

## Supplementary file S1

Review protocol (January 2014)

### Effectiveness of Chronic Care Models for the Management of Type 2 Diabetes Mellitus in Europe: a Systematic Review

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#### 1. BACKGROUND

A growing number of European citizens suffer from diabetes, constituting a growing health, social, and economic burden. The number of individuals with diabetes in Europe in 2013 was estimated by the International Diabetes Federation to be 56.3 million, or 8.5% of the adult population (20-79 years), and is expected to increase to 68.9 million people, or 10.3% by the year 2035 [1]. It is generally believed that lifestyle, with diets high in saturated fat and decreased physical activity, together with an increased longevity, are the main factors in the current increase in T2DM. In individual, as well as in societal terms, the burden of T2DM is enormous, resulting in increased morbidity and mortality [1].

Historically, health care systems were developed to respond rapidly and efficiently to acute diseases. The focus was on the immediate problem, a rapid diagnosis, and the initiation of professional treatment; a process in which the patient's role was largely passive. However, with the rapid aging of the population and the growing prevalence of chronic diseases, improvement in quality of chronic care requires more than evidence about effective diagnostic procedures and treatments. Despite much progress in clinical and behavioral interventions, it is suggested that many chronically-ill patients do not profit from these advances [2].

In the current health care systems in European countries, a shift from disease management to chronic care management may prevent costly complications and frailty in elderly with T2DM, enabling them to live independent, healthy and active lives as long as possible. With the aim of describing essential elements for improving outcomes in care of chronic diseases, the Chronic Care Model (CCM) was developed in the mid-1990s and was further refined in 1997 [3,4]. As such, CCM is a primary care-based comprehensive model, advocating evidence-based changes in health care of patients with chronic disease. The model is based on the assumption that improvements in care require an approach that incorporates patients, health care providers, and system level interventions. It can be applied to a variety of chronic illnesses, health care settings and target populations, with the goal of healthier patients, more satisfied providers, and cost savings.

The CCM comprises six components deemed essential for providing high-quality care to patients with chronic disease:

1. health care organization (i.e. providing leadership for securing resources and removing barriers to care),
2. self-management support (i.e. facilitating skills-based learning and patient empowerment),
3. decision support (i.e. providing guidance for implementing evidence-based care),
4. delivery system design (i.e. coordinating care processes),
5. clinical information systems (i.e. tracking progress through reporting outcomes to patients and providers), and
6. community resources and policies (i.e. sustaining care by using community-based resources and public health policy).

Reports indicate a widespread application of CCM to multiple illnesses [5,6], yet, to date, only one study has reviewed how CCM has been applied in diabetes care in primary care settings and what the outcomes were of this implementation [7]. This systematic review showed that CCM approaches in the United States have indeed been effective in improving the health of individuals with diabetes who receive care in primary care settings. Regarding quality of diabetes care in Europe, observational studies have been performed in different European countries [8-11]. The recently published GUIDANCE study [12] reported encouraging levels of adherence to the main recommended process measures in diabetes care, e.g. HbA1c levels <7%, blood pressure <130mmHg (systolic) and <80 mmHg (diastolic), and LDL cholesterol concentrations <2.6 mmol/l. The level of actual achievement of these target goals by the individual patients was, on the other hand, much lower. Findings from the GUIDANCE study supported previously made suggestions [13-15] that process adherence may only have a limited influence in terms of reaching target goals (risk factor control) or enhanced management, e.g. appropriate adjustments to medication. Also, the existence of substantial between-country variation in quality of diabetes care in Europe was confirmed by the GUIDANCE study [12].

## **2. AIMS**

This systematic review will focus on the scientific evidence regarding the specific treatment and care of elderly suffering from T2DM and associated comorbidities. Its aim is to summarize previous research on the effects of current European disease management models specifically related to the complex interaction between T2DM and comorbidities in the elderly, and on improving outcomes of interest.

## **3. OBJECTIVES (Research Question)**

To assess the effects of chronic care models with a duration of at least 6 months on the following outcomes in older patients with T2DM and diabetes-related comorbidities:

- biophysical outcomes (e.g. serum HbA1c concentrations, and change in BMI),
- patient-reported outcomes (e.g. diabetes-related quality of life),
- diabetes complications (e.g. micro- and macrovascular complications),

compared to routine diabetes care.

#### 4. METHODS

In the case of substantial clinical or statistical heterogeneity, study results will be combined in a narrative review only. Without substantial clinical and statistical heterogeneity, study results will be combined in a meta-analysis, following the approach described below. The subsequent reporting of the systematic review will be conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) statement [16].

##### **Criteria for considering studies for this review**

###### *Types of studies*

Studies will be eligible for inclusion if they are a randomized clinical trial (RCT). Only studies that have assessed outcome measures six months or more from baseline will be investigated.

###### *Types of participants*

Individuals, regardless of gender and ethnicity, with diagnosed T2DM with or without one of the following comorbidities, assessed and reported at baseline:

- Mental health problems (stress, depression, anxiety)
- Cancer
- Cardiovascular disease
- Osteoporosis
- Rheumatic arthritis
- Chronic obstructive pulmonary disease
- Neurological diseases
- Kidney diseases.

Ideally, the diagnostic criteria for T2DM are described in the study and were established using the standard criteria that were valid at the beginning of the trial (ADA 1997, NDDG 1979, WHO 1980, WHO 1985, WHO 1999), in order to be consistent with changes in T2DM classification and diagnostic criteria throughout the years.

We will include only studies in which the average age of the study population is  $\geq 60$  years, given that this is the usual age of diagnosis for most patients in Europe.

###### *Type of interventions*

Chronic care models/programs that meet the following criteria:

- specific for individuals with T2DM,
- based on guidelines,
- providing integrated (multi-disciplinary) care,
- addressing patient empowerment,
- providing quality management (e.g. patient registry systems, recording of process measures/adherence to guidelines, achievement of treatment goals),
- delivered in primary care and secondary care.

### *Type of controls*

The intervention group will be compared with those participants undergoing routine diabetes care (standard care recommended in that particular country, e.g. regular follow-up with the required health professional and a full diabetes annual review).

## **Types of outcome measures**

### *Primary outcomes*

#### Biophysical outcomes:

- Metabolic control: hypoglycemia, serum HbA1c concentrations, serum lipids levels (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides), blood pressure, and glomerular filtration rate
- Change in BMI and other anthropometric measures (waist circumference, waist to hip ratio)

#### Patient-reported outcomes:

- Diabetes-related quality of life
- Participation in life style changing programs
- Communication
- Patient empowerment

#### Diabetes complications:

- Microvascular complications: retinopathy, nephropathy, and neuropathy
- Macrovascular complications: cardiovascular disease, cardiovascular risk scores, and cerebrovascular disease
- Diabetes-related mortality: total mortality and mortality due to major adverse cardiac events

### *Secondary outcomes*

#### Mental Health:

- Depression
- Cognitive dysfunction or dementia
- Anxiety

#### Functionality:

- Frailty index
- Self-management skills: dietary habits, physical activity, medication administration, use of equipment
- Nutritional status
- Dependency on care

#### Contact to Health Care System:

- Number of yearly hospital visits
- Hospitalization: number of emergency admissions, and number and duration (days) of hospital stays.
- Adherence to treatment recommendations
- Quality of care
- Polypharmacy

## **Search methods for identification of studies**

### *Electronic searches*

Electronic databases will be searched from January 2000 until January 2014. We will use the following sources for the identification of trials:

- CENTRAL (the Cochrane Central Register of Controlled Trials)
- MEDLINE
- EMBASE
- CINAHL

### *Searching other resources*

We aim to further identify studies by searching the reference list of each relevant trial and systematic review identified. First authors are contacted whenever additional information is required.

## **Data collection and analysis**

### *Selection of studies*

To determine which studies are to be assessed further, two reviewers (BB, WR) will independently scan the titles, abstracts and key words of every record retrieved. Full text articles will be retrieved if the title/abstract/key words suggest that the trial:

- included patients with T2DM, and
- evaluated a chronic diabetes care model.

In case of any doubt regarding these criteria from the information given in the title and abstract, or if the abstract was absent, the complete article will be retrieved for clarification. Studies will be eliminated if both reviewers agree that the criteria for considering studies for the review are not being met. Inter-rater agreement for study selection will be measured using the Kappa statistic [17]. Any differences in opinion will be discussed and, if necessary, resolved by a third reviewer (KM).

### *Data extraction and management*

A structured data extraction form will be developed including the following information:

- General information: published/unpublished, title, authors, source/reference, contact address, country, language of publication, year of publication, sponsoring.
- Trial characteristics: design, duration, (method of) randomization, use of validated questionnaires, (method of) blinding (if appropriate).
- Intervention: comparison group included (routine care/no intervention), intervention (duration, timing).
- Participants: method of sampling, exclusion criteria, total number (also for comparison group(s)), sex, age, body mass index, ethnicity, pre-existing comorbidities/other medical conditions, standards of diabetes care (HbA1c concentration, serum glucose levels, lipid profile, blood pressure), diagnostic criteria T2DM, duration of T2DM, baseline comparison of the groups (including comorbidities), withdrawal from study/losses to follow-up, assessment of subgroups.

- Outcome: as specified above, main outcome as assessed in the trial, other outcomes/events assessed, quality of reporting the outcomes.
- Results: reported for outcomes and times of assessment.

If there is missing information, the authors of the article will be contacted. Differences in data extraction at item level will be resolved by discussion and if consensus is not reached, the third reviewer (KM) will take the final decision.

#### *Assessment of risk of bias in included studies*

The quality of reporting of each experimental trail will be assessed by two review authors independently (BB, WR). Risk of bias will be assessed using the Cochrane Collaboration's tool [18]. In particular, the following factors will be studied.

##### Minimization of selection bias

- Randomization procedure (*if applicable*): the procedure will be scored adequate if the resulting sequences were unpredictable (computer generated schemes, coin tossing, and tables of random numbers).

##### Minimization of attrition bias

- Handling of drop-outs: will be considered adequate when the trial reports a complete description of all patients failing to participate until the end of the trial and if the data were analyzed on intention-to-treat (ITT) (thus with all randomized patients included). An overall drop-out rate less than 15%, and a selective drop-out rate less than 10% (the at risk groups), will be considered justifiable.

##### Minimization of detection bias

- Method of blinding for the outcome: will be considered adequate if the outcome assessors were completely blind for the intervention.

#### *Assessment of heterogeneity*

Variation between studies (heterogeneity) will be examined to answer the question whether the combination of the different studies is meaningful.

Clinical heterogeneity of the selected studies will be evaluated according to key characteristics of the study participants (age, gender, diabetes duration, blood glucose levels), the intervention, and study outcomes. Statistical heterogeneity will be estimated by visual inspection of the forest plots (the less overlap of confidence intervals, the more likely the presence of heterogeneity). Furthermore, heterogeneity will be assessed using the  $I^2$ -statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance or sampling error [19]. It allows for calculation across studies of varying sizes, study types and with varying outcome data. In case there is significant heterogeneity ( $I^2$  values >75%), more emphasis will be placed on the results of a random-effects model, despite that the given model cannot overcome the problem of heterogeneity.

#### *Data synthesis*

Data will be summarized statistically if they are available, sufficiently similar, and of sufficient quality.

### *Subgroup analysis and investigation of heterogeneity*

To explore potential source of (clinical) heterogeneity, subgroup analyses will be performed. Where performed, subgroup analysis will have a tentative (hypothesis-generating) purpose. The following subgroup analyses will be considered:

- Gender
- Duration of the intervention
- Duration of diabetes below and over five years (individuals who have diabetes for a longer time are likely to have more advanced disease and increased insulin resistance, and more complications; hence any forms of care may have a smaller effect in more advanced disease)
- Number of comorbidities

### *Sensitivity analysis*

We will perform sensitivity analyses in order to explore the influence of certain factors on effect size:

- Repeating the analysis excluding unpublished studies (if selected and included).
- Repeating the analysis taking risk of bias into account.
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results.
- Repeating the analysis excluding studies by using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

The robustness of the results will further be tested by repeating the analysis using different measures of effects size (risk difference, odds ratio, etc) and different statistic models (fixed and random effects models).

## **5. OUTLOOK**

As the population ages, the burden of chronic disease is expected to grow continuously. While healthcare organizations need to find effective ways to deal with increased care demands, the CCM has been developed to advocate evidence-based changes in health care of patients with chronic disease. The findings of the current systematic review will contribute to our understanding of the relationship between application of CCM and qualitative and quantitative T2DM outcomes in European primary care settings. Finally, the results can provide insights into new approaches to further integrate the CCM into primary health care initiatives in diabetes.

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