# Self-Determination Theory Interventions Versus Usual Care in People With Diabetes: A Protocol for a Systematic Review With Meta-Analysis and Trial Sequential Analysis

**Anne Sophie Mathiesen** ( asmathiesen@gmail.com )
University of Copenhagen https://orcid.org/0000-0002-1354-1012
**Mette Juel Rothmann**
Steno Diabetes Center Copenhagen
**Vibeke Zoffmann**
Rigshospitalet
**Janus Christian Jakobsen**
Rigshospitalet
**Christian Gluud**
Rigshospitalet
**Jane Lindschou**
Rigshospitalet
**Mette Due-Christensen**
Steno Diabetes Center Copenhagen
**Bodil Rasmussen**
Deakin University
**Emilie Marqvorsen**
Rigshospitalet
**Thordis Thomsen**
Herlev Hospital

**Protocol**

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# Abstract

**Background** Existing self-management and behavioural interventions for diabetes vary widely in their content, and their sustained long-term effectiveness is uncertain. Autonomy supporting interventions may be a prerequisite to achieve 'real life' patient engagement and more long-term improvement through shared decision making and collaborative goal setting. This is the goal of self-determination theory and guided self-determination interventions. Self-determination theory has been reviewed but without assessing both benefits and harms and accounting for the risk of random errors using trial sequential analysis. The guided self-determination has not yet been systematically reviewed. The aim of this protocol is to investigate the benefits and harms of self-determination theory-based interventions versus usual care in adults with diabetes.

**Methods/design** We will conduct the systematic review following The Cochrane Collaboration guidelines. This protocol is reported according to the PRISMA checklist. A comprehensive search will be undertaken in the CENTRAL, MEDLINE, EMBASE, LILACS, PsycINFO, SCI-EXPANDED, CINAHL, SSCI, CPCI-S, and CPCI-SSH to identify relevant trials. We will include randomised clinical trials assessing interventions theoretically based on guided self-determination or self-determination theory provided face-to-face or digitally by any health care professional in any setting. The primary outcomes will be quality of life, mortality, and serious adverse events. The secondary will be diabetes distress, depressive symptoms, and adverse events not considered serious. Exploratory outcome will be glycated haemoglobin. Outcomes will be assessed at the end of the intervention and at maximum follow-up. The analyses will be performed using Stata version 16 and Trial Sequential Analysis. Two authors will independently screen, extract data from, and perform risk of bias assessment of included studies using the Cochrane risk of bias tool. Certainty of the evidence will be assessed by GRADE.

**Discussion** Self-determination theory interventions aim to promote a more autonomous patient engagement and are commonly used. It is therefore needed to evaluate the benefit and harms according to existing trials.

**Systematic review registration** The protocol has been registered in PROSPERO ID nr. 181144 (submitted to PROSPERO 24th April 2020)


# Background

Diabetes affects 425 million people worldwide, and of these, type 2 diabetes accounts for 90% [1]. The prevalence and incidence of both type 1 and type 2 diabetes are rapidly increasing [1]. Likewise, the aging populations contributes to a substantial rise in the number of people with diabetes.

Type 2 diabetes is caused by a genetic disposition in combination with a sedentary lifestyle and overweight [3]. These risk factors lead to insulin resistance, which initially prompts an increase in insulin production but causes decreased insulin secretion over time. More than 80% are overweight at the time of diagnosis [4]. The risk of developing type 2 diabetes increases from 50% to 75% when one or both

parents, respectively, have type 2 diabetes [5]. With age being the single largest risk factor for developing type 2 diabetes, the number of people living with type 2 diabetes and various combinations of comorbidities is also increasing.

Complications to diabetes include macrovascular complications such as ischaemic stroke or coronary heart disease [6]. Microvascular complications comprise retinopathy, neuropathy, and nephropathy [7]. While tight glycaemic control is associated with reduced microvascular complications [6, 7], this association is less clear in relation to macrovascular complications [8]. Due to the early onset of type 1 diabetes, complications of type 1 diabetes are more susceptible to develop [9]. In people with type 2 diabetes, macrovascular complications are associated with age, male sex, obesity, dyslipidaemia, and smoking [10]. Up to one third of people with type 2 diabetes have developed one or more complications of type 2 diabetes at the time of diagnosis [10]. A longer pre-detection period for unrecognised type 2 diabetes in people with low educational status infers a prolonged time for the complications of diabetes to develop [11].

Unhealthy lifestyle behaviours and body mass index may explain up to 45% of the social inequality in type 2 diabetes [4]. Within type 1 diabetes no social gradient exits [9], but still some interventions may potentially broaden the gap between social groups [12-15]. In this systematic review, we plan to investigate a potential differential impact of included interventions because social inequality is an issue in people with type 2 diabetes. As the interventions under investigation require a level of literacy and language skills they may potentially further increase inequity [14].

The human and economic drain from diabetes is excessive, not only because of direct costs, but also due to indirect costs like managing complications of diabetes, sick days, and early retirement. From a socioeconomic viewpoint, there appears to be convincing incentives to invest in people with diabetes and comorbidities, as the expenses for each individual disease may accumulate, resulting in total costs that exceeds the expenses for each individual disease [16]. Due to this effect, the return of investment is often underestimated when intervening in these patients [16].

## Description of the interventions

The management plan for people with diabetes should consider the person's age, cognitive abilities, literacy, social and financial situation, cultural factors, diabetes complications and comorbidities, health priorities, and preferences of care [17]. Autonomy supporting interventions may be a prerequisite to achieve 'real life' patient engagement and more long-term improvement through shared decision making and collaborative goal setting. Intrinsic motivation is a key concept, and an approach based on respect for the individual's autonomy is essential as it is connected to success to reach and sustain treatment targets [18, 19].

Existing self-management and behavioural interventions for diabetes vary widely in their content, and their sustained long-term effectiveness is uncertain [20, 21]. Reviews suggest that interventions that are

grounded in behavioural change theory are more effective than those that are not [19, 22]. Educational interventions, psychological interventions, and health educational tools are based on different theoretical grounding, training, clinical skills, and are delivered by different specialists in diverse settings. Educational interventions use didactic and enhanced learning methods to improve self-management of diabetes by reducing identifiable gaps in knowledge [23]. Psychological therapies use the therapeutic alliance between patient and therapist, in which the patient's problems are understood in terms of emotions, cognitions, and behaviors [24], yet, psychological interventions have not proven effective on glycated hemoglobin (HbA1c) in people with type 1 [25] or type 2 diabetes [20]. Health educational tools that aim at translating person-centered care into practice and finding ways to enhance intrinsic motivation may lead to greater long-term behavior change than tools solely relying on external motivation [26]. This is the goal of the guided self-determination method [27-30] and self-determination theory [31].

We aim to assess the effects of the guided self-determination intervention developed by Zoffmann [27-29, 32] and self-determination theory by Deci and Ryan [31]. Guided self-determination is an empowerment-based method recognised as a life-skills approach clinically applicable in patient-provider relationships. The guided self-determination method was empirically developed on the basis of grounded theory [27-30, 32] and formal theories including self-determination theory and life skills theory. The self-determination theory is based on comprehensive empirical research [31]. For transparency, the guided self-determination method and self-determination theory are described according to the model of analyses based on the criteria shown in table 1. These criteria were originally proposed by the *'Knowledge translation theories research group*' [33, 34] and later modified by Zoffmann et al. [35].

Table 1: The translational potential of the guided self-determination and the self-determination theory

| | The guided self-determination method | The self-determination theory |
|---|---|---|
| Determining the origin of the theory including development in a clinical setting | Guided self-determination was developed as an empowering decision-making and problem-solving method through a four-stage research program in difficult diabetes care in 1996–2004. | Self-determination theory has been developed from empirical motivational research [31]. It began with basic laboratory research and was gradually applied to education, to work organisations, and to health care [36]. |
| The main concepts of the theory | Three grounded theories: 1) keeping life and disease apart [28]; 2) relational potential for change [29]; and 3) a communication and reflection model [27].<br><br>General theories: humanistic values theory, self-determination theory, life skills, balanced self-determinism, dynamic judgement building. | The basic components of the self-determination theory consist of 6 mini theories:<br><br>1 and 2) cognitive evaluation theory I and II; 3) organismic integration theory; 4) causality orientations theory; 5) basic psychological needs theory; 6) goal contents theory [37]. |
| The consistency of the theory including the overarching goal and supportive processes<br><br>- | The person with diabetes to develop life skills to manage the condition. The supportive processes of guided self-determination method consist of seven stages: (1) establishing a mutual relationship with clear boundaries; (2) self-exploration; (3) self-understanding; (4) shared decision-making; (5) action; (6) feedback from action; and (7) translating evidence for productive patient behaviour in an autonomy-supportive way. | Human beings have three essential psychological needs: autonomy, competence, and relatedness for ongoing psychological growth, integrity, and well-being. The quality of motivation is central to<br><br>self-determination theory. The fundamental distinction is between autonomous and controlled forms of motivation and behavioural regulation. The predominant feeling is often referred to as 'willingness'. By contrast, in controlled motivation, the predominant feeling is pressure, which is often associated with ambivalence or resistance. |
| The degree of generalisability and parsimony of the theory including general principles, strategies or tools for engaging peoples | The person with diabetes-healthcare provider relationships can be released through self-reflection, mutual reflection, shared decision-making, dynamic judgment building, and autonomous motivation leading to self-concordance. Requires changes by both health care professional and person with diabetes in their relationship. | 1) Autonomy support: *relevance*,<br><br>*respect, choice, and avoidance of control.*<br><br>2) Structure (support for competence): *clarity of expectations*, o*ptimal challenge, feedback,*<br><br>*instrumental and practical skills-training*, *guidance and support*.<br><br>3) Involvement (support for relatedness):<br><br>*empathy, affection, attunement*, *dedication of resources, dependability.* |

| | | |
|---|---|---|
| How the theory is tested in empirical research including reported effects<br><br>- | The guided self-determination method has not yet been systematically reviewed or meta-analysed. The method has been tested in 4 randomised clinical trials and people with type 1 diabetes. Results showed significant improvement in glycemic control and life-skill, reduced diabetes distress, and improved diabetes competences [30, 38]. | Three meta-analyses [18, 19, 39] including diverse participants, primarily health people. Self-determination theory-based interventions have been tested in people with type 2 diabetes, showing an effect in women on HbA1c and quality of life [40]. A study reports effect on eating behavior but not on HbA1c in adolescents with type 1 diabetes [41]. |
| The usefulness and practicability of the theory including health care professionals' background and training and fidelity assessment | The health care professionals go through 32 hours of structured and supervised training to become certified guided self-determination facilitators. They document their ability to use the reflection sheets and communication skills in two full courses with patients. Figures from grounded theories are used as fidelity assessment tools. | No formal training of personal or fidelity testing.<br><br>Fidelity tools from motivational interviewing have been applied [19]. |

## How the interventions might work

In the guided self-determination approach, the person with diabetes has a primary role preparing for consultations at home, filling in reflection-sheets. This means that the person needs to clarify and prioritise what is important to change, thus becoming able to express their thoughts in communication with the health care professionals. Guided self-determination intervention are likely to improve clinical outcomes through the following pathways [30, 42]: increased perceived autonomy support from the health care professionals, a higher frequency of self-monitored blood glucose, increased perceived competence in managing diabetes, decreased diabetes-related distress, and ultimately improved glycaemic control [27-30].

According to the self-determination theory, when the three basic psychological needs: competence, autonomy, and relatedness are satisfied this leads to enhanced autonomous motivation and mental health [31, 37, 43]. Self-determination theory proposes a continuum for the internalisation of motivation, whereby individuals become more autonomous (or self-determined) to engage in behaviours over time. The pathways of mechanisms are built on a theoretical model [31], which argues, first, that social-contextual events (e.g. feedback, communications, rewards) that conduce toward feelings of competence during action can enhance intrinsic motivation for that action. Accordingly, optimal challenges, tailored feedback, and lack from demeaning evaluations are hypothesised to facilitate intrinsic motivation and thereby promote autonomy [31].

# Why is it important to do this systematic review

We conducted preliminary literature searches in PubMed and the Cochrane Database of Systematic Reviews using the search terms: diabetes, theory-based interventions, self-determination theory, guided self-determination and person-centred in different combinations. From these searches, we identified three reviews including studies that provided self-determination theory for behaviour change in the health domain [18, 19, 39]. None of the reviews were systematic reviews. The three reviews investigating self-determination theory [18, 19, 39], included trials investigating the effect of the self-determination theory-based intervention assessing at least one self-determination theory variable. All three reviews [18, 19, 39] included trials from different populations, primarily with healthy people and multiple experimental designs. Nevertheless, whether an improvement can be attributed to the intervention, can only be established in randomised clinical trials. An overview of the characteristics of the three reviews are shown in table 2. None of the reviews had a registered or published protocol, none were based on unrestricted searches, bias risk was only assessed in two reviews, using domains adopted from the Cochrane Handbook for conducting and reporting systematic reviews and meta-analyses [44, 45]. None of the reviews controlled the risks of random errors using Trial Sequential Analysis, the outcomes reported were limited to specific self-determination theory constructs, and none of the reviews assessed adverse effects. In the review of Ntoumanis et al. [18], the authors concluded that changes in autonomous motivation and perceptions of need support were associated with small positive changes in health behaviours at the end of the intervention, but small to medium changes at follow-up, which may indicate the potential of a sustained behaviour change [18].

Table 2: Self-determination theory reviews

| | Ng et al. (2012) | Gillison et al. (2018) | Ntoumanis et al. (2020) |
|---|---|---|---|
| Designs included | 184 independent datasets, primarily non-experimental design. | 74 studies including a control group (59 of randomised clinical trials (RCTs) or cluster RCTs). | 73 independent datasets, 58 RCTs (20 of these were cluster RCTs). |
| Number of trials including people with diabetes | Seven trials [30, 46-51]. | One trial [40]. | Six trials [40, 41, 50, 52-54]. |
| Registered in PROSPERO | No | No | No |
| Protocol published | No | No | No |
| Restricted searches | PsycINFO, PsycARTICLES and PubMed, citation searches (ISI web of knowledge). | Web of Science, PsychINFO, PubMed, Cochrane Database, DARE, Biomed Central, Sociological abstracts, ProQuest | PsycINFO, PsycARTICLES and PubMed/Medline |
| Assessment of bias risk | Not performed | A modified version of the Cochrane risk of bias tool (random group allocation, treatment allocation concealment, groups similar at baseline, blinded outcome assessor, intention-to-treat analyses, risk of bias) | A modified version of the Cochrane risk of bias tool (random group allocation, group allocation concealment, blinded outcome assessor, handling of missing data, selective reporting, other bias) |
| Assessment of random errors, using Trial Sequential Analysis | No | No | No |
| Outcomes | Specific self-determination theory constructs | Specific self-determination theory constructs | Specific self-determination theory constructs |
| Assessment of adverse effects | No | No | No |

Regarding guided-self-determination, we found no systematic reviews but we identified four randomised clinical trials providing guided self-determination for people with diabetes [30, 38, 53, 55]. Of these, one randomised clinical trial investigating the effect of guided self-determination in young adults with type 1 diabetes identified a larger effect on HbA1c and diabetes distress at follow-up compared to immediate after the intervention in women, but not in men [38]. Due to the limitations of the existing reviews outlined in table 2 and the fact that guided self-determination intervention method had not yet been systematically reviewed, we find it justified to conduct a systematic review including Trial Sequential Analysis and GRADE for assessing the potential of a long-term effect, specifically targeting people with diabetes.

## Objective

The objective is to investigate the benefits and harms of guided self-determination and self-determination theory interventions versus usual care in people with diabetes.

# Methods

This protocol has been registered in the PROSPERO database ID nr. 181144 (submitted on the 24$^{th}$ April 2020) and is reported according to the preferred Reporting Items for Systematic reviews and Meta-analysis Protocols (PRISMA-P) 2015 statement [56]. (Checklist as additional file).

## Criteria for considering studies for this review

### Types of studies

We will include randomised clinical trials and cluster randomised trials irrespective of publication status, reported outcomes, publication date, publication type, and language conducted in any setting for assessment of benefits and harms. We will not include quasi-randomised studies or observational studies [44].

### Types of participants

People with a diagnosis of type 1 diabetes or type 2 diabetes as defined by trialists. The participants should be described as adolescents or adults by trialists. Trials including participants described as children will be excluded.

### Types of interventions

Experimental interventions theoretically based on guided self-determination or self-determination theory provided face-to-face or digitally by any health care professional in any setting. The trials must refer to either guided self-determination or self-determination theory as their primary theoretical framework. Additionally, the trials must use the reflection sheets and the communication forms that are basic to the guided self-determination method.

## Control group interventions

Control interventions may be 'no intervention', wait list, or standard care as defined by trialists (e.g. standard healthcare provision). We will also accept attention placebo control [57], which is a control intervention that is not related to enhancing autonomy support but include a similar number of contacts with the interventionists [57].

### Outcomes

## Primary outcomes

- Quality of life (continuous data) measured by either any validated diabetes-specific questionnaire such as the diabetes quality of life [58] or any validated generic outcome measure such as the WHO-5 questionnaire [59].
- All-cause mortality (dichotomous data).
- Proportion of participants with one or more serious adverse events (dichotomous data), defined as any untoward medical occurrence that resulted in death, was life-threatening, required hospitalization or prolonging of existing hospitalization and resulted in persistent or significant disability or jeopardized the patient [60]. If the trialists do not use the ICH-GCP definition, we will include the data if the trialists use the term "serious adverse event." If the trialists do not use the ICH-GCP definition nor use the term serious adverse event, then we will also include the data, if the event clearly fulfils the ICH-GCP definition for a serious adverse event.

## Secondary outcomes

- Diabetes distress (continuous data) measured with any validated instruments such as the diabetes distress scale or the problem areas in diabetes scale [61, 62].
- Depressive symptoms (continuous data) measured with any validated instruments such as the Patient Health Questionnaire (PHQ-9)[63] or the hospital anxiety and depression scale [64]
- Proportion of participants with at least one adverse event (dichotomous data) not considered serious [60].

## Explorative outcomes

- HbA1c (continuous data).

## Assessment time points

The primary assessment time points for all outcomes will be closest to the end of intervention. We will secondly assess all outcomes at maximum follow-up.

# Search methods for identification of studies

## Electronic searches

We will search Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medical database (EMBASE), Latin American and Caribbean Health Sciences Literature (LILACS), PsycINFO, Science Citation Index Expanded (SCI-EXPANDED), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Social Sciences Citation Index (SSCI), Conference Proceedings Citation Index—Science (CPCI-S), and Conference Proceedings Citation Index—Social Science & Humanities (CPCI-SSH) to identify relevant trials. We will search all databases from their inception to the present. For a detailed search strategy for all electronic databases, see Additional file 2. The search strategy for PsycINFO will be given at the review stage.

## Searching other resources

The reference lists of relevant publications will be checked for any unidentified randomised trials. We will contact the authors of included studies by email asking for unpublished randomised trials. Further, we will search for ongoing trials on the following:

- gov (www.clinicaltrials.gov)
- Google Scholar (https://scholar.google.dk/)
- The Turning Research into Practice (TRIP) Database (https://www.tripdatabase.com/)
- European Medicines Agency (EMA) (http://www.ema.europa.eu/ema/)
- US Food and Drug Administration (FDA) (www.fda.gov)
- China Food and Drug Administration (CFDA) (http://eng.cfda.gov.cn/WS03/CL0755/)
- Medicines and Healthcare Products Regulatory Agency (https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatoryagency)
- The World Health Organization (WHO) International
- Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/)
- Cochrane Database of Systematic Reviews
- http://www.evidencebasedpsychotherapies.org/index.php?id=25

Additionally, we will hand search conference abstracts from diabetes conferences for relevant trials. We will also consider relevant-for-the-review unpublished and grey literature trials if we identify these. Reference lists of reviews and meta-analyses retrieved from the searches will also be screened. The latest search will be performed in May 2020 supplemented with ongoing alerts from the databases when new studies within the search matrix are published. We will end inclusion in June 2020.

# Data collection and analysis

We will conduct the review following The Cochrane Collaboration guidelines [44]. The analyses will be performed by the use of Review manager 5.3 [65]. The analyses will be performed using Trial Sequential Analysis [66] and Stata version 16 [67].

### Selection of studies

All potentially eligible trials identified in the literature searches will be imported into the systematic review management program, Covidence [68] or a reference management program. Two authors (ASM) and a co-author will independently screen potentially eligible studies on title and abstract. All full text studies will be retrieved and independently assessed by the two reviewers. Reasons for exclusion will be recorded. Any disagreements will be solved by discussion or by consulting a third author. Trial selection will be displayed in a flow diagram according to the PRISMA-P [56].

### Data extraction and management

Two authors will independently extract data from included trials. Disagreements will be solved by discussion or by consulting a third author. We will assess duplicate publications and companion papers of a trial together, to evaluate all data simultaneously (to maximize data extraction and correct bias assessment). We will contact all trial authors by email to specify any additional data, which may not be reported sufficiently or at all in the publication.

## Trial characteristics

The following data will be extracted: trial design (parallel, factorial, or crossover), number of intervention groups, lengths of follow-up, risk of bias components, and inclusion and exclusion criteria.

## Participants characteristics and diagnosis

We will extract the following data: number of randomised participants in each intervention group, adherence to intervention, age range (mean or median), sex ratio, type of diabetes, diabetes treatment, number of comorbidities (complications of diabetes/other comorbidities) and socioeconomic status/educational level.

# Intervention group

We will extract the following data: type of intervention, treatment duration of intervention group, number of sessions (or dose), intensity, and treatment format provided to the intervention group.

## Education and training of the interventionists

The intervention could be provided by any interventionist. Data on who is providing the intervention will be extracted. The training of the interventionists providing the method will be reported. Assessment of fidelity will be reported.

## Co-intervention characteristics

We will extract the following data: type of co-intervention, treatment duration of co-intervention, number of sessions (or dose), and treatment format.

## Control group intervention

We will extract the following data: type of control group intervention, treatment duration of control group, number of sessions (or dose), intensity, and treatment format provided to the control group. Any reported beneficial and harmful effects of the control intervention will be derived and described.

## Outcomes

For each outcome, we will extract the number of analysed participants, the number of participants lost to follow-up/withdrawals/crossover in the experimental and the control group.

## Notes

Funding of the trial and notable conflicts of interest of the trial authors will be extracted, if available. Unusual reporting of outcome data will be noted in the 'Characteristics of included studies' table. Two reviewers (ASM and co-author) will independently extract and transfer data into Review Manager [65]. Disagreements will be solved through discussion or by consulting a third author.

### Risk of bias assessment

Risk of bias in included RCTs will be assessed based on the domains described below [44, 69-79]. This assessment will be done separately for each outcome and comparison and will then be considered in relation to overall reliability of the evidence. This will be done in pairs by two independent review authors (ASM and co-author).

## Random sequence generation

- Low risk of bias: study authors performed sequence generation using computer random number generation or a random numbers table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if an independent person not otherwise involved in the study performed them
- Unclear risk of bias: study authors did not specify the method of sequence generation
- High risk of bias: sequence generation method was not random or quasi-randomised. Such studies will be excluded for the assessment of benefits.

## Allocation concealment

- Low risk of bias: participant allocations could not have been foreseen in advance of, or during, enrolment. A central and independent randomisation unit controlled the allocation. Investigators

were unaware of the allocation sequence (e.g. if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes)

- Unclear risk of bias: study authors did not describe the method used to conceal the allocation, so intervention allocations may have been foreseen before, or during, enrolment
- High risk of bias: it is likely that investigators who assigned participants knew the allocation sequence

## Blinding of participants and personnel

- Low risk of bias: either of the following: no blinding or incomplete blinding, but review authors judged that the outcome was unlikely to have been influenced by lack of blinding *or* blinding of participants and key study personnel ensured, and it was unlikely that the blinding could have been broken
- Unclear risk of bias: either of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; *or* the trial did not address this outcome
- High risk of bias: either of the following: no blinding or incomplete blinding, and the outcome was likely to have been influenced by lack of blinding; *or* blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to have been influenced by lack of blinding

## Blinding of outcome assessment

- Low risk of bias: either of the following: no blinding of outcome assessment, but review authors judged that the outcome measurement was not likely to be influenced by lack of blinding (we will consider self-reported questionnaires more prone to be affected by lack of blinded outcome assessor and hba1c less likely to be affected by lack of blinded outcome assessor) *or* blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
- Unclear risk of bias: either of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome
- High risk of bias: either of the following: no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; *or* blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding

## Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The study used adequate methods, such as multiple imputation, to handle missing data or had <5% missing data.
- Unclear risk of bias: information was insufficient to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results

- High risk of bias: results were likely to be biased due to missing data

### Selective outcome reporting

- Low risk of bias: a protocol is published or a trial has been registered in a trial register (e.g. clinicaltrials.gov) before or at the time the trial is begun and the outcome called for in the protocol or trial registration is reported on.
- Unclear risk of bias: study authors did not report all pre-defined outcomes fully, or it was unclear whether study authors recorded data on these outcomes
- High risk of bias: study authors did not report one or more pre-defined outcomes

### Other bias

- Low risk of bias: the trial appeared free of other factors that could have put it at risk of bias
- Unclear risk of bias: the trial may or may not have been free of other factors that could have put it at risk of bias
- High risk of bias: other factors in the trial could have put it at risk of bias

We will judge a trial to be at low overall risk of bias if assessed as having low risk of bias in all of the above domains. We will judge a trial to be at high overall risk of bias if assessed as having unclear or high risk of bias in one or more of the above domains.

We will assess the domains ‘blinding of outcome assessment’, ‘incomplete outcome data’, and ‘selective outcome reporting’ for each outcome result. Thus, we can assess the bias risk for each outcome assessed in addition to each trial. Our primary conclusion will be based on the results of our primary outcome results with overall low risk of bias.

# Differences between protocol and the review

Any deviations between the published protocol and the review will be reported in the ‘Differences between the protocol and the review’ section of the systematic review.

# Measures of treatment effect

## Dichotomous outcomes

We will calculate risk ratios (RRs) with 95% confidence interval (CI) for dichotomous outcomes, as well as the Trial Sequential Analysis-adjusted CIs (see below).

#### Continuous outcomes

We will calculate the mean differences (MDs) and consider calculating the standardized

mean difference (SMD) with 95% CI for continuous outcomes. We will also calculate trial sequential analysis-adjusted CIs (see below).

# Dealing with missing data

We will, as the first option, contact all trial authors to obtain any relevant missing data (i.e., for data extraction and for assessment of risk of bias, as specified above). Second, we will investigate the effects of missing data in sensitivity analyses, see below.

## Dichotomous outcomes

We will not impute missing values for any outcomes in our primary analysis. In our sensitivity analyses (see paragraph below), we will impute data.

## Continuous outcomes

We will primarily analyse scores assessed at single time points. If only changes from baseline

scores are reported, we will analyse the results together with follow-up scores [44]. If standard deviations (SDs) are not reported, we will calculate the SDs using trial data, if possible. We will not use intention-to-treat data if the original report did not contain such data. We will not impute missing values for any outcomes in our primary analysis. In our sensitivity analysis (see paragraph below) for continuous outcomes, we will impute data.

### Assessment of heterogeneity

We will primarily investigate forest plots to visually assess any sign of heterogeneity. We will secondly assess the presence of statistical heterogeneity by $chi^2$ test (threshold $P < 0.10$) and measure the quantities of heterogeneity by the $I^2$ statistic [80, 81]. We will investigate possible heterogeneity through subgroup analyses. We may ultimately decide that a meta-analysis should be avoided [44].

# Assessment of reporting bias

We will use a funnel plot to assess reporting bias if ten or more trials are included [82]. We will visually inspect funnel plots to assess the risk of bias. We are aware of the limitations of a funnel plot (i.e., a funnel plot assesses bias due to small sample size). From this information, we assess possible reporting bias. For dichotomous outcomes, we will test asymmetry with the Harbord test [83] if $I^2$ is less than 0.1 and with the Rücker test if $I^2$ is more than 0.1. For continuous outcomes, we will use the regression asymmetry test [84] and the adjusted rank correlation [85].

### Unit of analysis issues

We will only include randomised clinical trials. For trials using crossover design, only data from the first period will be included [44, 86]. We will include cluster-randomised trials after adjusting the original sample size of the trial to the effective sample size using the intracluster correlation coefficient from the 'design effect' [44]. Therefore, there will not be any unit of analyses issues.

# Data Synthesis

# Meta-analysis

We will undertake the meta-analysis according to the recommendations stated in the Cochrane Handbook for Systematic Reviews of Interventions [44], Keus et al. [87], and the eight-step assessment suggested by Jakobsen et al. [88]. We will assess our intervention effects with both random-effects meta-analyses [89] and fixed-effect meta-analyses [90]. We will use the more conservative point estimate of the two [88]. The more conservative point estimate is the estimate closest to zero effect. If the two estimates are similar, we will use the estimate with the widest CI. We assess a total of three primary, three secondary outcomes and one explorative outcome, and we will therefore consider a P value of 0.014 or less as the threshold for statistical significance [88]. We will investigate possible heterogeneity through subgroup analyses. Ultimately, we may decide that a meta-analysis should be avoided [44]. We will use the eight-step procedure to assess if the thresholds for significance are crossed [88]. Our primary conclusion will be based on results with low risk of bias [88]. Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons are combined in the same meta-analysis, we will halve the control group to avoid double-counting [44]. Trials with a factorial design will be included. If quantitative synthesis is not appropriate due to considerable heterogeneity or a small number of included trials, we will report the results narratively.

### Trial Sequential Analysis

Traditional meta-analysis runs the risk of random errors due to sparse data and repetitive testing of accumulating data when updating reviews. We wish to control the risks of type I errors and type II errors and thereby the risk of potential false-positive findings of meta-analyses [91]. We will therefore perform Trial Sequential Analysis on the outcomes, in order to calculate the required information size (that is, the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) and the cumulative Z-curve's breach of relevant trial sequential monitoring boundaries [66, 91-98]. A more detailed description of trial sequential analysis can be found in the trial sequential analysis manual [98] and at http://www.ctu.dk/tsa/.

For dichotomous outcomes, we will estimate the required information size based on the observed proportion of patients with an outcome in the control group (the cumulative proportion of patients with an event in the control groups relative to all patients in the control groups), a relative risk reduction of 20%, an alpha of 1.4% for all our outcomes, a beta of 10%, and the observed diversity as suggested by the trials in the meta-analysis. For continuous outcomes, we will in the trial sequential analysis use the

observed SD, a mean difference of the observed SD/2, an alpha of 1.4% for all outcomes, a beta of 10%, and the observed diversity as suggested by the trials in the meta-analysis.

**Subgroup analysis and integration of heterogeneity**

# Subgroup analysis

The subgroup analyses are moderator analyses that explore effect heterogeneity. Results from subgroup analyses should therefore be interpreted cautiously. The following exploratory subgroup analyses will be conducted when analysing the primary outcomes (Quality of life, mortality and serious adverse events):

Participants:

1. Type of diabetes. Trials including participants with type 1 compared to trials including participants with type 2.
2. Socioeconomic status defined according to trialists, e.g. educational level. Low socioeconomic status is an umbrella term including educational level and household income which will be used as a proxy for equity if information on educational level is not reported [44]. An equity-focused review must present both relative and absolute differences between groups [15]. We will investigate trials including participants with low socioeconomic status compared to trials including participants with high socioeconomic status.
3. Number of co-morbidities defined as complications of diabetes or other chronic conditions [99].
4. Effect in men compared to women.
5. Effect in adolescents (13 to 18 years) compared to adults > 18 years.

Intervention:

6. Trials investigating self-determination theory compared to trials investigating guided self-determination method.
7. Trials with an experimental intervention above and below the mean difference in intervention length.
8. Trials investigating individual interventions compared to trials investigating group interventions.
9. Type of control intervention (no intervention, standard care or placebo attention control)

Risk of bias:

10. Trials at overall high risk of bias compared to trials at overall low risk of bias

We will use the formal test for subgroup interactions in Stata [85].

# Sensitivity analysis

### Dichotomous data

To assess the potential impact of the missing data for dichotomous outcomes, we will perform the two following sensitivity analyses on both the primary and secondary outcomes.

1. 'Best-worst-case' scenario: we will assume that all participants lost to follow-up in the experimental group did not die, had no serious adverse events or non-serious adverse events. We will assume the opposite for all participants lost to follow-up in the control group
2. 'Worst-best-case' scenario: we will assume that all participants lost to follow-up in the experimental group died, had a serious adverse event or a non-serious adverse event. We will assume the opposite for all participants lost to follow-up in the control group.

We will present results of both scenarios in our review.

### Continuous data

When analysing the robustness of a continuous 'beneficial' outcome e.g. quality of life, we will impute the group mean plus two standard deviations (SDs) of the group mean. When dealing with a 'harmful outcome' we will impute the group mean minus two SDs of the group mean [88]. We will present results of both scenarios in our review. Other post hoc sensitivity analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results [78].

# The quality of evidence

# Summary of findings table

We will assess the quality of the evidence on the primary outcomes (Quality of life, mortality, serious adverse events), the secondary outcomes (diabetes distress, depressive symptoms, and non-serious adverse events), and the explorative outcome (HbA1c) using the five GRADE considerations: Risk of bias, consistency, imprecision, indirectness, and publication bias.

We will assess imprecision using trial Sequential Analysis or if that is not an option, two authors, ASM and TT, will independently evaluate the quality of the evidence using GRADEpro GDT [100], recommended by the Cochrane Handbook for Systematic Reviews of interventions [44]. Potential disagreements will be solved by an arbiter (JCJ, MR or VZ). We will report all decisions to downgrade the quality of studies by footnotes to add to the reader's understanding of the decisions. Findings tables will be based on trials with low risk of bias and the results based on all trials.

# Discussion

This is a protocol for a systematic review that aims at synthesising the evidence for the beneficial and harmful effects of guided self-determination or self-determination theory interventions for adults with diabetes and comorbidity in any healthcare setting assessed in randomised clinical trials.

The primary outcomes will be quality of life, mortality, serious adverse events, the secondary outcomes diabetes distress, depressive symptoms and non-serious adverse events and the explorative outcome HbA1cThis protocol has several strengths. The predefined methodology is based on the Cochrane Handbook for Systematic Reviews of Interventions [44], the eight-step assessment suggested by Jakobsen et al. [88], Trial Sequential Analysis [66], and GRADE assessment [105–107]. Hence, this protocol considers both risks of random errors and risks of systematic errors.

Our protocol also has some limitations. The primary limitation is the potential for large heterogeneity as a result of including both type 1 and type 2 diabetes and all ways of delivery and interventionists. Therefore, we may ultimately decide that a meta-analysis is not warranted. Further, diabetes management always consists of multiple treatment elements [17] and it is likely that different interventions have different effects. Hence, if we show a difference between the interventions applying self-determination or self-determination method compared strategies, it will be difficult to conclude what exactly caused the difference in effect. To minimize this limitation, ten subgroup analyses are planned, but results of subgroup analyses should always be interpreted with great caution. Another limitation is the large number of comparisons which increase the risk of type 1 error. A further limitation is our exclusion of quasi-randomised studies and observational studies in the assessments of adverse events. By focusing on randomised clinical trials that are unlikely to identify late and rare adverse events, we run the risks of focusing too much on benefits and too little on harms. Therefore, if we identify benefits of the interventions, new systematic reviews focusing on the risks of harms in quasi-randomised studies and observational studies should be conducted to achieve a more balanced evaluation of benefits and harms.

Regarding the health equity subgroup analyses, it has been reported that only 20% report a differential impact of interventions that may increase the social gradient [15]. Thus, we might find that studies do not report on the proxy equity measures for evaluating a differential impact of the interventions described in this protocol [15]. We have adjusted our thresholds for significance according to the number of primary outcomes, but as mentioned, we have also included multiple subgroup analyses. This large risk of type 1 error will be considered when interpreting the review results. Further, we expect that no trials will have blinded treatment providers and patients. Even though blinding of patients should be relatively easy, blinding of treatment providers is theoretically possible but much more difficult to carry out, especially in psychosocial interventions [57].

# Declarations

## Ethical approval and consent to participate

Not applicable

## Consent for publication

Not applicable

## Availability of data and materials

We will publish all data including code in the supplementary material of the systematic review.

## Competing interests

The authors declare that they have no competing interests.

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## Authors contributions

ASM wrote up the protocol with regular supervision from MJR, VZ, TT, JL, CG and JCJ. JL, CG and JCJ wrote the methods section. MDC contributed with expert knowledge on type 1 diabetes and psychosocial interventions. BR and EM read and commented on the final manuscript before it was submitted for publication. All authors read and approved the final manuscript.

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