REVIEW ARTICLE

DiabetesFlex™ – the effect of PRO-based telehealth and user involvement in care management of patients with type 1 diabetes: Trial protocol for a non-inferiority randomised controlled study

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Abstract

Background: This trial focuses on management of care for patients with type 1 diabetes, patient involvement and use of patient-reported outcome (PRO)-based telehealth. Despite available knowledge on the use of different kinds of PRO measures in diabetes care, studies that use PRO in remote monitoring in diabetes management are scarce.

Objective: The aim of this pragmatic randomised controlled non-inferiority study is to investigate the effect using a PRO-based telehealth intervention, DiabetesFlex, on health outcome, user involvement and healthcare utilisation in patients with type 1 diabetes.

Methods: This trial plans to recruit 400 patients with type 1 diabetes treated at an outpatient clinic at Aarhus University Hospital. The participants will fill in an electronic questionnaire covering health outcome and patient involvement at baseline and at end of the study period (15 month). Data on HbA_{1c}, blood pressure, urine albumin/creatinine ratio and resource (number of contacts and consultations) will be drawn from the patients' medical records at baseline and at 4, 8, 12 and 15 months. Patients will be randomised to either DiabetesFlex™ (a patient-initiated and PRO-driven protocol) or standard care. The patient perspective on the use of DiabetesFlex™ will be explored in a qualitative study.

Conclusion: This study will seek to outline significant knowledge on what matters to the people with diabetes in relation to involvement in care planning. As well as factors related to patients' experiences concerning the use of PRO measures. This is important components in diabetes care management.

Trial registration: ClinicalTrials.gov. NCT03202732

Keywords: Type 1 diabetes, Patient-reported outcome Measures, Patient involvement, Diabetes management, Outpatient follow-up, Randomised controlled trial, Interpretive Description.

INTRODUCTION

Diabetes is a chronic disease, and the provision of individual and effective care is a major challenge, as it requires a wide range of different kinds of care including team-based medical care with planned visits, lifestyle interventions, patient self-management support and decision support.[1, 2] In Denmark, around 30,000 people have type 1 diabetes [3]. Worldwide, 425 million people have diabetes, here of approximately 10 % with type 1 diabetes.[4] Diabetes care and self-management are vital to prevent critical acute complications and to reduce the risk of long-term complications such as cardiovascular disease, nephropathy, retinopathy and neuropathy, which can lead to chronic morbidities and mortality.[1]

Changes in management and care of type 1 diabetes have attracted considerable attention as healthcare systems begin to rethink the understanding of the relationship between patients and healthcare professionals with a clearer and more systematic focus on patient involvement and personalised care planning.[1, 2] This includes actions considering the rights and benefits of patients to play a central role in the healthcare process, as well as a collaborative process in which patients and healthcare professionals can identify and discuss problems and develop an individualised plan to address these.[1, 2].

Traditional diabetes management and care is based on routine follow-up initiated by healthcare professionals.[1, 5] According to American Diabetes Association Standards of Medical Care in Diabetes 2018, follow-up visits should occur at least every 3-6 months and should be individualised for each patient.[1] This corresponds with the Danish recommendations that persons with type 1 diabetes should attend care in an outpatient clinic 3 to 4 times a year to be followed-up by a team consisting of an endocrinologist, a diabetes nurse and a dietician.[3]. Still, there is a lack of evidence on the optimal frequency of follow-up visits as well as assessment of the impact of different kinds of follow-up.

An alternative to routine follow-up initiated by healthcare professionals is the use of patient-reported outcome (PRO)-based telehealth where PRO measures in clinical practice are used as a basis to follow-up, or the use of patient-initiated follow-up where the patients initiate appointment when perceiving a need.[6].

PRO is defined as *"a measurement based on a report that comes from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's report by a clinician or anyone else"*.[7] The PRO measures can includes both the patient's physical symptoms and psychosocial well-being as well as questions related to self-management and health behaviour.[8] PRO instruments have been introduced in many different settings and conditions as a tool to evaluate the need for outpatient follow-up.[9-11] PRO measures can be used as a foundation for decision-making regarding follow-up as the PRO measures often include a PRO-based automated decision algorithm. Based on the reply the patients and the healthcare professionals make decisions regarding treatment and care need.[8] The use of PRO in routine clinical care for patients with diabetes is limited as PRO measures in diabetes care are mostly used as a screening tool and in research.[12]. Still, studies show that the use of PRO influences the care and can be valuable for both the care team and the patient with diabetes as the use of PRO allows the patients to report systematically on symptoms and provide healthcare professionals with a better insight of the patient's perceptions of their health and their disease.[12]. This is consistent with additional studies including patients with other chronic conditions, which demonstrate how use of PRO in routine care can be an effective way for healthcare professionals to understand the patient's perspective on the disease, including psychosocial and behavioural problems, support individualisation of treatment, optimise communication and monitor the effect of treatment.[10, 12-14]. Patient-initiated follow-up may increase patient involvement as it allows patients to have a central position in care planning.[6]. To our knowledge, no studies on patients with type 1 or type 2 diabetes have systematically investigated the use of patient-initiated follow-up. Other studies on patients with breast cancer, inflammatory bowel disease and rheumatology diseases concluded that patient-initiated follow-up resulted in significantly fewer outpatient appointments, similar or improved patient satisfaction, quality of life and clinical outcomes.[5, 6] Studies investigating the use of PRO measures and different kinds of follow-up in relation to patients with type 1 diabetes are needed.[6]

Even though individual people with type 1 diabetes may have different care needs and may receive different treatments, all people with type 1 diabetes have to some extent symptoms and burdensome conditions. Their condition could triggered by poor blood glucose regulation, the burden of being in medical treatment or living with a chronic disease which requires constant focus.[1] Hence, self-management is vital in diabetes care [15] and is defined as "the individual's ability to manage symptoms,

treatment, physical and psychosocial consequences and life style changes inherent in life with long term conditions".[16] Therefore, the choice of PRO tools must cover several topics and symptoms, including both similarities and differences across individual needs of patients with type 1 Diabetes. Furthermore, the PRO tools must take account of the broad needs for dialogue, treatment support and self-management support. To deal with topics and symptoms related to the health outcome for patients with diabetes, a focus on health status and psychological well-being is needed.[17]

Ensuring safe and easy collection of the patients' PRO measurements in clinical practice is vital.[18] PRO-based telehealth Benefits of online or electronic collection of PRO include safe, easy, real-time data collection and symptom monitoring.[12] One example of PRO-based telehealth is when patients use communication and information technologies to complete a PRO questionnaire outside the clinical setting.[19]. For instance, in Denmark, the AmbuFlex telehealth system is implemented in more than twenty diagnostic groups, including more than 31,000 patients and disease-specific questionnaires that have been developed for each diagnostic group.[8, 18] The rationale underlying the use of AmbuFlex method is two-fold in most diagnostic groups. AmbuFlex questionnaire supports patients and healthcare professionals in decision-making concerning the need for a consultation. AmbuFlex supports as well the dialogue between the patient and the healthcare professional during the consultation.[9] In this way, PRO-based telehealth is based on collaboration between the patient and the healthcare professional. It represents a new model for management of care where the patients' PRO measures constitute the basis for making decisions regarding the need for care and contact to the healthcare professional.[2, 20] Therefore, it is worth investigating the use of PRO-based telehealth to collect the PRO measures from patients with diabetes and subsequently use that PRO data to make decisions regarding follow-up in routine care.

Despite the valuable knowledge on the use of different kinds of PRO in diabetes care and the fact that the use of PRO in clinical practice is fast increasing, knowledge in this area is still limited. Especially concerning the use of PRO-based telehealth follow-up in clinical practice for patient with type 1 diabetes, the impact on patient involvement and patients' self-management needs further investigation.[5] This study focuses on testing a diabetes management system called DiabetesFlex™ using PRO-based telehealth follow-up with the aim to improve health outcomes (health status, psychological well-being, HbA1c), self-management, patient involvement and healthcare utilisation. We hypothesise that DiabetesFlex™ makes it possible for patients to influence the diabetes care they need as well as the form and content of the consultation without compromising clinical outcome and patient safety.

The aim of this pragmatic randomised controlled non-inferiority study is to investigate the effect of the use of DiabetesFlex™ on health outcome, user involvement and healthcare utilisation. We hypothesise that the use of DiabetesFlex™ is non-inferior compared to standard care with respect to glycaemic control (HbA1c), and that it will lead to a higher degree of patient involvement and a decrease in total number of consultations. Furthermore, we aim to identify if any specific sub-population within the type 1 diabetes population would benefit significantly from using DiabetesFlex.

2. METHODS

2.1 Design

This is a pragmatic, two-armed, parallel group, randomised non-inferiority controlled trial.[21] Participants will be randomised to either DiabetesFlex™ Care or standard care. The study

follows the standard protocol items recommendation for clinical trials (SPIRIT) and Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension.[22]

2.2 Setting

The study is conducted in Denmark where the routine care of persons with type 1 diabetes is managed at publicly financed outpatient hospital clinics. The study will be conducted at the adult outpatient clinic, Steno Diabetes Centre Aarhus (SDCA), Aarhus University Hospital. Approximately 1,600 patients with type 1 diabetes are treated at SDCA.

2.3 Development of DiabetesFlex™ Intervention

From May 2016 to April 2018, healthcare professionals (endocrinologists, diabetes nurses and dieticians) and the AmbuFlex team developed and tested DiabetesFlex™ and the AmbuFlex Diabetes specific PRO Questionnaire (Table 1) in collaboration with patients from Steno Diabetes Centre Aarhus (SCDA), Aarhus University Hospital.

The development and test of DiabetesFlex™ followed a systematic approach.[8, 9] The AmbuFlex Diabetes specific PRO Questionnaire is based on both validated PRO instruments as the 36-Item Short Form Health Survey (SF-36), WHO-Five Well-being Index (WHO-5) and Problem Area In Diabetes (PAID)[14, 23] and study-specific questions developed based on clinical consensus (e.g. questions regarding regular eye check, regular food check, erectile dysfunction). The AmbuFlex Diabetes Questionnaire aims to support the patient and the healthcare professionals in the evaluation of the patient's condition and to estimate the need for care. The content of the questionnaire is designed to allow substitution for a consultation. A team of doctors, nurses, dieticians and the AmbuFlex project manager developed the questionnaire after identifying relevant domains. After consensus was reached concerning the questionnaire, 12 patients were interviewed as part of the initial pilot test of the questionnaire. Cognitive interviewing was used as a framework for testing the questionnaire.[24] The patients were asked to think aloud while completing the questionnaire. Afterwards, a semi-structured interview was performed, considering relevance of the questionnaire and aspects such as questions that were difficult to understand or to answer. The patients were also asked whether they would consider using the questionnaire as a part of the follow-up appointments. The pilot test led to minor changes in questionnaire.

A group of 22 patients, 11 doctors and 4 diabetes nurses then started to use the ”DiabetesFlex™" and "AmbuFlex Diabetes Questionnaire". Two months after, focus group interviews were performed with patients and healthcare professionals, aiming to provide information of both the patient perspective and the clinical perspective on implementing PRO-based telehealth follow-up. The focus group interviews was performed among healthcare professionals and concerned matters such as the use of PRO-data in follow-up appointments, workflow, documentation and use of the AmbuFlex system. Patients were interviewed concerning their experiences of using the website and technical matters considering receiving and completing the questionnaire. In addition, patients were interviewed about aspects of using the questionnaire as a basis for the consultation. Based on the focus groups, guidelines were made covering DiabetesFlex™, how to handle the AmbuFlex system and how to conduct a DiabetesFlex™ consultation. In addition, patients’ information was scrutinized for minor revisions.

The user interface and website are similar to other AmbuFlex PRO-based telehealth systems.[8, 9]

Table 1 The content of AmbuFlex Diabetes questionnaire for fixed or optional consultations

Fixed consultation (The first and the fourth)		Optional consultation (the second and the third)	
Page 1	SF36 well-being question [14]	Page 1	SF36 well-being question [14]
	WHO-5 Well-being Index [23]		WHO-5 Well-being Index [23]
Page 2	HbA_{1c}	Page 2	HbA_{1c}
	Home-based blood pressure monitoring		Home-based blood pressure monitoring
	Weight		Weight
Page 3	Incidents of hypoglycaemia (Defined by ADA's classification of hypoglycaemia, Level 1-3 [1])	Page 3	Incidents of hypoglycaemia (Defined by ADA's classification of hypoglycaemia, Level 1-3 [1])
	Diabetes complications (experienced pain in the chest, pain in the legs, breathlessness or wounds)		Diabetes complications (experienced pain in the chest, pain in the legs, breathlessness or wounds)
Page 4	Regular eye check, regular food check, erectile dysfunction (only men) and peripheral neuropathy.	Page 4	The patients' evaluation of the need for diabetes care (Options: a face-to-face consultation, a telephone consultation or no consultation).
Page 5	The PAID scale [14]	Page 5	The patients' evaluation of which healthcare professional they wish to consult (Options: an endocrinologist, a diabetes nurse or a dietician).
Page 6	The PAID scale continued [14]	Page 6	Topics patients may want to talk with the healthcare professional about: adjustment of insulin dose, dietary issues, weight, diabetes medicine, social support and expectations to the healthcare professional
Page 7	Topics patients may want to talk with the healthcare professional about: adjustment of insulin dose, dietary issues, weight, diabetes medicine, social support and expectations to the healthcare professional		

2.3 Participants

- Persons with type 1 diabetes treated at SDCA, Aarhus University Hospital, who meet the inclusions criteria (Table 2), will be sequentially enrolled.

Table 2 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Participants of 18 years or older • More than 1 year of a Type 1 diabetes diagnosis • Ability to use the Danish National Health web-site on healthcare www.sundhed.dk • Mentally well-functioning • Ability to understand, read and write Danish	• Cognitive impairment • Pregnancy

2.4 Randomisation

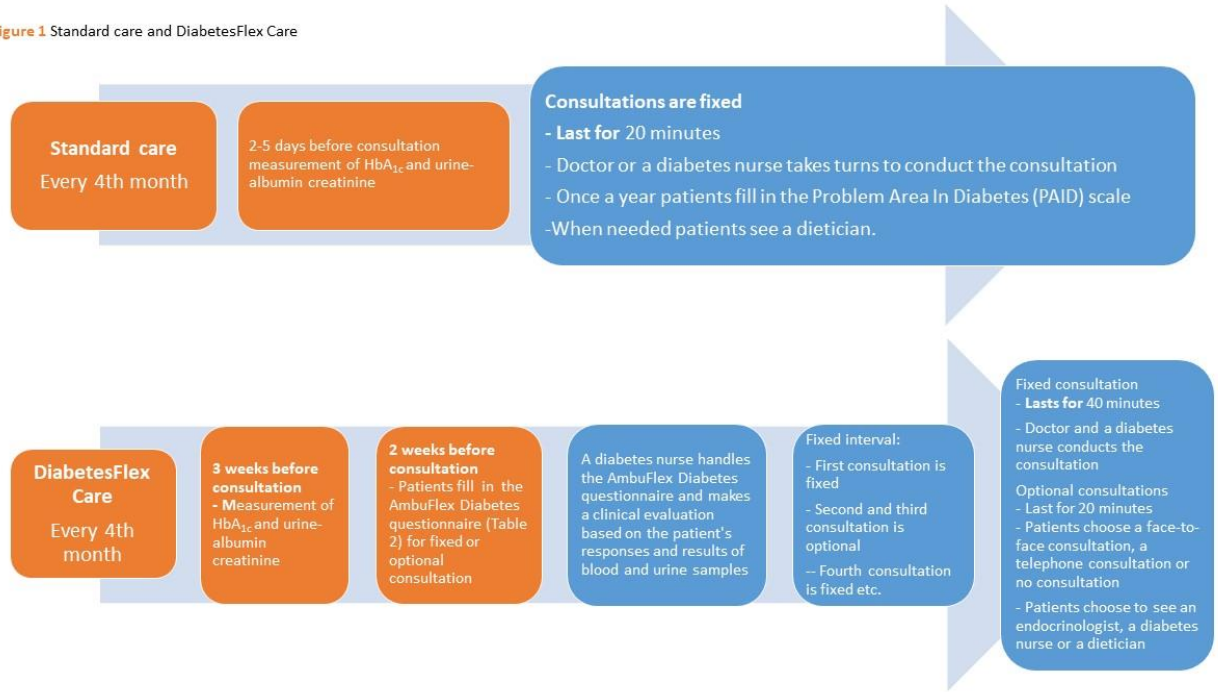
The participants will be randomised 1:1 to standard care or the intervention (DiabetesFlex™ care), stratified on the HbA_{1c} level (< 59 mmol/mol or >58 mmol/mol). This level of HbA_{1c} (58 mmol/mol) was chosen as it is the treatment goal for patients with higher rates of acute and chronic diabetes complications.[1, 3]

2.5 Intervention

2.5.1. Standard care arm

The standard care (Fig. 1) consists of routine face-to-face consultations every fourth months with either a doctor or a diabetes nurse; the healthcare professionals initiate consultations. Furthermore, based on the judgement of either the patient or the healthcare professionals, patients also see a dietician.

Figure 1 Standard care and DiabetesFlex Care



2.5.2 Intervention arm

DiabetesFlex™ is diabetes care (Fig. 1) which incorporates the AmbuFlex PRO-based telehealth system and the use of the AmbuFlex Diabetes specific PRO Questionnaire (Table 1).

When assigned to DiabetesFlex™, patients are offered pre-scheduled consultations every fourth month during the 15 month observation period. Two weeks prior to each consultation, patients fill in the AmbuFlex Diabetes specific PRO Questionnaire for either fixed or optional consultation electronically (Table 1). The first consultation in DiabetesFlex™ is a face-to-face consultation with an endocrinologist and a diabetes nurse. The last two consultations in the annual cycle are optional, and the patient may choose to have a face-to-face consultation, change the consultation to a telephone consultation or cancel the consultation. The first of two optional consultations are scheduled with participation of a diabetes nurse and the second with an endocrinologist.

Prior to the three consultations and before the patients fill in the AmbuFlex Diabetes questionnaire for either a fixed or an optional consultation electronically (Table 1), patients use the Danish National Health website (http://www.sundhed.dk) to check the results of their recent HbA_{1c} test. Patients self-measure their blood pressure and weight. To increase the response rate, up to three reminders are sent to non-respondents automatically, before non–responders are contacted directly by a diabetes nurse by telephone and are asked to fill in the questionnaire. A diabetes nurse handles all questionnaires. In relation to the optional consultation, the diabetes nurse makes a clinical evaluation based on the patient's response to the questionnaire. If there are any doubts or discrepancies between the patient's response and the clinical evaluation, the nurse will contact the patient by phone. Otherwise, based on the clinical evaluation, the diabetes nurse assigns the patient to a face-to-face consultation, a telephone consultation or no consultation including a scheduled date to fill in the next questionnaire and for the outpatient consultation.

2.6 Outcomes

The primary outcome is non-inferiority with respect to HbA_{1c}. Pre-specified secondary outcomes for Health outcome is SF36 well-being questions , WHO-5 Well-being Index[23] , The Patient Areas In Diabetes Scale (PAID) [14], blood pressure and urine albumine/creatinine ratio. Outcomes for "Patient involvement" is five generic questions concerning patient involvement[25], The Patient Activation Measure (PAM)[26] and The Health Literacy Questionnaire[27]. Outcome for use of resources includes number and type of consultations, registered non-attendance and healthcare professionals involved in the consultations. Table 3 outlines the three outcome areas: 1) Health outcome, 2) Patient involvement and 3) Resources.

Table 3 Design of the DiabetesFlex trial according to the SPIRIT checklist

	STUDY PERIOD						
	Enrolment	**Allocation**	**Post-allocation**				**Closeout**
TIMEPOINT:	***M0***	**$M0_1$**	***M0***	***M4***	***M8***	***M12***	***15t***
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation	X						
INTERVENTIONS:							
DiabetesFlex: Deliver blood sample and urine sample, blood pressure self-measurement, read result of HbA_{1c}, answer AmbuFlex Diabetes questionnaires (Table 1)			X	X	X	X	
Standard care: Deliver blood sample and urine sample			X	X	X	X	
ASSESSMENTS:							
Health outcome							
HbA_{1c}, blood pressure, urine Albumine/creatinine ratio	X		X	X	X	X	x
The SF36 well-being questions [14]	x						x
WHO-5 Well-being Index [23]	X						X
The Patient Areas In Diabetes Scale [14]	X						X
Patients involvement	X						X

Five generic questions concerning patient involvement [25]							
The Health Literacy Questionnaire (HLQ) sub scales 6 and 9 [27]	X						X
The Patient Activated Measure (PAM) [26]	X						X
Healthcare utilisation							
Consultation: Number, type, non-attendance, healthcare professional involved in the consultations		X	X	X	X		X
Patients characteristics							
Socio-demography	x						x
Treatment and monitor device							

2.7 Sample size

The non-inferiority design means that the sample size calculation is based on an expectation of no change in HbA1c level (baseline to 15 month) between DiabetesFlex™ and Standard care. The difference is defined as DiabetesFlex™ - Standard care. The upper limit of the 95% CI difference (the non-inferiority margin) is defined as 0.4% following the standard practice in diabetes research.[28]

Given a statistical power of 90%, p-value 0.05 and allocation ratio 1:1, the estimated sample size is 109 patients in each group. To our knowledge, this is the first RCT-study on patients with diabetes and the use of PRO-based telehealth, and we are short on knowledge regarding dropouts. Therefore, to account for attrition, loss to follow-up, we plan to recruit 400 participants.

2.8 Recruitment

Patients' pathway from inclusion to data collection is outlined in Table 3, which provides an overview of recruitment, randomisation and study timeline.

Patients will be invited to participate in the study by electronic mail. The invitation will contain an invitation to be informed orally and in writing about the study and a link to answer if the patient wishes to hear more about the study. If patients do not reply to the electronic invitation, they will be invited at their next consultation in the outpatient clinic.

2.8 Randomisation and allocation

Patients who agree to participate will fill in the baseline questionnaire before randomisation (Table 3).

Then participants will be sequentially randomised to DiabetesFlex™ or Standard care. The randomisation procedure will be handled using the RedCap randomisation module (36). To increase the statistical power, groups will be stratified for HbA_{1c} (< 59 mmol/mol or >58 mmol/mol).

No blinding of treatment allocation will be possible because the patients and healthcare professionals are explicitly involved and because the intervention and the standard care are obviously different.

Depending on the outcome of the randomisation, patients in the intervention group receive extended information about DiabetesFlex™, the use of AmbuFlex PRO-based telehealth, self-measurement of blood pressure, and information on how to use the health website Sundhed.dk. The information will be based on the website of the project "www.DiabetesFlex.auh.dk".

2.9 Study timeline, data collection and analysis

2.9.1 Study timeline

The duration of the data collection period for each patient is 15 months. Recruitment started in October 2017 where the first patient was included, and the last patient was included in February 2019. Final data collection will be finished in June 2020. Attempts to minimise loss to follow-up will be handled by e-mailing the participant two weeks before the end of the study. Table 3 clarifies the design of the DiabetesFlex trial according to the SPIRIT checklist.[22]

2.9.2 Data collection methods

All data will be stored within Redcap, which is a secure web application for managing online surveys and databases [29]. Data on Health outcome, patient involvement and patient characteristics will be collected electronically by using RedCap. Data on healthcare utilisation and some patient characteristics will be collected from the patients' medical record. Patients will fill in this questionnaire electronically either at home or at the outpatient clinic (Table 3).

2.9.3 Statistical methods

Our analysis will be by intention-to-treat. The primary outcome (HbA1c) will be analysed by a random effect model including random intercept and slope to account for the repeated measurement within individuals. If the differences of HbA1c (DiabetesFlex™-Standard Care) are below 0.4%, the DiabetesFlex™ care is considered to be at least equal to standard care. Characteristics of the patients (PRO score and use of consultations) will be summarized using descriptive statistics (means and standard deviations, medians and interquartile ranges, or frequencies and percentages as appropriate), and a comparison of these data will be made between DiabetesFlex™ and Standard Care. The estimates will be presented with 95% confidence interval, and the results will be considered significant if $p< 0.05\%$. All statically, analyses will be performed in Stata14.

3. PATIENTS' PERSPECTIVES ON THE USE OF DIABTESFLEX™

In addition to the RCT, a qualitative Interpretive Description (ID)[30] study of the patients' perspectives of the DiabetesFlex™ intervention will be carried out. The study includes 25 patients from the DiabetesFlex™ intervention group. To increase power of the study, patients will be purposively sampled with a focus on age, gender, HbA_{1c} and preferred patient role. All 25 patients will be interviewed approximately two weeks after the end of the RCT study. The interviews will take place in the participant´s home or at the outpatient clinic. An interview-guide based on literature concerning the use of

PRO measures, diabetes care and the patients' use of and responses to the AmbuFlex Diabetes questionnaire will be developed. As a minimum, the interview-guide will cover the following themes: 1) Patient involvement; 2) Content of the consultations; 3) Changes in the patient's role in diabetes care; 4) Confidence in diabetes care based on DiabetesFlex.

In accordance with ID , data analysis will be inductively performed concurrently with data collection and include memo-writing, synthesising, theorising, and re-contextualising.[30] The analysis and process of coding will lead to a coherent interpretation of the characteristic patterns of the patients' experience of DiabetesFlex™ compared to previous experiences with diabetes care. The software programme Nvivo12 will support the organisation and analysis of data.

4. Dissemination

The study results will be disseminated through peer-reviewed publications and conference presentations. Also none scientific articles will be published in relevant journals.

5. Patient and public involvement

Patients were involved in the development and test of DiabetesFlex. All participants will be invited to a meeting to hear and discuss the result of the study.

6. Discussion

In this study, the success criteria are to generate knowledge and directions for ways to reframe or to optimise the future management of diabetes care. This is a pragmatic trial in the sense that the intervention is conducted within the framework of the organisational and clinical strengths and weaknesses of the endocrinology outpatient clinical service [21].

The pragmatic clinical trial design is chosen in this study because it is especially designed to help to choose between options for care and not only to generate knowledge regarding one biological change.[21] This means that the result may not only be valid and useful for others but also be highly applicable in other outpatient clinics. Healthcare professionals can immediately use the results to optimise the management in diabetes care.

Knowledge on what matters to the people with diabetes in relation to involvement in care planning and factors related to patients' experiences concerning the use of PRO measures are important components in diabetes care management [31]. As Reaney and colleagues outlined, it is important to look beyond just biomedical efficacy to understand the true impact of treatment strategies in diabetes [31]. Incorporating the use of PRO in diabetes care will provide knowledge on the patients' experiences of living with diabetes. It may be a vital component when patients and healthcare professionals make diabetes healthcare decisions.

In conclusion, the DiabetesFlex™ study is a pragmatic randomised controlled trial aiming to generate evidence-based knowledge on the use of PRO-based telehealth follow-up and user involvement in diabetes care management.

7. Ethics Approval and Consent to Participate

The study is conducted in accordance with the Declaration of Helsinki II.[32] The study is approved by the Danish Data Protection Agency (record no. 2012-58-006) and by the Central Denmark Regional Committee on Health Research Ethics (record no. M- 2017-139-17). Patients are informed orally and in writing about the content, aim and possible side effects of the study. Participants are informed that participation is voluntary. Refusal to participate will involve no penalty or loss of benefits to

which the subject is otherwise entitled. Furthermore, participants may discontinue participation at any time without any consequences or loss of benefits, to which the subject is otherwise entitled. The study is registered with clinicalTrials.gov. NCT03202732.

8. Funding

This research is funded by the Novo Nordic Foundation (Reference number: NNF16OC0022382), by Aarhus University Hospital, Department of Endocrinology and Internal Medicine and by Aarhus University Hospital, Steno Diabetes Centre Aarhus

9. Conflict of Interest Statement

The authors declare to have no conflict of interest.

10. Authors' contribution

ALJ has contributed to the development of DiabetesFlex, the planning of the study, study design, the preparation of the manuscript and approvement of the final version. KL has contributed to the planning of the study, study design, the preparation of the manuscript and approvement of the final version. KL has contributed to the development of DiabetesFlex, the planning of the study, study design, the preparation of the manuscript and approvement of the final version. NHH has contributed to the planning of the study, study design, the preparation of the manuscript and approvement of the final version. NHH has contributed to the development of DiabetesFlex, the planning of the study, study design, the preparation of the manuscript and approvement of the final version. TKH contributed to the planning of the study, study design, the preparation of the manuscript and approvement of the final version. LMVS has contributed to study design, the preparation of the manuscript and approvement of the final version. LBO has contributed to the development of DiabetesFlex, the preparation of the manuscript and approvement of the final version. TL has contributed particularly with the statistical analysis.

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