association avec l'adhésion thérapeutique.

Dans le projet SISCare-DT2, les questionnaires de qualité de vie liée à l'état de santé générique SF-12 et spécifique au diabète ADDQoL sont administrés aux patients lors de l'inclusion dans l'étude (baseline), puis à six et 12 mois. Ceci nous permettra d'une part de comparer la qualité de vie liée à l'état de santé entre les patient « adhérents » et « non-adhérents » et d'autre part, d'étudier son évolution durant la période de suivi.

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ANNEXES

Annexe 1: Revue des études sur l'association entre l'adhésion thérapeutique (évaluée au moyen des données de renouvellements ou de remboursements d'ordonnances) et l'HbA1c (n=10 résultats pour 10 études)

Références	Type d'étude	Adhésion		Hba1c (%)		Adhésion en fonction de l'HbA1c	Autres résultats
		Suivi (mois)	Mesure	Population générale	Adhérents *vs* non-adhérents		
Shah et al. 2009 (USA, n=1'132, ADO et injectables, patients naïfs, DT n/s)	Cohorte	1	Initiation	-	Baseline : 8.3±1.9 vs 7.7± 1.5, p=0.004 A 12 mois : 7.0± 1.1 vs 7.3± 1.5, p=0.061 Diminution 3.5 fois plus importante (p=0.0001)	Les patients HbA1c ≥ 9.0% avaient 2.6 fois plus de chance de d'initier leur traitement que HbA1c < 9.0%	-
Lawrence et al. 2006 (USA, n=1'668, ADO, DT2)	Cohorte	9	MPR	Metformine : 7.8±2.1 Sulfonylurées : 7.9±2.0	-	Les patients HbA1c > 7.0% avaient un MPR non ajusté moins élevé que les patients HbA1c ≤ 7.0% (Metformine : 62% vs 77%, p<0.05, Sulfonylurées : 72% vs 82%, p<0.05)	Une augmentation du MPR engendrait une diminution de l'HbA1c (p<0.001)
Adams et al. 2008 (USA, n=1'806, ADO, patients naïfs, DT2)	Cohorte	12	Autre	Ethnie noire 9.8 ±2.4 vs caucasienne 8.9 ±2.1 ,p<0.001	-	Une meilleure adhésion était associée à une valeur d'HbA1c plus faible	Une augmentation de l'adhésion de 25% engendrait une diminution HbA1c 0.06%
Cohen et al. 2010 (USA, n=526, ADO, DT2)	Transversale	12	MPR (et MMAS-4)	-	Q50 8.6 (Q25 8.0 -Q75 9.6). vs Q50 8.9 (Q25 8.0 -Q75 10.7)	Les patients MPR < 42% avaient 1.7 (IC95% 1.2-2.6,p=0.008) fois plus de chance d'avoir HbA1c plus élevé que ceux avec MPR ≥ 42%	Des MPR <42% étaient associés à des HbA1c plus élevés, mais l'association était non significative lorsque l'adhésion était auto-déclarée
Kindmalm et al. 2007 (Suède, n=187, ADO, DT2)	Transversale	12	Autre	-	6.4 vs 6.3, ns	-	-
Penning-van Beest et al. 2008 (Pays-Bas, n=2'012, ADO, patients naïfs, DT2)	Cohorte	12	Persistance et non-persistance	8.9±1.8	6.9±0.9 vs 7.2±1.1, résultat de significativité non reporté	% de patients avec une HbA1c<7% Baseline : 0% (population totale) A 248 jours : 56.9% vs 46.8% A 12 mois: 67% (population totale)	Les patients non persistants avaient un risque de 18% de plus de HbA1c ≥ 7% que les patients persistants (RRajsuté=0.82, IC95% 0.74-0.91)
Rozenfeld et al. 2008 (USA, n=2'741/ pour HbA1c n=249, ADO, patients naïfs, DT2)	Cohorte	12	Autre	Baseline : 8.0±1.5%	-	-	Une augmentation de 10% de l'adhésion était associée à une diminution de l'HbA1c de 0.1% (p=0.0004)
Ho et al. 2006 (USA, n=11 532, ADO, DT2)	Cohorte	12	PDC				Chaque augmentation de 25% de l''adhésion aux ADO est associée à une diminution de l'HbA1c de -0.05% (IC95% -0.08% à -0.01%)
Trinacty et al. 2009 (USA, n=1'906, ADO, patients naïfs, DT2)	Cohorte	24	Autre	Ethnie noire 7.8 ±1.6% vs caucasienne 7.6±1.5%, p<0.05		Les patients HbA1c (7.0-9.0%) avaient un taux de discontinuation plus faible que les patients < 7.0% RRSulfonylurées 0.8 (IC95% 0.6-1.3) RRMetformine 0.4 (IC95% 0.05-3.1)	-
Pladevall et al. 2004 (USA, n=308, ADO, patients naïfs, DT2)	Transversale	36	CMG	A 3 ans : 8.0±1.4	8.0±1.2 vs 8.5±1.6, p<0.01	-	Coefficient de corrélation: Pearson = 0.25, p<0.01 Spearman = 0.21, p<0.01

							Une augmentation de 10% du CMG (adhésion moins bonne) était associée à une augmentation significative de l'HbA1c de 0.14%

ADO=Antidiabétiques Oraux ; DT n/s=Diabétiques, Type non spécifié ; DT2=Diabétiques de Type 2 ; IC95%=Intervalle de Confiance à 95% ; HR=Hazard Ratio ; MMAS-4/8=Morisky Medication Adherence Scale à 4 ou 8 items ; MPR=Medication Possesion Ratio ; n/s=non spécifié ; ns=non significatif ; OR=Odd Ratio ; RR= Risque Relatif

Annexe 2: Revue des études sur l'association entre l'adhésion thérapeutique (évaluée par les piluliers électroniques ou par comptage) et l'HbA1c (n= 2 résultats pour 2 études)

Références	Type d'étude	Adhésion		Hba1c (%)		Adhésion en fonction de l'HbA1c	Autres résultats
		Suivi (mois)	Mesure	Population générale	Adhérents *vs* non-adhérents		
White et al. 2012 (Royaume-Uni, n=60, ADO, DT2)	Cohorte	2	Piluliers électroniques	Baseline : Q_{50} 7.8 (Q_{25} 7.2- Q_{75} 8.6)	HbA1c à baseline % de jours de prises de médicaments comme prescrits : Q_{50} 7.2 (Q_{25} 6.9- Q_{75} 8.4) *vs* Q_{50} 8.2 (Q_{25} 7.7- Q_{75} 9.4) % de doses prescrites prises : Q_{50} 7.9[1] *vs* Q_{50} 7.8 (Q_{25} 6.8- Q_{75} 8.6)	-	Coefficient de corrélation de Spearman : % de jours de prises de médicaments comme prescrits : r= -0.13, ns % de doses prescrites prises : r= -0.29, p=0.02
Farsaei et al. 2011 (Iran, n=248, ADO, DT2)	Cohorte	3	Comptage (et questionnaire d'auto-évaluation)	A la fin du suivi : 7.4±1.3%	7.2±1.2[2] *vs* 7.9±1.4[2], p<0.05	% de patients avec HbA1c>7% *vs* HbA1c≤7% (p=0.001) Adhérents: 55.3% (n=121) *vs* 44.7% (n=98) Non-adhérents: 73.1% (n=98) *vs* 26.9% (=36) *Classification adhérent/non-adhérent et comptage/self-report : non spécifié*	-

[1]Valeur pondérée en fonction des groupes de patients ; [2]Valeur non pondérée ; ADO=Antidiabétiques Oraux ; DT2=Diabétiques de Type 2 ; IC95%=Intervalle de Confiance à 95% ; ns=non significatif

Annexe 3: Revue des études sur l'association entre l'adhésion thérapeutique (évaluée par questionnaire) et l'HbA1c (n=11 résultats pour 11 études)

Références	Mesure	Hba1c (%)		Adhésion en fonction de l'HbA1c	Autres résultats
		Population générale	Adhérents *vs* non-adhérents		
Aikens et al. 2013 (USA, n=287, ADO et/ou insuline, DT2)	MMAS-4	7.7±1.7	-	-	Une augmentation de 1 point sur l'échelle MMAS (=adhésion moins bonne) était associée à une augmentation de l'HbA1c de 0.16% (ou 1.8 mmol/mol) (β=1.77, P=0.025)
Krapek et al. 2004 (USA, n=301, ADO et/ou insuline, DT2)	MMAS-4	-	7.65[1] *vs* 8.79[1], *résultat de significativité non reporté*	-	Un score de Morisky ≥ 3 (bonne adhésion) était associé à un taux d'HbA1c total inférieur de 10% (β=1.105, P=0.0003)
Cohen et al. 2010 (USA, n=526, ADO, DT2)	MMAS-4 (et MPR)	Q_{50} 8.6 (Q_{25} 8.0 - Q_{75} 10.0)	Q_{50} 8.5 (Q_{25} 7.9 -Q_{75} 9.9). *vs* Q_{50} 8.8 (Q_{25} 8.1 -Q_{75} 10.2)	-	Association non significative mais significative pour le MPR :des MPR <42% étaient associés à des HbA1c plus élevés
Raum et al. 2012 (Allemagne, n=1'142, ADO et/ou insuline, DT2)	MMAS-4	-	-	*Résultats contradictoires* Le groupe non-adhérent a 1.5 (IC95% 1.24-1.93, p<0.05) fois plus de chance d'avoir une HbA1c≥7.5% par rapport au groupe non-adhérent p<0.05 Hommes : non-adhérents ont presque 2 (IC95% 1.46-2.49, p=0.01 fois plus de chance d'avoir une HbA1c≥7.5% vs adhérents Femmes : pas de différence significative	-
Al-Qazaz et al. 2011 (Malaisie, n=505, ADO, DT2)	MMAS-8	Q_{50} 7.6 (Q_{25} 6.7 - Q_{75} 8.9)	-	Score médian de MMAS-8 (p<0.001) : Avec HbA1c≤6.5%: 8.0 (Q_{25} 6.7- Q_{75} 8.0) Avec HbA1c>6.5%: 5.75 (Q_{25} 4.7- Q_{75}7.0)	Coefficient de corrélation de Spearman : r=-0.505,p<0.01
Alvarez et al. 2008 (EU, n=1'709, ADO, DT2)	Autre	7.1±1.1	-	% de patients « adhérents » (=ayant signalés qu'ils ont toujours pris leurs médicaments comme prescrits par le médecin) (p=0.0186) Avec HbA1c<6.5%: 73.3% Avec HbA1c≥6.5%: 67.4%	-
Farsaei et al. 2011 (Iran, n=248, ADO, DT2)	Autre (et comptage)	A la fin du suivi : 7.4±1.3%	7.2±1.2[2] *vs* 7.9±1.4[2], p<0.05	% de patients avec HbA1c>7% *vs* HbA1c≤7% (p=0.001) Adhérents: 55.3% (n=121) *vs* 44.7% (n=98) Non-adhérents: 73.1% (n=98) *vs* 26.9% (=36) *Classification adhérent/non-adhérent et comptage/self-report : non précisé*	-
Kreyenbuhl et al. 2011 (USA, n=74, ADO et/ou insuline, DT2)	Autre	-	7.6±1.8 *vs* 7.4±1.8, p=0.75	-	-
Ngo-Metzger et al. 2012 (USA, n=976, ADO et insuline, DT2)	Autre	-	-	Les patients non-adhérents ont un taux d'HbA1c 1.5 (1.06-2.08, p<0.05) fois plus important que les patients adhérents	-
Piette et al. 2004 (USA, n=766, ADO et/ou insuline, DT n/s)	Autre	-	7.9±1.7% *vs* 8.7±1.9%, p<0.0001	-	La non-adhésion a été associée à une augmentation absolue de 0.6% (0.2-0.9, p<0.001) des taux d'HbA1C des patients

Tiv et al. 2012 (France, n=3'637, ADO et/ou insuline, DT2)	Autre	-	-	-	Une faible adhésion (réponse négve pour au moins 3 des 6 questions) était associée à un taux d'HbA1c>8% (p=0.01)

[1]Valeur pondérée en fonction des groupes de patients ; [2]Valeur non pondérée ; ADO=Antidiabétiques Oraux ; DT n/s=Diabétiques, Type non spécifié ; DT2= Diabétiques de Type 2 ; IC95%= Intervalle de Confiance à 95% ; MMAS-4/8=Morisky Medication Adherence Scale à 4 ou 8 items ; MPR=Medication Possesion Ratio

Annexe 4: Revue des études sur l'association entre l'adhésion thérapeutique (évaluée par questionnaire) et la glycémie à jeun (n=2 résultats pour 2 études)

Références	**Méthode de mesure**	**Glycémie (mg/dL): adhérents *vs* non-adhérents**	**Autres résultats**
Adisa et al. 2011 (Nigeria, n=114, ADO et/ou insuline, DT2)	Autre	137.09±59.3 *vs* 143.92±87.6, p=0.095	-
Pascal et al.2012 (Nigeria, n=120, ADO, DT2)	Autre	-	% de patients adhérent *vs* non-adhérent (p=0.025) • Glycémie entre 70 et 130 mg/dL : 91.9% *vs* 8.1% • Glycémie <70 ou >130 mg/dL 41.3% vs 58.7%

ADO=Antidiabétiques Oraux ; DT2=Diabétiques de Type 2

Annexe 5: Revue des études sur l'association entre l'adhésion thérapeutique et les hospitalisations toutes causes (n=23 résultats pour 18 études)

Références	Durée de suivi (mois)	Méthode de mesure de l'adhésion	Statistiques descriptives	Résultats
ASSOCIATION SIGNIFICATIVE : ↓ OUTCOME D'HOSPITALISATION				
Antécédent d'hospitalisation				
Huber et al. 2016 (Suisse, n=26'713, ADO, DT2)	12	PDC	Près de 10% étaient hospitalisés 1 fois ou plus au cours de l'année précédant le suivi de l'adhésion	Hospitalisation antérieure plus fréquente si non-adhérent (PDC<80%) 10.9% vs adhérent (PDC≥80%) 7.7% (p≤0.01)
Probabilité d'hospitalisation				
Balkrishnan et al. 2006 (USA, n=4'710, ADO, DT2, patients naïfs)	12	MPR	Probabilité d'hospitalisation après initiation du traitement (durée de suivi de 30 mois) de 56 à 64% (en fonction de l'ADO)	Une augmentation du MPR de 10% était associée à une diminution relative de 6.8% de la probabilité d'hospitalisation (OR=0.32, IC95% 0.25-0.41, p significatif non spécifié)
Shenolikar et al. 2008 (USA, n=3'137, ADO, DT2, patients naïfs)	12	MPR	Près de 37% des sujets étaient hospitalisés	Une augmentation du MPR de 10% était associée à une diminution relative de 6.9% de la probabilité d'hospitalisation (OR=0.31, IC95% 0.23-0.41, p significatif non spécifié)
Sokol et al. 2005 (USA, n=3'260, AD, DT n/s)	12	MPR	-	• Les patients adhérents (MPR ≥80%) étaient significativement moins susceptibles d'être hospitalisés que les patients non adhérents (MPR<80%) (p<0.05) • Probabilité d'hospitalisation : MPR=80-100% : 30% ; MPR =60-79% : 39% ; MPR=40-59 : 42% ; MPR=20-39% : 47% ; MPR=1-19% : 55%
Huber et al. 2016 (Suisse, n=26'713, ADO, DT2)	12	PDC	Près de 10% étaient hospitalisés 1 fois ou plus au cours de l'année précédant le suivi de l'adhésion	Réduction relative de 7% de la probabilité d'hospitalisation chez les patients adhérents (PDC≥80%) par rapport aux patients non adhérents (PDC<80%) (RR=0.93, p≤0.001)
Encinosa et al. 2010 (USA, n=56 744, ADO, DT2)	12	RCR Persistance	Une augmentation de l'adhésion de 50 à 100% réduit le taux d'hospitalisation de 23.3% (réduction de 15 à 11.5%).	
Lo-Ciganic et al. 2015 (USA, n=33 130, ADO, DT2)	12	PDC	Le risque d'être hospitalisé diminue si l'adhésion augmente (différents % de réduction du risque d'hospitalisation en fonction du fait d'être adhérent selon un seuil influencé par des co-facteurs=catégorisation de la population), hospitalisation toute cause	● Si pas d'historique d'hospitalisation ou visites aux urgences, pas d'insuline ou dernière utilisation supérieur à 90j mais ≥ 7 prescriptions par mois et ≥1complication liée au diabète: 48% de moins de risque d'être hospitalisté si le PDC≥62% que si le PDC<62% (OR=0.52, IC95% 0.42-0.64): 22.4% (groupe adhérent) vs 35.9% (groupe non-adhérent) ● Si pas d'historique d'hospitalisation ou visites aux urgences, utilisation d'insuline ≥90j, et<13prescriptions/mois: 32% de moins de risque d'être hospitalisté si le PDC≥59% que si le PDC<59% (OR=0.68, IC95% 0.60-0.77): 20.7% (groupe adhérent) vs 28.6% (groupe non-adhérent) ● Si historique d'hospitalisation ou visites aux urgences, <7prescriptions/mois, pas de complication liée diabète: 22% de moins de risque d'être hospitalisté si le PDC≥94% que si le PDC<94% (OR=0.48, IC95% 0.34-0.67): 12.4% (groupe adhérent) vs 23.9% (groupe non-adhérent) ● Si historique d'hospitalisation ou visites aux urgences, <7prescriptions/mois, et ≥1complication liée au diabète: 38% de moins de risque d'être hospitalisté si le PDC≥83% que si le PDC<83% (OR=0.62, IC95% 0.50-0.76): 23.3% (groupe adhérent) vs 34.7% (groupe non-adhérent) ● Si historique d'hospitalisation ou visites aux urgences, ≥7prescriptions/mois, pas de complication liée au diabète: 31% de moins de risque d'être hospitalisté si le PDC≥46% que si le PDC<46% (OR=0.69, IC95% 0.59-0.80): 31.9% (groupe adhérent) vs 42.8% (groupe non-adhérent) ● Si historique d'hospitalisation ou visites aux urgences, ≥7 mais <13 prescriptions/mois, et ≥1complication liée au diabète: 38% de moins de risque d'être hospitalisté si le

				PDC≥83% que si le PDC<83% (OR=0.62, IC95% 0.54-0.70): 38.2% (groupe adhérent) vs 54.2% (groupe non-adhérent)
Ho et al. 2006 (USA, n=11 532, ADO, DT2)	12	PDC		Analyses multivariables : Risque d'hospitalisations toute cause plus élevé chez les non-adhérents aux ADO (OR=1.38, IC95%1.21-1.58,)
Jha et al. 2012 (USA, n=135 639, ADO, DT2	24	MPR	Une augmentation de l'adhésion est associée à presque 13% de risques en moins d'être hospitalisé ou d'avoir des urgences médicales.	Une augmentation de 10% du MPR est associée à une réduction de 1.2% des survenues d'hospitalisations et d'urgences médicales (p=0.05) (quand variable catégorielle) Les patients qui sont restés adhérents avaient le plus bas taux d'hospitalisations ou d'urgences médicales (27.8%), alors que ceux qui sont restés non-adhérents avaient 3% de risques absolus en plus (30.6%), p<0.001 Une diminution de 10% du MPR est associée à une augmentation de 4% du risque d'hospitalisation et/ou d'urgence médicale (p<0.001) (quand variable continue)
Hong et Kang 2011 (Corée du Sud, n=40 082, ADO, DT2, patients naïfs)	24	MPR		Patients non-adhérents pendant les 2 premières années avaient plus de risques d'hospitalisations toutes causes durant la 3ème année (OR=1.21, IC95%1.13-1.31)
Durée d'hospitalisation				
White et al. 2004 (USA, n=67'029, ADO, DT2)	12	MPR	Durée moyenne de l'hospitalisation (en jours): 1.06±4.68	Durée moyenne d'hospitalisation (en jours) en fonction du taux de MPR>95%, >75 et ≤95%, ≤75% • Cohorte DT : 0.23±1.46, 0.38±2.25, 0.47±3.01(p<0.001) • Cohorte DT et CV : 2.17±5.76, 3.51±7.90, 4.55±10.64 (p<0.001)
Encinosa et al. 2010 (USA, n=56 744, ADO, DT2)	12	Refill	Une augmentation de l'adhésion de 50 à 100% réduit le nombre de jours d'hospitalisation de7.4 à 5.6 jours (diminution de 24%)	
Nombre d'hospitalisation				
Balkrishnan et al. 2006 (USA, n=4'710, ADO, DT2, patients naïfs)	12	MPR	Probabilité d'hospitalisation après initiation du traitement (durée de suivi de 30 mois) : 56 à 64% (en fonction de l'ADO)	Une augmentation du MPR de 10% était associée à une diminution du nombre d'hospitalisation de 8.0% (β=-1.60 → 0.79 pour 100% MPR, p<0.01)
White et al. 2004 (USA, n=67'029, ADO, DT2)	12	MPR	Nombre moyen d'hospitalisation : 1.13±3.86	Nombre moyen d'hospitalisation en fonction du taux de MPR>95%, >75 et ≤95%, ≤75% • Cohorte DT : 0.36±1.68, 0.43±1.84, 0.53±2.47 (p<0.001) • Cohorte DT et CV : 2.31±4.62, 3.39±6.06, 4.45±8.52 (p<0.001)
Balkrishnan et al. 2007 (USA, n=1'705, ADO, DT2, patients naïfs)	30	MPR	Probabilité d'hospitalisation après initiation du traitement (durée de suivi de 30 mois) de 55 à 57% (en fonction de l'ADO)	Une augmentation de 10% du taux d'adhésion était associée à une diminution relative de 6.6% du nombre moyen d'hospitalisation (p<0.05)
ASSOCIATION NON SIGNIFICATIVE				
Antécédent d'hospitalisation				
Kreyenbuhl et al. 2010 (USA, n=22'014, ADO, DT2)	12	MPR	% de patients hospitalisés lors de l'année précédant le suivi (avec *vs* sans trouble schizophrénique) : • Médicale, liée au DT : 12 *vs* 8% • Médicale, non liée au DT : 18 *vs* 10% • Psychiatrique : 18 *vs* 0.7%	Pas d'influence des hospitalisations de l'année précédant le suivi de l'adhésion sur la non-adhésion ($OR_{MPR<80\% \ vs \ 80\text{-}120\%}$ =1.01, p=0.867)
Durée d'hospitalisation				
Parada et al. 2012 (n=302, ADO et insuline, DT2)	n/a	MMAS-4!	• Médiane (et range) du nombre de nuits hospitalisés durant les 6 derniers mois : 0(30) • 4% (n=12) ont été hospitalisés au moins une nuit durant les 6 derniers mois	Pas d'influence du nombre de nuits d'hospitalisation des 6 derniers mois sur la non-adhésion ($OR_{adhésion \ vs \ non\text{-}adhésion}$=1.14, IC95% 0.88-1.48, p=0.32)
Nombre d'hospitalisation				

Gibson et al. 2010 (USA, n=55'356, ADO, DT2)	18	PDC	Moyenne du nombre d'hospitalisation durant les 2 ans après le suivi de l'adhésion : 0.26±0.70	Taux d'hospitalisation des 2 années suivant le suivi de l'adhésion était non différent pour les patients adhérents *vs* non-adhérents (IRR $_{PDC\geq80\%\ vs\ PDC<80\%}$=0.946, IC95% 0.733-1.221, p=0.972)
ASSOCIATION CONTRADICTOIRE				
Probabilité d'hospitalisation				
Colombi et al. 2008 (USA, n=2'052, ADO, DT2)	12	MPR	% de patients avec au moins une hospitalisation variait (en fonction de la quote-part) : • <65 ans : de 10 à 17% • ≥ 65 ans : de 23 à 38%	• ≥65 ans : Diminution significative du risque relatif d'hospitalisation de 29% chez les patients avec un MPR≥80% *vs* MPR<80%, OR=0.71, IC95% 0.51-0.98, p=0.0375) • <65 ans : NS (OR=0.75, IC95% 0.51-1.10,p=0.1435)
Karve et al. 2008 (USA, n=4'943, ADO, DT2)	12	MPR PDC CMG Autres méthodes[1]	% de patients avec: • une hospitalisation : 19% • plus d'une hospitalisation : 8% • au moins une hospitalisation (total) : 27%	MPR, PDC, MPRm≥80% étaient associés à une diminution relative de la probabilité d'hospitalisation de respectivement 38.8, 38.2 et 35.3% (pour OR voir article, p≤0.004) mais non significatif pour les mesures d'adhésion suivantes RCR, CR, CSA. Une adhésion médiocre (CMG et CMOS<20%) étaient associés à un risque accru d'hospitalisation de 63.5% et de 61.9% (p≤0.001).
Stuart et al. 2009 (USA, n=7'441, ADO, DT1/2)	84	Autre méthode[1]	% de patients hospitalisés par année • Anciens ADO (Met et Sul) : 27.4% • Nouveaux ADO (Tzd, Meg, Iag) : 30.8%	Chaque remplissage additionnel d'anciens ADO (=Met et Sul) et de nouveaux ADO (= Tzd, Meg, Iag) modifiait le risque d'hospitalisation respectivement de -0.3% (p<0.05) et de 0.1% (NS)
Durée d'hospitalisation				
Stuart et al. 2009 (USA, n=7'441, ADO, DT1/2)	84	Autre méthode[1]	% de patients hospitalisés par année • Anciens ADO (Met et Sul) : 27.4% • Nouveaux ADO (Tzd, Meg, Iag) : 30.8%	Chaque remplissage additionnel d'anciens ADO (=Met et Sul) et de nouveaux ADO (= Tzd, Meg, Iag) modifiait les jours d'hospitalisation respectivement de -0.04 jours (p<0.001) et de 0.02 jours (NS)
Nombre d'hospitalisation				
Hepke et al. 2004 (USA, n= 57'687, ADO et insuline, DT n/s)	12	MPR	14% de la population a eu au moins une hospitalisation	• Les patients avec un MPR de 1% à 19% et de 20 à 39% étaient respectivement 1.26 et 1.23 fois plus susceptibles d'avoir une hospitalisation par rapport à un MPR=0%. • Pour un MPR≥1%, une augmentation de l'adhésion était associée à une diminution du nombre d'hospitalisations.

[1]Autre(s) méthode(s) de mesure de l'adhésion à partir des données de renouvellement/de remboursements d'ordonnances ; ADO=Antidiabétiques Oraux ; CMG=Continuous Measure of Medication Gaps ; CMOS=Continuous Multiple interval measure of Oversupply ; CV =maladies cardiovasculaires ; CR=Compliance Ratio ; CSA=Continuous Single interval measure of medication Acquisistion ; DT n/s=Diabétiques, Type non spécifié ; DT2=Diabétiques de Type 2 ; IC95%=Intervalle de Confiance à 95% ; IRR=Incidence Rate Ratio ; Meg=Meglinides ; Met=Metformine ; MMAS-4/8=Morisky Medication Adherence Scale à 4 ou 8 items ; MPR=Medication Possesion Ratio ; MPRm=MPR, modified; NS=non signficatif ; OR=Odd Ratio ; PDC=Percentage of Days Covered ; RCR=Refill compliance rate ; Sul=Sulfonylurées ; Tzd=Thiazolidinediones ; Iag=Inhibiteurs de l'alpha-glucosidase

Annexe 6: Revue des études sur l'association entre l'adhésion thérapeutique et les hospitalisations liées au diabète (n=7 résultats pour 7 études)

Références	Durée de suivi (mois)	Méthode de mesure de l'adhésion	Statistiques descriptives	Résultats
ASSOCIATION SIGNIFICATIVE : ↓ OUTCOME D'HOSPITALISATION				
Probabilité d'hospitalisation				
Lau et al. 2004 (USA, n=900, ADO, DT2)	12	MPR	% de patients hospitalisés • Pendant l'année de suivi (toute cause) : 11.4% • Pendant l'année suivant le suivi de l'adhésion (liées au diabète ou à maladies cardiovasculaires) : 6.7%	***Liée au DT ou à des causes cardiovasculaires*** • Les patients non adhérents (MPR<80%) étaient 2.5 fois plus susceptibles d'être hospitalisées l'année suivante par rapport aux patients adhérents (OR=2.53, IC95% 1.38-4.64, p≤0.01) • Taux d'hospitalisation pour MPR=100%:4.1%; MPR=99 à 80%:5.2%; MPR 79 à 60%: 10.3%; MPR 59 à 40%: 11.9%; MPR<40%: 14.8%, p=0.01
Sokol et al. 2005 (USA, n=3'260, AD, DT n/s)	12	MPR	-	• Les patients adhérents (MPR ≥80%) étaient significativement moins susceptibles d'être hospitalisés que MPR<80% (p<0.05) • Probabilité d'hospitalisation : MPR=80-100% : 13% ; MPR =60-79% : 20% ; MPR=40-59 : 25% ; MPR=20-39% : 26% ; MPR=1-19% : 30%
Zhu et al. 2015 (USA, n=24 067, ADO, DT2)	24	MPR	17.9% de toute la population étudiée avaient au moins une hospitalisation en lien avec le DT2 Pourcentage d'hospitalisation des patients adhérents (16.6)% vs non-adhérents (18.1%)	La non-adhésion est significativement associée aux hospitalisations (OR=1.2, IC95%= 1.1-1.3, p<0.0001)
Hong et Kang 2011 (Corée du Sud, n=40 082, ADO, DT2, patients naïfs)	24	MPR		Patients non-adhérents pendant les 2 premières années avaient plus de risques d'hospitalisations liés au DT/CV/maladie rénale (OR=1.26, IC95%=1.08-1.47).
Nombre d'hospitalisation				
Cheng et al. 2013 (Taiwan, n=11 580, ADO, DT2, patients naïfs)	84	MPR		Meilleure adhésion : diminution des hospitalisations pour le diabète ou les problèmes cardio- ou cérébraux-vasculaires (OR =0.74, IC95% = 0.69-0.78) Durée du diabète modère significativement cette relation (OR=0.86, IC95% 0.76-0.97)
ASSOCIATION CONTRADICTOIRE				
Probabilité d'hospitalisation				
Karve et al. 2008 (USA, n=4'943, ADO, DT2)	12	MPR PDC CMG Autres méthodes[1]	% de patients avec • une hospitalisation : 5% • plus d'une hospitalisation : 1% • au moins une hospitalisation (total) : 6%	MPR, PDC, MPRm≥80% étaient associés à une diminution relative de la probabilité d'hospitalisation de respectivement 43.7, 42.5 et 42.5% (pour OR voir article, p≤0.036) mais non significatif pour les mesures d'adhésion suivantes RCR, CR, CSA. Une adhésion médiocre (CMG et CMOS<20%) étaient associés à un risque accru d'hospitalisation de 77.7% et de 73.9% (p≤0.009).
Nombre d'hospitalisation				
Hepke et al. 2004 (USA, n= 57'687, ADO et insuline, DT n/s)	12	MPR	14% de la population a eu au moins une hospitalisation (toute cause)	• Les patients avec un MPR de 1 à 100% étaient 4.32 à 1.78 fois plus susceptibles d'avoir une hospitalisation par rapport à un MPR=0%. • Pour un MPR≥1%, une augmentation de l'adhésion était associée à une diminution du nombre d'hospitalisations.

[1]Autres méthodes de mesure de l'adhésion à partir des données de renouvellement/de remboursements d'ordonnances ; ADO=Antidiabétiques Oraux ; CMG=Continuous Measure of Medication Gaps ; CMOS=Continuous Multiple interval measure of Oversupply ; CR=Compliance Ratio ; CSA=Continuous Single interval measure of medication Qcquisistion ; DT n/s=Diabétiques, Type non spécifié ; DT2=Diabétiques de Type 2 ; MPR=Medication Possesion Ratio ; MPRm=MPR, modified; OR=Odd Ratio ; RCR= Refill Compliance Rate

Annexe 7: Revue des études sur l'association entre l' adhésion thérapeutique et les visites aux urgences (n=9 résultats pour 8 études)

Références	Durée de suivi (mois)	Méthode de mesure de l'adhésion	Statistiques descriptives	Résultats
Hepke et al. 2004 (USA, n= 57'687, ADO et insuline, DT n/s)	12	MPR	17% ≥ 1 visite	***Toutes causes*** Les patients 80≤MPR≤ 99% avaient un risque diminué de 12% d'avoir une visite aux urgences par rapport à un MPR<80% (OR=0.88, p non spécifié) ***Liées au diabète*** Les patients avec un 1≤MPR≤100% étaient 1.58 à 4.21 fois plus susceptibles d'avoir une visite aux urgences que les patients avec un MPR=0% (p non spécifié). A partir d'un 20≤MPR≤39%, une augmentation de l'adhésion était associée à une diminution du nombre de visites aux urgences.
Shenolikar et al. 2008 (USA, n=3'137, ADO, DT2, patients naïfs)	12	MPR	40% ≥ 1 visite	***Toutes causes*** Une augmentation de l'adhésion de 10% était associée à une diminution de 5.1% des visites aux urgences (OR=0.49, IC95% 0.38-0.63, p non spécifié)
White et al. 2004 (USA, n=67'029, ADO, DT2)	12	MPR	Nombre moyen de visites aux urgences : 0.34±0.98	***Toutes causes*** Nombre de visites aux urgences en fonction du taux de MPR : >95%, >75 et ≤95%, ≤75% • Cohorte DT : 0.15, 0.18, 0.21 (p<0.001) • Cohorte DT et CV : 0.63, 0.85, 1.10 (p<0.001)
Encinosa et al. 2010 (USA, n=56 744, ADO, DT2)	12	RCR Persistance	Une augmentation de l'adhésion de 50 à 100% réduit le taux d'urgences médicales de 46.2% (réduction de 17.3 à 9.3%)	
Gibson et al. 2010 (USA, n=55'356, ADO, DT2)	18	PDC	Nombre moyen de visites aux urgences durant les 2 ans après le suivi de l'adhésion : 0.64±1.71	***Toutes causes*** Le nombre de visites aux urgences était plus faible chez les patients adhérents (RR $_{PDC\geq80\%\ vs\ PDC<80\%}$=0.80, IC95% 0.665-0.962, p=0.018)
Jha et al. 2012 (USA, n=135 639, ADO, DT2	24	MPR	Une augmentation de l'adhésion est associée à presque 13% de risques en moins d'être hospitalisé ou d'avoir des urgences médicales.	Une augmentation de 10% du MPR est associée à une réduction de 1.2% des survenues d'hospitalisations et d'urgences médicales (p=0.05) (quand variable catégorielle) Les patients qui sont restés adhérents avaient le plus bas taux d'hospitalisations ou d'urgences médicales (27.8%), alors que ceux qui sont restés non-adhérents avaient 3% de risques absolus en plus (30.6%), p<0.001 Une diminution de 10% du MPR est associée à une augmentation de 4% du risque d'hospitalisation et/ou d'urgence médicale (p<0.001) (quand variable continue)
Balkrishnan et al. 2007 (USA, n=1'705, ADO, DT2, patients naïfs)	30	MPR	-	***Toutes causes*** Une augmentation de 10% de l'adhésion était associée à une diminution relative de 3.6% du nombre moyen de visites aux urgences (p<0.05)
Cheng et al. 2013 (Taiwan, n=11 580, ADO, DT2, patients naïfs)	84	MPR		Meilleure adhésion : diminution des urgences médicales pour le diabète ou les problèmes cardio- ou cérébraux-vasculaire (OR=0.78, IC95%=0.73-0.84) [pas besoin d'inclure le résultat qui suit] Durée du diabète ne modère pas cette relation (OR=0.91, IC95% 0.79-1.05)

ADO=Antidiabétiques Oraux ; CV=maladies cardiovasculaires ; DT n/s=Diabétiques, Type non spécifié ; DT2=Diabétiques de Type 2 ; IC95%= Intervalle de Confiance à 95% ; MPR=Medication Possesion Ratio ; OR=Odd Ratio ; PDC=Percentage of Days Covered ; RCR=Refill compliance rate.

Annexe 8: Revue des études sur l'association entre l'adhésion thérapeutique et les visites médicales ambulatoires toutes causes (n=5 résultats pour 5 études)

Références	Durée de suivi (mois)	Méthode de mesure de l'adhésion	Statistiques descriptives	Résultats
Kreyenbuhl et al. 2010 (USA, n=22'014, ADO, DT2)	12	MPR	Nombre moyen lors de l'année précédant le suivi (avec *vs* sans trouble schizophrénique) : • Médicale, liée au DT : 6±8 *vs* 5±5 • Médicale, non liée au DT : 24±31 *vs* 14±17 • Psychiatrique : 25±58 *vs* 2±14	Rapport du nombre de visites médicales ou psychiatriques ambulatoires au cours de l'année précédant le suivi de l'adhésion : OR $_{\text{risque d'avoir un MPR<0.8 vs 0.8-1.2}}$=0.996, IC95% 0.995-0.997, p<0.0001
White et al. 2004 (USA, n=67'029, ADO, DT2)	12	MPR	Nombre moyen de visites: 8.93±9.25	Nombre de visites en fonction du taux de MPR>95%, >75 et ≤95%, ≤75% • Cohorte DT : 7.74±7.69, 7.36±7.86, 6.90±6.90 (p<0.001) • Cohorte DT et CV : 13.66±10.69, 13.73±11.12, 14.39±12.51 (p=0.001)
Gibson et al. 2010 (USA, n=55'356, ADO, DT2)	18	PDC	Nombre moyen pendant 2 ans après le suivi de l'adhésion: 12.04±9.25	Nombre de visites était plus élevé chez les patients adhérents (RR $_{\text{PDC≥80\% vs PDC<80\%}}$=1.670 IC95%1.481-1.883, p<0.001)
Hong et Kang 2011 (Corée du Sud, n=40 082, ADO, DT2, patients naïfs)	24	MPR		Les patients non-adhérents ont fait moins de visites (11.4 vs 20.7, P<0.001)
Balkrishnan et al. 2007 (USA, n=1'705, ADO, DT2, patients naïfs)	30	MPR	-	Pas d'association significative entre l'adhésion et le nombre de visites (p non spécifié)

ADO=Antidiabétiques Oraux ; CV=maladies cardiovasculaires ; DT n/s=Diabétiques, Type non spécifié ; DT2=Diabétiques de Type 2 ; IC95%= Intervalle de Confiance à 95% ; MPR=Medication Possesion Ratio ; OR=Odd Ratio ; PDC=Percentage of Days Covered ; RR=Risque Relatif

Annexe 9: Revue des études sur l'association entre l'adhésion thérapeutique et les coûts toutes causes (n=34 résultats pour 17 études)

Références	Durée de suivi (mois)	Méthode de mesure de l'adhésion	Statistiques descriptives	Résultats
Coûts totaux				
Balkrishnan et al. 2006 (USA, n=4'710, ADO, DT2, patients naïfs)	12	MPR	Coûts pendant la 1ère année : • Thiazolidinediones: 8'318.70$ ± 13'188.87$ • Sulfonylurées/Metformine : 8'396.55$ ± 14'346.45$ Coûts pendant la 2ème année : • Thiazolidinediones: 9'322.95$ ± 14'012.24$ • Sulfonylurées/Metformine :11'618.96$ ± 17'246.5$3	L'adhésion n'est pas un prédicteur des coûts médicaux totaux (β= -0.12, p NS).
Hepke et al. 2004 (USA, n= 57'687, ADO et insuline, DT n/s)	12	MPR	-	Un MPR>40% était un prédicteur de la hausse des coûts globaux, coûts les plus faibles pour les patients avec MPR=0%
Shenolikar et al. 2008 (USA, n=3'137, ADO, DT2, patients naïfs)	12	MPR	Coût total annuel : 10'000$	Aucune association n'a été trouvée entre l'adhésion thérapeutique et les coûts
Shenolikar et al. 2006 (USA, n=1'073, ADO, DT2, patients naïfs)	12	MPR	Coûts totaux annuels: • Année de l'initiation :7'906$ ±12'256$ • Année 2 de l'initiation : 9'546$ ±14'861$	Réduction relative des coûts (de l'année 2 après initiation) médicaux totaux de 2% pour chaque augmentation du MPR de 10% (β= 0.20, p <0.001)
Sokol et al. 2005 (USA, n=3'260, AD, DT n/s)	12	MPR	Coûts en fonction du MPR: • MPR=80-100%: 8'886$ • MPR=60-79%: 11'484$ • MPR=40-59: 12'978$ • MPR=20-39%: 13'077$ • MPR=1-19%: 16'498$	Les coûts totaux des soins de santé ont tendance à diminuer avec des niveaux élevés d'adhésion malgré l'augmentation du coût des médicaments (pas de test statistiques)
White et al. 2004 (USA, n=67'029, ADO, DT2)	12	MPR	Coût total: 11'534$± 36'023$ • Sans maladies cardiovasculaires : 5'215$± 18'990$ • Avec maladies cardiovasculaires: 30'816$± 61'404$	• Sans maladies cardiovasculaires Les coûts totaux moyens étaient les plus élevés pour les patients avec un MPR ≤75% (5'706$) contre 95%≥MPR>75 et MPR>95% (5'314$ et 4'835$, respectivement; p<0.001) • Avec maladies cardiovasculaires Les coûts totaux moyens étaient les plus élevés pour les patients avec un MPR ≤75% (37'648$) contre 95%≥MPR>75 et MPR>95% (31'547$ et 25'354$, respectivement; p<0.001)
Gentil et al. 2015 (Canada, n=301, ADO, DT2)	12	MPR	L'impact sur les coûts de la santé est plus important chez les non-adhérents avec dépression et/ou troubles d'anxiété Les coûts de la santé plus importants chez les non-adhérents sont induits par des coûts ambulatoires et hospitaliers, des honoraires de médecins et des coûts de médications plus importants.	Coûts médicaux totaux: Les patients non-adhérents induisent des coûts médicaux totaux supérieurs aux patients adhérents (9008$ vs 5428$) Après ajustement, les participants sans dépression et/ou troubles d'anxiété, la non-adhésion était associée avec coûts médicaux totaux plus élevées: 4477$ (IC95% 3754-5201), p<0.001
Hagen et al. 2014 (USA, n=4 978, ADO, DT2)	12	PDC	Les coûts totaux sont plus élevés chez les patients adhérents à cause de coûts en médicaments plus importants	Coûts totaux (médicaux et traitements) toutes causes étaient similaires entre patients adhérents (PDC≥80%: 7782$) et non-adhérents (PDC<80%: 7642$), p=0.7370
Encinosa et al. 2010 (USA, n=56 744, ADO, DT2)	12	RCR		Une augmentation de l'adhésion de 50 à 100% réduit les coûts hospitaliers de 13 977 à 10 715$ par patient hospitalisé. Une augmentation de l'adhésion

		Persistance		de 50 à 100% réduit les coûts attendus d'hospitalisation de 2 097$ à 1 232$ par patient, impliquant une économie de 865$ en coûts hospitaliers par patient diabétique par année. Une augmentation de l'adhésion de 50 à 100% augmentent les coûts en médicaments antidiabétiques de 325 à 1105$ (supplément de776$ par patient et par année). ==> 865$/776$=1.12=12%; pour chaque dollar dépensé pour les médicaments pour augmenter l'adhésion aux AD de 50% à 100%, l'assuré/le payeur fait des économies de 0.12$ dans les soins hospitaliers=gain net de 12% Une augmentation de l'adhésion de 50 à 100% réduit les coûts de visites aux urgences de 49$ (=.173, 283$) à 28$ (=.093, 297$) par patient. (économies de 21$ par patient et par année) ==> 865$ + 21$ = 886$ -> /776$=1.14=14%; pour chaque dollar dépensé pour les médicaments pour augmenter l'adhésion aux AD de 50% à 100%, l'assuré/le payeur fait des économies de 0.14$ dans les soins hospitaliers et les visites aux urgences=gain net de 14% Economie globale annuelle par patient de 886$ et compensation des coûts de 1.14$ pour chaque dollars additionnel dépensé en médicament antidiabétique. Pour chaque dollar dépensé pour les médicaments pour augmenter l'adhésion aux AD de 50% à 100%, l'assuré/le payeur fait des économies de 0.14$ dans les soins hospitaliers et les visites aux urgences=gain net de 14%
Hansen et al. 2010 (USA, n=108'592, ADO, DT2)	24	MPR	Coûts des patients adhérents (MPR≥80%) *vs* non-adhérents (MPR<80%) : 1ère année : • Metformine: 10'065$±13'630$ *vs* 11'260$±23'271$ • Pioglitazone : 15'062$±17'997$ *vs* 17'878$±32'884$ • Sulfonylurées : 11'423$±20'362$ *vs* 14'457$±32'093$ 2ème année : • Metformine: 10'619$±14'489$ *vs* 12'364$±27'065$ • Pioglitazone : 15'782$±24'746$ *vs* 19'920$±40'471$ • Sulfonylurées : 12'378$±21'386$ *vs* 16'812$±36'296$	• MPR≥80% = 12 412$ par an et MPR<80%=13'258$ (différence: 846$, IC95% 747-945$) • La réduction annuelle des coûts liés à l'adhésion (adhérent *vs* non-adhérent) était de 336$ avec la metformine, de 1'509$ avec les sulfonylurées et de 1'140$ avec la pioglitazone
Hong et Kang 2011 (Corée du Sud, n=40 082, ADO, DT2, patients naïfs)	24	MPR		Les coûts totaux étaient plus élevés chez les patients adhérents : Les patients adhérents pendant les 2 premières années tendent à avoir des coûts de santé moindres durant la 3ème année (beta=-0.127, P<0.001). Plus l'adhésion augmente, plus les coûts de santé diminuent (réf. MPR<40% ; 40%<MPR<60%, beta= -0.072, P=0.000 ; 60%<MPR<80%, beta= -0.161, P<0.001 ; 80%<MPR, beta = -0.218, P<0.0001)
Stuart et al. 2015 (USA, n=894, ADO, DT2)	24	PDC		Les économies en terme de coûts liés aux dépenses médicales incluant médicaments étaient de 1914$ mais pas de différence significative entre le groupe adhérent et non-adhérent. = coûts médicaux totaux
Balkrishnan et al. 2007 (USA, n=1'705, ADO, DT2, patients naïfs)	30	MPR	Coûts pendant la période de suivi : • Rosiglitazone : 43'029$ ±42'469$ • Pioglitazone : 45'233$ ±45'812$	Une augmentation du MPR de 10% était associée à une augmentation des coûts de 2.6% (β=0.23, p<0.001)

Egede et al. 2012 (USA, n=740'195, ADO et insuline, DT2)	30	MPR	-	L'amélioration de l'adhésion dans le groupe non-adhérent entraînerait des économies annuelles estimées de $661'10^6$ $ (MPR<60% *vs* ≥60%) à 1.16 10^9 $ (MPR<100% *vs* =100%) par année (estimations des économies potentielles du Veteran Health Administrations). MPR<90% *vs* ≥90% : 1.13 10^9 $ MPR<80% *vs* ≥80% : 994 10^6 $ MPR<70% *vs* ≥70% : 789 10^6 $
Balkrishnan et al. 2004 (USA, n=3'483, ADO, DT2)	36	MPR Persistance	Coûts pendant l'année pré-initiation • Thiazolidinediones: 8'283$± 13'137$ • Sulfonylurées/Metformine : 8'443$± 13'094$ Coûts pendant l'année post-initiation • Thiazolidinediones: 9'458$± 14'594$ • Sulfonylurées/Metformine : 10'629$± 15'731$ Pas de différence entre les 2 groupes pour la 1ère année mais p<0.05 pour la 2ème (autres ADO coûts plus élevés) Coûts plus élevés pour la 2ème année (*vs* 1ère) pour les deux groupes (p<0.05)	Les patients qui commençaient une thiazolidinedione ont une meilleure adhésion et persistance du traitement (augmentation relative de 13% et 10% respectivement, p<0.001) comparés aux patients qui commençaient un autre ADO (Sulfonylurées/Metformine). Les patients qui commencaient une thiazolidinedione avaient 16.1% moins de coûts annuel totaux de soins de santé (p<0.01) que les patients qui commençaient un autre ADO.
Cheng et al. 2013 (Taiwan, n=11 580, ADO, DT2, patients naïfs)	84	MPR		Durant les 4 années suivant le diagnostic, les patients plus adhérents tendent à avoir des dépenses de santé plus importantes, mais cette tendance s'atténue après 5 ans. Néanmoins, une meilleure adhésion est associée à une augmentation des dépenses de soins de santé pour toute condition [beta=0.09,P<0.001). Les dépenses réduites liées aux hospitalisations et/ou urgences ne compensent pas les dépenses liées au médicament ou aux visites médicales.
Coûts médicaux				
Coûts médicaux totaux				
Balkrishnan et al. 2007 (USA, n=1'705, ADO, DT2, patients naïfs)	30	MPR	Coûts pendant la période de suivi : • Rosiglitazone : 15'000$ ±11'148$ • Pioglitazone : 16'063$ ±12'258$ Coûts par membre par mois : • Rosiglitazone : 828$±1'157$ • Pioglitazone : 850$±1'204$	Une augmentation du MPR de 10% était associée à une diminution des coûts de 2.1% (β=-0.23, p<0.01)
Hepke et al. 2004 (USA, n= 57'687, ADO et insuline, DT n/s)	12	MPR	-	Les coûts des soins médicaux ont augmenté lentement jusqu'à un MPR de 20 à 39% (effet seuil), une fois ce niveau atteint, il y a eu une diminution constante des coûts
Karve et al. 2008 (USA, n=4'943, ADO, DT2)	12	MPR PDC CMG Autres méthodes[1]	Coûts annuels : 5'497$± 9'030$	Aucune mesure d'adhésion ou de non-adhésion n'était significativement associée aux coûts totaux médicaux non pharmaceutiques.
Sokol et al. 2005 (USA, n=3'260, AD, DT n/s)	12	MPR	Coûts en fonction du MPR • MPR=80-100%: 6'377$ • MPR=60-79%: 9'363$ • MPR=40-59: 11'008$ • MPR=20-39%: 11'200$ • MPR=1-19%: 15'186$	Les coûts totaux des soins de santé ont tendance à diminuer avec des niveaux élevés d'adhésion (p<0.0001).
White et al. 2004 (USA, n=67'029, ADO, DT2)	12	MPR	Coût total : 10'089$± 35'842$ • Sans maladies cardiovasculaires : 4'090$ ± 18'835$	• Sans maladies cardiovasculaires (p<0.001) MPR>95% : 3'406$; 75%<MPR≤95% : 4'157$; MPR≤75% : 4'944$ • Avec maladies cardiovasculaires (p<0.001) MPR>95% : 23'326$; 75%<MPR≤95% : 29'815$; MPR≤75% : 36'332$

			• Avec maladies cardiovasculaires : 29'108$± 61'297$	
Gentil et al. 2015 (Canada, n=301, ADO, DT2)	12	MPR		Coûts des visites ambulatoires: Les patients non-adhérents induisent des coûts supérieurs aux patients adhérents (2654$ vs 1304$) Après ajustement, les participants sans dépression et/ou troubles d'anxiété, la non-adhésion était associée avec coûts médicaux totaux plus élevées: 1518$ (IC95% 1362-1675), p<0.001 Coûts hospitalisations : Les patients non-adhérents induisent des coûts supérieurs aux patients adhérents (2854$ vs 658$) Après ajustement, les participants sans dépression et/ou troubles d'anxiété, la non-adhésion était associée avec coûts médicaux totaux plus élevées: 2836$ (IC95% 2318-3353), p<0.001 Coûts des médecins : Les patients non-adhérents induisent des coûts supérieurs aux patients adhérents (1002$ vs 520$) Après ajustement, les participants sans dépression et/ou troubles d'anxiété, la non-adhésion était associée avec coûts médicaux totaux plus élevées: 568$ (IC95% 516-619-5201), p<0.001
Hagen et al. 2014 (USA, n=4 978, ADO, DT2)	12	PDC	Les patients adhérents ont des coûts médicaux plus faibles	Coûts médicaux toutes causes (hors médicaments) étaient plus faibles chez les patients adhérents (PDC≥80%: 4627$) vs les patients non-adhérents (PDC<80%: 5974$), p=0.0008
Stuart et al. 2015 (USA, n=894, ADO, DT2)	24	PDC		Les économies en terme de coûts liés aux dépenses médicales hors médicaments étaient de 12% (égale à 3033$, p<0.10) entre les patients adhérents vs non-adhérents. = coût médicaux hors pharmacies
Coûts hospitaliers				
Encinosa et al. 2010 (USA, n=56 744, ADO, DT2)	12	RCR Persistance		Une augmentation de l'adhésion de 50 à 100% réduit les coûts hospitaliers de 13 977 à 10 715$ par patient hospitalisé. Une augmentation de l'adhésion de 50 à 100% réduit les coûts attendus d'hospitalisation de 2 097$ à 1 232$ par patient, impliquant une économie de 865$ en coûts hospitaliers par patient diabétique par année.
Egede et al. 2012 (USA, n=740'195, ADO et insuline, DT2)	30	MPR	Coûts MPR≥80% *vs* MPR<80% : • Année 1 : 9'581.68$ *vs* 13'105.18$ • Année 2 : 9'689.92$ *vs* 14'189.15$ • Année 3 : 9'860.49$ *vs* 14'830.71$ • Année 4 : 10'002.85$ *vs* 15'113.41$ • Année 5 : 10'138.80$ *vs* 15'337.75$	Groupe MPR<80% a été associée à une augmentation relative des coûts de 41% *vs* MPR≥80% (OR=1.41, p<0.001)
Coûts ambulatoires				
Egede et al. 2012 (USA, n=740'195, ADO et insuline, DT2)	30	MPR	Coûts MPR≥80% *vs* MPR<80% : • Année 1 : 3'546.59$ *vs* 3'220.40$ • Année 2 : 3'602.27$ *vs* 3'501.96$ • Année 3 : 3'681.66$ *vs* 3'676.24$ • Année 4 : 3'751.08$ *vs* 3'762.64$ • Année 5 : 3'818.63$ *vs* 3'835.13$	Groupe MPR<80% a été associée à une diminution relative des coûts de 7% *vs* MPR≥80% (OR=0.93, p<0.001)
Coûts des médicaments				
Gentil et al. 2015 (Canada, n=301, ADO, DT2)	12	MPR		Les patients non-adhérents induisent des coûts inférieurs aux patients adhérents (2498$ vs 2945$) Après ajustement, les participants sans dépression et/ou troubles d'anxiété, la non-adhésion était associée avec coûts médicaux totaux moins élevées: moindre coûts de 444$ (IC95% -526 à -363), p<0.001
Hagen et al. 2014 (USA, n=4 978, ADO, DT2)	12	PDC		Coûts liés aux médicaments toutes pathologies sont plus importants chez les patients adhérents (PDC≥80%: 3155$) que non-adhérents (PDC<80%: 1668$), p<0.0001

Balkrishnan et al. 2007 (USA, n=1'705, ADO, DT2, patients naïfs)	30	MPR	Coûts pendant la période de suivi : • Rosiglitazone : 28'029$±37'432$ • Pioglitazone : 29'171$±40'442$ Coûts par membre par mois : • Rosiglitazone : 435$±311$ • Pioglitazone : 459$±334$	Une augmentation du MPR de 10% était associée à une augmentation des coûts de 12.7% (β=0.82, p<0.001)
Egede et al. 2012 (USA, n=740'195, ADO et insuline, DT2)	30	MPR	Coûts MPR≥80% *vs* MPR<80% : • Année 1 : 1'671.83$ *vs* 970.85$ • Année 2 : 1'689.06$ *vs* 1'050.12$ • Année 3 : 1'717.11$ *vs* 1'096.53$ • Année 4 : 1'740.19$ *vs* 1'116.33$ • Année 5 : 1'762.11$ *vs* 1'131.79$	Groupe MPR<80% a été associée à une diminution relative des coûts de 37% *vs* MPR≥80% (OR=0.63, p<0.001)
Hepke et al. 2004 (USA, n= 57'687, ADO et insuline, DT n/s)	12	MPR	-	Lorsque le niveau d'adhésion thérapeutique augmentait, les coûts pharmaceutiques augmentaient
Sokol et al. 2005 (USA, n=3'260, AD, DT n/s)	12	MPR	Coûts en fonction du MPR • MPR=80-100%: 2'510$ • MPR=60-79%: 2'121$ • MPR=40-59: 1'970$ • MPR=20-39%: 1'877$ • MPR=1-19%: 1'312$	Les coûts augmentent avec des niveaux d'adhésion plus élevée (p<0.0001)
White et al. 2004 (USA, n=67'029, ADO, DT2)	12	MPR	Coût total : 1'265$± 1'269$ • Sans maladies cardiovasculaires : 1'125$ ± 1'183$ • Avec maladies cardiovasculaires : 1'709$± 1'419$	• Sans maladies cardiovasculaires Les coûts moyens des pharmacies étaient les plus élevés pour les patients avec un MPR>95% (1'429$) contre 95%≥MPR>75 et MPR<75% (1'157$ et 762$ respectivement, p<0.001). • Avec maladies cardiovasculaires Les coûts moyens des pharmacies étaient les plus élevés pour les patients avec un MPR>95% (2'027$) 95%≥MPR>75 et MPR<75% (1'732$ et 1'317$ respectivement, p<0.001).

[1]Autre(s) méthode(s) de mesure de l'adhésion à partir des données de renouvellement/de remboursements d'ordonnances ; ADO=Antidiabétiques Oraux ; CMG=Continuous Measure of Medication Gaps ; CMOS=Continuous Multiple interval measure of Oversupply ; CR=Compliance Ratio ; CSA=Continuous Single interval measure of medication Acquisistion ; DT n/s=Diabétiques, Type non spécifié ; DT2=Diabétiques de Type 2 ; IC95%=Intervalle de Confiance à 95% ; MPR=Medication Possesion Ratio ; MPRm=MPR, modified; NS=non significatif ; OR=Odd Ratio ; PDC=Percentage of Days Covered ; RCR= Refill Compliance Rate

Annexe 10: Revue des études sur l'association entre l'adhésion thérapeutique et les coûts liés au diabète (n=13 résultats pour 8 études)

Références	Durée de suivi (mois)	Méthode de mesure de l'adhésion	Statistiques descriptives	Résultats
Coûts totaux				
Hansen et al. 2010 (USA, n=108'592, ADO, DT2)	24	MPR	Coûts MPR≥80% *vs* MPR<80%: 1ère année : • Metformine: 1'440$±3'854$ *vs* 1'686$±8'413$ • Pioglitazone : 3'845$±8'280$ *vs* 4'179$±15'351$ • Sulfonylurées : 1'813$±8'312$ *vs* 2'730$±13'457$ 2ème année : • Metformine: 1'528$±3'230$ *vs* 1'990$±9'981$ • Pioglitazone : 4'071$±13'801$ *vs* 5'278$±22'620$ • Sulfonylurées : 2'073$±9'590$ *vs* 3'531$±17'546$	MPR≥80% = 2'230$ et MPR<80%=2'284$ (différence: 55$, IC95% 33-77$) • Metformine : pas de différence significative • Sulfonylurées : non-adhérents avaient un coût augmenté de 271$ (p<0.05) par rapport aux adhérents • Pioglitazones : non-adhérents avaient un coût diminué de 433 (p<0.05) par rapport aux adhérents
Hepke et al. 2004 (USA, n= 57'687, ADO et insuline, DT n/s)	12	MPR	-	Un taux d'adhésion plus élevé était un prédicteur des coûts élevés liés au diabète
Shenolikar et al. 2006 (USA, n=1'073, ADO, DT2, patients naïfs)	12	MPR	Année 2 de l'initiation : 4'576$ ±8'208$	Réduction relative des coûts (de l'année 2 après initiation) médicaux en lien avec le diabète de 4% pour chaque augmentation du MPR de 10% (β=-0.575, p <0.001).
Sokol et al. 2005 (USA, n=3'260, AD, DT n/s)	12	MPR	Coûts en fonction du MPR • MPR=80-100%: 4'570$ • MPR=60-79%: 6'291$ • MPR=40-59: 6'522$ • MPR=20-39%: 7'124$ • MPR=1-19%: 8'867$	Les coûts totaux des soins de santé ont tendance à diminuer avec des niveaux élevés d'adhésion malgré l'augmentation du coût des médicaments (p<0.05).
Coûts médicaux				
Hepke et al. 2004 (USA, n= 57'687, ADO et insuline, DT n/s)	12	MPR	-	Les coûts des soins médicaux ont augmenté lentement jusqu'à un MPR de 20 à 39% (effet seuil), une fois ce niveau atteint, il y a eu une diminution constante des coûts mais coûts les plus faibles pour les patients avec MPR=0%
Karve et al. 2008 (USA, n=4'943, ADO, DT2)	12	MPR PDC CMG Autres méthodes[1]	Coûts annuels liés au diabète et non pharmaceutiques : 667$± 1'908$	2/6 mesures d'adhésion (MPR, PDC) ont montré qu'une augmentation des coûts était associée à une augmentation de l'adhésion (p<0.001). 4/6 autres mesures (CR, RCR, MPRm, CSA) n'ont montré aucune association significative. Les deux taux de non-adhésion (CMG, CMOS) ont montré qu'une diminution (p<0.001) des coûts était associée à une plus mauvaise adhésion.
Sokol et al. 2005 (USA, n=3'260, AD, DT n/s)	12	MPR	Coûts en fonction du MPR • MPR=80-100%: 3'808$ • MPR=60-79%: 5'887$ • MPR=40-59: 6'237$ • MPR=20-39%: 6'959$ • MPR=1-19%: 8'812$	Les coûts médicaux des soins de santé ont tendance à diminuer avec des niveaux élevés d'adhésion (p<0.0001).
Cheng et al. 2013 (Taiwan, n=11 580, ADO, DT2, patients naïfs)	84	MPR		Patients adhérents ont des dépenses liées aux hospitalisations et urgences médicales (diabète ou problèmes cardio- ou cérébraux-vasculaire) moins importantes (beta= -0.56, P<.001).
Coûts des médicaments				

Hepke et al. 2004 (USA, n= 57'687, ADO et insuline, DT n/s)	12	MPR	-	Lorsque le niveau d'adhésion thérapeutique augmentait, les coûts des médicaments augmentaient
Sokol et al. 2005 (USA, n=3'260, AD, DT n/s)	12	MPR	Coûts en fonction du MPR • MPR=80-100%: 763$ • MPR=60-79%: 404$ • MPR=40-59: 285$ • MPR=20-39%: 165$ • MPR=1-19%: 55$	Les coûts augmentent avec des niveaux d'adhésion plus élevée ($p<0.0001$).
Hagen et al. 2014 (USA, n=4 978, ADO, DT2)	12	PDC		Coûts liés aux médicaments AD sont plus importants chez les patients adhérents (PDC≥80%: 2168$) que non-adhérents (PDC<80%: 614$), $p<0.0001$ (toute la période d'observation)
Encinosa et al. 2010 (USA, n=56 744, ADO, DT2)	12	RCR Persistance		Une augmentation de l'adhésion de 50 à 100% augmentent les coûts en médicaments antidiabétiques de 325 à 1105$ (supplément de776$ par patient et par année). ==> 865$/776$=1.12=12%; pour chaque dollar dépensé pour les médicaments pour augmenter l'adhésion aux AD de 50% à 100%, l'assuré/le payeur fait des économies de 0.12$ dans les soins hospitaliers=gain net de 12%
Cheng et al. 2013 (Taiwan, n=11 580, ADO, DT2, patients naïfs)	84	MPR		Patients adhérents ont des dépenses liées au médicament ADO plus importantes (beta=0.52, P<.001).

[1]Autre(s) méthode(s) de mesure de l'adhésion à partir des données de renouvellement/de remboursements d'ordonnances ; ADO=Antidiabétiques Oraux ; CMG=Continuous Measure of Medication Gaps ; CMOS=Continuous Multiple interval measure of Oversupply ; CR=Compliance Ratio ; CSA=Continuous Single interval measure of medication Acquisistion ; DT n/s=Diabétiques, Type non spécifié ; DT2=Diabétiques de Type 2 ; IC95%=Intervalle de Confiance à 95% ; MPR=Medication Possesion Ratio ; MPRm=MPR, modified; NS=non significatif ; OR=Odd Ratio ; PDC=Percentage of Days Covered ; RCR= Refill compliance rate

Annexe 11: Revue des études sur l'association entre l'adhésion thérapeutique et l'état de santé (n=5 résultats pour 5 études)

Références	Méthode de mesure	Durée de suivi (mois)	Méthode de mesure (état de santé)	Statistiques descriptives	Résultats
Bailey et al. 2012 (USA, n=59, AD, DT n/s)	MMAS-8	n/a	« *Comment considérez-vous votre état de santé ?* *Excellent, bon, satisfaisant, mauvais ?* »	• Excellent : 7.0% • Bon : 45.6% • Satisfaisant : 33.3% • Mauvais : 14.0%	Un mauvais état de santé était associé à une non-adhésion (score MMAS de 0 à 6) (p=0.0028)
Parada et al. 2012 (USA, n=302, ADO et insuline, DT2)	MMAS-4	n/a	État de santé autoévalué : échelle continue de 1=faible à 5=excellent	Score moyen: 2.10±0.81 (~satisfaisant)	• Population entière : pas d'influence de l'état de santé sur l'adhésion (OR=1.38, IC95% 0.94-2.01, p=0.10) • Sous-population latino-américaine à prédominance espagnole (nés à l'étranger, n=238) : pour chaque augmentation de score de l'auto-évaluation d'une unité, la probabilité de non-adhésion augmentait d'un facteur 1.6 (OR=1.6, IC95% 1.05-2.44, p=0.03)
Park et al. 2010 (Corée, n=265, ADO et insuline, DT2)	MMAS-4	n/a	État de santé subjectif: « *bonne santé* » *vs* « pas bonne santé »	-	Pourcentage de patients « adhérents » (score MMAS-4=4) en fonction de leur état de santé (« bonne » *vs* « pas bonne santé ») : • Hôpital tertiaire : 68.6% *vs* 57.5% (p=0.271) • Cliniques privées : 47.5% *vs* 41.9% (p=0.536)
Raum et al. 2012 (Allemagne, n=1'141, ADO et insuline, DT2)	MMAS-4	n/a	« *Comment décrivez-vous votre état de santé général* ? *Faible, moins bon, bon, très bon, excellent* »	• Excellent ou très bon : 8.9% (n=102) • Bon : 57.4% (n=655) • Moins bon : 30.2% (n=344) • Faible : 3.5% (n=40)	Pourcentage de patients « non-adhérents » (score MMAS≥1) en fonction de l'état de santé (p=0.11) • Excellent ou très bon : 17.5% (n=17) • Bon :22.4% (n=140) • Moins bon : 28.0% (n=94) • Faible : 25.0% (n=10)
van Dijk et al. 2007 (Pays-Bas, n=2'194, ADO, DT2)	MPR	12	« *Comment percevez-vous votre état de santé ?* *Faible/modéré* (score=0), *bon/excellent* (score=1) »,	-	Etat de santé non associé à la non-adhésion ($OR_{\text{pour un score bon à excellent, MPR>80\% vs MPR≤80\%}}$=1.17, IC95% 0.99-1.37, p>0.05 NS)

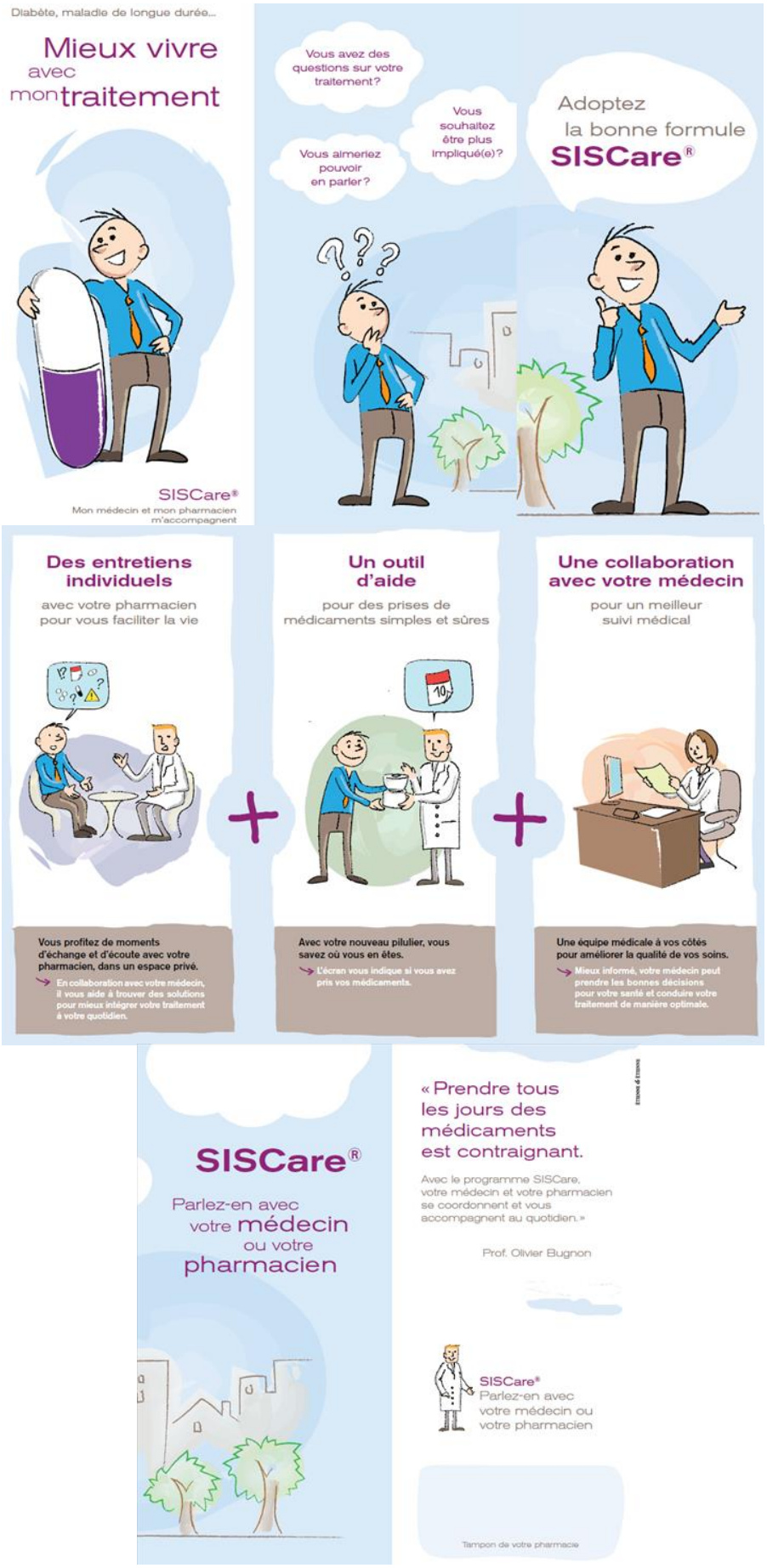
AD=Antidiabétiques ; ADO=Antidiabétiques Oraux ; DT n/s=Diabétiques Type non spécifié ; DT2=Diabétiques de Type 2 ; IC95%=Intervalle de Confiance à 95% ; MMAS-4/8=Morisky Medication Adherence Scale à 4 ou 8 items ; MPR=Medication Possesion Ratio ; NS=non significatif ; n/a= non applicable. OR=Odd Ratio

Annexe 12: Revue des études sur l'association entre l'adhésion thérapeutique et la qualité de vie liée à l'état de santé (n=3 résultats pour 3 études)

Références	Méthode de mesure (adhésion)	Durée de suivi (mois)	Méthode de mesure (qualité de vie)	Statistiques descriptives	Résultats
Piette et al. 2004 (ADO et insuline, n=766, ADO et insuline, DT n/s)	Autre méthode[1] (auto-évaluation)	n/a	SF-12 : score de 0 à 100 (les scores les plus élevés indiquent une meilleure qualité de vie)	-	Association entre la non-adhésion et la qualité de vie • Composante physique : β=-0.3, IC95% -3.0 à 3.5, p>0.05 NS • Composante mentale : β=-0.2, IC95% -3.3 à 2.9, p>0.05 NS
Florez et al. 2010 (USA, n=360, ADO, DT2, patients naïfs)	MPR	6	SF-36 : score de 0 (mauvais) à 100 (bon)	-	Seule la composante mentale du score était associé de façon significative (p<0.05) à l'adhésion
Martinez et al. 2008 (Mexique, n=238, ADO, DT2)	Comptage	1	Qualité de vie mesuré par le questionnaire WHOQOL-100 : score de 0 à 100 (les scores les plus élevés indiquent une meilleure qualité de vie)	Score moyen : de 63.1 (=niveau d'indépendance) à 73.9 (domaine spirituel)	Pas de différence significative du score moyen des patients « adhérents » (>90% ou <105%) *vs* « non-adhérents » (<90% ou >105%): • Santé physique: 67.5±16.3 *vs* 63.5±17.4 • Psychologique: 70.4±14.9 *vs* 67.2±13.4 • Niveau d'indépendance: 64.4±14.7 *vs* 62.9±13.3 • Relations sociales : 73.0±11.7 *vs* 70.4±11.6 • Environnement : 69.4±11.2 *vs* 66.7±9.8 • Croyances spirituelles/religieuses/personnelles : 74.8±20.5 *vs* 73.8±16.3

[1]Autre(s) méthode(s) de mesure de l'adhésion par auto-évaluation que ceux mentionnés dans la partie I (spécifique à l'étude) ; ADO=Antidiabétiques Oraux ; DT n/s=Diabétiques Type non spécifié ; DT2=Diabétiques de Type 2 ; IC95%=Intervalle de confiance à 95% ; MMAS-4/8=Morisky Medication Adherence Scale à 4 ou 8 items ; MPR=Medication Possesion Ratio ; NS=non significatif ; OR=Odd Ratio ; SF-12/36= Short Form Health Survey à 12 ou 36 items ; WHOQOL-100= World Health Organization Quality of Life à 100 items

Appendix 3 - Flyer to promote Siscare



Appendix 4 - Ethics approval

canton de vaud
COMMISSION CANTONALE
D'ÉTHIQUE DE LA RECHERCHE
SUR L'ÊTRE HUMAIN
CER-VD
Av. de Chailly 23
1012 Lausanne

Prof. Olivier Bugnon
Policlinique Médicale Universitaire
Rue du Bugnon 44,
(Bureau BU44/05/2412)
1011 Lausanne

Lausanne, le 9 mars 2016
Réf. AP/cc/fch/sm

Décision de la Commission cantonale (VD) d'éthique de la recherche sur l'être humain (CER-VD)

No de protocole	2016-00110
Titre	Évaluation d'un programme d'accompagnement interprofessionnel des patients diabétiques de type 2 et de son implémentation en Suisse romande
Investigateur principal	Prof. Olivier Bugnon
Date de soumission	26.01.2016 et 25.02.2016

I. Procédure

La CER-VD a statué en :

Procédure ordinaire	☐	
Procédure simplifiée	☑	02.02.2016
Décision présidentielle	☑	09.03.2016

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II. Décision

La décision concerne: **VD** **PMU**

☑ **Autorisation accordée**

Signification: L'étude peut commencer selon le plan de recherche accepté. Elle doit être menée dans le cadre des dispositions légales en vigueur.

III. Classification

☑ **Projet de recherche au sens de l'ORH:**

recherche sur des personnes	Catégorie ☑ A	☐ B
réutilisation du matériel biologique ou des données personnelles liées à la santé		☐
personnes décédées		☐
embryons et des fœtus		☐
avec rayonnements ionisants		☐

IV. Justifications de la décision/Remarques

Pas de remarque

V. Taxes et émoluments

Déjà facturé

VI. Voies de recours

La présente décision peut faire l'objet d'un recours au Tribunal cantonal, Cour de droit administratif et public. L'acte de recours doit être déposé auprès du Tribunal cantonal dans les **30 jours** suivant la communication de la décision attaquée ; il doit être signé et indiquer les conclusions et motifs du recours. La décision attaquée est jointe au recours. Le cas échéant, ce dernier est accompagné de la procuration du mandataire.

VII. Communication au requérant, et en plus à:

Promoteur	☐ Swissmedic	☐ OFSP ☐
Autres	☑ Bawab Noura, Noura.Bawab@hospvd.ch Perraudin Clémence. clemence.perraudin@hospvd.ch	

VIII. Composition de la Commission lors de la prise de décision

Décision Présidentielle: Prof. Patrick Francioli, Président

Prof. Patrick Francioli
Président

La décision de la CER-VD se base sur les documents soumis via BASEC. Selon vos indications il s'agit de:

4. Study plan (protocol), signed and dated

Protocole_OFSP_DT2_v2_24.02.2016_C.docx	24/02/2016	2		
Protocole_OFSP_DT2_v2_24.02.2016_TC.docx	24/02/2016	2		
Protocole_OFSP_DT2_v2_24.02.2016_signé.pdf	24/02/2016	2		

11. Other documents handed over to study participants

Annexe_15.3_Annonce d'EI suspectés d'un médicament_v12_01.08.2015.docx			24/02/2016	1
Annexe_15.4_Document de refus du programme SISCare DT2_v2_24.02.2016_C.docx	24/02/2016	2		
Annexe_15.5_Intro_questionnaires-patient_v2_24.02.2016_C.docx	24/02/2016	2		
Conditions-CER-VD_v1_24.02.2016.docx	24/02/2016	1		
Annexe_15.5_Intro_questionnaires-patient_v2_24.02.2016_TC.docx	24/02/2016		2	
Annexe_15.4_Document de refus du programme SISCare DT2_v2_24.02.2016_TC.docx	24/02/2016	2		
Annexe_15.2_Formulaire d'information et de consentement_v1_24.02.2016_.docx			24/02/2016	1

La CER-VD s'aligne sur les principes ICH GCP

Obligations du requérant (promoteur ou investigateur):
1. En cas de révision :
- Les documents révisés sont mis à disposition des autorités compétentes pour approbation.
- Les documents révisés doivent être soumis une fois en mode « suivi des modifications » et une fois en mode « modifications acceptées » (« track changes » et « clean »).
- Les informations sur le projet de recherche ainsi que les nouveaux documents sont à soumettre via le compte de soumission électronique du projet de recherche (BASEC). Veuillez vous référer à l'article « How to submit amendments, new documents or update fields of a submission? » disponible dans la page de support dans l'interface de soumission.

2. Les événements indésirables graves, la fin ou l'arrêt prématuré d'un essai clinique et les modifications essentielles sont annoncés via le compte de soumission électronique du projet de recherche selon les dispositions légales en vigueur.
3. Pour les essais cliniques, le rapport final est soumis à la CER-VD via le compte de soumission électronique du projet de recherche dans un délai d'un an au plus tard.
4. Les essais cliniques sont enregistrés dans un registre primaire de l'OMS (puis dans la banque de données complémentaire de la Confédération (Swiss National Clinical Trials Portal [SNCTP]).

Appendix 5 - Pharmacy assessment grid for telephone interviews during the preparation stage, at 5 weeks (call 1) and 12 weeks (call 2) after the start of patient inclusion

Thèmes	Sous-thèmes	Questions	Réponses	Questions	Réponses	Questions
Organisation	Information de l'équipe	Avez-vous informé toute l'équipe de la pharmacie du projet SISCare-DT2?	Oui	Avez-vous utilisé le support mise en place par SISPha?	Oui	Comment cela s'est-il déroulé? Avez-vous modifié quelque chose à la
					Non	Pourquoi?
			Non	Quelle en est la raison?		
Organisation (Appel 2 - uniquement si applicable)	Stockage	Avez-vous contrôlé le stock de piluliers électroniques et de flacons? Et éventuellement complété le stock? Avez-vous mis en place une stratégie pour organiser le stockage des emballages des patients?				
	Horaire	Avez-vous défini des jours/plages horaires lors desquels vous fixer de préférence des rendez-vous (présence de deux pharmaciens) Où enregistrer vous ces rendez-vous?				
	Accueil	Avez-vous défini une procédure d'accueil des patients lors des rendez-vous? (où les diriger, qui avertir, lecture des piluliers)				
Préparation	Liste de patients éligibles	Avez vous établi la liste de patients éligibles?	Oui	Avez-vous rencontré des problèmes?	Qu'avez-vous fait avec la liste de patients éligibles?	
			Non	Quelle en est la raison?		
	Contact-médecins	Avez-vous pris contact avec les médecins?	Oui	Par quel(s) moyens? Avez-vous eu des réponses positives ou négatives?	Combien de médecins avez-vous contacté? Combien de médecins vous ont répondu positivement, négativement ou pas répondus?	
			Non	Quelle en est la raison? Par quel(s) moyen(s) envisagez-vous de le faire?		
		Avez-vous fixé un rendez-vous avec un ou des	Oui	Quand et avec qui?		
			Non	Pourquoi?		
	Présentation du projet	Avez-vous présenté le projet aux médecins?	Oui	Avez-vous utilisé le support mise en place par SISPha?	Oui	Comment cela s'est-il déroulé? Avez-vous modifié quelque chose à la présentation? Combien de présentation avez-vous faites? Combien de médecins
					Non	Pourquoi?
			Non	Quelle en est la raison?		
		Avez-vous présenté le projet aux assistantes médicales?	Oui	Avez-vous utilisé le support mise en place par SISPha?	Oui	Comment cela s'est-il déroulé? Avez-vous modifié quelque chose à la présentation? Combien de présentations avez-vous faites? Combien d'assistantes
					Non	Pourquoi?
			Non	Quelle en est la raison?		
Mise en place	Patient test	Vous êtes-vous familiarisé avec la plateforme en créant un patient test?	Oui	Avez-vous rencontré des problèmes?		
			Non	Quelle en est la raison?		
	Flyer	Avez-vous utilisé le flyer?	Oui	Comment?		
			Non	Quelle en est la raison?		
Inclusion	Inclusion-patient	Avez-vous inclus des patients?	Oui	Combien? Comment avez-vous proposé aux patients de participer à l'étude? Ont-ils accepté de rentrer dans l'étude immédiatement? Combien de médecins différents sont impliqués par patient et pour tous les patients? Avez-vous envoyé le rapport d'inclusion au médecin? Avez-vous reçu des valeurs cliniques en retour? Avez-vous introduit ces valeurs cliniques dans la plateforme SISPha?		
			Non	Comment comptez-vous procéder?		

Appendix 6 - Interview grid for the first focus group sessions during the preparation stage

Thèmes	Sous-thèmes	Questions
MOTIVATION		
Quelles sont les raisons qui vous ont motivées à participer au programme d'accompagnement pour les patients diabétiques? Quelles sont les facteurs motivants à la mise en place du programme d'accompagnement pour les patients diabétiques?		
Facteurs de motivation	Annonce officielle de l'OFSP/communication au grand public	
	Projet pilote (aspect scientifique)	
	Séance de discussion	
FAISABILITÉ: FACILITATEURS		
Facilitateurs	Quels sont les facteurs qui ont facilité l'implémentation du programme?	
Barrières	Quelles sont les difficultés rencontrées à l'implémentation du programme?	
Organisation au sein de la pharmacie	Position du responsable du projet SISCare-DT2	En tant que responsable du projet SISCare-DT2, quelle est votre position au sein de la pharmacie (au niveau du pouvoir de décision dans la mise en place de ce projet)?
	Implication des membres de l'équipe	Comment sont impliqués les autres membres de la pharmacie au sein du projet?
	Répartition du travail	Comment avez-vous réparti le travail entre les différentes personnes présentes à la pharmacie? Dans quels rôles les assistantes sont-elles impliquées? Comment se sentent-elles face à ce projet?
	Manque de temps	Dans quelle mesure est-ce que le manque de temps est un problème auquel vous faites face dans le cadre du projet?
	Fidelité (adaptations)	Quelles sont les adaptations que vous avez éventuellement faites au programme et quelles en sont les raisons?
Patients	Proposition de participation au patient	Comment se passe la proposition de participation au patient?
	Refus de participations des patients	
	Faible taux de patients éligibles	
	Facturation de la prestation	
	Relations-patients	Comment décrieriez-vous vos relations avec vos patients?
	Fréquence de rencontre	A quelle fréquence rencontrez-vous les patients qui ont intégré ce programme?
		Comment avez-vous établi cette fréquence?
Relations professionnelles	Comment décrieriez-vous vos relations avec les médecins?	
	Quels sont les types de contact que vous avec eu ces professionnels de santé dans le cadre de ce programme?	
	Taux de réponse	Quel est le taux de réponses des professionnels de la santé à vos envois (courrier, rapport, autre)? Quel est votre ressenti/avis par rapport ce taux de réponse?
		Comment serait-influencé votre pratique si le médecin enverrait des patients à votre pharmacie pour un suivi de l'adhésion sous pilulier?
	Autres professionnels	Avez-vous eu des contacts avec des autres professionnels de la santé que les médecins dans le cadre du projet SISCare-DT2? Qui sont ces professionnels? Quels sont les types de contact que vous avez eu? Pour quelles circonstances?
	Rapport d'entretien	Comment transmettez-vous les rapports d'adhésion au médecin?
SUPPORTS		
***Formation initale SISCare-DT2 mars 2016 *Documents SISPha/PMU *Newsletter mensuelle *Formation SISPha septembre 2016**	Est-ce que ces supports ont été bien conçues pour une utilisation concrète dans la pratique?	
	Est-ce que ces supports sont appropriés?	
	Est-ce que ces supports sont efficaces?	
	Est-ce que ces supports sont suffisantes/Est-ce que ces supports répondent à vos besoins?	
RECOMMANDATIONS		
Recommandations	Quelles seraient vos propositions d'amélioration par rapport aux ressources mises en places par SISPha? Quels seraient vos besoins complémentaires par rapport aux ressources mises en places par SISPha?	
INTÉGRATION EN ROUTINE		
Intégration en routine	Comment décrieriez-vous l'intégration de ce programme dans l'activité de routine de la pharmacie?	

Appendix 7 - Interview grid for the second focus group sessions during the operation stage

Thèmes	Sous-thèmes	Questions
BARRIERES ET FACILITATEURS		
- Quelles sont les facilitateurs à la réalisation de la prestation ? - Quelles sont les barrières à la réalisation de la prestation ?		
1. Individuel (IBM ; Information Behaviour Motivation)	Motivation	Qu'est-ce qui vous parle dans ce projet ? A quel niveau cela vous motive-t-il ?
	Satisfaction	Quelles sont les satisfactions qui découlent du programme dans le cadre de l'activité officinale ?
	Compétences	Qu'est-ce qui rend l'entretien compliqué pour vous ?
2. Pharmacie	Facteurs facilitants/barrières	- Au sein de la pharmacie, quelles sont les facteurs facilitants qui vous ont permis la réalisation du programme en routine ? - Quelles sont les barrières ?
	Organisation	- Comment sont impliqués les autres membres de la pharmacie ? - Comment avez-vous réparti le travail entre les différentes personnes présentes à la pharmacie ? - Dans quels rôles sont impliquées les assistantes ?
3. Contexte local	Relation avec le patient - impact sur le patient ?	- Comment décririez-vous vos relations avec vos patients ? - Est-ce que cette relation a évolué ? Dans quel sens ? - Quels sont les feedbacks des patients ?
	Collaboration interprofessionnelle	Cf partie ci-dessous
4. Système	-	Cf partie ci-dessous
5. Service=programme (fidélité)	-	Cf partie ci-dessous
DIVERS		
Entretiens	Fréquence des entretiens	- Est-ce que vous arrivez à faire les entretiens de manière régulière ? - Et à quelle fréquence ? - Comment avez-vous établi cette fréquence ?
	Plateforme	Est-ce que tous les champs sont remplis de manière systématique dans la plateforme ?
	Données cliniques	Est-ce que vous remplissez les valeurs d'Hémoglobine glycquée ?
	Rapport	- Est- ce que le rapport d'entretien est envoyé au médecin ? Est-il envoyé systématiquement ? - Si le rapport est envoyé, sous quel format (document imprimé depuis SISPha, document personnalisé, etc) est envoyé le rapport d'entretien ?
	Adapations	- Quelles sont les adaptations que vous avez éventuellement faites au programme ? - Quelles en sont les raisons ?
Facturation Sispha	-	Quelle est votre position par rapport à la facturation du programme ?
Formations SISPha	-	Est-ce que les formations (suivi, entretien) ont été utiles pour vous ?
Collaboration interprofessionnelle	-	- Comment décrieriez-vous vos relations avec les médecins ? - Est-ce que cette relation a évolué ? Si oui, comment ? Dans quel
Maintenance	-	- Est-ce que vous continuez à inclure des patients ? - Si oui, quel type de patients ? - Si non, pour quelles raisons ?
Recommendations	-	Quelles seraient vos propositions d'amélioration par rapport aux ressources disponibles ?

Appendix 8 - Data collection protocol for pharmacy on-site audit during the operation stage

Date: Nom de la pharmacie:

1. **Questionnaire à remplir avec le chef de projet de la pharmacie**

   A. **En lien avec la pharmacie (en général)**

Pharmacien.ne interviewé.e

- Nom et prénom:
- ☐ Homme ☐ Femme
- Âge: ans - Nombre total d'année d'expérience (pharmacien): ans
- Pourcentage d'emploi: %
- Fonction: ☐Propriétaire ☐Gérant ☐ Adjoint ☐ Autre:
- Animateur d'un cercle de qualité médecins-pharmaciens:

☐ Oui ☐ Non ☐ Autre personne:

Pharmacie

		Nombre de personnels	Equivalent temps plein
Pharmacien.nes	Au sein de la pharmacie		
	Participant au projet		
Assistant.es	Au sein de la pharmacie		
	Participant au projet		

- Type de pharmacie:

☐ Indépendante ☐ Réseau/Groupement (=rassemblement économique de pharmacies indépendantes)[1] ☐ Chaîne (=pharmacie gérée par une entreprise privée)[1] ☐ Autre:

- Certification qualité:

☐ QMS ☐ En cours ☐Aucune ☐ Autre:

- Situation géographique

☐ Canton: Chef-lieu: ☐ Oui ☐ Non

☐ Rurale (>10 000 habitants)1 ☐ Urbaine (≤ 10 000 habitants)	☐ Centre-ville ☐ Centre commercial ☐ Autre:

[1] Selon thèse de J. Marquis (page 116, tableau caractéristiques des pharmacies)

- Espace confidentiel: ☐ Oui ☐ Non

  - ☐Au front office ☐ En back office
  - ☐ Assis ☐ Debout
  - Dans une pièce privée: ☐ Oui ☐ Non
  - Avec un ordinateur: ☐ Oui ☐ Non

- Délivrez-vous d'autre(s) prestation(s) pharmaceutique(s) ?

☐ Semainier ☐ Entretiens PMC ☐ Netcare ☐ Vaccination

☐ Dépistage allergies ☐ Dépistage cancer du colon ☐ Cardio Test

☐ Soins des plaies ☐ Désaccoutumance tabagique ☐ Mesure de la tension

☐ Autres :

B. En lien avec les propositions aux patients

Proposition

- Qui propose le programme au patient?

☐ Tout le monde au sein de la pharmacie ☐ Une partie du personnel

☐ Pharmacien ☐ Assistant ☐ Stagiaire en pharmacie ☐ Apprenti

- Comment?

☐ A la suite d'un PMC

☐ Au comptoir : ☐ Flyer

☐ Feuille d'information pour les patients

☐ Discussion

☐ Autre:

☐ Autre:

Commentaires:

- Allez-vous continuer de proposer la prestation aux patients?

☐ Oui, pour les DT2 ☐Oui, pour les autres pathologies ☐ Non ☐ Je ne sais pas

Commentaires:

Documentation des refus

- Avez-vous documenté les refus des patients ?

☐ Oui, toujours → Récolte de données (impression document(s) Word)

☐ Oui, parfois → Récolte de données (impression document(s) Word)

☐ Non, jamais

☐ Je ne sais pas

→ Estimation du nombre de refus :

Raisons:

C. En lien avec les inclusions

Confirmation du nombre d'inclusions

	Nombre de patients inclus		
	Total	Sous MEMS	Sous semainier seul
Sous "SISCare-DT2"			
Sous "Syndrome métabolique"			

[Enquêteur: *valider chaque inclusion lors du contrôle de la pochette; si discordance → question*]

- Patients inclus dans d'autres programmes pour suivi de l'adhésion (aujourd'hui):

Pathologie(s) concernées :

- Avez-vous eu des patients suivis par le programme SISCare avant le début de l'étude?

☐ Oui, nombre .... ☐ Non

- Avez-vous prévu de continuer le suivi de vos patients inclus après leur 15 mois de suivi (fin de l'observation pour l'étude)?

D. Organisation à l'officine

Documentation du temps

- Avez-vous documenté le temps consacré à l'ensemble du projet ?

☐ Oui, toujours → Récolte de données (impression document(s) Word ou copie sur clé du document Excel)

☐ Oui, parfois → Remplir le document 11c pendant la visite (approximation)

☐ Non, jamais → Remplir le document 1 c pendant la visite (approximation)

☐ Je ne sais pas

Répartition des tâches

- Avez-vous défini le rôle de chacun dans la prise en charge du patient ?

☐ Oui → ☐ Procédure écrite ☐ Accord oral ☐ Autre:

☐ Non

☐ Je ne sais pas

- Comment est-ce que vous vous organisez pour la répartition des tâches à la pharmacie ?

Activité	Personne chargée de l'activité		
	Pharmacien	Assistante	Autre (*à spécifier*)
Lecture du pilulier et comptage	☐	☐	☐
Préparation du pilulier	☐	☐	☐
Entretien patients	☐	☐	☐

Commentaires (autres tâches réparties):

E. Ressources disponibles

Documents généraux SISPha

Dans quelle mesure les documents mis à votre disposition vous ont-ils été utiles ?

	Utilité					Commentaire
Document	Très utile	Plutôt utile	Plutôt inutile	Inutile	Je ne sais pas	
01- Check-list organisationnelle pour implémentation à l'officine	☐	☐	☐	☐	☐	
02- Brochure patients SISCare	☐	☐	☐	☐	☐	
03- Argumentaire pour l'équipe de la pharmacie	☐	☐	☐	☐	☐	
06a- Consultation d'adhésion - Première visite	☐	☐	☐	☐	☐	
06b- Consultation d'adhésion - Rédaction du rapport	☐	☐	☐	☐	☐	
06c- Consultation d'adhésion - Visites de suivi	☐	☐	☐	☐	☐	
09b- Déroulement pratique avec le médecin	☐	☐	☐	☐	☐	
09d- Information pour les assistantes médicales	☐	☐	☐	☐	☐	
09e- Argumentaire pour les médecins	☐	☐	☐	☐	☐	
10a- Agenda pour la pharmacie	☐	☐	☐	☐	☐	
10b- Identification des patients éligibles via DP Ofac	☐	☐	☐	☐	☐	
10d- Histogramme de suivi d'inclusion des patients	☐	☐	☐	☐	☐	
10e- Information pour les patients (mis en place suite à la demande d'une pharmacie)	☐	☐	☐	☐	☐	

	Utilité					Est-ce que le document a été modifié?		
Document	Très utile	Plutôt utile	Plutôt inutile	Inutile	Je ne sais pas	Oui	Non	Commentaire
08a- Slides de la formation aux pharmaciens SISCare DT2	☐	☐	☐	☐	☐	☐	☐	
08b- Slides de présentation pour les médecins	☐	☐	☐	☐	☐	☐	☐	
08c- Slides de présentation pour les assistantes médicales	☐	☐	☐	☐	☐	☐	☐	
08d- Slides de présentation pour l'équipe de la pharmacie	☐	☐	☐	☐	☐	☐	☐	
09a- Courrier d'information aux médecins	☐	☐	☐	☐	☐	☐	☐	
09c- Mails d'accompagnement pour envois de documents au médecin	☐	☐	☐	☐	☐	☐	☐	
10c- Courrier aux patients éligibles	☐	☐	☐	☐	☐	☐	☐	

Documents spécifiques à l'étude

Avez-vous des commentaires sur les documents spécifiques à l'étude ?

Document SISPha spécifiques à l'étude	**Avez-vous un commentaire ?**
04- Diagramme d'inclusion d'un patient au projet SISCare DT2	
05- Diagramme de suivi d'un patient inclus dans le projet SISCare DT2	
07- Algorithme de choix des médicaments à inclure dans les MEMS	
11a- Procédure documentation du temps	
11b- Documentation du temps à remplir	
11c- Documentation du temps à remplir	
Document PMU spécifiques à l'étude	**Avez-vous un commentaire ?**
I- PMU - Calendrier de suivi des patients inclus dans le projet SISCare DT2	
II- PMU - Document de refus de participation au programme SISCare DT2	
III- PMU - Questionnaire ADDQoL	
IV- PMU - Questionnaire SF12	
V- PMU - Formulaire d'information et de consentement	
VI- PMU - Protocole de l'étude SISCare DT2	

"Offres SISPha"

Avez-vous (ou votre collègue) bénéficié de cette offre ?								
Oui	Non	Offre	Très utile	Plutôt utile	Plutôt inutile	Inutile	Je ne sais pas	Commentaires – Impact sur les inclusions?
☐	☐	Mailing organisé	☐	☐	☐	☐	☐	
☐	☐	Spot publicitaire	☐	☐	☐	☐	☐	
☐	☐	Affiche format A1	☐	☐	☐	☐	☐	
		Annonces d-journal (2) (3.03.2017 et 25.04. 2017)	☐	☐	☐	☐	☐	
		Newsletter	☐	☐	☐	☐	☐	
☐	☐	Appel SISPha	☐	☐	☐	☐	☐	
☐	☐	Formation proposition 12.09.2016	☐	☐	☐	☐	☐	
☐	☐	Formation proposition 31.01.2017	☐	☐	☐	☐	☐	
☐	☐	Formation proposition 7.03.2017	☐	☐	☐	☐	☐	
☐	☐	Formation proposition 13.03.2017	☐	☐	☐	☐	☐	
☐	☐	Formation consultation adhésion 27.03.2017 + 06.04.2017	☐	☐	☐	☐	☐	
☐	☐	Formation entretien de suivi 16.05.2017 AM	☐	☐	☐	☐	☐	
☐	☐	Formation entretien de suivi 16.05.2017 PM	☐	☐	☐	☐	☐	

[*A juger par l'enquêteur*] Est-ce que l'offre SISCare est visible ?

Flyer ☐ Oui ☐ Non

Affiche ☐ Oui ☐ Non ☐ Non applicable

Spot publicitaire ☐ Oui ☐ Non ☐ Non applicable

F. Entretiens réalisés avec les patients :

i. Durée des entretiens

- Avez-vous documenté la durée des entretiens avec vos patients ?

☐ Oui, toujours ☐ Oui, parfois ☐ Non, jamais ☐ Je ne sais pas

Source d'informations : ☐ Documentation réelle ☐ Estimation

Résultats:

Entretiens d'inclusion (N_{tot}=…)→ Moyenne: min Min: min Max: min

Entretiens de suivi (N*=…..) → Moyenne: min Min: min Max: min

[N : Nombre de patients par semaine ou par mois en moyenne à préciser]

Source d'informations : ☐ Documentation réelle ☐ Estimation

Commentaires:

ii. Méthodologie

- Comment qualifieriez-vous les entretiens avec vos patients ?

Structuré							Spontané

☐ Guidé selon la plateforme SISPha

☐ Approche de type motivationnel

☐ Autre:

Participatif							Directif
Motivant							Démotivant

- Est-ce que vous discutez du graphique d'adhésion pendant l'entretien avec le patient? ☐ Oui, toujours ☐ Oui, parfois ☐ Non, jamais ☐ Je ne sais pas

Commentaires:

iii. Fréquence des entretiens

Comment fixez-vous la fréquence des entretiens avec les patients ?

iv. Facturation des entretiens

Est-ce que vous facturer une prestation aux patients suivis?

G. Plateforme informatique SISPha

i. Utilisation de la plateforme

- Est-ce que les données issues de l'entretien sont introduites dans la plateforme?

☐ Oui, toujours → ☐ Lors des entretiens ☐ Après les entretiens
☐ Oui, parfois → ☐ Lors des entretiens ☐ Après les entretiens
☐ Non, jamais
☐ Je ne sais pas

Commentaires :

ii. Documentation

- Documentez-vous les données de la plateforme en lien avec ...?

	Toujours	Parfois	Jamais	Je ne sais pas	Commentaires
Les facteurs facilitants et barrières (smileys)	☐	☐	☐	☐	
Les symptômes et les effets indésirables	☐	☐	☐	☐	
Les paramètres cliniques	☐	☐	☐	☐	
L'appréciation	☐	☐	☐	☐	
Le plan de traitement Est-ce que tout l'historique médicamenteux a été documenté?	☐	☐	☐	☐	

Est-ce que tous les traitements antidiabétiques oraux ont été mis sous piluliers?

☐ Oui ☐ Non

Si ce n'est pas le cas et que la documentation de l'historique médicamenteux n'a pas été faite systématiquement → relevé les données des posologies pour les antidiabétiques oraux pour les patients concernés.

iii. Lecture du pilulier et mesure de l'adhésion

- Est-ce que, lors de la lecture du pilulier, le champ "Comprimés restant dans le pilulier à scanner" est systématiquement renseigné selon le nombre de comprimés rapportés par le patient?

☐ Oui, toujours ☐ Oui, parfois ☐ Non, jamais ☐ Autres:

Commentaires :

- Est-ce que la valeur d'adhésion électronique est systématiquement reportée à chaque lecture du pilulier?

☐ Oui, toujours ☐ Oui, parfois ☐ Non, jamais ☐ Autres:

Commentaires :

- Est-ce que l'utilisation des piluliers par le patient est validée à chaque entretien ?
(Rubrique: Utilisation du pilulier électronique par le patient
Questions:

- *Temps habituel entre ouverture du pilulier et ingestion du médicament*
- *Doses préparées à l'avance*
- *Périodes non monitorées)*

☐ Oui, toujours ☐ Oui, parfois ☐ Non, jamais ☐ Autres:

Commentaires :

- Lorsqu'un patient est pressé (pas le temps de faire un entretien) et que vous lui délivrez des comprimés, comment procédez-vous sur la plateforme?

☐ Prolongation de la préparation en cours

☐ Création d'une nouvelle préparation

☐ Pas renseigné systématique

☐ Autre:

- Est-ce que des piluliers ont été défectueux au cours du suivi de patients SISCare-DT2?

☐ Oui ☐ Non

Si oui, pour quel patient?

Qu'avez-vous fait avec les piluliers?

H. Collaboration interprofessionnelle

i. <u>Présentation du projet</u>

- Est-ce que vous avez contacté les médecins pour les informer du projet?

☐ Oui ☐ Non

=> Méthode de contact : ☐ Fax ☐ Courrier postal ☐ Mail ☐ Autre :

Nombre de médecins contactés:

Comment avez-vous sélectionné ces médecins?

☐ Médecins du quartier ☐ Amis, bonnes connaissances ☐ Autre:

Commentaires:

- Suite à cet envoi, est-ce que vous avez eu des réponses des médecins?

☐ Oui, toujours ☐ Oui, parfois ☐ Non, jamais ☐ Je ne sais pas

Nombre:

Commentaires:

- Est-ce que vous avez rencontré des médecins pour présenter le projet?

☐ Oui ☐ Non

Nombre de rencontres:

Nombre de médecins rencontrés:

Où? A quelle occasion?

☐ Cercle de qualité ☐ Réunion spécifique pour le projet

☐ Autre:

Commentaires:

ii. Transmission des rapports d'entretien

- Est-ce que les rapports d'entretien sont envoyés au médecin référent du patient ?

☐ Oui, toujours ☐ Oui, parfois ☐ Non, jamais ☐ Je ne sais pas

=> Méthode d'envoi : ☐ Fax ☐ Courrier postal ☐ Mail ☐ Autre :

=> ☐ Rapport généré par SISPha ☐ Autre rapport:

Commentaires:

- Est-ce que vous avez des réponses du médecin suite à l'envoi du rapport ?

☐ Oui, toujours ☐ Oui, parfois ☐ Non, jamais ☐ Je ne sais pas

=> Par : ☐ Fax ☐ Courrier postal ☐ Mail ☐ Autre :

Commentaires:

iii. Communication

- Avez-vous des contacts avec les assistantes médicales? Dans quel cadre?

☐ Oui, toujours ☐ Oui, parfois ☐ Non, jamais ☐ Je ne sais pas

Commentaires:

Avez-vous d'autres échanges avec les médecins référents des patients suivis ?

Par exemple: cercle de qualité

☐ Oui, toujours ☐ Oui, parfois ☐ Non, jamais ☐ Je ne sais pas

Commentaires:

Appendix 9 - Report of the first focus group sessions during the preparation stage

Focus groupe 1 – 14.11.2016, Neuchâtel – 6 participants, 4 pharmacies

Focus groupe 2 – 22.11.2016, Lausanne – 11 participants, 8 pharmacies

Implémentation du programme SISCare-DT2 dans l'activité officinale

Lors de ces deux focus groupes, trois principaux facteurs sont apparus comme important dans l'implémentation du programme au sein des pharmacies : la perception de l'utilité du programme, la logique d'investissement/rentabilité, l'organisation à l'officine. Ces trois facteurs sont liés, puisque plus la prestation va être intégrée dans la stratégie d'entreprise, dépendamment de la perception du pharmacien propriétaire de son utilité et de sa rentabilité, et plus des moyens seront mis en œuvre au sein de l'organisation à l'officine pour mettre en place et délivrer le programme de façon optimale (p.ex. aménagement du temps des pharmaciens impliqués, soutien à l'équipe face aux patients et aux médecins, intégration des assistantes).

- **Perception de l'utilité du programme**

La perception de l'utilité du programme/de l'accompagnement comme une plus-value pour le patient est un facteur de motivation qui incite les pharmaciens à s'investir dans sa délivrance. Au plus cette vision est partagée/diffusée au sein de l'équipe, et notamment par le pharmacien propriétaire, au mieux l'implémentation du programme sera favorable.

- **Logique d'investissement/rentabilité**

Plusieurs pharmaciens rapportent le manque de rentabilité comme un problème et que la rémunération actuelle ne permet pas de couvrir les coûts engendrés par la mise en place du programme, qui sont importants (p.ex. organisation dans l'officine, temps professionnel, abonnement Sispha). Le fait d'intégrer la prestation/le programme Siscare dans la stratégie d'entreprise et de le percevoir comme un investissement pour le futur, dans le cadre de l'avenir de la profession, favorise sa mise en place. Sans cela, d'autres projets semblent plus prioritaires au détriment du programme SISCare-DT2. Néanmoins, même si le pharmacien propriétaire ne perçoit pas le projet comme prioritaire, les pharmaciens chef de projet présents lors de ces focus groups, semblent motivés, et souvent, le projet dépend alors uniquement d'eux.

- **Organisation à l'officine**

Certains pharmaciens rapportent des dysfonctionnements dans l'organisation de la pharmacie qui perturbe la bonne mise en place et le bon déroulement du programme : tensions au sein de l'équipe, interruptions lors des entretiens, dépendance du programme à un seul pharmacien chef de projet. La mise en place d'un véritable « plan d'action » pour intégrer le programme dans l'activité de l'officine (p.ex. communication au sein de toute l'équipe, proposition d'inclusion des patients par les assistantes au comptoir) est favorable à son implémentation.

Formation

La majorité des pharmaciens présents ont partagé le sentiment d'un manque de compétences pour créer la relation avec le patient et mener les entretiens. Ils ne se sentent pas à l'aise face à cette « sortie de zone de confort » et partagent le fait que des prérequis sont nécessaire pour créer le lien avec le patient (p.ex. phrase d'accroche), de même que pour la relation avec les médecins (p.ex.

communication). Des besoins en cours pratiques plutôt que théoriques sont identifiés pour s'exercer (exemple avec la comédienne), pour débuter l'entretien ainsi que pour le contenu. Un intérêt a été montré pour des formations courtes et répétées.

Relation avec le patient

Les stratégies d'inclusion des patients ne sont pas les mêmes dans chaque pharmacie. Le fait de proposer plusieurs fois le programme au patient peut être perçu comme nécessaire, mais certains pharmaciens n'en voient pas l'intérêt ou ne se sentent pas à l'aise pour le faire. Les pharmaciens rapportent une difficulté pour ouvrir le dialogue avec les patients qui auraient véritablement besoin de la prestation, ceux qui ne se dévoilent pas facilement. La prestation est aussi parfois proposée suite à un PMC, permettant de créer le lien avec le patient. Plusieurs pharmaciens supportent l'idée que les refus ne doivent pas être pris personnellement.

De plus, la sélection des patients avec 3 médicaments chroniques restreint le nombre de patients éligibles. Certains pharmaciens identifient le questionnaire patient comme une barrière pour l'inclusion à cause de sa longueur et de sa complexité de compréhension. Certains pharmaciens le remplissent avec le patient, ce qui est long (15 à 20 minutes).

La combinaison d'un ou de plusieurs piluliers à un semainier est compliquée pour certains patients, les pharmaciens estiment que les patients perdent leur autonomie.

Collaboration interprofessionnelle

La collaboration est quasi inexistante pour l'instant, le taux de réponse est assez bas. La relation est unilatérale Cela apparait pour une grande majorité comme un facteur de démotivation.

Appendix 10 - Report of the second focus group sessions during the operation stage

FG 2a – 23.04.2018, Lausanne – 7 participants (5 pharmaciens, 1 assistante, 1 pharmacienne-stagiaire), 5 pharmacies

FG 2b – 30.04.2018, Lausanne – 6 participants (6 pharmaciens), 6 pharmacies

Entretien téléphonique a – 15.05.2018 – 1 pharmacienne (n=14 patients)

Entretien téléphonique b – 17.05.2018 – 1 pharmacienne (n= 29 patients)

⇨ Représente 48% des pharmacies (n=13/27) et 61% des patients (n=130/212)

Ce rapport a été rédigé par les animateurs des focus groupes. Il ne s'agit pas d'une analyse selon la méthode de la recherche qualitative mais d'un rapport préliminaire à l'attention de Ofac/Sispha afin de pouvoir mettre en œuvre des plans d'action dans un bref délai. L'analyse qualitative suivra.

Niveau individuel

- **Motivation**

La phase d'inclusion a été vécue comme très confrontante par une majorité des pharmaciens, notamment en raison du manque de compréhension des patients de cette nouvelle prestation, de la difficulté à se placer dans cette démarche propositionnelle qui diffère de la routine, et de la crainte d'être confronté à un éventuel refus (réelle ou imaginée) (cf. rapport des FG1).

Facteurs favorisant la motivation

La phase de mise en routine des prestations a été perçue comme plus facile et est globalement bien vécue. Le type de pratique semble différer selon les pharmacies et le nombre de patients suivis (cf. organisation). Pour rendre cette intervention faisable, des indices laissent à penser que l'intervention a parfois été adaptée dans les pharmacies.

Le fait que le projet soit soutenu par l'OFSP est un facteur de motivation fortement exprimé. Une partie de la motivation tient au fait que c'est une étude pilote. Cet argument est aussi un outil supplémentaire pour la pharmacie pour convaincre le patient d'adhérer et de continuer le suivi. Au-delà de l'étude, cette source de motivation risque de disparaître. A la fin de la période de suivi, certains pharmaciens souhaitent ajouter ces prestations comme des prestations disponibles parmi d'autres dans l'offre de la pharmacie, qui seraient destinées aux personnes qui ont des problèmes d'adhésion. Au vu de la pratique du projet pilote, cette prestation ne serait donc pas proposée de manière « systématique » comme cela a pu être le cas pendant la période d'étude. Les pharmaciens mettent en avant la relation avec le patient comme source de motivation pour ces prestations.

Freins à la motivation

Certains patients peuvent exprimer des réticences vis-à-vis du projet, en particulier liées au sentiment de se sentir contrôlé via le pilulier électronique. Le pilulier électronique est souvent vu par le patient (et en miroir par les pharmaciens) comme un outil peu pratique, bien qu'il puisse parfois être très utile pour soutenir la motivation du patient (discussion sur le graphique) et vérification de la prise (écran LCD). D'un autre côté, la collaboration interprofessionnelle avec les autres professionnels partageant la prise en charge du patient est inexistante, à de rares exceptions près. Ensuite, les difficultés techniques liées à la plateforme Sispha (manque de réactivité perçue du service unanimement reconnu) donnent le sentiment de ne pas être épaulé par l'équipe du projet. Enfin, notons que certains doutes sur la légitimité

du programme subsistent, en particulier par rapport aux patients qui ont déjà une très bonne adhésion au traitement et une parfaite régularité. Toutes les pharmacies ont été confrontées à une attrition de leur échantillon (parfois allant jusqu'à la moitié de l'échantillon) et constatent par les faits que la prestation ne convient pas à tous les types de patients.

L'ensemble de ces barrières donne parfois l'impression que les pharmaciens se retrouvent dans la mission de porter le programme « envers et contre tous », dans un contexte où ni les patients, ni les médecins, ni même le support technique de la plateforme ne facilitent la mise en œuvre, alors même que ces prestations sont largement réalisées à perte. Des doutes sur la durabilité de la motivation des pharmaciens peuvent ainsi légitimement être soulevés.

- **Compétences et formation**

Les visites effectuées à la pharmacie par Ming Yan et Blaise se sont révélées utiles, mais le moment n'était pas approprié (pendant les heures d'ouverture de la pharmacie). Une organisation pendant les horaires de fermeture (midi ou soirée) ou dans un endroit externe aurait été plus approprié.

Les formations de suivi et interprofessionnelles ont été appréciées par les pharmaciens. Elles permettent de s'exercer tout en ayant un coaching. Une participation régulière est nécessaire pour pouvoir en tirer profit de manière continue.

Un besoin de formation et un guide d'utilisation concernant la plateforme informatique sont ressortis comme nécessaires, tant pour le pharmacien que pour l'assistante. Les fonctionnalités de la plateforme évoluent et il semble y avoir un manque de communication quant aux nouveautés offertes par la plateforme (p.ex. possibilité d'accéder à Sispha depuis GolgenGate sans login par sms)

La simulation d'un entretien complet lors d'une formation (entretien motivationnel et utilisation de la plateforme) a été suggérée. La technique de l'entretien motivationnel devrait faire l'objet de rafraîchissement régulier. Les cours ont pour effet d'augmenter la maîtrise de ces techniques, mais aussi la motivation à les mettre en œuvre de retour à la pharmacie. Des aspects comme la durée de l'entretien, la gestion des débordements de temps, l'intégration des outils Sispha dans l'entretien (pour potentialiser ses effets), la diversité des profils de personnalité des patients devraient être traités avec un soin particulier dans ces formations.

Pour certains pharmaciens (p.ex pharmaciens adjoints récemment impliqués dans le projet), un manque de compétences dû à un manque d'expériences est relaté.

Si les avis sont partagés sur la quantité idéale de formations « officielles » à donner (offre Sispha notamment), une formation continue, sur le terrain et constante des cadres de la pharmacie auprès des collaborateurs est nécessaire pour faire entrer en routine les automatismes nécessaires à la délivrance de la prestation. Plus le « coaching » à l'interne par les pharmaciens cadres est élevé et moins les demandes en formations externes sont exprimées.

Pharmacie

- **Organisation à l'officine**

Les assistantes ont presque systématiquement été impliquées lors de la phase d'inclusion des patients.

Pour le suivi, le mode d'organisation varie principalement en fonction du nombre de patients inclus. Si le nombre de patients est faible, la prestation est généralement réalisée par le seul pharmacien en charge du projet. L'« 'implémentation » (entendue comme une transformation de l'organisation et des

pratiques dans la pharmacie toute entière), reste dans ce cas assez limitée. La prestation est essentiellement l'affaire d'une seule personne.

L'augmentation du nombre de patients implique par contre la mise en place d'une réponse coordonnée et collaborative. La collaboration avec l'assistante semble être une aide : son rôle va de la préparation du pilulier (déblistérer les médicaments) au remplissage de la plateforme (sur base des notes du pharmacien). Cependant certains pharmaciens n'ont pas formé leurs assistantes car cela demanderait trop de temps pour peu de rentabilité (peu de patients inclus). Avec une préparation anticipée du pilulier par le pharmacien, le temps de la partie technique pendant la présence du patient est réduit. Dans certains cas, les patients savent que cela peut prendre du temps et certains reviennent plus tard dans la journée pour l'entretien et pour récupérer leur pilulier.

L'irrégularité dans la manière dont les patients viennent au rendez-vous représente un défi pour les pharmaciens, particulièrement celle où seule une personne est en charge de la prestation. Les patients ne sont vraisemblablement pas habitués à prendre rendez-vous dans leur pharmacie.

La mise en place d'une collaboration dans la pharmacie est facilitée par le fait que le personnel est déjà habitué à collaborer ensemble, p.exe dans le cadre d'autres prestations. Les qualités de collaboration, de réaction et de débrouillardise d'un collaborateur-clé peuvent s'avérer déterminants pour la mise en en place de la collaboration. Le fait que la responsabilité soit diffusée sur l'ensemble des collaborateurs semble être un facteur facilitateur, particulièrement pour les pharmacies en situation de sous-effectif.

Le travail en équipe, rendu efficient par une culture collaborative et l'intégration de tous les collaborateurs dans le projet, est primordial et permet de mettre en place de telles prestations pour un large échantillon de patients.

Des séances de formations continues et d'information des pharmaciens adjoints et des assistantes doivent être organisées régulièrement à l'interne.

- **Soutien et vision du pharmacien chef**

Le soutien du pharmacien chef/propriétaire et du pharmacien chef de projet est indispensable pour implémenter ce projet en groupe au sein de la pharmacie. Sans cela, le pharmacien responsable du projet, qui est souvent pharmacien adjoint, ne se sent pas soutenu et peine à légitimer sa participation active du projet.

L'implémentation doit répondre à un projet partagé et communiqué au niveau de la pharmacie. Il doit être clairement explicité comme une des priorités stratégiques pour la pharmacie en entier. Durant la phase d'inclusion, l'établissement d'un objectif de nombre de patients à inclure par mois ou par année avait permis de favoriser l'implication des membres de l'équipe. Un très fort degré de conviction porté par la direction de la pharmacie que le pharmacien a son rôle à jouer dans la prise en charge du patient par ces prestations, au niveau de la pharmacie, permet de passer outre bien des barrières : motivation et formation des autres pharmaciens adjoints et assistants en pharmacie, manque de reconnaissance des médecins, doutes réels ou potentiels des patients, problèmes de rentabilité, etc. Ce haut degré de motivation porté par la direction semble très lié au nombre de patients inclus par chaque pharmacie. Les formations Sispha ont leur rôle à jouer dans le rappel des motivations, de même que les messages de figures emblématiques unanimement reconnues dans le milieu professionnel (par exemple et en particulier les fondateurs de Sispha).

La vision de l'utilité et de la pertinence de la prestation par le pharmacien chef/propriétaire et le pharmacien chef de projet est un point clé. Le rôle bien-fondé de la prestation doit être présentée à l'ensemble de l'équipe officinale. Le contenu du programme doit aussi être connu pour tous les membres de l'équipe. Les pharmacies qui organisent en équipe la délivrance de la prestation, qui ont déjà établi une culture de la gestion de projets d'équipe dans la pharmacie, arrive à prendre en charge les patientèles les plus nombreuses. L'encadrement offert par les pharmaciens cadres aux employés de la pharmacie, le rôle de modèle qu'ils jouent, le rappel du caractère prioritaire de la prestation sont des facteurs clés pour transmettre l'information, la motivation et les compétences. Reconnaître que les autres pharmaciens de la pharmacie sont compétents pour faire les entretiens (évidemment avec une formation et une expérience adéquate) est un pas nécessaire pour passer d'une implémentation du projet limitée à un pharmacien à un projet de la pharmacie entière. De règle générale, un leadership adéquat, coopératif, inclusif et qui met en sens le changement, semble très prédicteur de la facilité d'implémentation du changement.

Contexte local

- **Relation avec le patient**

Les pharmaciens sont satisfaits de la relation avec les patients qui participent au suivi. Ces patients sont très contents d'avoir un moment privilégié avec leur pharmacien. Cette relation est aussi gratifiante pour le pharmacien. Elle crée un lien privilégié de connaissance mutuelle qui dépasse la relation conventionnelle.

Certains patients ont quitté l'étude en raison de la lourdeur et rigidité de la procédure et/ou de la gestion du pilulier. La difficulté principale réside notamment dans la gestion de la polymédication ; l'existence d'un semainier électronique serait une amélioration souhaitable. Certaines pharmacies fournissent des médicaments supplémentaires pour permettre aux patients de pouvoir remplir leur pilulier et leur offrir plus de souplesse quant au moment de venue la pharmacie.

Il y a probablement un biais d'auto-sélection important des patients qui restent à long terme dans les suivis. Les patients sont décrits comme ayant beaucoup de temps à leur disposition (pour revenir à la pharmacie p.ex) ou un large besoin de sociabiliser (parler pendant 40 minutes de leur vécu). Il se peut donc que les populations retraitées ou sans situation professionnelle soient surreprésentées.

Les autres raisons de l'arrêt du suivi sont : déménagement, arrêt du traitement, prise en charge par le CMS, problèmes d'ordre psychologique, facturation, pilulier encombrant. Un certain nombre de patients sont contents de pouvoir « aider » en participant à une étude.

Le contexte particulier d'une pharmacie (départ à la retraite de plusieurs médecins du quartier et peu de temps à disposition de la part des médecins pour faire le suivi du patient) montre clairement le rôle et l'importance du pharmacien dans l'accompagnement de patients chroniques.

- **Collaboration interprofessionnelle**

Les rapports sont souvent envoyés au médecins, parfois munis de questions concernant le suivi du patient. Suite à ces rapports, très peu reçoivent de réponses. Parfois, les rapports ne sont envoyés que quand un problème a été rencontré (adhésion, effet indésirable, non atteinte de l'objectif thérapeutique, etc.). Un pharmacien appelle toujours avant d'envoyer le rapport pour avertir le médecin ou l'assistante médicale, ce qui favorise la collaboration. L'absence de réponse suite à l'envoi de rapport est démotivante. Certains pharmaciens sont étonnés de savoir que l'infirmière reçoit plus d'information sur

le patient de la part du médecin que les pharmaciens. La place du pharmacien dans le diabète est remise en cause du fait de la présence d'un médecin généraliste, d'un spécialiste diabétologue et d'une infirmière spécialisée en diabétologie.

Dans deux cas seulement, la collaboration interprofessionnelle est jugée satisfaisante. Dans ces deux cas, un contact en face à face a eu lieu avant le début de la collaboration. Dans un cas, pharmacien et médecin ont une relation amicale personnelle, dans l'autre, un entretien de face à face a été organisé pour présenter les prestations. La rencontre personnelle semble donc une un élément favorisant la collaboration interprofessionnelle. Il est vraisemblable que le contexte villageois favorise de telles relations.

- **Contexte central vs périphérique**

Dans des régions périphériques, la pharmacie peut représenter le seul accès « bas seuil » à de l'information de santé. Dans ce contexte, il est plus aisé pour les pharmaciens-chefs de consolider une vision dans laquelle la pharmacie a un rôle de santé public central à jouer, davantage encore au travers de prestations d'accompagnement comme le suivi DT2.

Système

- **Plateforme Sispha et soutien informatique**

La plateforme peut poser des problèmes : impossibilité de lire le pilulier, problème d'introduction des valeurs cliniques, longueur du temps de chargement (surtout au début de l'étude). Le temps d'attente pour la hotline Ofac est long et parfois sans réponse. En cas de problèmes ou de questions urgents, les réponses ne sont pas immédiates (délai de 10 jours). Les changements (p.ex. suppression de données introduites par erreur) ne sont pas faits après la première demande. Ceci est décourageant pour les pharmaciens et demande un investissement important.

- **Facturation et rémunération**

Les pharmaciens facturent la prestation au cas par cas en fonction du nombre de médicaments. Ils essayent dans la mesure du possible de pouvoir être rémunéré la plupart du temps via la position tarifaire « semainier ». Cependant cette rémunération ne permet pas de couvrir les coûts engendrés par le suivi du patient, même s'il y a plus de 10 patients suivis.

Service

- **Inclusion**

Les pharmaciens ont principalement arrêté d'inclure les patients. La proposition demande un investissement important. Pour certains, il y avait une mauvaise compréhension et ils pensaient que l'inclusion était limitée jusqu'en juin 2017 et applicable uniquement aux patients diabétiques de type 2. Pour d'autres, la charge de travail avec les patients déjà inclus était trop importante. Inclure est un défi majeur pour tous les pharmaciens.

- **Pilulier**

Le pilulier est une barrière pour le patient lorsque celui-ci doit prendre beaucoup de médicaments. Dans ce cas le semainier semble être mieux adapté mais ne permet pas une méthode de mesure objective de l'adhésion. A l'avenir, il est souhaitable d'opter pour un autre mode de suivi de l'adhésion que le pilulier.

- **Bénéfice pour le patient**

Certains pharmaciens expriment le bénéfice de la prestation pour le patient : détection et gestion d'effets indésirables, non atteinte de l'objectif thérapeutique et échange d'information avec le médecin. Pour d'autres pharmaciens, le champ d'action face à la maladie du diabète semble limité et être un frein pour ce programme.

Suggestions pour la prochaine newsletter

- Soutenir la proposition et l'inclusion de patients au-delà de l'étude : p.ex se fixer un objectif d'inclusion par mois, proposer à d'autres patients que DT2, commencer par proposer des PMC car c'est une bonne porte d'entrée.
- Effectuer un entretien à la pharmacie des Troistorrents par rapport à leur organisation à l'officine : la pharmacienne a une assistante de gestion qui prend les rendez-vous, prépare les piluliers, introduit les données dans la plateforme.
- Rapporter la satisfaction des patients quant à leurs entretiens avec le pharmacien.
- Proposition de nouvelles formations (cf. ci-dessus)
- Expliquer les problèmes survenus avec la hotline et mesures pour y remédier
- Réaffirmer le soutien aux pharmaciens investis et féliciter la personne responsable du projet dans la pharmacie.

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Dissemination of Research

Peer-reviewed journal publication

2020 **Implementation and Effectiveness of an Interprofessional Support Program for Patients with Type 2 Diabetes in Swiss Primary Care: A Study Protocol.** N. Bawab, J.C. Moullin, C. Perraudin, and O. Bugnon. *Pharmacy (Basel),* 2020;8(2). 10.3390/pharmacy8020106

Peer-reviewed conference proceedings

2020 **Implementation study of an interprofessional support programme for patients with type 2 diabetes in a Swiss primary care setting.** N. Bawab, J.C. Moullin, C. Perraudin, and O. Bugnon. *3rd UK Implementation Science Research Conference*, London, United Kingdom (held virtually), 16-17 July. Oral presentation. *Implementation Science*, under publication.

2018 **Implementation science to promote the contribution of the Swiss community pharmacists in chronic care management.** N. Bawab, A. Georges, C. Rossier, C. Perraudin, and O. Bugnon. *BPSPPR Conference*, Lisbon, Porto, 25-27 June. 3-minute thesis oral presentation. *Pharmacy Practice 2018*, Jun;16 (Suppl1):1339; p.8:3mT020. 10.18549/PharmPract.2018.s1.1339

2017 **Evaluation of the implementation of an interprofessional type 2 diabetes adherence program in Swiss primary care setting.** N. Bawab, C. Rossier, C. Perraudin, and O. Bugnon. *10th PCNE Working Conference*, Bled, Slovenia, 1-4 February. Poster. *Int J Clin Pharm* 39(3):p.617-618. 10.1007/s11096-017-0462-2

Submitted papers in peer-reviewed journals

2020 **Interest in and Use of Person-centred Pharmacy Services - a Swiss Study of People with Diabetes** N. Bawab, E. Zuercher, T. Carron, L. Chinet, O. Bugnon, J. Berger, and I. Peytremann-Bridevaux. Under review in *BMC Health Services Research* since 19 May.

2020 **Implementation Evaluation of an Interprofessional Programme for Supporting Patients (Siscare) with Type 2 Diabetes in a Swiss Primary Care Setting.** N. Bawab, J.C. Moullin, C. Perraudin, and O. Bugnon. To be submitted to *Research in Social and Administrative Pharmacy*.

2020 **Effectiveness of an Interprofessional Programme (Siscare) for Supporting Patients with Type 2 Diabetes.** N. Bawab, M.P. Schneider, P. Ballabeni, I. Locatelli, O. Bugnon, C. Perraudin. To be submitted to *BMJ Open Diabetes Research & Care*.

2020 **Building Interprofessional Collaborative Practices through Support Programme for Patients with Type 2 Diabetes in Primary Care.** N. Bawab, J.C. Moullin, S. Jotterand, C. Rossier, M.P. Schneider, O. Bugnon, C. Perraudin. To be submitted to *Journal of Interprofessional Care.*

Papers in preparation for peer-reviewed journals

2020 **Literature Review (Part I): Methods of Measurement, Prevalence and Determinants of Medication Adherence in Patients with Type 2 Diabetes.** N. Bawab, C. Perraudin, and O. Bugnon.

2020 **Literature Review (Part II): Association between Medication Adherence and Clinical Outcomes, Healthcare Utilisation/Costs, and Health status/Quality of Life in Patients with Type 2 Diabetes.** N. Bawab, C. Perraudin, and O. Bugnon.

Research report

2019 **Final expert report.** *Evaluation du projet pilote Siscare-DT2 et de son implémentation dans l'offre de soins ambulatoires en Suisse romande. Promouvoir l'adhésion thérapeutique et la sécurité des patients diabétiques de type 2*. N. Bawab, C. Rossier, C. Perraudin, and O. Bugnon, *Federal Office of Public Health*. Full report

Communications to scientific meetings without proceedings

2020 **Implementation and effectiveness of an interprofessional support program for patients with type 2 diabetes in Swiss primary care settings.** N Bawab, M.P. Schneider, I. Locatelli, P. Ballabeni, C. Rossier, C. Perraudin, and O. Bugnon, *Eurodurg 2020 Conference*, Szeged, Hungary, 4-7 March. Poster Prize Nomination: Intervention-Implementation Category

2019 **Adherence to oral antidiabetics: a cohort study of patients participating in an interprofessional chronic patients support program in Switzerland.** N Bawab, M.P. Schneider, I. Locatelli, P. Ballabeni, C. Rossier, C. Perraudin, and O. Bugnon, *ESPACOMP 23th Conference*, Porto, Portugal, 21-23 November. Best Student Contribution Award for oral presentation

2019 **Medication adherence and clinical outcomes of type 2 diabetes patients supported by an interprofessional program (Siscare-DT2 program).** N. Bawab, C. Perraudin, and O. Bugnon, *33rd Seminar in Pharmaceutical Sciences "Me, MYSELF & I"*, Zermatt, Switzerland, 2-5 September. 5-minute thesis oral presentation

2019 **Evaluation of the implementation of an interprofessional support program for type 2 diabetes patients in the French-speaking part of Switzerland.** N. Bawab, A. Georges, C. Rossier, C. Perraudin, O. Bugnon, PhD Day, Geneva, Switzerland, 12 June. Oral presentation

2017 **Implementation of an interprofessional type 2 diabetes medication adherence program in Swiss primary are setting: focus on the patient inclusion phase**. N. Bawab, A. Georges, C. Rossier, C. Perraudin, and O. Bugnon, *ESPACOMP 21th Conference*, Budapest, Hungary, 30 November - 2 December. Poster

Outreach activities

2019 **Certificate of Advanced Studies in Clinical pharmacy**: *Prestations dans les soins de base - Module 7: Implémentation des prestations pharmaceutiques avancées*; *Phases de préparation et de réalisation d'une prestation pharmaceutique*, Geneva, Switzerland, 7 November | Workshop Moderator

2019 ***Forum Médecin-Pharmacien***: *Programme d'accompagnement des patients Siscare, Implémentation auprès des patients diabétiques de type 2*, Montreux, Switzerland, 3 October | Workshop Moderator

2018 **Certificate of Advanced Studies in Clinical pharmacy**: *Prestations dans les soins de base - Module 7: Implémentation des prestations pharmaceutiques avancées*; *Phases de préparation et de réalisation d'une prestation pharmaceutique*, Geneva, Switzerland, 8 November | Workshop Moderator

2017 **Evaluation of the implementation of an interprofessional support program for type 2 diabetes patients in the French-speaking part of Switzerland (SISCare-DT2).** Seminary of Clinical Pharmacy, Basel, Switzerland, 2 November | Presenter (knowledge transfer activity)

2016 ***Forum Pharmacie 2016*** - *Notre rôle dans les soins médicaux de premier recours : Décide-toi – application de tes compétences*, Lausanne, Switzerland, 26 November | Workshop Moderator

2016 **Siscare-DT2: initial training for the launch of the interprofessional program and scientific evaluation**. Vevey 3 March, Neuchâtel 11 March and Geneva 16 March, Switzerland | Moderator

Curriculum Vitae

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EDUCATION

2015-2020 **PhD-candidate in Life Sciences** (Pharmaceutical Sciences), University of Geneva, Unisanté (CH), thesis defence on September 11

2013-2015 **Master in Pharmacy**, Université Libre de Bruxelles (BE), research option | Great distinction

- 2015: 1-month internship in Erasmus Hospital Pharmacy, Brussels (BE)
- 2014-2015: 10-week research work on *Potential of "serious games" in the acquisition of skills of pharmacy students in pharmacy practice* at Unisanté (Pharmacy), Lausanne (CH)
- 2013-2015: 5-month internship in the community pharmacy Zombek, Brussels (BE)

2010-2013 **Bachelor in Pharmacy,** Université Libre de Bruxelles (BE) | The greatest distinction

2004-2010 **General secondary education**, Lycée Maria Assumpta, Brussels (BE), Science and languages option | Distinction

EMPLOYMENT

Since 2016 **Deputy pharmacist**, Unisanté, Pharmacy, Lausanne (CH)

- Validation of prescriptions, management of drug related problems, patient counseling
- Pharmaceutical assistance: drug information centre for health professionals and caregivers
- Medication adherence consultation: interviews based on motivational interviewing techniques, face-to-face with patients in a confidential consultation box | in training

PRICES | AWARDS | FELLOWSHIPS

2020 **Poster Prize Nomination: Intervention-Implementation Category (II6)** for a poster presentation on *Implementation and effectiveness of an interprofessional support program for patients with type 2 diabetes in a Swiss primary care setting*, EuroDURG 2020 Conference, Szeged (HU) | Presenter

2019 **Best Student Contribution Award** for: *Adherence to oral antidiabetics: a cohort study of patients participating in an interprofessional chronic patients support program in Switzerland*; 23rd ESPACOMP Conference, Porto (PT) | Presenter

2015 **Grant** for: *Evaluation of the Siscare-DT2 pilot project and its implementation in primary care in the French-speaking part of Switzerland*; from Swiss Federal Office Of Public Health & Fonds de qualité et de recherche RPB IV/1 (CH) | Investigator

2014 **Scholarship** for an exchange within the G3 agreement between Switzerland, Belgium and Canada | Master internship

LANGUAGES

native French | Dutch
fluent English
intermediate Italian | Arabic
beginner German

INFORMATICS

general Mac OSX | Microsoft Windows | Office
programming Access | Stata | R | R Studio | ITyStudio (ITycom)
pharmacy Golden Gate (Pharmatic) | Carefolio (Siems) | Sispha | Medamigo