Bicycle Exercise and Lifestyle Intervention in Newly Diagnosed Diabetes

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BELIFE Study

Clinical Study Protocol

Study Type:	Randomized, multi-center, proof-of-concept study
Study Categorisation:	Risk category A
Study Registration:	EKNZ 2018-01920 ClinicalTrials.gov: NCT03827382 Swiss National Clinical Trials Portal (SNCTP) SNCTP000003087
Study Identifier:	BELIFE-Study
Sponsor, Sponsor-Investigator or Principal Investigator:	Prof. Dr. med. Marc Y. Donath, University Hospital Basel, Endocrinology, Diabetes and Metabolism Petersgraben 4, CH-4031 Basel,
Investigational Product:	n/a
Protocol Version and Date:	Version 1.10 of 30.10.2023

Signature Page

Study number	EKNZ 2018-01920
Study title	Bicycle Exercise and Lifestyle Intervention in Newly Diagnosed Diabetes– BELIFE Study

The sponsor-investigator and trial statistician have approved the protocol version 1.10 of 30.10.2023 and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Sponsor-investigator:

Prof. Dr. med. Marc Y. Donath, University Hospital Basel, Endocrinology, Diabetes and Metabolism, Petersgraben 4, CH-4031 Basel

Basel	21.11.2023 | 16:42 CET	Marc Donath	
Place/Date		Signature	

Local principal investigator at study site:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Site	Cantonal Hospital Solothurn, Clinic Olten, Baslerstrasse 150, CH-4600 Olten, +41 62 311 44 94
Principal investigator	Dr. med. Matthias Hepprich, Leitender Arzt

Basel	21.11.2023 | 14:28 MEZ	Matthias Hepprich
Place/Date		Signature

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STUDY SYNOPSIS

Sponsor / Sponsor-investigator	Prof. Marc Donath, MD
Co-Investigators	Prof. Roland Bingisser, MD Prof. Philipp Schuetz, MD Prof. Gottfried Rudofsky, MD Dr. Matthias Hepprich, MD
Study Title:	Bicycle Exercise and Lifestyle Intervention in Newly Diagnosed Diabetes
Short Title / Study ID:	BELIFE
Protocol Version and Date:	Version 1.10 of 30.10.2023
Trial Registration:	ClinicalTrials.gov, Swiss National Clinical Trials Portal (SNCTP) EKNZ 2018-01920
Study Category	A
Clinical Phase:	N/A
Background and Rationale:	Lifestyle intervention is a fundamental aspect in the treatment of type 2 diabetes. Implementation of lifestyle changes early after diagnosis often suffices to control metabolic dysregulation and may even have a durable impact. However, implementation of these changes is often difficult for multiple reasons including noncompliance as well as doubt on efficacy of sport and diet changes compared to drugs. Furthermore, most patients with type 2 diabetes remain asymptomatic for a prolonged period of time. Thus, they lack an immediate relief of symptoms and do not feel the benefit of changes in lifestyle. Often, untreated type 2 diabetes first manifests itself with symptoms of polyuria and polydipsia. This offers a unique opportunity to demonstrate the potential of lifestyle changes. However, in daily practice, symptomatic patients with polyuria and polydipsia or with HbA1c levels >10% at diagnosis are typically referred to an emergency room, hospitalized and treated with drugs as a first line treatment. In the present study, we aim to implement a lifestyle intervention as a first-line treatment in recent onset type 2 diabetes. In the emergency room, the bed will symbolically be removed and the patient requested to perform a bicycle exercise. Non-ER patients will be invited to perform the bicycle exercise as soon as possible. We expect from this educational trigger that patients will realize the therapeutic power of sport. Preliminary interventions using this approach at our emergency room demonstrated the potential of such an intervention. However, internal and external validation, efficacy and safety of a lifestyle intervention in an emergency room remain to be shown in a multi-center controlled study.
Objective(s):	The aim of the study is to test the efficacy, feasibility, and safety of a bicycle exercise followed by an intensive lifestyle intervention for 3 months in patients with recent onset and medically untreated type 2 diabetes.

Outcome(s):	**Primary:**
	The primary endpoint of this study is achievement of metabolic control without anti-diabetic medication 3 months after study enrollment. For the purpose of this study, metabolic control is defined as an HbA1c below a target stratified for three groups according to HbA1c at baseline: HbA1c >14% → target < 10%; HbA1c < 14% and > 10% →target < 8%; HbA1c < 10% →target < 7.5%
	
	Secondary:
	- Absolute HbA1c reduction per stratification group (groups consist of HbA1c > 14 %, HbA1c < 14 % and > 10 % and HbA1c < 10 %)
	- Change of HbA1c at 6 and 12 months after enrollment compared to control group
	- Proportion of patients achieving target per stratified group after 3 and 6 months without anti-diabetic medication other than Metformin
	- Changes in pH, base excess and bicarbonate 90 minutes after bicycle exercise compared to baseline
	- Change of weight at 3, 6 and 12 months after enrollment compared to baseline and to standard of care
	- Changes in blood glucose at the end of, as well as 30 and 90 minutes after bicycle exercise compared to baseline
	- Feasibility of bicycle exercise at study enrollment in the ER, defined as absence of problem reports through the study team (e.g. patient cooperation)
	- Safety of bicycle exercise, defined as:
	  o Absence of SAEs during the exercise
	  o No signs of acute cardiopulmonary decompensation in patients during bicycle exercise
	  o No necessity to prematurely terminate the bicycle intervention because of other health or safety concerns
	- Safety of intensive lifestyle intervention within 3 months following study enrollment, with the following endpoints:
	  o Number of SAEs in the intervention group compared to the control group
	  o Number of rescue medication administered in the intervention group compared to the control group
	- Length of initial hospitalization, as well as number and length of re-hospitalizations and unplanned re-consultations within 3 months after initial consultation
	- Changes in physical activity at 6 months compared to baseline assessed by SIMPAQ questionnaire (Endpoint: hours of physical activity)
	- Changes in physical activity at 3 and 6 months compared to baseline assessed by actigraph (Endpoint: Stepgoal reached)
	- Number of anti-diabetic medication at 30, 60, 90 days, as well as 6 months and one year compared to baseline in both arms
	- Proportion of patients receiving insulin therapy after 6 months and one year in the intervention group compared to the control group
	- Absolute health-care related costs at 3, 6 and 12 months in both arms
	- Quality of life at 6 months in the intervention group compared to standard of care as assessed by SF-36 questionnaire.

Study Design:	Randomized, multicenter, proof-of-concept study.

Inclusion / Exclusion Criteria:	**Inclusion criteria:** - Informed consent as documented by signature - Type 2 diabetes diagnosed within the last two years according to the American Diabetes Association (ADA) criteria - Age ≥ 18 years - HbA1c ≥ 7.5 % **Exclusion criteria:** • Clinically instable patient as defined by the physicians on duty including signs of new cardiac ischemia in the ECG, systolic blood pressure ≥ 200 mmHg, fever ≥ 38.5 °C, symptoms of SIRS or reduced vigilance. • Anti-diabetic medication for ≥ 24 hours • Inability to perform a bicycle exercise during 30 minutes • Previous lifestyle-intervention by an endocrinologist • Engagement in physical activity more than five times per week • Enrollment in other interventional study
Measurements and Procedures:	Measurement of clinical parameters (heart rate, blood pressure), venous blood gas analysis (pH, pCO2, base excess, bicarbonate) at baseline and 120 min after beginning of bicycle exercise. Blood glucose levels at baseline and 30, 60 and 120 min after beginning of bicycle exercise. Blood glucose levels, vital parameters, concomitant medication after 2, 7, 30, 60 and 90 days; HbA1c at baseline, 2 (only intervention group), 3 and 6 months and one year; physical activity at baseline, 3 and 6 months. In the intervention group additional self-measurements of blood glucose levels during the first week and within the week before visit at day 30 and 90 after randomization.
Study Product/Intervention:	Patients will be randomized either to standard care or to a bicycle exercise followed by an intensive lifestyle intervention on top of non-pharmacological standard care. After rehydration, patients allocated to the intensified lifestyle intervention group will be instructed to perform 30 minutes of bicycle exercise at 60 % of the calculated maximum heart rate (according to Franckowiak et al.)[20] followed by an intensive lifestyle intervention. Patients will be discharged if the clinical status is stable and no comorbidities require further hospitalization. Follow-up visits at the Clinic of Endocrinology for further instructions and consultation will be carried out after 2, 7, 30, 60 and 90 days, half a year and a year. In order to monitor blood glucose levels, patients will be instructed on visit 2 to take measurements at home and will be asked to send their fasting glucose levels of the first week to the study team for monitoring of the metabolic situation. This will also be done in the week before visits of day 30 and 90. The schedule for the intervention arm consists of 3 to 5 aerobic training sessions (duration 15-40 minutes each) and 2 resistance trainings per week, as well as weekly motivational coaching via telephone by the study psychologist. Everyday activity will be objectively monitored using the patient's mobile phone and a blinded actigraph (activity tracker). Exercise sessions will be monitored by weekly phone calls and documented. To assess baseline physical activity all patients will fill in the SIMPAQ questionnaire at baseline and at 6 months.
Control Intervention (if applicable):	The control arm will consist of the standard care delivered by the involved centers.

Number of Participants with Rationale:	The aim of this study is to assess whether bicycle exercise followed by an intensive lifestyle intervention can sufficiently restore metabolic control without anti-diabetic drugs at 3 months after study enrollment as compared to a standard of care control group. Based on our clinical experience we expect that 80 % in the intervention group will reach the primary endpoint of metabolic control with no anti-diabetic drugs compared to only 40% in the usual care control group. The inclusion of 28 patients per group (n total 62 patients including 10 % lost to follow-up) will provide 80 % power at an alpha level of 0.05.
Study Duration:	The primary endpoint will be assessed at 3 months. The overall study duration is 1 year.
Study Schedule:	11/2018 of First-Participant-In (planned) 12/2025 of Last-Participant-Out (planned)
Investigator(s):	Investigators: Beckey Trinh, MD, Jonathan Mudry, MD-PhD, and Matthias Hepprich, MD Division of Endocrinology, Diabetes and Metabolism Department of Internal Medicine University Hospital Basel, Switzerland +41 61 265 25 25 beckey.trinh@usb.ch jonathan.mudry@usb.ch matthias.hepprich@usb.ch
Study Centers:	Department of Medicine, University Hospital Basel Department of Medicine, Cantonal Hospital Olten Hôpital du Jura - site de Delémont
Statistical Considerations:	All subjects will be considered on a per-protocol basis. For our primary analysis, we will compare the two arms with a Fisher's exact test and we will also estimate effect size with a logistic regression model reporting odds ratios (OR) and corresponding 95% confidence intervals. All tests will be two-tailed; $p<0.05$ will be defined as significant. Data will be analyzed using Graph Pad Prism, STATA and IBM SPSS.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

ABBREVIATIONS

ADA	American Diabetes Association
AE	Adverse event
ASR	Annual safety report
BASEC	Business Administration System for Ethical Committees, (https://submissions.swissethics.ch/en/)
BGA	Blood gas analysis
CA	Competent authority (e.g. Swissmedic)
CEC	Competent ethics committee
ClinO	Ordinance on Clinical Trials in Human Research *(in German: KlinV, in French: OClin, in Italian: OSRUm)*
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
CTU	Clinical Trial Unit
DSBG	Departement für Sport, Bewegung und Gesundheit
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EKNZ	Ethikkommission Nordwest- und Zentralschweiz
ER	Emergency room
GCP	Good clinical practice
H_0	Null hypothesis
H_1	Alternative hypothesis
HbA1c	Glycated hemoglobin A
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISF	Investigator site file
ISO	International Organisation for Standardisation
MHR	Maximum heart rate
SAE	Serious adverse event
s.c.	Subcutaneous
SIMPAQ	Simple physical activity questionnaire
SIRS	Systemic inflammatory response syndrome
SNCTP	Swiss National Clinical Trials Portal
SUSAR	Suspected unexpected serious adverse reaction
TMF	Trial master file

STUDY SCHEDULE

Study Periods	ER	Intervention Period								Follow-up	Telephone FU
Visit	1	2	3		4		5		6	7	8
Time (day)	0	2 +/- 1	7 +/- 3	weekly	30 +/- 7	weekly	60 +/- 14	weekly	90 +/- 14	180+/-14	1 year +/-45
Patient information and informed consent	x										
Demographics	x										
Medical history	x										
Medication	x				x		x		x	x	x
ECG (electrocardiograph)	(x)										
In- /exclusion criteria	x										
Physical examination	x										
Vital signs	x	x	x		x		x		x	x	only weight
Fasting blood samples (including glucose, insulin and c-peptide)		x							x	x	
Glycated hemoglobin A1c	x						x		x	x	x
Randomization	x										
Bicycle intervention	x										
Diabetes counselling (i. e. general information, self glucose measurements)		x	(x)								
Nutrition counselling			x								
Telephone (coaching) interview				x		x		x			
Report about physical activity (SIMPAQ)		x								x	
Adverse events	x	x	x		x		x		x	x	
Actigraph readout			x						x	x	
Quality of life questionnaire SF-36		x								x	
Start of Metformin therapy									(x)		

Table 1 Study schedule of the intervention group. (x) optional

Study Periods	ER	standard care period	Follow-up	Telephone FU
Visit	1	6	7	8
Time (day)	0	90 +/- 14	180+/-14	1 year +/-45
Patient information and informed consent	x			
Demographics	x			
Medical history	x			
Medication	x	x	x	x
ECG (electrocardiography)	(x)			
In- /exclusion criteria	x			
Physical examination	x			
Vital signs	x	x	x	only weight
Fasting blood samples (including glucose, insulin and c-peptide)	x	x	x	
Glycated hemoglobin A1c	x	x	x	x
Randomization	x			
Diabetes counselling (i. e. general information, self glucose measurements)	(x)	x		
Nutrition counselling	(x)	x		
Report about physical activity (SIMPAQ)	x		x	
Adverse events	x	x	x	
Quality of life questionnaire SF-36	x		x	
Start of Metformin therapy	(x)	(x)		

Table 2 Study schedule of the control group. (x) optional

1. STUDY ADMINISTRATIVE STRUCTURE

Sponsor, Sponsor-Investigator

Prof. Dr. med. Marc Y. Donath, University Hospital Basel, Endocrinology, Diabetes and Metabolism
Petersgraben 4, CH-4031 Basel

Principal Investigator(s)

Prof. Dr. med. Marc Y. Donath, University Hospital Basel, Endocrinology, Diabetes and Metabolism
Petersgraben 4, CH-4031 Basel, +41 61 265 50 78

Dr. med. Matthias Hepprich, Endocrinology, Department of Medicine Cantonal Hospital Olten
Baslerstrasse 150, CH-4600 Olten, +41 62 311 44 94

Statistician

Prof. Dr. med. Philipp Schütz, Endocrinology, University Department of Internal Medicine Cantonal Hospital Aarau
Tellstrasse 25, CH-5001 Aarau, +41 62 838 41 41

Laboratory

Laboratory analysis will be done by the associated laboratories of the study centers. For the University Hospital Basel: Labormedizin, University Hospital Basel, Petersgraben 4, CH-4031 Basel.

Cantonal Hospital Olten, Central Laboratory, Baslerstrasse 150, CH-4600 Olten, +41 62 311 51 01

Hôpital du Jura - site de Delémont, Laboratoire, Fbg des Capucins 30, 2800 Delémont.

Monitoring Institution

Monitoring will be performed by an independent, professional and certified monitor within the University Hospital Basel.

There will be a total of two visits from the monitor at each study site containing an initiation and a final monitoring visit.

Data Safety Monitoring Committee

Not applicable.

2. ETHICAL AND REGULATORY ASPECTS

The decision of the competent ethics committee (CEC) concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

Study Registration

The study will be registered on clinicaltrials.gov and the Swiss National Clinical Trials Portal (SNCTP) on www.kofam.ch

Categorisation of Study

This is a randomized, multicenter, proof-of-concept study with the risk category A.

Competent Ethics Committee (CEC)

The clinical study will be reviewed and approved by the CEC “Ethikkommission Nordwest- und Zentralschweiz” (EKNZ). Approval by the EKNZ will cover the planned centers Basel and Olten.

Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of good clinical practice (GCP) issued by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), in case of medical device: the European directive on medical devices 93/42/EEC and the ISO Norm 14155 and ISO 14971, the Swiss law and Swiss regulatory authority’s requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

Declaration of Interest

This is an investigator driven study without conflicts of interest.

Patient Information and Informed Consent

The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.

The participant must be informed that his/her medical records may be examined by authorized individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and an informed consent form (ICF) describing the study and providing sufficient information for participant to make an informed decision about their participation in the study.

The formal consent of a participant, using the approved ICF, must be obtained before the participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the ICF, and should be given a copy of the signed document. The ICF must also be signed and dated by the investigator (or his designee) at the same time as the participant sign, and it will be retained as part of the study records.

Participant Privacy and Confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilizing subject identification code numbers to correspond to treatment data in the computer files.

For data verification purposes, authorized representatives of an ethics committee (EC) may require direct access to parts of the medical records relevant to the study, including participants' medical history.

Early Termination of the Study

The sponsor-investigator may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- early evidence of benefit or harm of the experimental intervention

Protocol Amendments

Substantial amendments are only implemented after approval of the CEC and CA respectively.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC/CA. Such deviations shall be documented and reported to the sponsor and the CEC/CA as soon as possible.

All non-substantial amendments are communicated to the CA as soon as possible if applicable and to the CEC within the annual safety report (ASR).

3. BACKGROUND AND RATIONALE

Background and Rationale

Current standards for diabetes care recommend the initiation of pharmacological therapy[16] as well as lifestyle interventions at new onset of type 2 diabetes mellitus[12]. The implementation of regular physical activity and dietary measures are effective in the treatment of type 2 diabetes, resulting in stabilization of plasma glucose in the acute phase, increase in lean body mass and reduction of insulin resistance and glycated hemoglobin A1c. While physical activity is broadly promoted[19] in the medical community as an effective prevention and treatment of glucose intolerance, many patients fail to include lifestyle changes into their daily routines. A study by Morrato et al. discovered that only 38 % of type 2 diabetes patients in the United States engage in regular physical activity, leaving the majority of patients inactive, thus, putting strong emphasis on the need for further efforts to promote physical activity in the diabetes population[13].

The beneficial effects of physical activity on glucose tolerance and blood sugar levels have been shown by several studies. Ried-Larsen et al. did not find equivalence of lifestyle intervention compared to standard diabetes care in respect to glycemic control at 12-months follow-up. However, in the lifestyle intervention group, a reduction of oral anti-diabetic medication was reached in significantly more patients compared to the standard care group[14]. Physical activity has not only been shown to be effective in long-term improvement of metabolic parameters[17], but also has a direct effect on blood glucose levels shortly after by increasing insulin sensitivity of peripheral tissues[18].

In addition to overall health benefits to diabetes patients, lifestyle interventions such as physical activity and dietary measures show the potential to have a cost-reducing impact on the health care system. The “Look AHEAD” trial by Espanlad et al. assessed the impact of lifestyle interventions in diabetic patients on the development of their healthcare costs. They found that applied lifestyle interventions led to a reduction of healthcare costs mainly on the ground of reduced and shorter hospitalizations and fewer needed medications[15].

We believe it is crucial to stress the importance of lasting lifestyle changes for metabolic control from the very point of diagnosis. Intervention early in the course of the disease often suffices to control metabolic dysregulation and may even have a durable impact. However, as mentioned above, multiple reasons including non-compliance as well as doubt about the efficacy of sport and diet changes compared to drugs make a lasting change in lifestyle difficult. Furthermore, most patients with type 2 diabetes remain asymptomatic for a prolonged period of time, leaving patients in doubt about the immediate benefit of lifestyle changes. Often, untreated type 2 diabetes manifests itself for the first time with symptoms of polyuria and polydipsia. This offers a unique opportunity to demonstrate the potential of lifestyle changes. However, in daily practice, symptomatic patients with polyuria and polydipsia are typically referred to an emergency room and are treated with drugs and hospitalized. With this study, we therefore aim to implement lifestyle intervention as first line treatment in new onset type 2 diabetes patients. We expect to achieve a durable educational impact with this approach and to increase the patients’ motivation for glycemic control through healthy lifestyle while keeping pharmacological aids at a minimum.

Investigational Product (Treatment, Device) and Indication

No investigational products are used in this trial.

Preclinical Evidence

Not applicable.

Clinical Evidence to Date

Refer background and rationale.

Explanation for Choice of Comparator (or Placebo)

The control treatment used in this trial is based on the current standard of care for diabetes according to national and international guidelines (American Diabetes 2012). There is no medical disadvantage for the participants of the control group.

Risks/Benefits

Subjects will only be performing the bicycle exercise when they are found to be eligible by the responsible medical doctor with concern to their clinical status. During the remaining study period patients are encouraged to be physically active. This may increase the risk for physical activity associated accidents (i.e. adverse events) but does not represent a greater risk within the study compared to general physical activity in the normal population.

It is expected that intensified lifestyle intervention will generally be beneficial to the subjects and especially with respect to the medical treatment of diabetes and associated co-morbidities. Patients in the intervention group will be monitored closely by the study physicians and psychologist. With the results of this study, bicycle exercise may become an important educational intervention in the emergency setting and thereby of outstanding importance for the further course of diabetes management.

There are no specific risks or benefits for the standard care group receiving routine treatment.

Justification of Choice of Study Population

A total of 62 patients with new onset of type 2 diabetes mellitus will be included in this study.

4. STUDY OBJECTIVES

4.1 Overall Objective

This is a proof-of-concept study to test the efficacy, feasibility, and safety of a bicycle exercise followed by an intensive lifestyle intervention for the following three months in patients with newly diagnosed or medically untreated type 2 diabetes.

4.2 Primary Objective

The primary objective is to investigate whether an intensive lifestyle intervention in untreated type 2 diabetes can adequately lower blood glucose and HbA1c levels compared to conventional standard of care anti-diabetic treatment.

4.3 Secondary Objectives

Secondary objectives are

- To implement methods to monitor patients' activity levels and support motivation for the following training sessions
- To test the impact of an intensive lifestyle intervention on HbA1c-levels and its dependency on the level at baseline
- To assess change of weight at 3, 6 and 12 months after enrollment compared to baseline and to standard of care
- To evaluate changes in heart rate, blood pressure, blood glucose, pH, base excess and bicarbonate after a 30-minute bicycle exercise
- To evaluate re-hospitalization and unplanned re-consultation rate during the study in both arms
- To evaluate changes in physical activity during and after the study intervention compared to baseline
- To evaluate number of anti-diabetic medication at 30, 60, 90 days, as well as 6 months and one year compared to baseline in both arms
- Cost-effectiveness
- To compare changes in quality of life in the intervention group to the standard-of-care group.

4.4 Safety Objectives

- To test the safety and feasibility of a 30-minute bicycle exercise in hyperglycemic patients
- To test the safety of an intensive lifestyle intervention within 3 months following study enrollment

5. STUDY OUTCOMES

5.1 Primary Outcome

The primary endpoint of this study is achievement of metabolic control with intensive lifestyle intervention 3 months after study enrollment. For the purpose of this study, metabolic control is defined as a fasting glucose < 7.6 mmol/l and an HbA1c below a target stratified for three groups according to HbA1c at baseline: HbA1c > 14 % → target < 10 %; HbA1c < 14 % and > 10 % → target < 8 %; HbA1c < 10 % → target < 7.5 %.

5.2 Secondary Outcomes

Secondary outcomes are as follows:

- Absolute HbA1c reduction per stratification group (groups consist of HbA1c > 14 %, HbA1c < 14 % and > 10 % and HbA1c < 10 %)
- Change of HbA1c at 6 and 12 months after enrollment compared to control group
- Proportion of patients achieving target per stratified group after 3 and 6 months without anti-diabetic medication other than Metformin
- Changes in pH, base excess and bicarbonate 90 minutes after bicycle exercise compared to baseline
- Change of weight at 3, 6 and 12 months after enrollment compared to baseline and to standard of care
- Changes in blood glucose at the end of, as well as 30 and 90 minutes after bicycle exercise compared to baseline
- Feasibility of bicycle exercise at study enrollment in the ER, defined as absence of problem reports through the study team (e.g. patient cooperation)
- Safety of bicycle exercise, defined as:
    - Absence of SAEs during the exercise
    - No signs of acute cardiopulmonary decompensation in the patient during bicycle exercise
    - No necessity to prematurely terminate the bicycle intervention because of other health or safety concerns
- Safety of intensive lifestyle intervention within 3 months following study enrollment, with the following endpoints:
    - Number of SAEs in the intervention group compared to the control group
    - Number of rescue medication administered in the intervention group compared to the control group
- Length of initial hospitalization, as well as number and length of re-hospitalizations and unplanned re-consultations within 3 months after initial consultation
- Changes in physical activity at 6 months compared to baseline assessed by SIMPAQ questionnaire (Endpoint: hours of physical activity)
- Changes in physical activity at 3 and 6 months compared to baseline assessed by actigraph (Endpoint: Stepgoal reached)
- Number of anti-diabetic medication at 30, 60, 90 days, as well as 6 months and one year compared to baseline in both arms
- Proportion of patients receiving insulin therapy after 6 months and one year in the intervention group compared to the control group
- Absolute health-care related costs at 3, 6 and 12 months in both arms
- Quality of life at 6 months in the intervention group compared to standard of care as assessed by SF-36 questionnaire.

6. STUDY DESIGN

General Study Design and Justification of Design

This is an investigator-initiated, randomized, parallel design trial with one intervention arm (bicycle exercise followed by intensive lifestyle modification) and one standard-of-care arm in patients with newly diagnosed or medically untreated type 2 diabetes mellitus. The bicycle intervention at enrollment

comprises approximately two hours with pre- and post-preparations and 30 minutes of moderate physical activity on a bicycle. The whole study period takes one year for both arms. Subjects in the intervention arm will be contacted by the study psychologist by telephone on a weekly basis for coaching and follow-up. Actigraph data readout will occur at baseline, 3 and 6 months. Additionally, everyday physical activity will be assessed by the SIMPAQ questionnaire at baseline and 6 months. Regular routine follow-up visits will be done for both groups in the respective hospitals, outpatient clinics or by the subjects' responsible general practitioner to acquire data on vital signs, glucose values and medication as well as adverse events. See **Table 1** for further details.

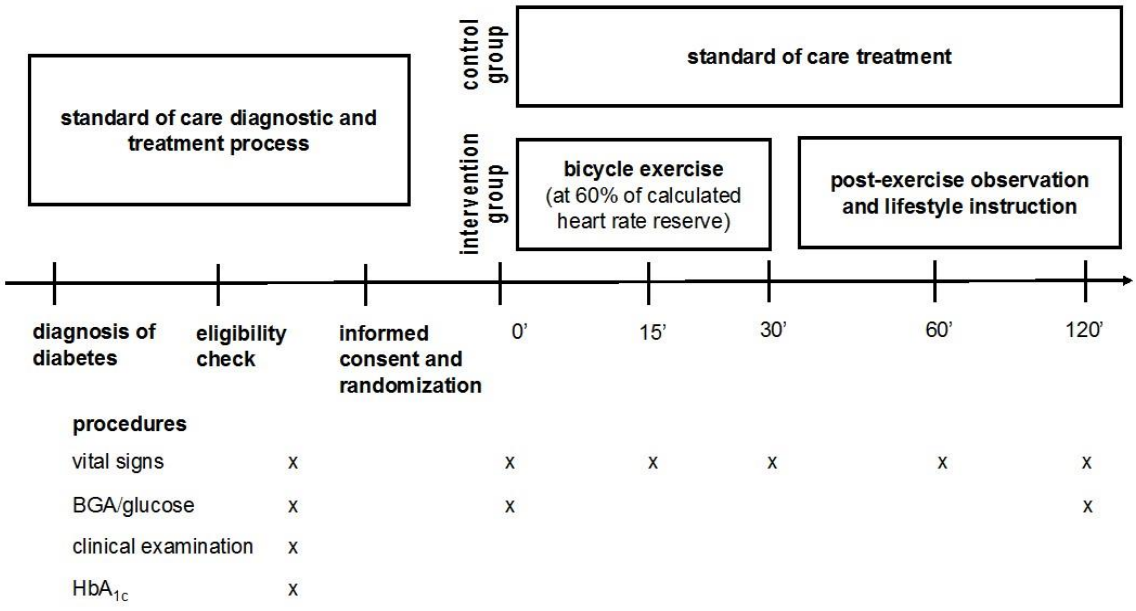

Figure 1 *Schematic overview of study enrollment and initial intervention.*

Methods of Minimizing Bias

6.1.1 Randomization

Participants will be randomized into the "lifestyle intervention" or "conventional anti-diabetic treatment" arm using a computer-generated random number in the electronic data managing application secuTrial®. Participants will be randomized 1:1 to the study groups.

6.1.2 Blinding Procedures

Blinding of patients and study personal is not possible for this study.

7. STUDY POPULATION

Eligibility Criteria

Participants fulfilling all of the following inclusion criteria are eligible for the study

- Able to give informed consent as documented by signature (Appendix ICF)
- Type 2 diabetes diagnosed within the last two years according to the ADA-criteria
- Age ≥ 18 years
- HbA1c ≥ 7.5 %

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:

- Clinically instable patient as defined by the physicians on duty e. g. signs of new ischemia in the ECG, systolic blood pressure ≥ 200 mmHg, fever ≥ 38.5 °C, symptoms of SIRS or reduced vigilance.
- Anti-diabetic medication for ≥ 24 hours
- Inability to perform a bicycle exercise during 30 minutes
- Previous lifestyle intervention by an endocrinologist
- Engagement in physical activity more than five times per week
- Enrollment in other interventional study

Recruitment and Screening

Patients are recruited after seeking medical consultation at the emergency room, medical outpatient clinic of the respective study centers or their general practitioners. Patients will be assessed and enrolled in the study by the study team.

Assignment to Study Groups

Patients are randomized to the intervention or the control arm using a computer-generated number after agreeing to participate in the study.

Criteria for Withdrawal/Discontinuation of Participants

Participants may withdraw or be withdrawn at any time. Subjects who discontinue participation may be replaced. Reasons for discontinuation are:

- Participant withdraws informed consent
- Participant does not comply with study treatment or the concomitant procedures. Non-compliance for this study is defined as completion of less than 50% of the training program during two weeks
- Pregnancy
- Participant is no longer willing to continue the study because of any reason
- The incidence or severity of adverse events (AEs) indicate a potential health hazard to the participant

Withdrawal will be documented in the database with all other study data.

8. STUDY INTERVENTION

Identity of Investigational Products (Treatment/Medical Device)

There is no investigational product nor medical device used.

8.1.1 Experimental Intervention

In this study's interventional group no drugs except for the patient's original medication and Metformin starting after 3 months are used. The 30 minutes bicycle exercise will be performed on a standard bike home trainer.

8.1.2 Control Intervention (Standard Treatment)

Standard therapy for type 2 diabetes usually consists of a variation of oral anti-diabetic medication and/or s. c. insulin therapy as well as a limited lifestyle intervention according to national and international guidelines (American Diabetes 2018)[12].

Administration of Experimental and Control Interventions

8.1.3 Experimental Intervention

Patients allocated to the intervention arm will be instructed to perform 30 minutes of bicycle exercise at 60 % of the calculated maximum heart rate (MHR: 208 x (0.7 – age))[20]. During the following 3 months they will take part in an intensive lifestyle intervention. Patients in the intervention group may also start Metformin therapy (titrated to 1000 mg 1-0-1 unless there is medical contraindication) 3 months after study enrollment. The schedule for the intervention arm consists of 3 to 5 aerobic training sessions (duration 15-40 minutes each) and 2 resistance trainings per week, as well as weekly motivational coaching via telephone by the study psychologist. The training sessions will be put together by a team from the department of physical education of the University of Basel (DSBG, Departement für Sport, Bewegung und Gesundheit). All Patients in the intervention group will receive a training adapted to their capabilities by trainers from the DSBG. The overall physical activity level during the course of the study will be monitored by an actigraph provided by the DSBG and read out at baseline, 3 and 6 months. The weekly step count goal is 70'000 steps per week. Additionally, overall physical activity will be monitored by weekly telephone interviews as not all physical activity (i.e. bike hometrainer) is recorded by the actigraph.

8.1.4 Control Intervention

The control arm for this study will receive standard type 2 diabetes treatment after study enrollment. This treatment usually consists of a limited lifestyle intervention and oral anti-diabetic medication (i.e. Metformin, SGLT2-inhibitors, DPP-Inhibitors, GLP-1-receptor agonists etc.) or insulin therapy.

Dose/Device Modifications

Therapy for the participants of the intervention group has to be reassessed if:

- glucose values remain elevated above 15 mmol/l for more than 7 consecutive days
- in case of symptomatic hyperglycemia or re-hospitalization

In these cases, standard of care according to national and international guidelines will be implemented.

Compliance with Study Intervention

Patients in the intervention arm will be motivated by a specially trained psychologist and provided with an actigraph to monitor daily step count, overall physical activity and the scheduled training sessions. Personal motivation for the training sessions will be supported through telephone interviews, during study visits and with continuous self-evaluation. If the bicycle exercise is not completed or completed partly, this will be documented in the CRF.

Data Collection and Follow-up for Withdrawn Participants

Participants may withdraw or be withdrawn at any time. Subjects who discontinue participation will not be replaced. Withdrawal will be documented in the database with all other study data. All gathered data and samples until withdrawal of informed consent will be used anonymously for analysis. Follow-up will not take place if the patient has withdrawn informed consent, in all other cases follow-up will take place as planned.

Trial-specific Preventive Measures

Participants of the bicycle and intensive lifestyle modification group will, in addition to the general clinical visits, be closely monitored and coached with weekly telephone calls, thereby ensuring appropriate glucose management. If needed, standard of care medical treatment will be initiated also in the interventional group. All patient specific data will be recorded in an electronic case report form (eCRF).

Patients who were randomized into the intervention group will be instructed in correct self-measurement of blood glucose by a member of the study team at study enrollment or on visit 2. They will receive a blood glucose monitor to document fasting glucose every morning during the first week of the study. This way the study team is able to supervise the metabolic situation and may start rescue medication if needed.

Concomitant Interventions (Treatments)

Permitted concomitant treatments are all medication the patient has taken prior to the initial visit. We expect no influence on the study by treatment of other diseases. Not permitted are any oral anti-diabetic drugs (except for Metformin) or Insulin for the intervention group, except in case it needs to be administered as rescue medication.

9. STUDY ASSESSMENTS

Study Flow Chart and Table of Study Procedures and Assessments

Please refer to **Table 1** and **Figure 1**.

Assessments of Outcomes

9.1.1 Assessment of Primary Outcome

Glycated hemoglobin A1c will be measured by the same means (POCT or venous blood sampling) as done at baseline, and 3 months after enrollment.

9.1.2 Assessment of Secondary Outcomes

Please refer to chapters 5.2.

9.1.3 Assessment of Safety Outcomes

9.1.3.1 Adverse Events

We consider the risks of this study to be very low. Possible risks may occur if glycemic control cannot be achieved and maintained with lifestyle intervention. Consequently, the patient may experience symptoms of hyperglycemia requiring further medical attention. Patients will be systematically questioned about the occurrence of AEs at each study visit. The patients' safety will be monitored by assessment of blood sample parameters and the recording and evaluation of all study related AEs.

9.1.3.2 Laboratory Parameters

Laboratory parameters to be monitored for patient safety will be blood glucose, glycated hemoglobin A1c, pH, bicarbonate and base excess.

9.1.3.3 Electrocardiography

Patients will receive electrocardiographic diagnostics before enrollment into the study if deemed necessary by the treating physician.

9.1.3.4 Vital Signs

Blood pressure, heart rate and body weight will be measured at each study visit. Additionally, blood pressure will be measured during bicycle intervention in 15-minute intervals. The intervention will be stopped if systolic pressure exceeds 240 mmHg. A member of the study team will be present at all times during the bicycle exercise.

Please refer also to chapter 5.2.

9.1.4 Assessments in Participants who Prematurely Stop the Study

Patients who prematurely withdraw from the study will be substituted. Withdrawal will be documented in the database with all other study data. Follow-up will not take place if the patient has withdrawn informed consent, in all other cases follow-up will take place as planned.

Procedures at Each Visit

9.1.5 Visit 1: Day 0 – Initial Consultation

All Patients will be recruited at the ER department or outpatient clinic of a participating study center or by their personal practitioner after presenting with a newly diagnosed or untreated type 2 diabetes mellitus. The treating physician will assess whether the patient is clinically fit to participate in the study and will order an ECG if necessary.

If the patient meets all of the inclusion and none of the exclusion criteria, he or she is required to sign the ICF. The patient will then be randomized 1:1 to the intervention or the control group.

Medical history is taken followed by a physical examination and drawing of blood samples for a venous blood gas analysis (pH, pCO_2, base excess, bicarbonate, glucose) and a baseline HbA1c (may be up to 14 days old).

Patients allocated to the intervention group will then perform a 30-minute bicycle exercise at 60 % of the age-adjusted maximal heart rate. Blood samples will again be drawn at the end of the exercise as well as 30 and 90 minutes after its completion to determine blood glucose levels and to do a venous BGA at 90 minutes after the bicycle exercise.

All participants of the intervention group will receive a structured plan for an intensive lifestyle intervention for the following 3 months as well as an actigraph provided by the DSBG to monitor daily physical activity between study visits.

Patients allocated to the control group will receive the standard diabetes care practiced at the study center according to national and international guidelines.

Patients will be discharged when clinically stable and no comorbidities require further hospitalization.

9.1.6 Visit 2-6: Day 2/7/30/60/90 – Study Visits

At each study site the study visits will take place at the respective endocrine or medical policlinic. Study visit 2 will be combined with specific diabetes consultation where patients learn how to measure their blood glucose.

Further study visits will be combined with regular check-ups for newly diagnosed diabetes patients.

1. Vital signs (heart rate, blood pressure and body weight) will be measured at any study visit
2. Patients will be questioned about the occurrence of AEs or other difficulties with the conduct of the study at any study visit
3. HbA1c will be measured at visits 5 and 6
4. Intervention group participants will be instructed in correct self-measurement of blood glucose by a member of the study team at study enrollment or on visit 2 and will receive a blood glucose monitor to document fasting glucose every morning during the first week of the study
5. Patients will be instructed on when and how to measure their blood glucose at home by the diabetes counseling. For the study they will be asked to write down a diurnal profile of their blood glucose measurements three days before each study visit in addition to their regular measurements. For the diurnal profile fasting glucose in the morning as well as before each principal meal should be measured. To increase adherence they will receive reminders from the study team by telephone
6. The self-evaluation of the lifestyle intervention will be discussed with the patient at visit 2
7. Home measured blood glucose values will be discussed with the patients of the intervention group at any study visit
8. SIMPAQ and SF-36 questionnaires will be filled out at visit 2
9. In between visits 2-6 weekly coaching by phone will be held to improve the adherence to the lifestyle interventionActigraph readout will be conducted at visit 6
10. Re-hospitalizations and unplanned physician consultations will be assessed through questioning at visit 6 in both arms
11. Participants allocated to the control group will be monitored at 3 and 6 months after study entry. This means they do not participate in visits 2-5 and will only be seen by the study team for visit 6 and 7 after enrollment. They will therefore not be as closely monitored as the intervention group and will not receive weekly phone calls by the study psychologist

9.1.7 Visit 7: Day 180 – Follow Up

1. Vital signs (heart rate, blood pressure, temperature) and weight will be measured
2. Blood glucose and current HbA1c will be measured
3. A blood sample will be drawn for asservation
4. Patients of both study groups will fill out the SIMPAQ- and SF-36 questionnaire to evaluate quality of life and daily physical activity compared to baseline
5. Anti-diabetic medication of the patient will be assessed through questioning
6. Re-hospitalizations and unplanned physician consultations will be assessed through

questioning

7. Patients who participated in the intervention group will be questioned about current physical activity levels and if they maintained the intense lifestyle intervention during the 3 months without weekly phone calls and further support by the study team
8. Actigraph readout will be done

9.1.8 Visit 8: 1 Year – Telephone Follow Up

Telephone follow-up visit with the general practitioner, treating endocrinologist or participant to inquire about HbA1c, weight and medication one year after study enrollment. This visit will be held for both groups.

10. SAFETY

During the entire duration of the study, all serious adverse events (SAEs) are collected, fully investigated and documented in source documents and case report forms (CRF). Study duration encompasses the time from when the participant signs the informed consent until the last protocol-specific procedure has been completed, including a safety follow-up period.

10.1.1 Definition and Assessment of (Serious) Adverse Events and Other Safety Related Events

An **adverse event (AE)** is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. [ICH E6 1.2]

A **serious adverse event (SAE)** is classified as any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious. [ICH E2A]

SAEs should be followed until resolution or stabilization. Participants with ongoing SAEs at study termination (including safety visit) will be further followed up until recovery or until stabilization of the disease after termination.

Assessment of Causality

Both investigator and sponsor-investigator make a causality assessment of the event to the study drug, based on the criteria listed in the ICH E2A guidelines:

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Suspected Unexpected Serious Adverse Reactions (SUSARs)

The sponsor-investigator evaluates any SAE that has been reported regarding seriousness, causality and expectedness. If the event is related to the investigational product and is both serious and unexpected, it is classified as a SUSAR.

Assessment of Severity

The grades for severity described in the Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0) are used.

10.1.2 Reporting of SAEs and Other Safety Related Events

Reporting of SAEs

All SAEs must be reported immediately and within a maximum of 24 hours to the sponsor-investigator of the study. The sponsor-investigator will re-evaluate the SAE and return the form to the site.

If it cannot be excluded that the SAE is attributable to the intervention under investigation, the Investigator reports it to the EC via BASEC within 15 days. If the SAE occurs at one of the study sites, the coordinating investigator reports the events to the CEC within 15 days. The other ECs involved in the trial receive SAEs resulting in death in Switzerland via sponsor-investigator via BASEC within 7 days.

Exemptions from expedited reporting may be possible if the SAE is either a clear result of the underlying disease or well-known and described in the currently approved product information (mainly for phase IV studies). Please define those SAEs that are exempted from expedited reporting.

Reporting of SUSARs

A SUSAR needs to be reported to the EC (local event via local investigator) via BASEC and to Swissmedic for category B and C studies (via sponsor-investigator) within 7 days, if the event is fatal, or within 15 days (all other events).

The sponsor-investigator must inform all investigators participating in the clinical study of the occurrence of a SUSAR. All ECs involved in the trial will be informed about SUSARs in Switzerland via sponsor-investigator via BASEC according to the same timelines.

Reporting of Safety Signals

All suspected new risks and relevant new aspects of known AEs that require safety-related measures, i.e. so called safety signals, must be reported to the sponsor-investigator within 24 hours. The sponsor-investigator must report the safety signals within 7 days to the EC (local event via local investigator) via BASEC and to Swissmedic in case of a category B or C study.

The sponsor-investigator must immediately inform all participating investigators about all safety signals. The other ECs involved in the trial will be informed about safety signals in Switzerland via the sponsor-investigator.

Reporting and Handling of Pregnancies

Pregnant participants must immediately be withdrawn from the clinical study and substituted as gestational diabetes patients require a stricter blood glucose management and more likely an insulin therapy and therefore meet our exclusion criteria. Any pregnancy during the treatment phase of the study and within 30 days after discontinuation of the intervention will be reported to the sponsor-investigator within 24 hours. The course and outcome of the pregnancy should be followed up carefully, and any abnormal outcome regarding the mother or the child should be documented and reported.

Periodic reporting of safety

An ASR is submitted once a year to the local EC via local investigator from all sites. The sponsor-investigator prepares it, and then submits it to the participating investigators. The participating investigators submit it to the local committees.

10.1.3 Follow Up of (S)AEs

All subjects who experience AEs will be followed until the event resolves or until the subject's participation in the study ends. For those AEs judged to be unrelated to the study intervention, the outcome at last observation will be recorded on the appropriate pages of the CRF.

Subjects experiencing AEs that were judged to be possibly, probably, or definitely related to a study

intervention will be followed until the events resolve or until the event is judged to be chronic or stable. Resolution of such events will be documented on the appropriate pages of the CRF.

11. STATISTICAL METHODS

Hypothesis

We hypothesize that lifestyle intervention lowers HbA1c effectively without antidiabetic drugs. The null-hypothesis (H_0) is that there will be no significant difference between the proportions of patients achieving metabolic control in the intervention group and the control group. The alternative hypothesis (H_1) is that there will be significantly more patients achieving metabolic control in the intervention group. For the purpose of this study, metabolic control is defined as a fasting glucose < 7.6 mmol/l and an HbA1c below a target stratified for three groups according to HbA1c at baseline: HbA1c > 14 % → target < 10 %; HbA1c < 14 % and > 10 % → target < 8 %; HbA1c < 10 % → target < 7.5 %.

Determination of Sample Size

The aim of this study is to assess whether bicycle exercise followed by an intensive life style intervention can sufficiently restore metabolic control without anti-diabetic drugs as compared to a standard care control group.

Based on our clinical experience we assume that 80 % in the intervention group will reach the primary endpoint of metabolic control with no anti-diabetic drugs compared to only 40 % in the standard care control group.

A publication by Martinus et al.[21] on adherence to a study sport program for newly diagnosed type 2 diabetes mellitus patients, shows up to 80 % adherence for the group that was additionally supported by a psychologist for increased motivation. The adherence to the program was significantly better in the group with support by the psychologist, as were the results regarding improvement of physiological parameters such as body mass, fat mass or strength.

A review on the effect of physical exercise on glycemic control found an average decrease of HbA1c by 0.6 mmol/l through exercise[22] in diabetes patients at least one year after diagnosis and with a moderate hemoglobin elevation. Based on this data, our target ranges were extrapolated for patients with new-onset diabetes and higher HbA1c.

The inclusion of 28 patients per group (n total 62 patients including 10 % lost to follow-up) will provide 80 % power at an alpha level of 0.05. A number of 15 to 25 patients per center is envisaged.

Statistical Criteria of Termination of Trial

There will be no statistical criteria to terminate the trial early.

Planned Analyses

11.1.1 Datasets to be Analyzed, Analysis Populations

Data will be analyzed as intention to treat after all participants have finished the study.

11.1.2 Primary Analysis

Analysis will be done by the investigators. For our primary analysis, we will compare the two arms with a Fisher's exact test and we will also estimate effect size with a logistic regression model reporting odds ratios (OR) and corresponding 95% confidence intervals using STATA. All tests will be two tailed; $p < 0.05$ will be defined as significant.

11.1.3 Secondary Analyses

We will use the Wilcoxon Rank Sum test for not normally distributed data and Fisher's exact test for categorical data to compare changes between the two groups. All tests will be two tailed; $p < 0.05$ will be defined as significant. Data will be analyzed using STATA, Graph Pad Prism and IBM SPSS.

The parameters assessed via blood sampling during and after the bicycle exercise will be analyzed using descriptive statistics and appropriate graphical representation.

Values of pH, base excess and bicarbonate at 120 minutes after beginning of the bicycle exercise will be compared to the baseline values using medians and interquartile range as well as appropriate graphical representation. The statistical significance of the difference between the two medians will be tested using the Wilcoxon signed-rank test for paired data.

The same statistical procedure will be applied to the values of blood glucose at the end of, as well as 60 and 120 minutes after beginning of the bicycle intervention.

Safety outcomes (please refer to chapter 5.2) will be illustrated using descriptive statistics.

Re-hospitalization and uplanned re-consultation rate 3 months after study enrollment will be quantified by number of hospitalizations and/or physician re-consultations as well as total length of hospitalization(s) in days. Data will be tested using the Mann-Whitney U-test.

SIMPAQ questionnaire results will be depicted using descriptive statistics and medians of the two groups evaluated using the Mann-Whitney U-test.

Results of the actigraph readouts at baseline, 3 months and 6 months will be compared inter-individually to assess if the endpoint has been fulfilled or not.

Number of anti-diabetic medication at 1, 2, 3 and 6 months as well as one year compared to baseline will be depicted using Graph Pad Prism. Average number of medication in both groups will be compared at 3 and 6 months after baseline.

Health-care related costs will be calculated for each study arm based on actual costs in respective cantons for medication as well as according to Tarmed (outpatient-clinic tariff system).

SF-36 questionnaire will be evaluated using IBM SPSS and compared between the two groups using the Mann-Whitney U-test at baseline and after 6 months.

11.1.4 Interim Analyses

There are no interim analyses planned.

11.1.5 Safety Analysis

Descriptive analysis will be used. Please refer also to chapter 5.2

11.1.6 Deviation(s) from the Original Statistical Plan

Any deviation(s) from the original statistical plan will be described and justified in the protocol and reported to the EC.

Handling of Missing Data and Drop-outs

Results will be summarized using all available data. Multiple attempts will be made to obtain missing data. Missing data will not be imputed. Drop-outs will not be replaced.

12. QUALITY ASSURANCE AND CONTROL

Data Handling and Record Keeping/Archiving

12.1.1 Case Report Forms

A subject screening and enrollment log will be completed for all eligible or non-eligible subjects with the reasons for exclusion. For each subject enrolled a CRF must be completed and signed by the principal investigator or co-investigator. Data will be transferred from the source documents directly to the e-CRF.

All source documents, enrollment logs, p-CRFs, ICFs and other documents pertaining to the conduct of the study must be kept on file by the investigator for a minimum of 10 years after study termination. If a subject withdraws from the study, the reason must be noted in the enrollment log or p-CRF.

All participants receive an identification number (ID) and no person identifying data such as name or initials are collected in the p-CRF.

12.1.2 Specification of Source Documents

Source data (visit dates, ICFs, SAEs, AEs, concomitant medication, results of relevant examinations, laboratory values, glucose readings) will be available at the site to document the existence of the study participants. Source data will include the original documents relating to the study, as well as the medical treatment and medical history of the participant.

12.1.3 Record Keeping/Archiving

All study data must be archived for a minimum of 10 years after study termination or premature termination of the clinical trial.

Data Management

12.1.4 Data Management System

The study data collected in the p-CRF will be transferred to a web-based electronic data capture (EDC) system, named secuTrial® (version 5.3.4.6, 2018). Each EDC system of the participating centers runs on a server maintained by the appropriate IT-department of each hospital. The e-CRF is implemented by the research group in collaboration with the clinical trial unit (CTU) of the medical faculty at the University of Basel, Basel, Switzerland.

Authorized persons at the study sites are responsible for data entry into the EDC system.

12.1.5 Data Security, Access and Back-up

The EDC system is accessible via a standard browser on an web-connected device. Password protection ensures that only authorized persons can enter the system to view, add or modify data according to their permissions.

User administration and training is performed by the IT-department and CTU Basel according to predefined processes.

A regular backup of the EDC study data is performed according to the processes of the IT-department of the University Hospital Basel.

12.1.6 Analysis and Archiving

The EDC system will be locked after all data is monitored and all raised queries have been resolved.

Data is exported and transferred to the investigator by the CTU Basel according to internally defined

processes. The exported data will be archived by the investigator.

Data for analysis will be extracted from the database export and analysis will be conducted with Graph Pad Prism. Source data/documents and p-CRFs will be stored at study site for at least 10 years and be destroyed thereafter.

12.1.7 Electronic and Central Data Validation

Data is entered into the eCRF (version 5.3.4.6, 2018) and can be validated for completeness and discrepancies automatically.

An audit trail system maintains a record of initial entries and changes (reasons for changes, time and date of changes, user identification of entry and changes).

Data entered into the eCRF will be reviewed by the responsible investigator and an independent monitor will raise queries using the query management system implemented. Designated investigators have to respond to the query and confirm or correct the corresponding data. Thereafter the monitor can close the query.

Monitoring

There will be a monitoring of the study by an independent, professional, qualified study monitor from the University Hospital Basel. There will be one initiation visit and one close-out visit. The source data/documents are accessible to monitors and questions are answered during monitoring.

Audits and Inspections

Authorized representatives of the national or local health authorities and ECs will be permitted to inspect or audit the facilities, records and original data relevant to this study.

Confidentiality and Data Protection

All personal and medical information obtained for this study is confidential and disclosure to third parties other than those noted below is prohibited. Participant's data will be identified by study and subject ID number.

Upon the participant's permission, medical information will be given to his or her personal physician or other appropriate medical personnel responsible for her or his welfare.

Data generated by this study must be available for inspection upon request by representatives of the appropriate national and local health authorities, and the EC for each study site, if appropriate.

Source documents will be permitted to the study team and for purposes of monitoring, audits and inspections by local authorities and appropriate monitoring staff during and after the study. No third party will be given access to the source data. Data stored in the eCRF (secuTrial®, version 5.3.4.6, 2018) is anonymized.

Storage of Biological Material and Related Health Data

Health related data will be stored in an anonymized eCRF (secuTrial®, version 5.3.4.6, 2018). Additional samples will be taken and stored for 10 years, they will be destroyed thereafter.

13. PUBLICATION AND DISSEMINATION POLICY

The study will be published in an international peer-reviewed journal irrespective of whether its results were positive or negative.

14. FUNDING AND SUPPORT

Funding (third-party) will be applied for after approval from EC and are secured in house.

15. INSURANCE

All assessments and information material mentioned and the smart watch device in this protocol are free of charge for the subject.

The study procedures will be covered by the general liability insurance **Helvetia** of the University Hospital Basel, as will be certified by Legal Service, University Hospital Basel. A copy of the certificate will be filed in the investigator site file (ISF) and the trial master file (TMF).

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17. APPENDICES

17.1 SF-36 Questionnaire

17.2 SIMPAQ Questionnaire