PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between full monitoring of biomedical and lifestyle target indicators and HbA1c level in primary type 2 diabetes care: an observational cohort study (ELZHA-cohort 1)
AUTHORS	van Bruggen, Sytske; Rauh, Simone; Kasteleyn, Marise; Bonten, Tobias N.; Chavannes, Niels; Numans, Mattijs

VERSION 1 – REVIEW

REVIEWER	Prof Doris Young National University of Singapore, Singapore
REVIEW RETURNED	18-Nov-2018

GENERAL COMMENTS	This observational study examined the association between full monitoring of physiological and lifestyle target indicators and HbA1c level in primary type 2 diabetes care based on a cohort study (ELZHA-cohort 1) in the Western region of the Netherlands. This particular manuscript is of interest to policy makers and health services providers in other countries who are struggling to trial different funding models to achieve better outcomes for their type 2 DM patients. Providing support to private GPs to manage their DM patients better is vital to achieve better health outcomes and in this study, the authors chose HbA1C, BP and Lipids, physiological and biochemical measures in addition to lifestyle measures such as exercise smoking and BMI. The paper is well written though it can be improved by the following suggestions. In order to be of relevance to other international policy makers and practitioners, the authors need to clarify the health care funding model in their manuscript even though the authors referred to their previous publication but this should be explained again in the introduction. 1. Explain the health care system in the Netherlands a bit more in particular the funding model ie the insurance system and how GP care is funded and what is the contribution by the patients. In this care group model, is it only free service to the patients who enrolled to see these GPs who took it up or are GP services free to all patients with chronic diseases?

	2. Clarify the care group model: what is it and what incentives are there for GPs to sign up? Is it universal? A trial? Voluntary? How are patients enrolled? 3. How did the three HbA1C profile groups come about? What do you mean by professional GP guidelines? Reference 13 was quoted, Is it a local consensus by GPs in Netherlands? 4. Complete monitoring means all the targets are reported 4 times a year, is this a surrogate measure of continuity of care? Could incomplete monitoring data be due to other reasons eg patient saw different doctors? Went to see endocrinologists privately or public hospitals? Is this possible in the Dutch health care system or not? Below are some issues related to the measures used which need to be clarified? The term physiological refers to blood pressure but Lipids and HbA1C are biochemical measures so may be that can be clarified and reflected accurately in the title and throughout the study. Some Minor points: Even though the English writing is good, there are grammatical and other errors in the text eg page 5 lines 16 to 20 chronical? Care group 'collective or collected'? And some prepositions are missing in the sentences, terms used are also unique to perhaps the Netherlands, fundus vs retinal screening , allied health vs paramedics but I am not sure if you need to change those and will leave it to the editors to decide.

REVIEWER	Edoardo Mannucci Diabetology, Careggi Hospital, Florence, Italy
REVIEW RETURNED	26-Nov-2018

GENERAL COMMENTS	The manuscript reports the results of a retrospective study on a cohort of type 2 diabetic patients undergoing a GP-based structured program of diabetes management. The main result is that those patients with complete registration of indicators defined by the structured program have a lower A1c than those with incomplete registration. The authors conclude that regular data registration produces an improvement in glycemic control. The main problem of the paper is that the authors seem to draw conclusions on causal relationships, whereas this study design demonstrates only associations.it is certainly possible that a more accurate registration of some intermediate endpoints can induce physicians to a prompt therapeutic intervention, thus reducing A1c (a concept which could be expressed more clearly in Discussion). However, we can also formulate other hypotheses. Incompleteness in registration could be the effect of a reduced awareness of doctors in the relevance of diabetes management; this could produce a less reactive attitude toward intensification of therapy, whenever needed, and therefore to higher A1c levels. The use of drugs for diabetes (anche changes in therapy) should be recorded and used a potential confounded. In addition, it would be interesting to know the proportion of cases in which each doctor intensifies therapy when A1c is not within targets; this could be used as a further confounded in multivariate analysis. Another issue is patient compliance: some patients may have incomplete

	reco res because they did not perform some prescribed tests. It is conceivable that patients with a lower motivation, who miss some tests, also have a lower adherence to treatments, leading to a worse glycemic control. Minor points: 1. Number and main characteristics of patients excluded for incomplete data should be reported. 2. Statistical methods for comparisons between different A1c groups should be reported in methods. I would suggest to use a suitable method for detecting differences across multiple groups, rather than a comparison of each subgroup with the first subgroup, as reported in results.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:

This observational study examined the association between full monitoring of physiological and lifestyle target indicators and HbA1c level in primary type 2 diabetes care based on a cohort study (ELZHA-cohort 1) in the Western region of the Netherlands.
This particular manuscript is of interest to policy makers and health services providers in other countries who are struggling to trial different funding models to achieve better outcomes for their type 2 DM patients. Providing support to private GPs to manage their DM patients better is vital to achieve better health outcomes and in this study, the authors chose HbA1C, BP and Lipids, physiological and biochemical measures in addition to lifestyle measures such as exercise smoking and BMI.
The paper is well written though it can be improved by the following suggestions.
In order to be of relevance to other international policy makers and practitioners, the authors need to clarify the health care funding model in their manuscript even though the authors referred to their previous publication but this should be explained again in the introduction.

1) Explain the health care system in the Netherlands a bit more in particular the funding model ie the insurance system and how GP care is funded and what is the contribution by the patients. In this care group model, is it only free service to the patients who enrolled to see these GPs who took it up or are GP services free to all patients with chronic diseases?

Reply: We appreciate the reviewer's points and we agree that our explanation of the Dutch health care system, including the funding of structured diabetes primary care and the care group model, needs some more clarification.

In the Netherlands, for all citizens, a health care insurance is legally required. Health insurance companies are funded by periodical contributions of beneficiaries in combination with national governmental support. For all beneficiaries, access to primary care is fully covered by their insurers and, thus, free of charge.
For GPs, reimbursement is determined by the number of patients that is registered at a practice, combined with a fee-for-service (1).
To improve diabetes primary care in the Netherlands, GPs unified into care groups. These care groups negotiate on behalf of their GP members content, delivery and reimbursement of structured diabetes care protocols. Taking the preventive benefits of structured primary care for diabetes patients into consideration, insurers encourage delivery of structured diabetes care protocols; and, thus, GP participation in care groups.
Originally, care group protocols were specifically targeted at type 2 diabetes care. All patients diagnosed with type 2 diabetes mellitus and in absence of relevant comorbidities such as terminal diseases were eligible for inclusion. Last years, an increasing number of care groups also developed

structured primary protocols for patients with other chronic diseases such as COPD and cardiovascular diseases. For these diseases, a comparable inclusion model was applied.
All patients who receive diabetes care in GP practice are eligible for participation. The costs of this care protocol are fully covered by health insurance companies. Participation is free of charge for patients.

In the introduction, we revised this section (page 4, line 42 – page 5, line 14).
"It is known that implementing structured primary diabetes care and delegation of tasks to a nurse practitioner has considerable impact on the organization of the GP practice (20, 21). For example, in the USA, an evaluation of the recent Comprehensive Primary Care (CPC) program revealed a need to refine practice workflows, to incorporate new staff roles, and to overcome incompatibility of health technology systems (22). To improve the delivery of structured primary diabetes care in the Netherlands, most GPs have joined together in local 'care groups' (23) ~~*that provide logistic and quality support to individual GP practices. In addition,*~~ *Care groups negotiate collective structured diabetes care protocols* ~~*are negotiated*~~ *with the funding institutions of Dutch primary care, namely, local health insurance companies."*

Introduction (page 5, line 26 – 33):
"It is known that providing a structured diabetes care protocol is associated with better monitoring of patients (24). In addition, adequate registration of the diabetes-related patient health indicators is associated with improvement of the care process (25). The costs of this protocol are fully covered by health insurance companies. For patients, participation is free of charge."

2) Clarify the care group model:
   A) What is it and what incentives are there for GPs to sign up? Is it universal? A trial? Voluntary?

Reply: Across the whole country, local care groups have been initiated. For GPs, participation in a care group is not part of a scientific trial or universal, but rather a voluntary choice. Incentives to participate in a care group include logistic support to implement the care protocol and, based on the number of patients enrolled, reimbursements for four annual diabetes consultations at ward.

We adjusted the introduction section (page 5, line 13-24) as follows:
"For GPs, participation in a care group is voluntary. However, the logistic and quality support to individual GP practices which is part of the care group approach, might be seen as an incentive for care group participation. That is, the agreements between care groups and health insurance companies on structured diabetes care protocols enable GPs to offer high-quality intensive primary diabetes care. To illustrate, on an annual basis, four consultations at the GP practice with an explicit focus on lifestyle support are facilitated, as well as ~~*paramedical diabetes*~~ *complementary allied health (e.g. annual screening of fundus and feet)."*

   B) How are patients enrolled?

Reply: Within a care group setting, GPs are able to invite all their T2DM patients for this structured care protocol. Patients are invited to join this care protocol during a standard diabetes consultation or at time of diagnosis. Patients who provide consent to be enrolled can join the protocol.
We adjusted the article as follows:

In the introduction (page 5, line 24-26):
"All patients who receive diabetes care in GP practice are eligible for participation in the structured care protocol ~~*is free of charge for patients*~~*."*

In the methods section (page 6, line 48 – 55):
In short, within a care group setting, GPs are able to invite all their T2DM patients with primary care treatment for this structured care protocol. During a standard diabetes consultation or at time of diagnosis, patients are informed about this care protocol. Patients who provide consent to be enrolled, can join the structured primary care protocol. The protocol includes a quarterly diabetes consultation, in which diabetes-related target indicators are checked and lifestyle education is provided, combined with ~~*'paramedical care'*~~ *complementary allied health such as an annual foot check, fundus screening and dietician´s counselling.*

3) How did the three HbA1C profile groups come about? What do you mean by professional GP guidelines? Reference 13 was quoted, Is it a local consensus by GPs in Netherlands?

Reply: From the reviewer's comment, we understand that the professional GP guidelines model in the Netherlands requires more background information. In the Netherlands, a national scientific council of GPs determines, based on most recent scientific evidence, treatment guidelines for a wide range of diseases in primary care ((2)*, this represents reference 13 in the manuscript)*. All Dutch GPs adjust the delivery of their primary care in correspondence with these guidelines. In other words, all GPs follow these guidelines which are based on consensus among an expert panel of GPs. Accordingly, we added some clarification at two points.

In the introduction (page 4, line 24 – 32):
"Accordingly, in the Netherlands, a nationally acknowledged scientific council of GPs has determined professional guidelines for diabetes primary care (13) ~~guidelines for general practitioners (GPs).~~ In correspondence with the NICE guidelines (14), it is recommended ~~emphasize~~ to monitor at least once a year not only HbA1c levels, but also the ~~physiological~~ biomedical target indicators systolic blood pressure and LDL, as well as lifestyle-related indicators ~~(13, 14).~~"

In the methods section (page 8, line 14-38):
"Tailored on specific key patient characteristics (age, intensity of medication treatment, and disease duration) professional Dutch GP guidelines ~~distinguish~~ recommend differentiated HbA1c targets for three different patient profile groups ~~for HbA1c targets~~ based on age and prescribed medication. Details on the scientific determination of these target values are presented in the guidelines (13). To summarize, 1) for patients aged <70 years, and for older patients with a mild treatment regime (only metformin monotherapy prescription or lifestyle coaching), a target HbA1c value of 7.0% (53 mmol/mol) is recommended.~~.; ~~In the present study, since missing data on medication might reflect administrative omissions rather than absence of medication treatment, patients without data on medication were excluded.~~ 2) for patients aged ≥70 years who need more intensive treatment and were diagnosed with diabetes <10 years previously, a target HbA1c value of 7.5% (58 mmol/mol) is recommended; 3) for patients aged ≥70 years who need more intensive treatment and were diagnosed with diabetes ≥10 years previously, a target HbA1c value of 8.0% (64 mmol/mol) is recommended. In the present study, since missing data on medication might reflect administrative omissions rather than absence of medication treatment, patients without data on medication were excluded."

4) A. Complete monitoring means all the targets are reported 4 times a year, is this a surrogate measure of continuity of care?

Reply: We agree with the reviewer that full monitoring might be interpreted as a surrogate measure of continuity of care. We notice that some confusion might have risen regarding our definition of 'full monitoring', and that the current description requires more clarification. To specify, in our study, 'full monitoring' implies that each target indicator should have been registered at least once in one year (between January and December 2014). We adjusted the description of fully monitoring at two points:

In the introduction (page 4, line 24-32):
"Accordingly, in the Netherlands, a nationally acknowledged scientific council of GPs has determined professional guidelines for diabetes primary care (13). In correspondence with the NICE guidelines (14), it is recommended to monitor at least once a year not only HbA1c levels, but also the ~~physiological~~ biomedical target indicators systolic blood pressure and LDL, as well as lifestyle-related indicators."

In the methods section (page 7, line 18-25):
"In the present study, patients were regarded as 'fully monitored' when ~~at least one measure of~~ each ~~of the~~ target indicator~~s~~ was registered at least once between January and December 2014. If one or more target indicators were not registered minimally one time in calendar year 2014, patients were defined as ´incompletely monitored´."

B. Could incomplete monitoring data be due to other reasons eg patient saw different doctors? Went to see endocrinologists privately or public hospitals? Is this possible in the Dutch health care system or not?

Reply: Within the care group model, an individual patient can only participate in the structured diabetes care protocol at one specific GP practice at a time. During the calendar year, a patient might decide to move to another GP practice. In that case, at the previous practice, his participation in the diabetes protocol is automatically ended.
In the Netherlands, endocrinologists and other specialists are all embedded in public hospitals. For patients, a GP referral is required in order to have access to hospital care. When a patient requires specialized diabetes hospital care instead of the primary care protocol, a GP refers the patient to a hospital specialist and ends the protocol participation.
In our study, patients were excluded if they participated less than 12 months in the diabetes protocol. To conclude, incomplete monitoring could not be explained by variation in GP practices which were consulted by the patient.

In our view, the suggestions of the reviewer are of high relevance to interpret our findings correctly. Therefore, we adjusted the manuscript at two points as follows:

In the methods section (page 6, line 29-31):
"Patients receiving continuously structured primary diabetes care from January 2014 through December 2014 at the same GP practice were included."

In the discussion section (page 13, line 21- 26):
"Third, since patients were included if they participated for at least one year at the same GP practice, bias caused by intermediate moving or referral to hospital diabetes care was avoided - which contributes to the stability and, thus, the validity of our findings."

Below are some issues related to the measures used which need to be clarified? The term physiological refers to blood pressure but Lipids and HbA1C are biochemical measures so may be that can be clarified and reflected accurately in the title and throughout the study.

Reply: We thank the reviewer for her alertness with regard to the chosen terminology on the registration of diabetes target indicators. In our view, the term 'biomedical' measures is a more adequate way than 'physiological' to describe measures of systolic blood pressure, HbA1c and lipids. Subsequently, we replaced the word physiological by biomedical in the whole article.

Some minor points: Even though the English writing is good, there are grammatical and other errors in the text eg page 5 lines 16 to 20 chronical? Care group 'collective or collected'? And some prepositions are missing in the sentences, terms used are also unique to perhaps the Netherlands, fundus vs retinal screening , allied health vs paramedics but I am not sure if you need to change those and will leave it to the editors to decide.

Reply: Again, we appreciate the reviewer's suggestions regarding the use of grammar and other errors. Indeed, 'chronical' should be replaced by 'chronic'.
With regard to the description of the care group model as a collective: a care group involves a collective of GP practitioners. To specify, GPs unified themselves in care groups. These care groups negotiate with insurance companies on behalf of their members and provide collective support regarding the implementation of diabetes care protocols in individual practices. We understand that in the methods section, confusion may have risen when reporting 'data registry from a care group collective in the western part of the Netherlands.'

We adjusted the methods section (page 6, line 16-21) as follows:
"Data were used of type 2 diabetes patients from the observational Eerstelijns Zorggroep Haaglanden (ELZHA) cohort, which is based on primary care registry data from a care group ~~collected~~ in the western part of the Netherlands".

With regard to the terminology of 'allied health', we fully agree with the reviewer that 'allied health' is most accurate description of non-academically educated health care professionals – nurse practitioners, physiotherapists, dietitians - who are involved in the structured diabetes care protocol. We adjusted the manuscript at several points as follows:

In the introduction section (page 5, line 20-25):

"To illustrate, on an annual basis, four consultations at the GP practice with an explicit focus on lifestyle support are facilitated, as well as ~~paramedical diabetes care~~ complementary allied health (e.g. annual screening of fundus and feet)."

In the methods section (page 6, line 50 – page 7, line 12):
Patients who provide consent to be enrolled, can join the structured primary care protocol. The protocol includes a quarterly diabetes consultation, in which diabetes-related target indicators are checked and lifestyle education is provided, combined ~~'paramedical' care~~ complementary allied health such as an annual foot check, fundus screening and dietician´s counselling.

Regarding the use of the term 'fundus' screening, international ophtamology guidelines (3) refer to fundus examination in order to determine symptoms of diabetic retinopathy. If the editor prefers use of 'retina' instead of 'fundus', we are willing to adjust terminology.

Moreover, this revised paper has been corrected by a native English speaker who has experience in checking scientific manuscripts. The changes made by the English speaker, including the use of prepositions, are labelled as 'Language bureau' in the track changes version of the manuscript.

Reviewer #2.

The manuscript reports the results of a retrospective study on a cohort of type 2 diabetic patients undergoing a GP-based structured program of diabetes management. The main result is that those patients with complete registration of indicators defined by the structured program have a lower A1c than those with incomplete registration. The authors conclude that regular data registration produces an improvement in glycemic control.
The main problem of the paper is that the authors seem to draw conclusions on causal relationships, whereas this study design demonstrates only associations.it is certainly possible that a more accurate registration of some intermediate endpoints can induce physicians to a prompt therapeutic intervention, thus reducing A1c (a concept which could be expressed more clearly in Discussion). However, we can also formulate other hypotheses. Incompleteness in registration could be the effect of a reduced awareness of doctors in the relevance of diabetes management; this could produce a less reactive attitude toward intensification of therapy, whenever needed, and therefore to higher A1c levels. The use of drugs for diabetes (anche changes in therapy) should be recorded and used a potential confounded. In addition, it would be interesting to know the proportion of cases in which each doctor intensifies therapy when A1c is not within targets; this could be used as a further confounded in multivariate analysis. Another issue is patient compliance: some patients may have incomplete reco res because they did not perform some prescribed tests. It is conceivable that patients with a lower motivation, who miss some tests, also have a lower adherence to treatments, leading to a worse glycemic control.

Reply: To begin with, we thank the reviewer for his correct remark that our study does not allow any causal inferences. In addition, with his subsequent considerations, the reviewer introduces a framework which contributes strongly to a deeper understanding of our findings. His hypothesis regarding a potential relationship between diabetes management 'awareness' and reactivity of GPs and patients' Hba1c levels is worth further exploration.
As the reviewer suggests, use of diabetes drugs might be a relevant factor affecting HbA1c levels. In the Netherlands, recommended HbA1c levels are adjusted to drugs use: for patients older than 70 years with only prescription of metformin monotherapy, a stricter HbA1c level (maximally 53 mmol/mol) is recommended than for patients older than 70 years with other kind of diabetes drugs prescriptions (58 mmol/mol). In our study, we adjusted for drugs use by conducting stratified analyses regarding HbA1c profiles. We agree with the reviewer that it might be interesting to examine the proportion of cases in which GPs intensify therapy when HbA1c exceeds recommended target values. We fully agree that incomplete monitoring of patients might not only indicate no-show, but also missing of prescribed lab tests and limited overall adherence to diabetes treatment. This is especially relevant in our urban study population, which is characterised by poverty, poor education, health illiteracy and cultural diversity. And in our view, the reviewer's comment that this adherence problem is reflected in worse HbA1c control, is very important. We appreciate these interesting reflections. Accordingly, we adjusted the discussion on several points:

Discussion section (page 12, line 31 – 36):
"Thus, in general, incomplete monitoring of a patient should be interpreted as an important sign of diabetes-related health risks – especially since incomplete records might not only be caused by no-show, but also by low patient motivation, missing of prescribed lab tests and limited overall adherence to diabetes treatment."

Discussion section (page 12, line 36 – 42):
"As reported by others (36), a tailored approach based on data registry and adjusted to patient characteristics (e.g. monitoring completeness), is recommended. This might encourage awareness in GP practice regarding adequate diabetes management and might help GP's to overcome barriers on full adoption of the care group monitoring approach."

Discussion section (page 13, line 45-50):
In addition, from the GP perspective, examining potential barriers to complete monitoring, including potential benefits such as an increase of the proportion patients with HbA1c levels within recommended values, might provide keys to improvement of the monitoring process.

Minor points:

1. Number and main characteristics of patients excluded for incomplete data should be reported.

We agree that this information improves adequate understanding of our findings. The manuscript has been adjusted as follows:

Methods section (page 7, line 42-47):
"For patient characteristics, categorical variables were reported as numbers and percentages. Continuous variables were reported as means with standard deviation (SD) or, when non-normally distributed, as medians with interquartile ranges (IQR). Baseline characteristics of excluded patients were, if available, compared to the study population."

Results section (page 10, line 19-44):
"Comparing characteristics of the excluded patients (n = 12,103 patients) with the study population (n = 12,095 patients, see supplementary file, table 1), in excluded patients, mean HbA1c level (50.32 mmol/mol, SD = 12.8 mmol/mol; 6.76 % (SD = 3.32 %, 7.535 registrations missing) was slightly lower than in the study population (52.5 mmol/mol, SD=1.07 mmol/mol; 6.95 %, SD = 3.16). Comparing the median diabetes duration of excluded patients (5 years, IQR: 3 – 9, 63 registrations missing) to the study population (6 years, IQR: 3 – 10), no substantial differences were found. Regarding median age, excluded patients (71 years, IQR: 60 – 82, 2,917 registrations missing) were older than included patients (median: 64 years, IQR: 56 – 71 years) and slightly more often female (50 % (n = 4,251; 3,530 registrations missing) versus 45 % (n = 5,477). More detailed characteristics of our study population, classified by HbA1c profile and monitoring completeness, are presented in Table 1. Of patients who were incompletely monitored, information on physical exercise was most often missing, followed by smoking, BMI, LDL, and systolic blood pressure (Figure 2).
~~*Characteristics of our study population, classified by HbA1c profile and monitoring completeness, are presented in Table 1.*~~

2. Statistical methods for comparisons between different A1c groups should be reported in methods. I would suggest to use a suitable method for detecting differences across multiple groups, rather than a comparison of each subgroup with the first subgroup, as reported in results.

According to the reviewer's comments, we understand that our analyses were not described sufficiently clear.
To specify, we firstly conducted multiple multi-level analyses of the relation between monitoring completeness and HbA1c level for each of the different HbA1c profiles. In addition, to explore whether the magnitude of the potential effect in older patients with more complex treatment needs differed from relatively young and stable patient group, we tested with a non-stratified multi-level analysis whether the magnitude of the effect found in HbA1c profile 2 and 3 differed significantly from Hba1c profile 1.

We adjusted the methods section (page 8, line 40-47) as follows:
"In view of the relevance for clinical practice, separate multi-level analyses were conducted and reported for each of these HbA1c profile groups. In addition, in a non-stratified multi-level analysis, we tested ~~for a significant interaction effect between monitoring completeness and HbA1c profile group~~ whether the magnitude of the effect found in HbA1c profile 2 and 3 differed significantly from Hba1c profile 1."

In addition, we adjusted the heading of table 2 (page 20):

Table 2. Multilevel analyses evaluating the HbA1c difference of fully-monitored patients compared to incompletely monitored patients, stratified for HbA1c profile.

		Profile 1			**Profile 2**			**Profile 3**		
		B	**95% CI**	**p-value**	**B**	**95% CI**	**p-value**	**B**	**95% CI**	**p-value**
Model 1[a)]	mmol/mol	-1.95	-2.41,-1.49	<0.001	-2.03	-3.41, -0.66	0.004	-1.53	-2,96, -0.10	0.037
	%	-0.18	-0.22; -0.14		-0.19	-0.31; -0.06		-0.14	-0.27; -0.01	
Model 2[b)]	mmol/mol	-2.03	-2.53, -1.52	<0.001	-3.36	-5.28, -1.43	0.001	-1.89	-3.76, -0.01	0.049
	%	-0.19	-0.23; -0.14		-0.31	-0.48; -0.13		-0.17	-0.34; 0.00	

[a)] Crude analysis

[b)] Multilevel analysis adjusted for age, diabetes duration and gender

References

1. Changing landscape: From fee-for-service to value-based reimbursement: U.S. Department of Health and Human Services, National institute of diabetes and digestive and kidney diseases; 2018 [
2. Rutten GEHM DGW, Nijpels G, Houweling ST, Van de Laar FA, Bilo HJ, Holleman F,Burgers JS, Wiersma Tj, Janssen PGH. NHG-Standaard Diabetes mellitus type 2 (derde herziening). Huisarts en Wetenschap 2013;56(10):512-25.
3. Ico guidelines for diabetic eye care, update 2017. International Council of Ophtamology; 2017.

VERSION 2 – REVIEW

REVIEWER	Young , Doris National University of Singapore, Singapore
REVIEW RETURNED	13-Jan-2019

GENERAL COMMENTS	I am satisfied with the revised manuscript and felt that the authors have addressed my comments adequately. Their findings are informative for other researchers working in the same field.

REVIEWER	Edoardo Mannucci University of Florence, Italy
REVIEW RETURNED	07-Jan-2019

GENERAL COMMENTS	All the issues raised by this reviewer were fully addressed.