The aim of this thesis was to assess the effectiveness in the Netherlands of collaborative care for Major Depressive Disorder (MDD) with all the elements of the IMPACT-model and a patient tracking system. Secondary aims were the evaluation of cost-effectiveness and the influence of concomitant physical symptoms on the outcome of MDD treated according to the principles of collaborative care. The main findings of the thesis are described below.

1. Summary (main findings):

Effectiveness of collaborative care for MDD in the Netherlands

In Chapter 3 the effectiveness of collaborative care for MDD in the Netherlands was assessed. The model tested in the CC:DIP-trial proved to be more effective than care as usual after three and nine months. It also appeared to be more effective after six and twelve months, but the results were not statistically significant. This shows that there is still room for improvement, but the results after three and nine months are promising. The odds ratio (OR) for this effect was around 5 after both three and nine months, which means that the odds on reaching a favourable response to treatment (a reduction of at least 50% on the PHQ9 compared to baseline) were 5 times higher for patients in the collaborative care group than for patients who received care as usual. The number needed to treat (NNT) varied between 2 after three months and 3 after nine months. This implies that a general practitioner (GP) should provide collaborative care treatment for 2-3 patients to expect response to treatment in one extra patient (compared to care as usual). This is a good result: for instance, studies evaluating the effectiveness of interventions for hypertension with the goal of reducing cardiovascular morbidity and mortality generally report much higher NNT.204;205 Although this comparison might not be completely fair, the low NNT does show that treatment for depression can be just as successful as treatment for some chronic somatic conditions.

This promising result may, in part, be due to the fact that the percentages of patients who responded to treatment in the care as usual group were low. Only 10.5% of the patients in the care as usual group responded to treatment after three months. In the collaborative care group as a whole this percentage was 45.9%. In comparison, in the care as usual group in the IMPACT-study the percentage that responded to treatment after three months was 14.8%.12 These low response percentages in the care as usual groups might reflect on the availability of guideline based care for patients receiving care as usual. Indeed Prins and colleagues concluded that patients with depressive and anxiety symptoms requesting treatment in the primary care setting in the Netherlands receive guideline based care in less than half of cases.119 This may be due to certain characteristics of primary care such as the fact that consultations generally last no longer than 10 minutes (which leaves little time for psychosocial problems) and the issue of competing demands (somatic and psychiatric diseases 'compete' for attention, for instance when a patient suffers from diabetes and depression).38

Our study shows that collaborative care appears to deal successfully with some of these problems enhancing the effectiveness of primary care for MDD. Elements of care that are propagated by the guidelines for depression in the Netherlands11;18, are incorporated in the collaborative care model: e.g. monitoring of the course at least every two weeks, and encouraging pleasurable activities and achievable goals (addressed in the collaborative care model during PST and in the self-help manual). Adherence to the guideline is also facilitated when applying collaborative care because certain time consuming elements of...
effective treatment are delegated to a care manager, and because specialist advice (by a psychiatrist) is easily available. The collaborative care model may therefore be an important tool to achieve one of the goals of the Depression initiative, of which this project was part: implementation of the Multidisciplinary guideline for depression in the Netherlands. These are promising developments, but particularly in times of cutbacks on public spending implementation will still be be very difficult if collaborative care proves to be effective but expensive. This topic is explored below.

**cost-effectiveness of collaborative care for MDD in the Netherlands**

In Chapter 4 the cost-effectiveness of collaborative care was assessed. Both the direct medical costs and the indirect costs of collaborative care were lower than those for care as usual. The lower indirect costs were mainly due to the decrease of long-term absence in the collaborative care group (this particularly made a difference in the screened collaborative care group). As collaborative care was only slightly more effective in terms of Quality Adjusted Life Years (QALY, this roughly refers to 1 life year in good health that is gained), there is room for improvement in terms of effectiveness when quality of life is the outcome. Nevertheless from the societal perspective (when productivity costs were also assessed), the model became dominant over care as usual.

The implications of these findings will be discussed further on in this discussion, but not without noting one more finding regarding cost-effectiveness. When the collaborative care patients who were identified by their GP were added to the analyses the model was also dominant from a direct medical perspective. This implies that GPs might be capable of selecting patients who are particularly likely to benefit from the intervention. More research regarding the success of direct referral by the GP is necessary as was discussed in Chapter 3 of this thesis.

**The influence of medically unexplained physical symptoms**

70% of the patients who go to their GP with health complaints that later turn out to be at least partly associated with MDD, only present physical symptoms at first. In other words: the association of physical symptoms with MDD should not be ignored by researchers and clinicians as it is very common.

In Chapter 7 the results are presented from a pre planned secondary data analysis on the CC:DIP trial that took concomitant physical symptoms into account. These symptoms were clearly associated with a less favourable response to treatment in both groups in the trial. When the results all patients in the trial were analysed as belonging to one group (collaborative care + care as usual) the odds on a favourable response for patients not suffering from clinically significant concomitant physical symptoms were up to 7 times higher than for patients who did suffer from a clinically significant amount of such symptoms. So, in both groups (care as usual and collaborative care alike) concomitant physical symptoms were associated with much lower odds on response to treatment. The issue of co-occurrence of physical symptoms and depression thus may shed some light on the question why collaborative care induces a favourable response in 61% of the patients at best (after six months for the collaborative care total group, see Table 2 in Chapter 3 of this thesis), and why care as usual if only effective for 26% of the patients at best (after nine months).

A supplementary finding in Chapter 7, was the fact that the distinction between physical symptoms that were 'explained' by chronic medical disorders and the physical symptoms

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1 Direct medical costs refer to actual medical care that was given, such as medication that was pre prescribed or visits to a healthcare professional. Indirect medical costs for instance refer to productivity loss (absence from work).

2 Note that 61% is not a bad result. In the IMPACT-trial the maximum percentage of patients reaching a favourable response is 49%. 

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that were 'unexplained' did not prove to be relevant in the light of the outcome measure: a favourable response to treatment for depression. The severity of physical symptoms (scoring above or below the cut-off on the Physical Symptoms Questionnaire, PSQ, that was given in Chapter 7) turned out to be the factor interfering with effective treatment for MDD, and not the nature of the symptoms (explained by for instance diabetes or COPD, or 'unexplained', for instance unexplained abdominal pain, nausea, or headaches). This finding may be highly relevant, because researchers have pointed out that many studies that assess the epidemiology of medically 'unexplained' symptoms fail to correct for a possible medical explanation (in these cases symptoms are measured on a scale, such as the PSQ, but whether or not these symptoms are actually unexplained is not clear since a medical assessment is lacking). Crombez and colleagues have called this issue 'the unbearable lightness of somatisation'.35 We were able to circumvent this problem to a certain extent in Chapter 7 because we asked the participants in our study to list the chronic medical disorders they were suffering from at baseline. It is advisable that future studies also provide an assessment by a medical doctor at baseline, but at least our method is a step in the right direction.

Importantly, the findings from Chapter 7 are in line with those in Chapter 5 and 6 (although we were not able to address the issue of medically unexplained versus medically 'explained' symptoms in Chapter 5 and 6). In Chapter 5 the results from a systematic review were presented. It was concluded that the scientific literature points to a trend for a negative association of concomitant physical symptoms with the course of MDD. The effect might be considerable, but the studies that are available at present do not allow for statistical pooling. This could change in the future if more studies were to use the same outcome measures (for instance by defining a favourable response to depression treatment as a reduction of at least 50% on a validated questionnaire for depression severity).

Finally, in Chapter 6 we found that concomitant physical symptoms were a strong predictor of a poor outcome in both treatment groups in a trial that assessed the effectiveness of Problem Solving Treatment (PST) in primary care.180 This is an important finding because we also applied PST in our collaborative care algorithm in the CC:DIP-trial. This gives us reason to believe that it might be worthwhile to think about other types of treatment for patients with MDD who are suffering from concomitant physical symptoms. Moreover, given the fact that concomitant physical symptoms interfere with both the effectiveness of PST and collaborative care, PST could be replaced by a form of treatment that is effective for (medically unexplained) physical symptoms if these are also present (for instance if a patient scores above the cut-off for clinically significant physical symptoms on the Physical Symptoms Questionnaire, PSQ, as applied in Chapter 7). A more elaborate discussion of this topic will be provided below.

General discussion

This section provides a more in-depth look into the factors that influence the effectiveness of collaborative care in primary care and discusses future directions for research and possibilities for implementation of the model in the Netherlands.

The results with regard to the effectiveness of collaborative care (Chapter 3) are promising, particularly the low Number Needed to Treat (NNT). This means that it would be relatively easy to gain good results if collaborative care were to be implemented successfully. Furthermore, the results with regard to cost-effectiveness (Chapter 4) show that at least from a societal perspective (taking productivity costs into account) collaborative care is dominant over care as usual. Moreover, there is a good chance that cost-effectiveness can be further enhanced if GPs identify the patients eligible for collaborative care directly instead of by screening (screening is not common practice.
anyway). If the GP identified patients are included in the analyses collaborative care is also dominant from a direct medical perspective. More research into the benefits of GP identification instead of screening is necessary (for instance in a patient randomized trial in which all patients are identified by the GP), but the outlook is promising. Whether or not (cost)effectiveness could also be enhanced by adapting the model for patients suffering from concomitant physical symptoms is also an intriguing question.

So, should collaborative care be welcomed as if it were the holy grail of mental health care? We do not claim that it is, but the results indeed give reason to implement the model in the Netherlands. The demands stated in the sieve of Dunning (see introduction) are met: treatment for MDD is necessary in primary care (the prevalence of MDD is too high to be met exclusively in secondary care), collaborative care is more effective than care as usual, and the costs are reasonable. Not all problems are solved however. And as those of you who have knowledge of Problem Solving Treatment will agree, problems are a normal part of life. So, which issues do still remain?

I. Complete remission is still rare. Concomitant physical symptoms and personality disorders provide leads for future improvements

Firstly, collaborative care induces a relative improvement: it is more effective than care as usual, but this does not mean that all patients benefit. As mentioned before, the maximum percentage of patients with a favourable response to treatment is 61%. Furthermore, if we apply more strict criteria and look at complete remission of depressive symptoms (PHQ9<5), the maximum percentage goes down to 37.7% (the total collaborative care group after 9 months of treatment)! Put differently: 62.3% of the patients never experience a complete remission of depression during the trial! The conclusion should be that MDD can be treated more successfully applying collaborative care, but that more research is needed to increase the efficacy of treatment for MDD in general.

Increasing the remission percentages is of paramount importance, particularly because complete remission is associated with a decreased probability of relapse. Given that it has been stated that depression causes a decrease in quality of life of 50% compared to the general population, which is in the same range as after a severe stroke, preventing relapse and a chronic course should be the aim of treatment. Sobocki and colleagues observed that for patients who achieved remission both health care costs and quality of life increased with more than 40% as compared to non remitting patients.

Fortunately we are not completely in the dark on the way forward. The CC:DIP study provides two important leads that can be followed in the future. The first lead is connected to physical comorbidity. Chapter 7 showed that both care as usual and collaborative care are less effective for patients suffering from MDD and concomitant physical symptoms. The results from Chapter 6 point out that this might be connected to the fact that physical symptoms also limit the effectiveness of Problem Solving Treatment (PST), one of the prime ingredients of our collaborative care model.

So, could the effectiveness of collaborative care be enhanced by adapting the model to make it more suitable for patients suffering from concomitant physical symptoms? There is reason to assume that this may be the case. A study assessing the effectiveness of a collaborative care model for patients suffering from medically unexplained symptoms (and not necessarily depression) showed good results. In this trial all patients were seen by the GP and a consultant psychiatrist. In the CC:DIP-trial patients were only seen by the consultant psychiatrist in case of stagnation. One advice could therefore be that all patients who score above the cut-off on the Physical Symptoms Questionnaire (PSQ) are seen by the GP, the caremanager and the consultant psychiatrist before collaborative care treatment is initiated in primary care (and not just by the GP and the caremanager).
Another option (not necessarily excluding the previous one) would be to replace PST by a form of treatment that specifically targets medically unexplained physical symptoms if patients score above the cut-off for clinically significant physical symptoms on the PSQ. Referring these patients to a so-called psychosomatic physiotherapist could be an option, as these physiotherapists have been trained to recognize and influence the complex interplay between motor function, mental function, and psychosocial context. Unfortunately at present, to my knowledge, no randomised controlled trial has evaluated the effectiveness of psychosomatic physiotherapy. A collaborative care trial that incorporates this form of treatment as described above, comparing collaborative care without psychosomatic physiotherapy to collaborative care with psychosomatic physiotherapy, would be an excellent way to prove added value. Another option might be to replace PST by brief psychodynamic interpersonal psychotherapy, because this was found to be effective for patients suffering from multisomatof orm disorder. In that particular trial though, depression did not improve (the main improvement was a decreased physical component score on the SF36). But this could possibly change if brief psychodynamic interpersonal psychotherapy was incorporated in a collaborative care model that also focuses on depression.

Interestingly, during the exit-interviews after the CC:DIP-trial had finished, GPs did not mention concomitant physical symptoms as one of the factors that may interfere with the effectiveness of collaborative care. Instead they did mention comorbid personality disorders and history of traumatic experiences. Severe somatisation has been linked to personality disorders and traumatic experiences in early childhood. Perhaps GPs are indirectly linking severe medically unexplained physical symptoms (the cut-off on the PSQ applied in the CC:DIP trial points to severe concomitant physical symptoms) to personality disorders pointing to a group of patients that is hard to treat in primary care. This is an intriguing thought that could explain why GPs did not mention concomitant physical symptoms, but we did not ask them whether this was indeed what they meant. In any case expanding the role of the consultant psychiatrist appears to be necessary for both personality disorders and medically unexplained physical symptoms. Referral to secondary care, to a primary care psychologist (for instance for brief interpersonal psychodynamic psychotherapy), or to a psychosomatic physiotherapist should be options that the consultant psychiatrist keeps in mind in these cases depending on the specific clinical picture.

II. Will collaborative care help to decrease the prevalence and societal burden of Major Depressive Disorder?

Another issue altogether is that of the societal impact of collaborative care. In Section 1 of the general introduction of this thesis the case was made that MDD can be seen as a huge burden for society. If the burden is huge, then the benefits of effective treatment are also possibly large, even if there is room for improvement when looking at the remission percentages. Given the results regarding cost-effectiveness in primary care, there is reason to be hopeful.

Nevertheless, two questions arise with respect to this topic:

1. Is it possible to implement collaborative care successfully? Proving effectiveness in a trial is one thing. Implementation in everyday care is something else.

2. If collaborative care is implemented, will it reach a sufficient amount of possible patients to have an impact on prevalence and societal burden?

With regard to the first question, reimbursement will of course be of vital importance for successful implementation, but other (in part more practical) issues connected to everyday care should not be ignored either. Given the fact that collaborative care appears to be cost-effective, the outlook for reimbursement seems promising. This section will
therefore focus on practical issues that may influence implementation. One of the factors that has been associated with better depression outcomes after a collaborative care intervention was regular and planned supervision of care managers by a psychiatrist (quite probably this could also be a psychologist, for instance with respect to Problem Solving Treatment).209 This is relatively easy to organize for a trial, but might be a lot harder in every day care, especially if care managers are not employed by a mental health care institution.

Another practical issue is connected to the web-based patient tracking system that operated during the trial. GPs reported that they would be more inclined to use the system if this could be connected to the systems they already use to keep their electronic patient files. We were not able to achieve this during the trial (the systems operated next to each other). It should of course be possible to solve these technical problems, but this is somewhat more problematic than one would think at first glance. Several systems are used in primary care in the Netherlands (Medicom and Omnihis in our study) and nationwide implementation would imply connecting the web-based patient tracking system to all different types of electronic patient files.

This is one example of how one of the characteristics of primary care in the Netherlands could complicate implementation of collaborative care (and probably of many disease management models): in the Netherlands, every primary care practice is a small business unit with its own culture and rules (and electronic patients system). The number of GPs in one practice usually ranges from 1-5, 2 GPs on average.124,125 Although this appears to be changing rapidly many GPs are not co-located with other health care professionals such as psychiatric nurses, social workers, psychologists, or physiotherapists.16 Furthermore, the reimbursement system in the Netherlands demands regular negotiations between each health care provider and the various health care insurance companies.16 The UK, the other European country where the IMPACT collaborative care model was found to be effective, has a nationalized health service and a larger average number of GPs per primary care practice.121 This could make implementation of disease management models relatively easier. On the other hand, given the fact that GP-practices in the Netherlands are in essence small business units, collaborative care could be attractive to GPs if health care insurers (or other stakeholders) are willing to reward implementation of the model.

Implementation could also be influenced should the personal contribution to mental health care that patients had to pay in the Netherlands in 2012 return. This personal contribution is not part of the preliminary plans for 2013, but it might return in the light of the discussion on the ever increasing expenditure on health care (in any case, it will be interesting to compare 2012 to 2013 with regard to mental health care service use). The personal contribution in 2012 for mental health care in primary care was 20 Euros per session, which corresponded to 120 Euros for 6 sessions with a care manager (for instance a primary care psychologist). An exception was made for the mental health care-practice nurse (MHC-PN, or Praktijkondersteuner GGZ, POH-GGZ in Dutch) who works directly for the GP. It seems possible that patients would refuse primary mental health care that includes care management, should the personal contribution return and should the exception for MHC-PN disappear. This could lead to an increase of the prescription of antidepressant medication (without monitoring), an issue that is discussed below.

The second question that was posed above was whether or not collaborative care could reach a sufficient amount of possible patients to have an impact on prevalence and societal burden of MDD, if it were to be implemented. The answer might be yes if one looks at the prevalence of MDD in primary care, which is approximately 10%.5 Whether this is also the case for the general population remains to be seen, mainly because it is not always easy to convince patients who might have a depression to accept treatment for this condition. In her thesis Wittkampf proposed that there may be a relatively large group of patients that is not motivated for treatment. Some of the patients in her study
connected their symptoms to transient problems in their lives, such as financial troubles, worries about housing, or relationship problems. They claimed that their symptoms would improve when the problems were over.\textsuperscript{210}

Comparable to Wittkampf's findings it also proved remarkably hard to find a sufficient amount of patients to participate in the CC:DIP-study: only 25\% of the patients returned the screening questionnaire (the PHQ9). A screener had to be send out to almost 27,000 patients to include 93 screened patients\textsuperscript{5} in the trial! Indeed, quite a few patients were not motivated for treatment. It thus appears to be hard to target 'new' patients who are depressed according to the criteria for MDD, but who are not in care at the moment. This problem is not solved by collaborative care and screening for depression might not solve it either. Therefore, even though collaborative care is an effective intervention, its influence (if implemented on a wide scale) on the prevalence of depression might be modest.

As mentioned before, one of the reasons why patients often do not receive treatment for MDD may be that not everyone accepts 'the depression label'.\textsuperscript{210} Apparently some patients who suffer from MDD according to the DSM IV criteria do not feel that they have this disorder (or they associate their symptoms with something else). The finding by Wittkampf\textsuperscript{210} that at least some of them connect feelings of depression to transient problems and not to a medical disorder is reminiscent of the claim made by Horwitz and Wakefield (see general introduction Section 1) that the criteria for MDD may be overinclusive.\textsuperscript{4} In the future we might see a debate on whether or not the DSM-criteria for classifying MDD should be adapted.\textsuperscript{**} Feelings of depression may well be a normal reaction to for instance loss of a long lasting love relationship (and not just to a loss experience connected to bereavement) or to severe financial problems. In these instances coaching or internet interventions for specific problems (such as financial troubles) instead of a medical diagnosis could be less stigmatizing. Problem Solving Treatment could, for instance, easily be applied outside the context of MDD. The same goes for interventions that are focused on increasing happiness instead of curing sadness\textsuperscript{211}, and for instance for running therapy\textsuperscript{81} and other interventions focused on life style changes. If a person still has a depressed mood after the problems have passed, fails to address the problems adequately after help has been offered (for instance through an internet intervention for work related stress or by a financial coach), or still feels very sad months after a love relationship has ended, a diagnosis of depression may have more face validity.

Having said this, I do not agree that the symptoms that are currently used to diagnose MDD should be ignored. As noted in section one of the general introduction, the societal burden of these symptoms is very high.\textsuperscript{6,7} Symptoms such as concentration problems and insomnia could also be a bigger problem than they were some decades ago. For the majority of the workforce in the Western world, the nature of work has shifted from manual labor to knowledge-work. This is type of work is very difficult if you are, for instance, having concentration problems. Because of this it seems unwise not to apply the MDD-classification in its current form in health care settings, before a new paradigm for dealing with these problems has been established. Many effective interventions are based on the current MDD-criteria. These interventions may decrease the economic burden of MDD and, more importantly will decrease suffering for many patients. This may also be

\textsuperscript{5} The other 57 patients were included by direct referral by their GP. Figure 1 in Chapter 3 provides more in depth information on the screening and referral procedures.

\textsuperscript{**} In fact the American Psychiatric Association has published a footnote on the DSM-5 development website that might be added to the criteria voor Major Depressive Disorder in DSM-5 that is due for May 2013. In this footnote they state that 'the normal and expected response to an event involving significant loss (e.g. bereavement, financial ruin, natural disaster), including feelings of intense sadness, rumination about the loss, insomnia, poor appetite and weight loss, may resemble a depressive episode. The presence of symptoms such as feelings of worthlessness, suicidal ideas (as distinct from wanting to join a deceased loved one), psychomotor retardation, and severe impairment of overall function suggest the presence of a Major Depressive Episode in addition to the normal response to a significant loss.' (www.dsm5.org/ProposedRevisions, on October 13th 2012).
the case for collaborative care. The question of whether or not we should actively try to persuade the general population to visit their GP if they are feeling sad or blue (for instance through mass screening, and not targeting screening on high risk groups, such as patients suffering from diabetes, COPD, or somatoform disorders) is another question. The answer may well be no.212

Collaborative care could also play a part in dealing with one of the problems that is commonly associated with the medicalization of MDD, namely the fact that according to estimations approximately 1 million people in the Netherlands are using antidepressant medication.213 This may have something to do with the time constrained nature of primary care. A General Practitioner who has to deal with a patient's complex psychosocial problems within a ten minute consultation will generally not be very effective at doing this. If the possibility to delegate such 'time consuming' elements of care (to a caremanager) exists, a GP may less inclined to choose 'a quick solution' such a prescribing antidepressants. If care management and brief psychological treatment (such as Problem Solving Treatment) are available in the health care centre where a patient also consults his or her GP, this might also make it less difficult for him or her to accept treatment based on 'talking instead of medication' (or talking and medication instead of medication as standalone treatment). In the IMPACT-group this was known as the so called 'Rita down the hall effect', named after one the caremanagers who participated in the project.

Viewed this way collaborative care could be one of the facilitators that could help GPs to implements new guidelines for treatment of depression that are due in the Netherlands. Recently newspapers in the Netherlands reported that the Dutch College of General Practitioners is moving towards regulations that state that GPs should only prescribe antidepressant medication for relatively severe depressive symptoms because this type of medication does appear to be less effective for mild symptoms.214 This could well be the outcome of the before mentioned debate on the criteria for depression in the future: 'all or nothing' criteria (see box 1 in the general introduction) might not suffice. Diagnosing depression on a continuum could be the way forward (for instance by measuring depressive symptoms on a scale such as the PHQ9). Low intensity interventions (such as behavioral activation, motivational interviewing, PST, and perhaps running therapy) could be targeted at mild symptoms (for instance a PHQ9-score between 5 and 10), whereas antidepressant medication could be reserved for relatively severe symptoms (for instance a PHQ9-score of at least 10). Such an approach based on 'staging and profiling'215 seems promising. More research into this is necessary.

3. Conclusion

Summing up the main findings from this thesis, a concluding remark could be that treating depression should be a team effort in which the GP, the psychiatrist or clinical psychologist, a caremanager, and of course the patient collaborate. As was stated during the training the IMPACT-group provided at the start of the CC:DIP-project: "None is as smart as all of us." Another important finding is that it may be possible to enhance the effectiveness of collaborative care by adding elements to the model that increase its impact on concomitant physical symptoms.

Ten years ago the Netherlands commission on mental health care published the report 'A care of many' (in Dutch: zorg van velen)216 on the reasons for the increasing demand for mental health care in the general population. One of the recommendations was that specialized mental health care should be integrated with other health care settings and other organizations that promote wellbeing in the general population. Stepped care with specialized mental health care as the last step was noted as one of the methods to achieve such integration. Collaborative care incorporates stepped care and also facilitates cooperation between primary and specialized care. These are important reasons to
proceed with the implementation of the model (as well as the results from CC:DIP regarding cost-effectiveness).

Another recommendation in the report was that mental wellbeing should indeed be 'a care of many'\textsuperscript{216} and that the community should participate in this, perhaps against the societal trend of individualization. Feeling lonely is probably associated with depression. Here lies an important task for society as a whole.