A target-driven Collaborative care model for Major Depressive Disorder is effective in primary care in the Netherlands. A Randomised Clinical Trial from the Depression Initiative.
Abstract

Background: Practice variation in the primary care treatment of depression may be considerable in the Netherlands, due to relatively small and unregulated practices. We adapted the collaborative care model for the treatment of Major Depressive Disorder (MDD) to accommodate existing practice variation and tested whether this had added value over Care as Usual (CAU).

Methods: A cluster randomised controlled trial was conducted to compare an adapted target driven collaborative care model with Care As Usual (CAU). Randomisation was at the level of 18 (sub)urban primary care centers. The care manager and GP were supported by a web-based tracking and decision aid system that advised targeted treatment actions to achieve rapid response and if possible remission, and that warned the consultant psychiatrist if such treatment advice was not followed up. Eligible patients had a score of 10 or higher on the PHQ9, and met diagnostic criteria for major depression at the subsequent MINI Neuropsychiatric interview. A total of 93 patients were identified by screening. They received either collaborative care (CC) or CAU. Another 56 patients received collaborative care after identification by the GP. The outcome measures were response to treatment (50% or greater reduction of the PHQ9-total score from baseline) at three, six, nine and twelve months, and remission (a score of 0-4 on the PHQ9 at follow-up).

Results: Treatment response and remission in CAU were low. Collaborative care was more effective on achieving treatment response than CAU at three months for the total group of patients who received collaborative care [OR 5.2 ((1.41-16.09), NNT 2] and at nine months [OR 5.6 ((1.40-22.58)), NNT 3]. The effect was not statistically significant at 6 and 12 months.

Conclusions: Our adapted target driven CC was considerably more effective than CAU for MDD in primary care in the Netherlands. The Numbers Needed To Treat (NNT) to achieve response in one additional patient were low (2-3), which suggest that introducing CC at a larger scale may be beneficial. The relatively large effects may be due to our focus on reducing practice variation through the introduction of easy to use web based tracking and decision aids. The findings are highly relevant for the application of the model in areas where practices tend to be small and for mixed healthcare systems such as in many countries in Europe.

Trial registration: Dutch trial register ISRCTN15266438 (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=820)
**Introduction**

Although there remains enormous variation across the globe, recent reports have shown that the access to treatment of affective disorders, such as Major Depressive Disorder (MDD), is improving in many places in the world. This is important as numerous reports have demonstrated that depression has enormous public health damage, while being a highly treatable disorder. Even though access has improved, it was established that patients with depressive and anxiety symptoms presenting themselves in the primary care setting with the request for treatment receive guideline based care in less than half of cases in the Netherlands. The alternative, referring all patients asking for treatment of depression to specialty mental health settings, may not be preferable due to the heterogeneity and prevalence of depressive disorders in the primary care setting. Some may be first time depressive disorders, and may benefit from treatment in primary care; some may be related to comorbid somatic disorders that may be treated by the GP as well, allowing for integrated treatment in the primary care setting; some depressive disorders may be treatment resistant, recurrent or chronic. Establishing effective treatment models in the primary care setting for at least some of these patients, and establishing clear rules for referral of patients who may not benefit from treatment in the primary care setting, is needed to solve this problem. A disease management approach for depression, such as the collaborative care model may be suitable for this.

A well studied collaborative care model is the IMPACT-protocol in which a depression care manager (DCM) collaborates with a GP and a liaison psychiatrist in order to provide depression treatment in primary care. Effectiveness has been established in the US, mostly within a combined insurance company and health care provider setting such as Kaiser Permanente (KP). Collaborative care has so far been researched most extensively in countries with central steering and relatively large GP practice sizes. In the UK, with its nationalized health service and a larger average number of GPs per primary care practice than for instance in the Netherlands, France, and Germany, the model was effective as well. In Chile, where collaborative care was also found to be effective, practices are even larger with up to 60 physicians per practice. In the USA, Chile and the UK, primary care practices are also generally centrally organized units that are relatively large, and where some form of central regulation in terms of availability of treatment and reimbursement exists. In the Netherlands, every primary care practice is a small business unit with its own culture and rules. The number of GPs in one practice ranges from 1-5, 2 GPs on average, and the patients in one practice often receive reimbursement from a variety of health insurance companies, that have different reimbursement policies in terms of depression treatment. In the USA, an ongoing discussion is whether the IMPACT collaborative care model could be applied in such small, individual practices, which in the USA are mostly found in rural areas. The Dutch healthcare system provides an opportunity to evaluate these issues in mixed healthcare systems, where there is no single ownership of input and health and cost outcomes.

For this purpose, we adapted the collaborative care model for application in such a system. We maintained the architecture of the IMPACT CC model: a DCM, GP and a liaison psychiatrist; and the use of Problem Solving Treatment (PST) as intervention provided by the DCM. However, we made the CC model target driven, that is, aimed at fast treatment response or if possible remission in 18-24 weeks, as indicated by the
PHQ9 score. An efficient way to enhance the efforts of health care professionals in small scale primary care practices in a target-driven collaborative care model, may be the use of a decision aid that facilitates close following of a clearly defined stepped care protocol. Because in the Netherlands, primary care practices are numerous and because they use different electronic patient file systems that may not be compatible, this patient tracking system decision aid was made web-based and could be accessed from any practice on a secured website. The web-based decision aid might therefore not only be an important facilitator for the implementation of collaborative care in the Netherlands, but it might also be a highly relevant innovation with respect to the implementation of collaborative care in rural areas with small practices (such as, for instance, in the United States). Furthermore, providing decision support by way of a detailed algorithm might be an efficient way of reducing practice variation, which is likely to be disruptive in situations where there are small practices, operating without close cooperation or control (such as primary care in the Netherlands).

A stepwise algorithm was incorporated in the decision aid. Not only was the progress of the patient monitored, but also the adherence of the health care professional to the treatment protocol. Advice was provided on how and when to take a next treatment step, or to start or switch antidepressants, in order to improve adherence to antidepressant treatment by GPs in this decentrally organized primary care setting. Also, the web-based tracking system contains a protocol for handling suicidality as assessed by item 9 of the PHQ9, in order to enhance patient safety. It monitors if treatment in the primary care setting can be expected to still provide progress, or whether referral to the specialty mental health setting is needed, and when a psychiatrist should be consulted. Consultation by a psychiatrist occurs in cases where this decision aid does seem too rigid for the particular patient, i.e. in case of comorbidity. Another reason for psychiatric consultation would be non-adherence to the treatment protocol. The decision aid signals if a prescribed action was not taken by the health care professional, and the consultant psychiatrist would in that case receive an email that this was the case, and contact the professional and provide consultation advice.

The primary objective of this paper was to establish effectiveness of this target driven collaborative care model for MDD with a web-based decision aid, and consultant psychiatrist availability if treatment was not followed as intended, in the mixed healthcare setting in the Netherlands with small primary care practices, compared to usual care.
Methods

The design of the study has been described in more detail elsewhere, but is summarized below. Using cluster randomisation, 18 primary care centers (with a total of 82 GPs) were randomly assigned to either the collaborative care (CC) or the care as usual condition (CAU) by an independent statistician using a computer algorithm for allocation. We chose to deviate from our initial method of patient randomisation, as described in the design paper, in order to prevent contamination of the effect. A study by Richards and colleagues showed that there is a substantial risk of spill over of the effect to the control group when the effect of collaborative care is assessed in a patient randomised design.

GPs in Primary care centers randomised to the CC condition received training in the collaborative care model and the use of the web-based tracking system and got acquainted with the consultant psychiatrist. Patients of the respective practices could enter the trial in two ways: either by screening or after identification by their GP. Screening was done as follows: all patients who had consulted their GP during the past 6 months received the PHQ9 by mail, regardless of the reason for prior consultation. The reason for this broad approach is that literature suggests that patients suffering from Major Depressive Disorder (MDD) are more likely to visit their GP with miscellaneous somatic symptoms instead of the core symptoms of MDD.

After informed consent, patients were asked to return the questionnaire regardless of whether or not they still had any symptoms. At the moment of screening, patients were unaware of their allocation. Inclusion criteria were age > 17 years, PHQ9 score ≥ 10 and a classification of MDD according to the MINI neuropsychiatric interview, which was administered by telephone. The MINI interview was applied to avoid false positive diagnoses of MDD based on the PHQ9-score. Exclusion criteria were high risk of suicide, psychosis, dementia, drug or alcohol dependence, already being under specialty mental health treatment, or insufficient knowledge of Dutch to fill in the questionnaires.

Which method to use was a dilemma our research group faced at the beginning of the trial. Both methods (patient randomisation and cluster randomisation) have advantages and disadvantages. The advantage of cluster randomisation is that it is the absence of spill over of effect (If you randomise the patients, the result is that you get two groups in one health care centre. You are then asking the GP not to apply the new methods he or she has learned when he or she treats patients in the control group. If the GP is not very strict, dilution of the effect of the intervention compared to care as usual will often occur, and this is prevented by choosing cluster randomisation. On the other hand, a disadvantage of patient randomisation is that it is not very motivating for GPs to participate in a scientific study if they are randomised to the control group. Another disadvantage of cluster randomisation may be the problem of 'selection bias' if you ask GPs to refer patients to your study (It is almost impossible to blind GPs. They know that their patients will receive the new intervention or care as usual). How we dealt with this problem is described in the method section of this chapter (by also including through screening and not just through referral and by applying propensity scores).

When we wrote the study protocol (chapter 2) we decided that patient randomisation would be the best method for our trial, but before we actually started the trial we changed our thoughts (but the paper had been published by then). You only get one chance to get it right when you start a trial (once you have started to include patients it is impossible to change the method). The reason for the switch was the problem described above, namely that it is very hard to implement an organizational approach like collaborative care next to care as usual in one health care centre.
Outcome measures

Outcome measures were assessed by self-report questionnaire that was sent to the participants by mail three (T1), six (T2), nine (T3), and twelve (T4) months after their inclusion in the trial. The primary predefined outcome measure was whether or not a patient had reached a clinically relevant response on the PHQ9. The PHQ9 consists of 9 items referring to the DSM IV criteria for MDD. Each item is scored from 0 (not at all) to 3 (nearly every day). The total score thus varies from 0 to 27. A score of 10 or higher indicates depressive symptoms of at least moderate severity. A decrease of at least 50% on the PHQ9 compared with baseline on a follow up questionnaire was defined as a clinically relevant response to treatment. The secondary predefined outcome was remission, defined as a score of lower than 5 on the PHQ9.

Intervention:

Target driven Collaborative Care

The target driven collaborative care protocol used during this study has been described in detail elsewhere, and is also described in the Appendix. Target was to achieve remission (PHQ-9 < 5) within 18 to 24 weeks of treatment. If this was not achieved, referral to specialty mental health care, was advised. In case of suicidality, a suicidality protocol was followed, including consultation by the psychiatrist if needed. An antidepressant algorithm was provided by the decision aid tracking system, as described in the Appendix. The specific tasks of the Depression Care Manager (DCM), the GP, and the consultant psychiatrist are explained in the Appendix as well.

Usual care

Patients recruited in the usual care practices were informed as to their diagnosis and advised to seek treatment from their GP. There were no restrictions to treatment in any way. The GPs in the control condition were not informed about the presence of MDD in screened patients. Treatment in the usual care group was monitored during the course of the study.

Statistical analyses

Multi Level Analysis (MLA) was performed using MLwiN 2.0 multilevel software on the basis of the intention to treat analysis. Propensity scores were calculated to correct for selection bias due to the cluster randomisation. The amount of variance in the effect was established at the level of primary care centers, GPs and patients. Multilevel logistic regression analysis was used to assess the treatment response as well as the remission outcome at each administration after baseline. The effect of the intervention for the collaborative care group as a whole (CCtotal) was compared to CAU. We also estimated the effect for the screened collaborative care group compared to CAU (CCscreen vs. CAU), because these patients were included the same way (after screening instead of selection by GP). Based on this model, we calculated odds ratios and Numbers Needed to Treat (NNT) regarding the primary outcome measure 'response to treatment'. The Number Needed to Treat can be defined as the number of patients that have to be treated according to a new intervention (in this case collaborative care) compared to care as usual in order to achieve a clinically relevant outcome (in this case response to treatment) for one extra patient.

A composite score was computed based on the first time point to achieve treatment response. Differences between treatment groups on this score were also analyzed using MultiLevel Analysis.
Results are presented according to the CONSORT statement for cluster randomised trials.\textsuperscript{130}

**Study oversight** This RCT was part of the Depression Initiative, a national initiative to improve depression management in the Netherlands.\textsuperscript{16;17} The study progress was monitored by a steering group and advisory board on a 3 monthly basis.

## Results

### Participant flow

The inclusion phase of the trial started in September 2007 and ended in August 2009. 18 Primary care clinics agreed to participate in the trial. They were situated both in major urban areas such as Amsterdam and Haarlem and in smaller urban areas and more rural communities. 150 patients gave informed consent for the treatment phase, 49 patients participated in the CAU condition and 101 participated in one of the two collaborative care groups: 45 in the screened collaborative care group (CCscr) and 101 in the total collaborative care group (CCtotal, the 45 patients in the CCscreen group plus the 56 patients who received collaborative care after identification by their GP). Only one patient was included by the GP in the CAU group. Inclusion and trial flow according to the cluster-randomised CONSORT statement\textsuperscript{130} is shown in Figure 1. The 56 patients who received collaborative care after identification by their GP were treated as a separate group in the flowchart.

Of the 82 GPs that agreed to participate in the trial, 50 included patients in the final cohort. 18 GPs only included one patient. As mentioned in the method section we applied Multi Level Analysis (MLA) to correct for any disturbances in the data due to cluster effects. This method provides correct estimates even if the patient-to-site-ratio is small. Moreover the Intra Cluster Correlation (ICC), a measure for the variance in outcomes explained by the different levels, was 0.00 at both the level of Health Care Centers and at the level of individual GPs. This means that the level of variation that can be attributed to Health care centers and GPs is very low.

The average loss to follow up percentage (patients who did not return a questionnaire at one of the time points) was 36.5%. Patients who dropped out three and six months after inclusion did not have higher PHQ9-scores at baseline (T1, p=.799; T2, p=.577). Patients who dropped out at nine and twelve months after inclusion had on average a higher PHQ9-score at baseline, but this trend was the same for the patients in the collaborative care group and the patients who received CAU (T3, p=.575 ; T4, p=.547). This implies that there is no evidence for selective dropout in the trial, and because of this we decided not to impute missing data. Multilevel analysis has been shown to be very flexible when handling missing data. Multilevel analysis on an incomplete dataset might even be preferable compared with imputation methods.\textsuperscript{131}
**Baseline data**

Baseline characteristics and PHQ9 scores are displayed in Table 1.

### Table 1  Characteristics of the patients in the collaborative care groups, and in the care as usual group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Care as usual (CAU; N=49)</th>
<th>Collaborative care, total group (CC total; N=101)</th>
<th>Collaborative care screened (CCscr; N=45)</th>
<th>p-value CAU vs. CCtotal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (sd)</td>
<td>52.1 (14.8)</td>
<td>47.0 (13.5)</td>
<td>52.0 (13.0)</td>
<td>.023*</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>73.5</td>
<td>72.3</td>
<td>64.4</td>
<td>.979 (Chisq)</td>
</tr>
<tr>
<td>Living alone (%)</td>
<td>50.9</td>
<td>49.5</td>
<td>53.3</td>
<td>.773 (Chisq)</td>
</tr>
<tr>
<td>Non Dutch origin(%)</td>
<td>25.0</td>
<td>30.0</td>
<td>22.7</td>
<td>.528 (Chisq)</td>
</tr>
<tr>
<td>Level of education**</td>
<td>5.2 (2.9)</td>
<td>5.7 (2.6)</td>
<td>5.4 (2.5)</td>
<td>.304</td>
</tr>
<tr>
<td>PHQ9 at baseline (T0)</td>
<td>14.8 (4.8)</td>
<td>15.5 (4.8)</td>
<td>14.3 (4.8)</td>
<td>.369</td>
</tr>
<tr>
<td>Prior episode of depression (%)</td>
<td>56.2</td>
<td>56.2</td>
<td>58.5</td>
<td>.994 (Chisq)</td>
</tr>
</tbody>
</table>

Chisq=Chi square test
* Statistically significant: p<.05
**5 corresponds to only secondary school; 6 corresponds to a few years of education following secondary school

Most variables did not differ significantly between the four groups at baseline, except age. The patients in the CCtotal group were younger (p=.023). The patients in the CCscr group did not differ from the patients who received CAU with respect to any of the baseline variables. Adjusting the models for age did not influence the results.

**Response to treatment and remission**

The results regarding response to treatment and remission are displayed in Table 2.

Treatment response for CAU was low at first (10.5%), and took longer to come into effect than for CC. It increased at follow-up to a maximum of 25.8% at nine months. The response percentages were higher in both collaborative care groups. After twelve months, the effect of both care as usual and collaborative care subsided to a certain extent. At 3 months both the screened (CCscreen) and the total group of patients who received collaborative care (CCtotal) had a strong and statistically significant favourable odds ratio for response to treatment: 5.20 (CI: 1.41-16.09) for CTotal and 4.59 (CI: 1.15-18.34) for CCscreen. The strongest effect of collaborative care on response to treatment compared with CAU was found after nine months, with a statistically significant favourable odds ratio for response of 5.62 (CI: 1.40-22.58) for the CTotal group compared with CAU. Numbers Needed to Treat (NNT) calculated for the response percentages were 2 for the total CC group at 3 months and 3 for the total CC group at nine months. In the screened patients who showed response, the difference in time to first response between CCscr versus CAU was three months (4.4 versus 7.4 months).
Striking are the low remission percentages in CAU. The maximum remission percentage in CAU was 12.9% after nine months. The strongest effect of collaborative care on remission compared with CAU was found after six months, with a statistically significant favourable odds ratio for remission of 3.9 for CCtotal compared with CAU. As is shown in Table 3 the patients in the CAU-group did receive care. It is therefore not likely that absence of care was an important reason for the low remission percentages in this group. We can also provide some additional data on adherence to the collaborative care protocol by the caremanagers. 90.9% of the patients in the total collaborative care group visited the caremanager at least once. The average number of visits was 5.8 (sd 3.6). The psychiatrist was consulted for 8.8% of the patients. During the first weeks of the intervention an antidepressant was prescribed (or prescription was continued) to 26.4% of the patients.

**Table 2** Results for response to treatment and remission

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>CAU</th>
<th>CCtotal</th>
<th>CCscreen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Three months (T1)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>38</td>
<td>61</td>
<td>31</td>
</tr>
<tr>
<td>Response to treatment (%) T1</td>
<td>10.5%</td>
<td>45.9%</td>
<td>41.9%</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Ref. Cat.</td>
<td>(1.41-16.09)</td>
<td>(1.15-18.34)</td>
</tr>
<tr>
<td>NNT (only when P&lt;.05)</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Remission (%) T1</td>
<td>7.9%</td>
<td>26.2%</td>
<td>16.1%</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Ref. Cat.</td>
<td>(0.61-10.48)</td>
<td>(0.32-9.46)</td>
</tr>
<tr>
<td><strong>Six months (T2)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>39</td>
<td>63</td>
<td>31</td>
</tr>
<tr>
<td>Response to treatment (%) T2</td>
<td>25.6%</td>
<td>39.7%</td>
<td>29.0%</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Ref. Cat.</td>
<td>(.70-.567)</td>
<td>(.38-4.17)</td>
</tr>
<tr>
<td>Remission (%) T2</td>
<td>10.3%</td>
<td>23.8%</td>
<td>19.4%</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Ref. Cat.</td>
<td>(1.01-15.17)</td>
<td>(.42-19.83)</td>
</tr>
<tr>
<td><strong>Nine months (T3)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>31</td>
<td>59</td>
<td>28</td>
</tr>
<tr>
<td>Response to treatment (%) T3</td>
<td>25.8%</td>
<td>61.0%</td>
<td>50.0%</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Ref. Cat.</td>
<td>(1.40-22.58)</td>
<td>(.92-17.80)</td>
</tr>
<tr>
<td>NNT (only when P&lt;.05)</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Remission (%) T3</td>
<td>12.9%</td>
<td>37.3%</td>
<td>32.1%</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Ref. Cat.</td>
<td>(0.96-14.04)</td>
<td>(.71-13.00)</td>
</tr>
<tr>
<td><strong>Twelve months (T4)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>32</td>
<td>58</td>
<td>33</td>
</tr>
<tr>
<td>Response to treatment (%) T4</td>
<td>25.0%</td>
<td>39.7%</td>
<td>33.3%</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Ref. Cat.</td>
<td>(.61-5.42)</td>
<td>(.45-4.81)</td>
</tr>
<tr>
<td>Remission (%) T4</td>
<td>6.3%</td>
<td>20.7%</td>
<td>15.2%</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Ref. Cat.</td>
<td>(3.38)</td>
<td>(2.07)</td>
</tr>
</tbody>
</table>

CAU=Care as usual; CI=Confidence interval; CCtotal=Collaborative care, total group; CCscreen=Collaborative care, identified through screening; OR=Odds Ratio; NNT=Number Needed to Treat; Ref. cat.=Reference category

*p<.05
Table 3  Actual care given

<table>
<thead>
<tr>
<th></th>
<th>Care as usual</th>
<th>Collaborative care, total group</th>
<th>Collaborative care screened</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean number contacts</td>
<td>percentage of people (%)</td>
<td>Mean number contacts</td>
</tr>
<tr>
<td>GP</td>
<td>4.7 (4.9)</td>
<td>85.7</td>
<td>4.8 (4.4)</td>
</tr>
<tr>
<td>Mental Health Care Institute (RIAGG)</td>
<td>3.2 (11.7)</td>
<td>26.5</td>
<td>1.8 (4.4)</td>
</tr>
<tr>
<td>Private psychologist/psychiatrist</td>
<td>1.1 (3.1)</td>
<td>20.4</td>
<td>1.6 (4.3)</td>
</tr>
<tr>
<td>Psychologist/Psychiatrist at outpatient centre of hospital</td>
<td>0.3 (1.0)</td>
<td>10.2</td>
<td>0.9 (4.2)</td>
</tr>
<tr>
<td>Social Worker</td>
<td>0.8 (2.1)</td>
<td>18.4</td>
<td>2.2 (4.6)</td>
</tr>
<tr>
<td>Counselling centre for drugs alcohol</td>
<td>0.1 (0.4)</td>
<td>2.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Admission to (parttime) psychiatric day care</td>
<td>1.9 (13.2)</td>
<td>4.1</td>
<td>0.06 (0.5)</td>
</tr>
<tr>
<td>Admission to a psychiatric hospital</td>
<td>0.6 (2.2)</td>
<td>14.3</td>
<td>2.3 (22.4)</td>
</tr>
<tr>
<td>Psychiatric nurse</td>
<td>No information</td>
<td>-</td>
<td>1.7 (3.2)</td>
</tr>
<tr>
<td>Mental health care practice nurse</td>
<td>0.1 (0.6)</td>
<td>2.0</td>
<td>0.8 (2.4)</td>
</tr>
<tr>
<td>Medication (not necessarily an antidepressant)</td>
<td>-</td>
<td>79.6</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 1 Flowchart of participants in the trial in accordance with consort statement

Excluded (for all 3 groups):
- No MDD: 364
- Severe mental health problems: 8
- Primary substance dependent: 12
- Already receiving treatment in specialized mental health care: 77
- Refused treatment: 61
- Language problems during MINI: 8
- Other reason: 25 (for instance moved to another city)

Patients who received CC after identification by their GP: N=56 (actually received the intervention: N=45; 80%)

CCscr: N=45 (actually received allocated intervention: N=45; 100%)

CAU: N=49 (1 by the GP) (actually received allocated intervention: N=49; 100%)

Randomised: 18 primary care centres with 82 GPs who agreed to participate in the trial

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Randomised: 18 primary care centres with 82 GPs who agreed to participate in the trial
Discussion

This trial shows that our adapted target driven collaborative care (CC) model for the treatment of Major Depression in primary care is effective. We adapted the CC model to cope with practice variation that is inherent in a mixed health care model with small primary care practices, such as in the Netherlands. CC was most effective in the short term: the OR for response to treatment at three months was about 5, and the Number Needed to Treat (NNT) was 2-3. The strongest effect of collaborative care on response to treatment compared with CAU was found after nine months, with a statistically significant favourable odds ratio for response to treatment of 5.6 (CI: 1.40-22.58) for the collaborative care group in total compared with CAU. The average time to first response was three months shorter in the screened CC group compared to CAU. The effect of collaborative care, particularly for the screened group, subsided to a certain extent after twelve months, which might be explained by the fact that the intensity of the intervention was toned down at this point, and that the care as usual group started to catch up, although without surpassing the intervention group at any point. A stronger focus on maintaining response and remission may be needed in future research, e.g. a stronger focus on relapse prevention in the collaborative care algorithm.

It is striking that treatment response and remission in the CAU group are very low (the response percentages ranged between 10.5% and 25.8%). The results are comparable though to those in the IMPACT-study where treatment response in the CAU-group ranged between 14.8% and 30.9%.

In our current study, ‘depression’ may not have been on the patients’ agenda in their contacts with primary care in the CAU-condition, as these cases were detected by means of screening (although the patients in the CAU-group may have been more motivated to seek treatment because they knew they were suffering from MDD). In the time restricted primary care setting GPs and patients are often confronted with competing demands, e.g. hypertension or diabetes may ‘take away' the focus from depression. Moreover, patients' perceived needs for care are also strongly associated with the delivery of guideline-concordant care for depression.

Hence, care for depression might not have been high enough on the patients’ agenda during their appointments with their GPs (but this probably does not correspond to a major difference between care as usual in this study and care as usual in everyday care). Some of the patients who were included in the trial had been taking an antidepressant in the same dosage for years, without any monitoring or adjustment. In the collaborative care group monitoring and contacting patients was a task for the caremanager, which may have diminished the burden on the GP.

In our collaborative care model, more emphasis is put on following a precise algorithm and on treatment adherence and monitoring of the health care professional by the tracking system (decision aid). This is a new aspect in our current study that may facilitate implementation of target driven collaborative care in a mixed health care system and in a variety of primary care practices. It may also reduce practice variation, which is inherent to a primary care setting with relatively small practices acting independently to a large extent. Implementation efforts with regard to the webbased decision aid are needed though, in order to facilitate the uptake of this promising tool in everyday care. GPs in our study indicated that it would be easier for them to use the decision aid if compatibility with their current electronic patient files could be improved.
Limitations

An important limitation of the current study is the relatively high percentage of patients who did not return one or more follow-up questionnaires. However, no indication for selective non-response exists. In this cluster randomised trial, the screened patients were blinded for the intervention and thus the comparison between screened collaborative care versus screened CAU patients can be considered non-biased. Obviously the findings for the group of patients who were identified by their GP are hard to interpret, as only one patient was included in the trial by the GP in the CAU group. And thus there were almost no GP identified patients in the CAU group to compare the GP identified CC patients with. The more positive findings for the group of patients identified for CC by their GP may have to do with more motivation for treatment and with the capability of the GPs to select a group of patients for whom collaborative care is most likely to be beneficial. In any case, that the GP identified CC group outperformed the screened CC group is a promising result because these patients may closely resemble the patients GPs would select in everyday care. The results for the CC total group (in which the GP identified patients were included) imply that collaborative care may also be effective in everyday care, because the patients who were identified by their GP may closely resemble the patients they would refer for collaborative care in everyday practice. These patients have a ‘perceived need for care’ which might be more strongly associated with successful treatment than a positive score on a screener. More research into this is necessary. In any case, we were also able to compare a screened collaborative care group to a screened CAU group in the current trial, which allowed for a valid comparison.

Another limitation might be the strikingly low remission percentages in CAU. One could argue that this is due to recruitment bias, with patients in the CAU group told that they are depressed and that it was advisable to seek treatment, whereas patients in the CC group were contacted by the caremanager. However, this is not supported by the finding that when we excluded the CAU-patients who were not seen by their GP during the first three months of the intervention (39.4% in CAU as opposed to 21.8% in CC), the results for CAU did not improve: 10.0% of the CAU-patients who were seen by their GP achieved response, as opposed to 15.4% of those were not seen. The results remained strongly in favour of collaborative care (P<.01).

Implications for research and clinical practice

We conclude that target driven collaborative care for major depression in small primary care practices in a mixed healthcare system such as in the Netherlands can be very effective. The web-based tracking system and the precise decision aid based on an algorithm with follow up by the consultant psychiatrist, is a promising development in that respect. This way, an algorithm is combined with expert advice in case the algorithm is insufficient for a particular patient. The uptake of the decision aid by GPs could still be improved, which may even increase the effectiveness. Future research efforts might furthermore focus on expanding the model to other mental health problems, fine-tuning the model and on the identification of subgroups of patients for whom the intervention is less effective or particularly effective. What, for instance, are the outcomes for patients suffering from comorbid medical disorders and for patients
suffering concomitant medically unexplained physical symptoms? Recent studies have shown that this is an important issue. 133;134

The target driven collaborative care model with a web-based decision aid may be particularly useful for implementation in i.e. rural areas or areas with a large percentage of small primary care practices where collaborative care was so far considered not to be feasible, and in other mixed healthcare systems where clinical practice and reimbursement of treatment are not in one hand. Collaborative care may help to meet the need for effective, efficient and easy to use interventions to treat large numbers of patients with MDD in primary care. In places with a well developed, but relatively unregulated primary care, such as many parts of Europe, our adapted target driven model may be fruitfully introduced.
Appendix

ALGORITHM FOR TARGET DRIVEN COLLABORATIVE CARE

Target was to achieve remission (PHQ-9 < 5). If this was not achieved within 18 to 24 weeks of treatment, referral to specialty mental health care was advised. Subtargets were to achieve a decrease of at least 5 points on the PHQ9 within each 6 weeks, in a succession of 18-24 weeks (the target was remission if a step in the treatment algorithm had already resulted in a decrease of at least 5 points after six weeks). If this was not the case, a switch would be advised to a more intensive treatment step, either psychotherapy or antidepressant medication, as indicated in Figure 1 of this Appendix. In case of suicidality, a suicidality protocol was followed, and also an antidepressant algorithm was monitored by the decision aid tracking system, as described below. Monitoring of treatment progress and providing Problem Solving Treatment (PST) were the tasks of the Depression Care Manager (DCM), assisted by the decision aid. He or she discussed progress with the patients and the GP. The GP was responsible for treatment with antidepressant medication and the drawing up of a treatment plan together with the patient and the DCM. In case of adverse events, nonadherence or suicidality a consultant psychiatrist was to be consulted.

The DCM, the GP, and the consultant psychiatrist had access to the online patient tracking system that contained the decision aid that would indicate -based on the progress of the patient measured with the PHQ9-score- if a subsequent treatment step or psychiatric consultation was deemed necessary. Also, the tracking system could send out a signal to the consultant psychiatrist if proposed algorithm steps (such as the suicidality protocol and an agreed on treatment plan) were not followed, allowing the consultant psychiatrist to contact the DCM or GP for exploration of the problem and advice.

The process of the recruiting and the training of caremanagers for our study, as well as the issue of the impact of either approach (CAU or CC) on the organization, staffing, and resources of the GP’s practices, has been described extensively elsewhere.16;17

SUICIDALITY PROTOCOL

Every time the PHQ9 was assessed, suicidality was assessed as well by a subprotocol in case of a score of ≥ 2 in the 9th PHQ9 item, as shown in the box in Figure 1 of the appendix. In case of suicidality according to this item, the depression caremanager (DCM) was instructed to contact the GP and ask for assessment and management of the suicidality by the GP. If the DCM would not act accordingly within 24 hrs, the tracking system would alert the consultant psychiatrist who would contact the DCM at once in order to perform psychiatric consultation and give advice to DCM and GP concerning the suicidality. If the GP assessed that the suicidality was indeed of high risk, urgent referral to crisis specialty mental health care was advised. In case of low suicide risk, the patient could proceed with treatment in the primary care practice.

ANTIDEPRESSANT PROTOCOL

The antidepressant algorithm was in accordance with the Dutch guidelines for depression11;18, but it provided more specific information about dosage and management
of three antidepressants, from which the GP could make a choice. The antidepressant protocol was based on the following principles:

**Principles**

For the on-target collaborative care intervention an antidepressant algorithm was developed that fitted in the national guidelines for depression treatment but that gave more specific instructions to GPs and the DCMs for treatment and follow up based on monitoring with the PHQ9. It included a choice of antidepressants that could be chosen and recommendations for switching if after 6 weeks the medication did not produce enough improvement on the PHQ9. This 6 week evaluation was repeated every 6 weeks until 18-24 weeks.

Principle for treatment was that pharmacologic treatment of the depression should include treatment with an antidepressant rather than with a benzodiazepine. The GP should choose an antidepressant together with the patient. As correct dosage was deemed important, the GP received detailed suggestions for dosage for three antidepressants to choose from. The three antidepressants mentioned below were selected as

- they could be prescribed on a generic basis;
- there was no patent of a pharmaceutical company on the suggested antidepressant;
- the antidepressant was used frequently in the primary care practice setting;
- the antidepressant was easy to start and easy to stop without adverse effects,
- and should be applicable for the elderly as well,
- the medication should be safe in case of frequently occurring somatic comorbidity such as diabetes and cardiovascular disease.

According to these principles, as first step an SSRI was advised that was safe in case of somatic cardiovascular comorbidity and in the elderly. As second step a more broad spectrum antidepressant, namely a SNRI, was advised, or a TCA that was well tolerated in the elderly. The algorithm is shown in the box below.

**Box 1. Antidepressant algorithm**

**Step 1:** Citalopram, 1st week 20 mg, second week 40 mg daily

**response of at least 5 points drop in PHQ9 score after 6 weeks?**

**Yes:** continuation of treatment

**No:** step 2

**Step 2:** Venlafaxine,
1st week 75 mg, Second week 150 mg,

**response of at least 5 points drop in PHQ9 score after 12 weeks?**

**Yes:** continuation of treatment

**No:** step 3

4th week possibility to increase to 225 mg daily.

Alternative step 2: Nortriptyline,
1st week 50 mg
2nd week 100 mg
3rd week 150 mg daily

**Target was remission (PHQ9 score < 5) after 12 weeks of an antidepressant that produced response.**

After 18-24 weeks, treatment was only continued in primary care if optimization in primary care was deemed possible after consultation by a psychiatrist.
Figure 1 of the appendix. The flowchart treatment algorithm