

Aspects of cost-effectiveness and feasibility of primary care implementation

Aspects of cost-effectiveness and feasibility of implementations for care of depressed persons in primary care

Internet-based treatment and care manager organisation

Anna Holst

Department of Public Health and Community Medicine
/Primary Health Care
Institute of Medicine
Sahlgrenska Academy, University of Gothenburg

Gothenburg, Sweden 2019



UNIVERSITY OF GOTHENBURG

Anna Holst

Cover illustration

Photo by Sole Perez: *Minyons de Terrassa building a Castell.*

A *castell* is a human tower built traditionally in Catalonia, the Balearic Islands and Valencia. A *castell* is a complex construction consisting of layers of people, added stage by stage. To form the upper parts of the tower, stability of the base is crucial. Members of the base also act as a safety net if the tower structure collapses, cushioning the fall of people from the upper levels. Minyons de Terrassa says: ‘ We are people united for the collective work of building castells, a team task where everyone has their place regardless of age, sex, physical or social condition.’

Aspects of cost-effectiveness and feasibility of primary care implementations
© Anna Holst 2019
anna.holst@vgregion.se

ISBN 978-91-7833-284-7 (PRINT)
ISBN 978-91-7833-285-4 (PDF)
<http://hdl.handle.net/2077/58090>

Papers I, II and III are reprinted with permission from the publishers.
All photos published are licensed under Creative Commons, Flickr.

Printed by BrandFactory AB, Gothenburg, Sweden 2019

*General practice is the jazz of medicine,
the general practitioner is the bohemian among doctors,
states Marshall Marinker.*

*Approved – souls and blues are valuable parts
of general practice – but so must be: research,
construction of our scientific foundation
and self-critical appraisal.*

Per Fugelli

Abstract

Background: Depression is a major source of human suffering and a growing challenge for societies worldwide. The lion's share of depressed persons in Sweden are diagnosed and treated in primary care. There is an urgent need for new ways of treating and cooperating within and between care levels. Internet-mediated cognitive behavioural therapy (ICBT) and collaborative care with a care manager (CCCM) are two examples of implementations intended to meet the demands of reinforced continuity, accessibility and coordination in treatment and care of patients with mild to moderate depression.

Aim: The aim of this thesis was to evaluate ICBT and CCCM in the Swedish primary care setting from the perspectives of cost-effectiveness and feasibility including the experience of patients and staff.

Papers I–II: ICBT was compared to treatment as usual (TAU) in a cost-effectiveness analysis made from both health care and societal perspectives. The patient experience of ICBT was studied by means of focus groups and interviews. ICBT seemed to be an alternative as effective and cost-effective as TAU from both from health-care and societal perspectives. The largest cost in both groups was productivity loss related to sick leave. ICBT was shown to be an attractive treatment for some patients, but not for all. The freedom of ICBT was appreciated but the responsibility placed on the patient was considerable.

Papers III–IV: CCCM was compared to care as usual (CAU) in a cost-effectiveness analysis from both health-care and societal perspectives. Questionnaires including closed and open questions were used to study the experiences of primary care centre (PCC) directors and clinicians. CCCM was shown to be cost-effective compared to CAU from both health-care and societal perspectives. CCCM was also perceived to be effective and positive by both directors and clinicians. Facilitators for CCCM were support from colleagues and directors, cooperative skills and positive attitudes of care managers and clinicians. Barriers were high workload, shortage of staff and extensive requirements and demands from health-care management.

Conclusion: ICBT seems to be an acceptable alternative to TAU in terms of patient experience and cost-effectiveness. CCCM is highly cost-effective compared to CAU and both PCC clinicians and directors are generally positive to implementing – and working within – CCCM.

Keywords: primary care, cost-effectiveness, depression, ICBT, care manager, collaborative care, effectiveness, organisation, continuity, accessibility, coordination, Sweden

Sammanfattning på svenska

Depression är en stor källa till mänskligt lidande och över hela världen en växande utmaning för samhället. Människor med depression i Sverige söker hjälp, diagnostiseras och behandlas oftast i primärvården. I primärvård och allmänmedicin är kontinuitet, tillgänglighet och samordning ledstjärnor och vi vet att vårdkvaliteten ökar vid samtidig hög kontinuitet och tillgänglighet. Behovet av nya behandlingsmetoder och organisationsformer som stärker samarbete inom och mellan vårdnivåer för att uppnå bästa möjliga resultat vid behandling av depression, är stort. Internetmedierad kognitiv beteendeterapi (ICBT) och vårdsamordnare för psykisk ohälsa (CCCM) är två exempel på implementeringar som syftar till att stärka kontinuitet, tillgänglighet och samordning.

Syftet med denna avhandling var att utvärdera ICBT och CCCM som behandling vid depression i den svenska primärvården ur perspektiven kostnadseffektivitet och genomförbarhet. För att bedöma en behandlings genomförbarhet är patienters och personals upplevelser och erfarenheter viktiga.

Studie I–II: ICBT verkade vara effektiv och kostnadseffektiv i samma utsträckning som sedvanlig behandling både ur sjukvårds- och samhällsperspektiv. Den största kostnaden för både ICBT och sedvanlig behandling var relaterad till arbetsoförmåga och sjukskrivning. ICBT visade sig vara en attraktiv behandling för vissa patienter, men inte för alla. Friheten i ICBT var uppskattad men patientens ansvar för att behandlingen fortskred upplevdes som tungt.

Studie III–IV: CCCM visade sig vara höggradigt kostnadseffektiv jämfört med sedvanlig primärvård både ur sjukvårds och samhällsperspektiv. CCCM uppfattades som effektiv och positiv av vårdcentralspersonal och deras chefer. Stöd från kollegor, samarbetsförmåga och positiva attityder hos personal och vårdsamordnare verkade underlätta arbetet inom CCCM. Hög arbetsbelastning, personalbrist och omfattande och parallella krav uppifrån i organisationen upplevdes som hindrande faktorer.

ICBT verkar alltså vara ett acceptabelt alternativ till sedvanlig primärvård både vad gäller patientupplevelse och kostnadseffektivitet. Att ha flera goda behandlingsalternativ att välja mellan ligger helt i linje med de allmänmedicinska personcentrerade arbetsformerna. CCCM är mycket kostnadseffektivt jämfört med sedvanlig primärvård och både personal och chefer på vårdcentralerna är generellt positiva till CCCM.

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. Holst A, Björkelund C, Metsini A, Madsen JH, Hange D, Petersson EL, Eriksson MC, Kivi M, Andersson PÅ, Svensson M. Cost-effectiveness analysis of internet-mediated cognitive behavioural therapy for depression in the primary care setting: results based on a controlled trial. *BMJ Open* 2018;8(6):e019716.
- II. Holst A, Nejati S, Björkelund C, Eriksson MC, Hange D, Kivi M, Wikberg C, Petersson EL. Patients' experiences of a computerised self-help program for treating depression – a qualitative study of Internet mediated cognitive behavioural therapy in primary care. *Scand J Prim Health Care* 2017;35(1):46-53.
- III. Holst A, Ginter A, Björkelund C, Hange D, Petersson EL, Svenningsson I, Westman J, André M, Wikberg C, Wallin L, Möller C, Svensson M. Cost-effectiveness of a care manager collaborative care programme for patients with depression in primary care: economic evaluation of a pragmatic randomised controlled study. *BMJ Open* 2018;8:e024741.
- IV. Augustsson P, Holst A, Svenningsson I, Petersson EL, Björkelund C, Björk Brämberg E. Implementation of care managers for patients with depression in Swedish primary care – a staff survey of perceived use, facilitators and barriers. Submitted to *BMC Health Services Research*.

Content

ABBREVIATIONS	V
INTRODUCTION	1
Primary care	1
Primary care as the core of health care systems	1
Primary care is person-centred care	2
Historical perspective of primary care and general practice in Sweden..	3
Primary care in the Swedish health care system– organisation, economics and ethical principles	5
The real world – how to know what makes a difference	6
Depression in primary care	7
The depression disease	7
Assessing level of depression	8
Depression treatment and care according to the Swedish national guidelines.....	9
The need to break fresh ground	10
Internet-mediated cognitive behavioural therapy – ICBT	11
Care levels in collaboration	12
Collaborative care with a care manager.....	14
Cost-effectiveness in health care	15
Health care and societal perspectives	16
Pricing time.....	17
Quantifying health and life	17
Time perspective.....	18
Comparison of alternatives – the ICER	19
Visualization of cost-effectiveness – the cost-effectiveness plane	20
Assessing uncertainty	21
Net monetary benefit	22
AIM	23
General aim.....	23

Aspects of cost-effectiveness and feasibility of primary care implementation	
Specific aims.....	23
METHODS.....	25
The PRIM-NET study.....	26
Paper I – Cost-effectiveness analysis of ICBT vs TAU.....	26
Health outcomes	26
Cost outcomes.....	27
Cost-effectiveness analysis.....	27
Paper II – Patients experiences of ICBT – qualitative analysis	28
The PRIM-CARE study.....	29
Paper III – Cost-effectiveness analysis of collaborative care with a care manager vs CAU.....	31
Health outcomes	31
Cost outcomes.....	32
Cost effectiveness analysis	32
Paper IV – Director and clinician experiences of collaborative care with a care manager – descriptive and qualitative analysis	33
Ethical issues.....	35
RESULTS	37
Paper I – Cost-effectiveness of ICBT vs TAU	37
Health outcome.....	39
Cost outcome	40
Cost-effectiveness.....	41
Paper II – Patient experiences of ICBT	44
Paper III – Cost-effectiveness of collaborative care with a care manager vs CAU	49
Health outcome.....	49
Cost outcome	49
Cost-effectiveness.....	52
Paper IV – Director and clinician experiences of collaborative care with a care manager	54
Quantitative results	55

Qualitative results	56
DISCUSSION	59
Major findings.....	59
ICBT is an acceptable and feasible treatment for depression	59
Collaborative care with a care manager is an effective way of giving care for depression	60
General discussion	61
Cost-effectiveness of CCCM och ICBT	61
Productivity loss may be underestimated	62
Age and personality traits may matter, and depressive symptoms certainly do	63
The need for a helping hand	63
Cyberspace and hardware considerations	64
Blending care	64
Facilitators for implementing CCCM.....	65
Barriers to implementing CCCM.....	65
Methodological considerations – strengths and limitations	66
Paper I.....	66
Paper II	67
Paper III	69
Paper IV	70
Implications for healthcare	71
CONCLUSION	72
FUTURE PERSPECTIVES	73
ACKNOWLEDGEMENT	74
REFERENCES	76

Abbreviations

APA	American Psychiatric Association
BDI-II	Beck Depression Inventory II
CAU	Care as usual
CBT	Cognitive behavioural therapy
CCCM	Collaborative care with a care manager
CI	Confidence interval
DFD	Depression free days
EPR	Electronic patient records
EQ-5D-3L	EuroQol, five-dimension, three-level
GP	General practitioner
HRQoL	Health related quality of life
ICBT	Internet-mediated cognitive behavioural therapy
ICER	Incremental cost-effectiveness ratio
MADRS-S	Montgomery Åsberg Depression Rating Scale – self-rating version
NMB	Net monetary benefit
PCC	Primary care centre
PHQ-9	Patient health questionnaire 9
RCT	Randomised controlled trial
SBU	Swedish Agency for Health Technology Assessment and Assessment of Social Services (Statens beredning för medicinsk och social utvärdering)
SEI	Socio-economic index
SEK	Swedish kronor (€~0.1)

Anna Holst

TAU Treatment as usual

QALYs Quality adjusted life years

WHO World Health Organisation



Hippocrates of Kos

Photo: Kai Morgener

Introduction

A modern globalised world demands accessible, qualitative and coordinated health care. Achieving the best possible health and lowest possible morbidity for individuals is a major challenge for health care and society with limited resources. There is an urgent need for refined or new perspectives and working methods to be able to deal with this complex task. Health care needs to respond better – and faster – to the challenges of a changing world. There are major knowledge gaps regarding the care and treatment of fragile individuals and of chronic and multiple illnesses. This calls for the rapid development of knowledge in the areas of collaboration and coordination within health care. Research that goes beyond care levels and health care organisations should be based on primary care, which is the central node of the health care system. Primary care is the arena best suited to meet demands and lead development towards a modern and sustainable health care system. My research has been performed in this context. In this thesis I intend to present studies of examples of refined and new working methods from the real world of primary care.

Many decisions will need to be taken and many priorities selected. These should – as all decision making in health care – lean on the principles of justice, equality, cost-effectiveness, need and solidarity. Health care must not harm. Results from applicable high quality research should form the knowledge basis of decision-making. Such research should be performed upstream of – or at least in line with – decisions. Such research should be designed for effectiveness and consider clinical effects but also the important aspects of feasibility, cost-effectiveness and patient and staff experiences and preferences. The effectiveness approach has a high probability of creating value in the real world. In this thesis I intend to present examples of effectiveness studies.

Primary care

Primary care as the core of health care systems

Primary care is defined by the World Health Organisation (WHO) as a key process in any health care system. In 1978, at the Alma Ata WHO conference, all countries were encouraged to invest in primary care, with the ultimate goal of ‘better health for all’ (1). Primary care plays a central role in most health care systems world-wide, and strengthening primary care is widely seen as

central to enhancing equity and efficiency in health care (2). There is also considerable evidence that primary care systems contribute to overall health system performance and health. Primary care has been described as complex and multidimensional (3).

Primary care should be **the first contact**, **accessible** at the time of need. It should be **continuous** meaning that it focuses on the long-term health of a person rather than the short duration of a disease. It should be **comprehensive** meaning that it offers a broad range of services appropriate to the common problems of the respective population and meets the needs of all ages and individuals. This includes initial medical assessments, treatment and follow-up of illness and injuries that do not require hospitalisation, preventive measures, health promotion, rehabilitation, and death with dignity. Primary care should be **coordinative** in that it involves other specialists and social agents that the patient may need. Thus, primary care should be more than just a level of care or a gate-keeping function (2-5).

Primary care is person-centred care

Patient-centred care was mentioned already in the 60s by Mr and Mrs Balint (6) as a contradiction to the predominantly paternalistic model of the time, and was later described by Ian McWhinney as care in which ‘the physician tries to enter the patient's world, to see the illness through the patient's eyes’ (7). It has also been defined as ‘care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions’ (8). In recent years – aiming to encompass the entirety of a person's needs and preferences and not just the clinical or medical – there has been a move toward using the term person-centred, rather than patient-centred. A recent definition of person-centred care is ‘care where individuals’ values and preferences are elicited and, once expressed, guide all aspects of their health care, supporting their realistic health and life goals. Person-centred care is achieved through a dynamic relationship among individuals, others who are important to them, and all relevant providers. This collaboration informs decision-making to the extent that the individual desires.’ (9).

Primary care and general practice has a long and strong tradition of person-centred care. The open-ended commitment of the general practitioner (GP) is to the person, not to ‘the person with a certain disease’. The care is comprehensive in its response to the needs of the people and reasonably accessible in their neighbourhood. (10). The relationship between the patient and the GP has been the subject of many attempts to describe and define. One

model developed in the 1990s is characterized by sustained partnership. Some of the defining features of this model are:

- A focus on the whole person (i.e. the doctor attends to all health-related problems, either directly or through collaboration, regardless of the nature, origin, or organ system affected)
- The doctor's knowledge of the patient (i.e. the doctor knows not just the patient's medical history but his or her personal history, family, work, community and cultural context, as well as his or her preferences, values, beliefs and ideals about health care, including preferences for information and participation in clinical decision making)
- The choice of appropriately adapted care (i.e. the doctor tailors treatment recommendations to reflect the patient's goals and expectations regarding health and health care as well as the patient's beliefs, values and life circumstances)
- The patient's participation in decision making (i.e. the doctor encourages the patient to participate in all aspects of care, and treatment and referrals are agreed to by both the clinician and the patient. To the extent that the patient wishes, the clinician informs the patient about diagnosis, prognosis and treatment options and includes the patient in treatment decisions) (11).

In modern primary care, where close collaboration among care and patient is standard, this model is equally applicable.

While secondary care mainly treats different patients with similar diseases, primary care treats the same patients and their different conditions and diseases for long periods. It might be challenging for secondary care to adapt to the model of person-centred care. However, in primary care, person-centeredness has been the guiding principle for decades, and today most medical schools educate and supervise consultation skills that facilitate patient-doctor communication and make person-centred care possible and actual (12).

Historical perspective of primary care and general practice in Sweden

A governmental organisation of district medical officers was established in the seventeenth century and tasked with mediating medical care and monitoring the health and sanitary conditions of the population (13). The first district medical officer of Gothenburg was the Dutch Pieter á Naaldwyck, who entered

his service of the Gothenburg population at the time of the city's founding 1621 (14). By the year 1900, the majority of the Swedish medical profession consisted of district medical officers (responsible for one geographical district each) in private practice – there were few hospital doctors. Primary care was thus completely dominant. The work of the district medical officer was exhausting and isolated as he (there were only males until Marianne Lindstén became the first female district medical officer in Vilhelmina in 1946) was on call twenty-four hours a day seven days a week. The only requirement to be employed as a district medical officer after graduation from medical school was eight months of service at a hospital (15).

The first Swedish primary care centre (PCC) was established in Dalby, in the county of Skåne in 1968 (and was initially attached to the academy with a research commission). In the 1970s, PCCs were established throughout the country, and the organisational residence of primary care moved from national jurisdiction to the county councils. The requirements to be a GP (previously named district medical officer) were extended to three years at various hospital clinics. The PCCs typically employed GPs, nurses, physiotherapists and occupational therapists, and child and maternity care was integrated into the primary care organisations. Today these PCCs, with some extensions to the competence profile of the staff, are the predominant organisational form of the comprehensive primary care sector.

General practice became a specialty in 1981, requiring four and a half years of practice in different specialities including two years in general practice. In 1981 the first professorship in general practice was instituted at the Lund University in Skåne, and today research on general practice is conducted at all Swedish medical faculties. General practice is included in the basic education of all physicians and constitutes around a quarter of their internship (allmäntjänstgöring (AT)). The specialty of general practice today demands five years of internship (specialiseringstjänstgöring (ST)) following a comprehensive curriculum (16). An increasing number of GPs have been trained over the years – yet GP job vacancies prevail. One explanation could be the heavy workload and stressful working conditions of GPs. In a Commonwealth Fund survey of primary care physicians in several countries in 2015, 56% of Swedish GPs reported their work as very or extremely stressful, which was the second highest proportion among all countries surveyed, and more than double the proportion of several countries (17).

Primary care in the Swedish health care system– organisation, economics and ethical principles

In Sweden, the government is responsible for ensuring the health of all citizens according to the ethical principles stated in the Health Care Act (Hälso- och sjukvårdslagen) (18). Prioritization in health care should be based on the following principles:

- The principle of human dignity: The entire population should be given health care on equal terms regardless of functions in society or personal characteristics.
- The principle of need and solidarity: Those most in need of health care should be given priority.
- The principle of cost-effectiveness: Health care should be conducted cost-effectively. However, considerations in the individual case should only be made in compliance with the above-mentioned principles (18-20).

A national health care guarantee stipulates the patient's right to get in touch with health care in zero days, and to see a GP within seven days (21). Since 2010 the patient has the right to choose a primary care provider according to the Act on System of Choice in the Public Sector (Lagen om valfrihetssystem, (LOV)) (22). The health-care guarantee and choice of care together make it difficult to achieve the principles of equal care for everyone and priority for those most in need. The reforms have entailed improved contact opportunities with health-care services and more PCCs. However, this has mainly benefited patients of higher socio-economic status and with less care needs (20).

Health care expenditure is mainly tax funded (80%). Sweden had the highest health-care spending in the European Union in 2015: 11% of gross domestic product (bruttonationalprodukten (BNP)) compared to the EU average of 9.9% (23). However, accessibility, waiting times and person-centred care coordination across care providers are enduring issues. Sweden has a large number of doctors and nurses: 4.2 practicing doctors per 1,000 persons, compared to the EU average of 3.6, but only 15% of the doctors are GPs which is considerably lower than most EU countries (23). The difficulty of recruiting GPs is a national problem particularly in rural areas, and this has led to a growing market for locum physicians employed by staffing companies which in turn has had a negative impact on both staff costs and continuity of care for patients. There has been a long-term shift from inpatient to outpatient care in Sweden. For example, the number of hospital beds has gradually become fewer and is now the lowest in EU with 2.3 beds per 1,000 persons of the general population compared to the EU average of 4.2. Hospital admission rates for

chronic diseases are also below the EU average. Yet, primary care has not been bolstered to respond to the increased need for outpatient care to the same extent (23).

The funding and organisation of health care in Sweden lies largely (84%) on the twenty-one county councils/regions. The county councils are responsible for providing primary care to all county residents, and define the requirements to be met for primary care providers by means of regulations and reimbursement systems. The prerequisites to establish and run a PCC are the same whether it is funded privately or publicly.

The PCCs of Sweden typically employ many professional categories. In addition to an average of four to five GPs, the teams consist of nurses specialised in general practice/diabetes/asthma, assistant nurses, psychotherapists, physiotherapists, occupational therapists and rehabilitation coordinators. The teams cooperate to give care to – and to work preventively with – the patients. This includes maternity and child care. The PCC is also the health care instance with the greatest responsibility for coordinating care with a patient's additional carers. The PCCs cooperate closely with the local municipality in elder care, both for persons in nursing homes and those living at home. PCC staff also cooperate with authorities such as the Social Insurance Agency (Försäkringskassan) and the Public Employment Service (Arbetsförmedlingen) as well as patients' employers.

The real world – how to know what makes a difference

The task of primary care is to grow as the population's needs grow and as more care is provided at the primary care level. We need to learn to develop primary care that is more effective for the user, society and, preferably, staff. This presupposes clinical research within the real world of primary care. *Efficacy studies* are performed under controlled/ideal conditions and answer the question Can it work? Effectiveness studies answer the question Does it work? *Effectiveness studies* of regular medical services that are designed to shed light on as many important aspects as possible are more likely to create value in the real world, which is a very complex system (24). Effectiveness studies are also known to be the most informative for drawing economic and cost-effectiveness conclusions (25).

The WHO World Health Report 2008, entitled *Primary health care. Now more than ever* clearly articulates the need to mobilise knowledge on primary care level (26).

Depression in primary care

Depression is a major source of human suffering and a great and growing challenge for societies worldwide. Mental health problems account for 13% of the global burden of disease and are one of the leading causes of disability (27). From an economic point of view, depression puts a high burden on affected individuals and also on society, including health care costs, sick leave and disability pension (28). The total annual cost of mood disorders in Europe in 2010 was estimated at approximately EURO 113.4 billion, which corresponds to almost 1% of the gross domestic product of the EU (29). The largest component of the costs of depression in Sweden consists of productivity loss due to impaired work performance. Depression is one of the leading causes of sick leave (30). The majority of people with depressive symptoms in Western countries – 70% in Sweden (31) – seeks and obtain treatment in primary care (30, 32). In Sweden approximately 15%-20% of primary care patients suffer from depression or a depression-like state (30). Only 20% of patients with depression are referred to specialist psychiatry (33).

Primary care is the appropriate level for treating depression according to WHO, because it implies reduced stigma for mental health patients and their families, improved access to care, holistic management of co-morbidities, better treatment because of reduced losses to follow-up, lower patient-borne costs and improved overall capacity of the health care system to deal with mental health problems (28).

The depression disease

Existing national and international data on the prevalence of depression are not concordant; therefore, no reliable conclusion on the prevalence of depression in the general population can be drawn. For example, Swedish studies report the prevalence of depression in the general population of Sweden to be between 2.4% and 15% (30). Women are more often diagnosed with depression than men (34), and the risk of becoming depressed increases with age, more so for women more than for men (35). There are several risk factors for depression such as chronic somatic disease, major life changes and traumatic events, heredity and substance abuse (30).

The crucial difference between the brief mood swings of a healthy individual and depression is the quality of symptoms as well as the duration. A depression diagnosis is based on a clinical assessment in connection with the GP or psychologist consultation. ICD-10 (36) and DSM-IV (37) are the most

common systems of criteria for depression diagnostics internationally. The most used diagnostic criteria in Swedish primary care are the ones of ICD-10-SE (38). ICD-10-SE defines depression as a condition that lasts more than two weeks and includes drowsiness, reduced energy and loss of interest or pleasure in activities that are otherwise satisfying. Sadness, anxiety, guilt, suicidal thoughts and reduced appetite may also be included (33).

Depression is also associated with low quality of life, impaired functional capacity and work ability, sick leave, pain and increased risk of mortality (39, 40). Patients with depression are also at risk of not receiving adequate treatment for concurrent somatic diseases resulting in deteriorated health and premature death (31).

Regardless of the condition, depressed patients treated in the PCCs often function quite well and have capacity to work (41), unlike most patients in psychiatric secondary care. However, there are increasing numbers of people on sick leave for depression (42). In Sweden, a person can be on sick leave from work for one week without a sickness certificate. For a longer period of sick leave a sick note issued by a physician is needed. The employer pays benefits for the first two weeks of sick leave. Thereafter the Social Insurance Agency (Försäkringskassan) pays sick-leave benefits upon receiving an approved sick note. Part-time (25% -75%) or full-time sick leave is possible.

Assessing level of depression

There are several validated scales for assessing level of depression. The scales most used in clinical primary-care contexts are the self-rating version of the Montgomery Åsberg Depression Rating Scale (MADRS-S) (43) and the Patient Health Questionnaire 9 (PHQ-9) (44). The Beck Depression Inventory II (BDI-II) (45) is also used to a limited extent in primary care, but more often by psychologists and in research. The use of a self-assessment tool in recurrent consultations does not improve treatment results of depression in primary care compared to treatment as usual (TAU) (40, 46, 47), but it can strengthen the patient's perceptions about clarification, centredness and confirmation (48) as well as increase adherence to anti-depressant medication (46).

MADRS-S is used to assess the severity of depression and was developed as a self-rating version of MADRS. It is based on a questionnaire of nine items, each being valued from 0 (lower bound) to 6 (upper bound). Subscores are added for an overall score, which indicates the severity of depression (≤ 12 = no depression, 13 - 19 = mild, 20 - 34 = moderate, ≥ 35 = severe).

BDI-II is a self-assessment instrument that measures the level of depression. The BDI-II contains twenty-one items, and the patient assigns each item a score of 0-3. Maximum score is 63. The cut-off for mild depression is 14, for moderate depression 20 and for severe depression 29.

MADRS-S and BDI-II correlates well in assessing depression levels in all domains, but MADRS-S could be judged as a more rapid, inexpensive and easily administered tool compared to BDI-II (49). However, in clinical praxis, the BDI score of 29, classified as severe depression, seems to indicate a less severe condition than MADRS-S point 35 (49).

Depression treatment and care according to the Swedish national guidelines

The goal of all depression treatment is to free a person from the symptoms and regain a satisfactory level of functioning, including return to work. The severity of the symptoms determines whether the depression is graded as mild, moderate or severe. The severity together with the preferences of the patient then determines which treatment is appropriate.

The Swedish National Guidelines for Care in Cases of Depression and Anxiety Disorders of 2017 ranked actions to be taken in assessing and treating mild to moderate depression (the ranking of action is based on the severity of the condition, the effect of the action/intervention, and the cost-effectiveness) (33). Among the recommendations with the highest ranks were:

- High accessibility to health care for primary assessment.
- Active follow-up with scheduled return visits (continuity).
- Cognitive behavioural therapy (CBT).
- Antidepressant medication.

Thus, antidepressant medication and CBT are both recommended treatment for mild to moderate depression. However, there are studies showing that only a third of patients with – especially mild – depression fully respond to antidepressants (50), and that patients tend to favour psychotherapy to antidepressants (51). CBT is the form of brief psychological therapy with the strongest support in available evidence for persons with depression (31) and has been shown to be as effective as antidepressants in treating depression (30). Interpersonal therapy (IPT) is judged by a fraction of psychologists to be as effective as CBT, but there is less evidence on IPT.

In primary care, TAU for depression is based on the National Guidelines and consists of a diverse flora of treatment elements. The most appropriate elements are selected by the primary care team in close cooperation with the patient. TAU could include visits to the GP and/or nurse, antidepressants, face-to-face psychotherapy (or waiting list for), sick leave, recommendations of increased physical activity or combinations of these. Care as usual (CAU) is a term used to describe the provided care as a whole including its organisation.

Accessibility to and continuity of treatment for depression in primary care are well-known factors that increase the quality of care (33, 52). Continuity of care implies significant benefits to patients and staff (53). A Norwegian study in primary care showed that regularly occurring GP visits had a therapeutic effect similar to antidepressant medication (54).

The need to break fresh ground

The demands for accessible, continual, qualitative and coordinated health care are major challenges for health care and society to manage, given limited economic and personnel resources. There is a large gap worldwide between need and provision of depression care (28). Some of the main challenges facing the treatment and care of depression in primary care are related to accessibility, continuity and coordination. These challenges are especially relevant for depression and anxiety patients, whose symptoms often lower their access to care (55).

Increases in funding and supply of educated personnel would probably improve opportunities to cope with the challenges in primary care. Nonetheless, new ways are needed to treat patients and cooperate within and between care levels. New evidence-based treatment methods and organisational forms of care need to be evaluated at the primary care level.

Limited access and unacceptably long delays to psychotherapy is a severe problem for patients suffering from depression. The availability of CBT in primary care is low (31, 32), often due to a shortage of trained psychotherapists, and many patients therefore do not receive appropriate treatment (56). To be put on a waiting list for psychotherapy is a well-known disadvantage for recovery from depression and anxiety disorders (57). Patients also increasingly request online solutions for communication and treatment (58). Internet-mediated cognitive behavioural therapy (ICBT) has the potential to increase accessibility to CBT in primary care and to satisfy patients with requests for online treatment.

International studies conclude that isolated actions such as increased screening for depression, special training of doctors and nurses or increased psychological expertise in primary care do not result in higher quality of care or a better effect than CAU (59). Literature reviews by Cochrane and Swedish Agency for Health Technology Assessment and Assessment of Social Services (Statens beredning för medicinsk och social utvärdering (SBU)) have shown that only those organisational actions that include complex interventions have positive effects in reducing depression, improving patient satisfaction and quality of life compared to CAU in primary care (60).

As most patients with depression are diagnosed and treated in primary care, studies that target the primary care context are especially needed. Relatively few studies have been conducted on the management of depression in primary care. Recommendations for diagnosis and treatment have mainly been based on research at psychiatric clinics, where few patients with mild and moderate depression are treated (30).

Internet-mediated cognitive behavioural therapy – ICBT

ICBT is an online alternative to standard manualized face-to-face CBT and is described as feasible, effective and acceptable (61). In standard ICBT patients regularly read and download online materials arranged into a series of lessons or modules available on a secure web-site during a specified period. They receive homework assignments to complete before the next module is available. They also complete questionnaires, allowing the therapist to monitor progress, safety and outcomes (62). ICBT allows greater access, and possibly more effective health care than face-to-face CBT (i.e. shorter therapist time spent per patient) (63).

ICBT has been used as treatment for depression for many years (64-66) and is internationally accepted as a treatment for depression (63, 67-70). ICBT has been recommended by the National Board of Health and Welfare in Sweden (Socialstyrelsen) as the preferred treatment for mild to moderate depression (71).

There are effectiveness studies of ICBT as treatment for depression in the primary care setting with the clinically most relevant comparison group, in other words, TAU (73, 74), but the evidence for Swedish primary care clinical practice is still insufficient (75).

Cost-effectiveness

Several studies of the cost-effectiveness of ICBT as a treatment for depression have shown promising results in favour of ICBT (76-79). For example, McCrone et al. investigated the cost-effectiveness of ICBT compared to TAU in treating depression and anxiety in a randomised controlled trial (RCT) conducted in a primary care setting in the United Kingdom in 2004. They found that ICBT was more effective than TAU as provided by the primary care team at negligible additional cost. ICBT also reduced productivity loss caused by sick leave to lower levels than TAU (76). Recently, however, Gilbody et al. conducted an RCT concerning two different ICBT programs for depression in primary care in UK (the REEACT trial). No substantial improvement in depression outcomes could be seen compared to the usual GP care alone. The trial-based cost-effectiveness analyses suggested that none of the ICBT programs were cost-effective compared to usual GP care alone (74, 80). SBU has concluded that ICBT may be cost-effective, but whether it applies to Swedish primary care needs further investigation (75).

Patient experiences

How patients experience ICBT in the primary care context is important if we are to gain an understanding of the barriers and facilitators to successful treatment. Patients tend to be more positive to ICBT than psychotherapists (81). A study by Kivi et al (82) of the ICBT therapists' experiences showed that they considered ICBT a complementary part of face-to-face therapy. There is evidence that care combining ICBT with face-to-face support is more effective than ICBT without it in community and secondary care (72, 83).

Several studies of the patient experiences in ICBT (84-88) show the advantages and disadvantages of the treatment, but none have been made in the Swedish primary care context.

Care levels in collaboration

Collaboration, integration and coordination have become household terms. However, they do not mean the same thing to everyone. Cohen et al defined three interpersonal strategies (*Cs*) that primary care and behavioural health clinicians could practise to solve patients' problems:

- **Consult** meaning seeking advice, confirm perceptions of a patient's needs or validate care plans with another professional.

- **Coordinate** meaning two professionals giving care to a patient separately but cooperate in a parallel or back-and-forth fashion to achieve a common goal of the care.
- **Collaborate** meaning two or more professionals interacting in real time to discuss a patient's symptoms, communicating views on treatment and jointly develop a care plan.

Cohen et al. suggested that organisations execute all three Cs routinely in practice (89). Wagner et al. suggested an integrated system of chronic illness care leaning on five cornerstones: the use of evidence-based, planned care; reorganisation of practice systems and provider roles; improved patient self-management support; increased access to expertise; and greater availability of clinical information (91). This was further supported by WHO (28) and is the basis of the collaborative care model evaluated in this thesis.

In the primary care and in the literature of the United States (where, however, the task and organisation of primary care is essentially different from in Sweden) there are several concepts involving collaboration, integration and coordination as follows.

- **Coordinated care** is a broad term meaning organisation of patient care activities and information exchange between patient and provider, and between providers at different care levels.
- **Integrated care** is an umbrella term that is defined by the American Psychiatric Association (APA) as 'tightly integrated practice teams with a unified care plan. All aspects of the organisation and delivery of care are orchestrated to work effectively together to deliver whole-person care' (whole person care being 'care that is patient centred and addresses the full range of a patient's medical and behavioural needs, culture, values and preferences; helps patients become active participants in their own health care') (90).
- **Collaborative care** is a form of integrated care which does not mean the same thing to everyone. The APA definition is 'a specific type of integrated primary care that uses care registries and consulting psychiatrists to support a care team that includes a care coordinator and primary care physician typically located in the practice to treat common mental health conditions'.

Collaborative care with a care manager

To collaborate the core competencies of health care professionals for the patient is a well-established strategy of the primary care team. As mentioned above, Swedish primary care teams traditionally combine professions such as GPs, nurses, psychotherapists and physiotherapists. SBU recently published an evaluation of methods that can facilitate the introduction of evidence-based care for patients with depression in primary care (59). SBU identified an effective implementation strategy and referred to studies from the UK and US in which the primary care organisation was reinforced with a care manager and combined with other actions such as training of the care team and feedback between GP and patient. The care manager in these studies was described as a person especially trained for the task, such as a nurse, responsible for support and continual contact with patients with depression (60, 92). The care manager is a practice-based staff with direct patient contact, taking on the coordination and participate in both the clinical and nonclinical aspects of care. Care managers are sometimes referred to as care coordinators, patient navigators, or patient coaches (93). The care manager role referred to in this thesis has two types of important functions. One function is to increase accessibility and continuity of care for the patient at the PCC. The care manager then operates as a supporter and coordinator of care and not as a therapist. The other function is educational development at the PCC to improve communication and feedback within the PCC team and communication with secondary care (41, 94, 95).

SBU called for studies on collaborative care organisation with a care manager conducted in Swedish primary care (59), as complex interventions behave differently depending on context (96), and results from other health care systems may not be suitable for Swedish conditions.

Cost-effectiveness

Care managing has been shown to reduce patients' depression symptom burden, to increase the adequacy of antidepressant prescription and to be cost-effective both for the patient and the PCC (94, 97). Collaborative care was found to be cost-effective for the management of depressive disorders in a systematic review by Jacob et al. (92). Gilbody et al. concluded, in a systematic review of enhanced primary care for treating depression, that improved patient outcomes are expected in collaborative care, but at increased cost and investments (98). At present there are no Swedish studies of the cost-effectiveness of a care-manager programme for the treatment of depression in a Swedish primary-care context.

Director and clinician experience

The effect of implementation depends on the context and how the change process looks. Therefore, studies and systematic overviews should be complemented by methodologies that highlight contextual factors and the implementation process (59). Care manager interaction with patients and clinicians is affected by how well care management is defined and supported (97). Staff and organisational factors are known to be decisive for whether or not an implementation will succeed (99). According to previous studies, the facilitators of implementing collaborative care for depression in primary care are: strong leadership, standardised systematic clinical pathways, sufficient training and regular supervision of staff (95, 100) and accessible care managers on site (94, 97). The social and professional skills of the care managers are additional facilitating factors (101). Existing service structures, unfavorable financial structures (97, 100) lack of organisational, administrative and professional ability to change and implement, and lack of clarity of the responsibility of the care manager (102, 103) are barriers. At present there are no published Swedish studies on the experiences of staff in a care manager programme for the treatment of depression in a Swedish primary-care context.

Cost-effectiveness in health care

The Swedish health-care system abides by the priority principles of human dignity, need and solidarity, and cost-effectiveness. It is committed to ensuring the health of all citizens (21). Previously, clinical effectiveness was the only thing that counted in the field of medical research; and prioritization of resource use was not always necessary. Now we spend more money on health care than ever, and health-care resources are continual insufficient. Prioritization is unavoidable. The pressed budgets of the past two decades have granted economic evaluations increased prominence in health-care decision making (25). These evaluations provide frameworks for making the best economic use of clinical evidence through organised considerations of the health effects of available alternatives and health care costs.

The most commonly used form of economic evaluation in the field of primary care is the cost-effectiveness analysis (25). This method evaluates benefits/effects of alternative interventions/options relative to costs.

Some key concepts of cost-effectiveness analysis are described below.

Health care and societal perspectives

Perspective must be considered when deciding which costs and health benefits to include in an economic evaluation. One perspective could be the individual's; for example a cost could be what the patient needs to buy or pay to be healthy (out-of-pocket costs). In the Swedish context, however, health care (i.e. the county council) pays the lion's share of costs related to investigation and treatment of disease. In economic evaluations health care represents the payer.

The health care perspective comprises the payer's costs. In the example of depression, these costs might include the labour of health care personnel (e.g. GPs, psychotherapists and nurses), investigation (e.g. basic blood samples), treatment equipment (e.g. ICBT software) and medication.

The societal perspective includes the health care perspective but adds costs and benefits on a national level. Thus, the societal perspective includes all costs and effects related to the condition or disease irrespective of how and when they emerge. In the example of depression, societal costs might consist of production loss related to sick leave and/or health care visits and treatment. See Figure 1.

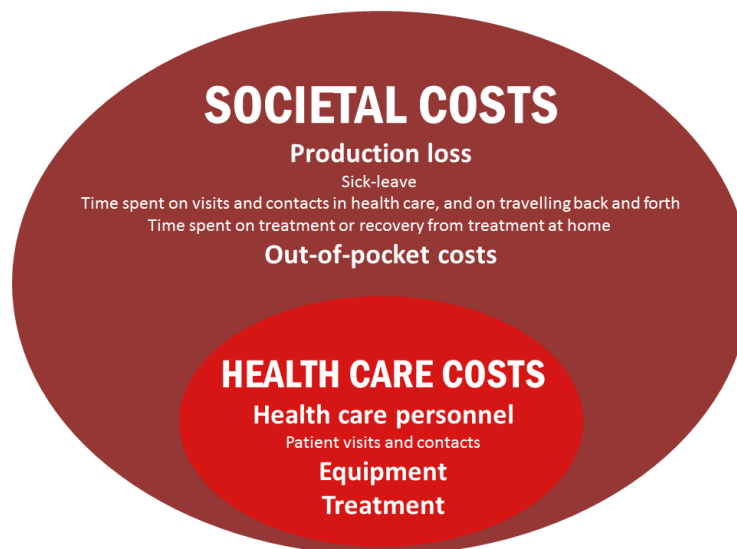


Figure 1. Costs from a societal and a health care (i. e. payer's) perspective. By Anna Holst, 2018.

Pricing time

Health care costs

In primary care the most valuable and most costly resource is the health care personnel (whereas in some secondary care, the medication or technical devices may comprise a larger part of the cost). Assessing the cost of an intervention therefore mainly involves the identification and valuation of utilizing health-care personnel (e.g. time spent on patient contact, treatment and follow-up). The cost of this utilization is calculated by combining salary data (gross wage plus social fees) per hour – defined as the hourly wage – with time spent (25). For example the cost of a 45-minute GP consultation equals hourly wage $653 \text{ SEK} \times \frac{45}{60} = 490 \text{ SEK}$.

Average standard costs are listed for several posts, such as GP visits. However, the actual time spent, if obtainable, would be more accurate in calculating true costs as described above.

Societal costs

The *human capital approach* (25) can be used to put a value on the productivity lost to illness and sick leave. This approach values work/productivity at the market price of what an employer is willing to pay per hour of labour (gross wage plus social fees). Some health economists claim that the human capital approach overestimates the value of productivity loss and advocate instead for the *friction cost approach* (104). Friction cost arises in the time period during which no one is producing. The friction cost starts when someone falls out of production and ends when replaced by another person.

The hourly wages of patients could be calculated from individual salary data or average gross wages for the context (in this case Sweden).

Quantifying health and life

To measure the health benefits of an intervention, disease-specific outcome measures can be used. (See Assessing level of depression, page 8). A benefit of disease-specific instruments, such as MADRS-S and BDI-II, is that they are used clinically to evaluate depression and can capture relatively minor changes in the disease state. The disadvantage, in assessing cost-effectiveness, is that the score is not translatable to other medical care, and there is no way to determine an effective cost-effective limit based on differences in points. Additionally, MADRS-S and BDI-II present only a snapshot of depression symptoms. Depression-free days (DFDs) (105) is a measure that

simultaneously captures treatment outcome and estimates the patient's experience of depression over time. DFDs are calculated by using linear interpolation to estimate daily depression severity across assessment points. In this manner, each day in the follow-up period is assigned a depression level, and days without depression can be counted using diagnostic instruments such as MADRS-S. DFDs are understood by clinicians and decision makers and are used in several cost-effectiveness studies of depression intervention (106).

In cost-effectiveness analysis, *quality adjusted life years (QALYs)* is recommended as an outcome measure (107, 108). QALYs is a tool developed in the US and Canada during the late 1960s (109) to evaluate the cost-effectiveness of treatments. It is central to health-care decision making in many countries. QALYs measures a person's health state regarding both health related quality of life (HRQoL) and length of life. The EuroQol, five-dimension, three-level (EQ-5D-3L) self-assessment instrument (110) is one of the generic preference-based measures used to assess HRQoL. A person uses EQ-5D-3L to assess health status in five dimensions (mobility, self-care, ability to undertake usual activities, anxiety and depression), with three levels of health state (no problems, some problems, extreme problems) in each dimension (111). Responses to the EQ-5D-3L instrument can be inserted in the index scale based on the often-used *Dolan-tariff* (112) and be assigned QALY weights. QALY weights can vary between 1 (perfect health) and 0 (death) (25). The sum of QALY weight values over a period of time, such as a depression episode, is calculated as *the area under the curve* as illustrated in Figure 2.

Time perspective

It is important to choose an evaluation period that is long enough to capture all relevant consequences of the intervention. Clinical knowledge and prior studies can provide important input to this decision.

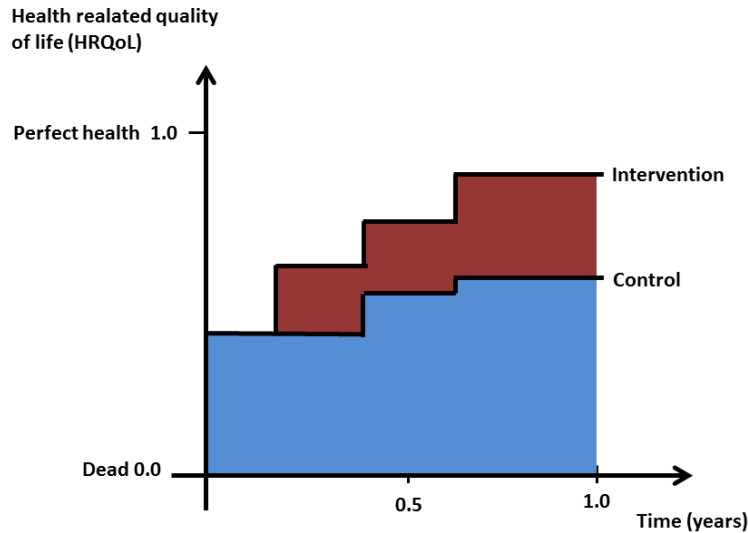


Figure 2. Example of QALY calculations. The two QALYs (control and intervention) are represented by the areas under the curves; blue area for the control and blue area plus brown area for the intervention. The brown area represents the difference in QALYs (Δ QALYs). By Anna Holst, 2018.

Comparison of alternatives – the ICER

In a cost-effectiveness analysis, costs and effects (health outcomes) of treatment options are compared to each other. The result is expressed as the *incremental cost-effectiveness ratio (ICER)* (25). The ICER is defined by the difference in cost (Δ cost) between two possible treatments (e.g. intervention vs control/TAU/CAU) divided by the difference in their effect (Δ effect) (see example in Figure 2 where Δ effect (Δ QALYs) is represented by the brown area) calculated as:

$$ICER = \frac{\Delta cost}{\Delta effect} = \frac{[Cost]_{intervention} - [Cost]_{control}}{([Health\ outcome]_{intervention} - [Health\ outcome]_{control})}$$

The ICER can be viewed as the price tag of a one unit increase in the health outcome measure (e.g. BDI-II score or QALYs). When prioritizing treatment

options, larger patient health gains may be achieved at a given budget if treatments with a lower ICER are recommended.

Visualization of cost-effectiveness – the cost-effectiveness plane

The *cost-effectiveness plane* (Figure 3) is used to visually represent the costs and effects of treatment options in two dimensions. Effects are plotted on the x axis and costs on the y axis (see ICER example V). The control/TAU/CAU is frequently plotted at the origin, so the x and y values represent incremental effects and incremental costs vs control/TAU/CAU.

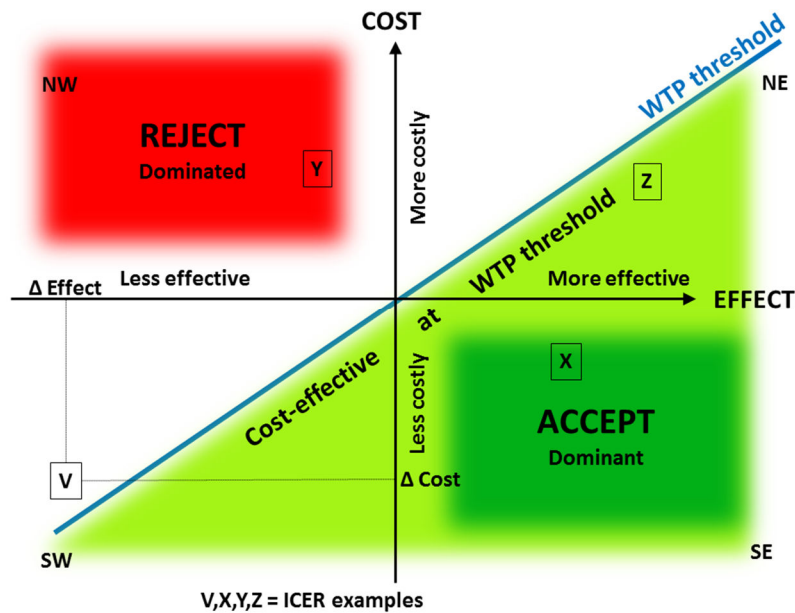


Figure 3. The cost-effectiveness plane. By Anna Holst, 2018.

SW=south-west, NW=north-west, NE=north-east, SE=south-east,

WTP=willingness to pay, ICER=incremental cost-effectiveness ratio

The cost-effectiveness plane is divided into four quadrants. Most cost-effectiveness analyses of new treatments show results in north-east (NE) quadrant (ICER example Z), meaning the new treatment generates more health but is also more expensive. Results in the south-east (SE) quadrant (ICER example X) should be accepted right away, as they are more effective and less costly. On the other hand, results in the north-west (NW) quadrant (ICER

example Y) should be rejected as they are both less effective and costlier. In the NE (ICER example Z) and the south-west (SW) (ICER example V) new treatment are assessed as cost-effective if below the willingness-to-pay (WTP) threshold (ICER example Z). The *WTP threshold* is defined as the decision makers' WTP for one health outcome unit, e.g. one QALY. The WTP threshold could be seen as a rule for determining whether an intervention should be implemented or not. WTP thresholds differ between countries and contexts. In Sweden there is no clearly defined WTP threshold, but National Board of Health and Welfare (Socialstyrelsen) have in some guidelines mentioned 500,000 SEK per QALY (113). Compare this with the UK NICE (National Institute for Health and Care Excellence) WTP of GBP 30,000 (347,000 SEK) per QALY (114).

Assessing uncertainty

The certainty of parameter estimates in data from trials is often too limited to enable a robust cost-effectiveness analysis. Sensitivity analysis of data should therefore be performed to quantify the level of confidence in the output of the analysis, in relation to uncertainty in the input data. Probabilistic sensitivity analysis (e.g. non-parametric bootstrapping) is often the method of choice when data are available on an individual level. This analysis is executed as a trial where random draws from input data are made, and the ICER is calculated from each draw. This is repeated many times (typically 1,000 to 10,000), resulting in a distribution of resampled ICERs that can be graphed as a cloud on a cost-effectiveness plane. It could also be presented on a cost-effectiveness acceptability curve illustrating the probability of an intervention being cost-effective for several WTP threshold values per health outcome unit (25).

Deterministic sensitivity analysis, or scenario analysis can be used to assess how cost-effectiveness would be affected by changes in relevant assumptions (e.g. different price levels of the ICBT programme).

The distribution of ICERs could be difficult to interpret if it spanned the dominant SE quadrant (lower costs and better health outcomes) and the dominated NW quadrant (higher costs and worse health outcomes). In that case it would be recommended to estimate the net monetary benefit instead (25).

Net monetary benefit

Net monetary benefit (NMB) translates the cost-effectiveness calculation into a linear expression and is calculated as: $V \times \Delta effect - \Delta cost$, where V is the WTP threshold value per health outcome unit (e.g. BDI-II score or QALY). If NMB is positive, the treatment is cost-effective; if the NMB is negative, the treatment is not cost-effective.

For example, imagine that the mean health gain of ICBT compared to TAU is 0.1 QALYs ($\Delta effect$) with an associated increase in costs of €1,000 ($\Delta cost$). Assume that the decision maker's WTP per QALY (V) is €30,000. In this situation, the ICER is $\text{€}1,000 / 0.1 = \text{€}10,000$, whereas the $NMB = (\text{€}30,000 \times 0.1) - \text{€}1,000 = \text{€}2,000$; in other words, it is positive. The conclusion is identical whether we look at the ICER or at the NMB – ICBT is cost-effective – because the ICER is below the decision maker's WTP per QALY and the NMB is positive. Conclusions based on the ICER and the NMB will always be identical, but the advantage of the NMB expression is that we do not confuse dominant with dominated outcomes and can therefore always calculate appropriate confidence intervals.

Probabilistic sensitivity analysis can also be used to assess the uncertainty of the NMB result as in the case of ICERs (115).

Aim

General aim

The aim of this thesis was to evaluate internet-based treatment and collaborative care organisation with a care manager in the primary care setting – examples of two implementations intended to raise the quality and quantity of treatment and care for patients with mild to moderate depression in Swedish primary care, from the perspectives of cost-effectiveness and patient and staff experiences.

Specific aims

I. To perform an economic evaluation of internet-mediated cognitive behavioural therapy (ICBT) compared to treatment as usual (TAU) as treatment for mild to moderate depression in the primary care setting, based on a pragmatic effectiveness trial performed in Swedish primary care. In particular, the objective was to assess the incremental cost-effectiveness ratio (ICER) of ICBT vs TAU at twelve-month follow-up, from health-care and societal perspectives.

II. To explore primary care patients' experiences of ICBT depression treatment.

III. To evaluate the cost-effectiveness of a care manager programme compared with care as usual (CAU) for treatment of mild to moderate depression in the Swedish primary care setting from health-care and a societal perspectives.

IV. To study primary health care clinicians' and directors' perceptions of implementing collaborative care with a care manager for patients with depression at the PCC. And secondly, to identify the barriers and facilitators, perceived by the personnel, influencing this implementation.



Figure 4. Word-cloud representing the most used words of the thesis. By Anna Holst, 2018.

Methods

Table 1. Summary of designs, materials and methods of the included studies.

	Design	Study group	Data collection	Data analysis
Paper I	Cost-effectiveness analysis alongside a pragmatic effectiveness trial	16 PCCs in Region Västra Götaland; 90 patients diagnosed with depression at the PCCs	Electronic patient records, patient research questionnaires (PRIM-NET), salary databases, drug pricing database	Cost-effectiveness analysis
Paper II	Qualitative cross-sectional study	13 patients having received ICBT for depression	Focus groups and semi-structured individual interviews	Systematic text condensation according to Malterud
Paper III	Cost-effectiveness analysis alongside a pragmatic cluster randomised controlled trial	23 PCCs in two regions of Sweden; 376 patients diagnosed with depression at PCCs	Electronic patient records, patient research questionnaires (PRIM-CARE), salary databases, drug pricing database	Cost-effectiveness analysis
Paper IV	Descriptive and qualitative cross-sectional study	36 strategically selected PCCs with care managers in Region Västra Götaland; 36 directors and 461 clinicians	Web-based questionnaires	Descriptive statistics and inductive manifest content analysis according to Graneheim et al.

The PRIM-NET study

The PRIM-NET study was a pragmatic effectiveness trial comparing ICBT to TAU as treatment for mild to moderate depression in Swedish primary care. It evaluated depressive symptoms, quality of life and sick-leave results in a three, six and twelve-month evaluation (116, 117).

The PRIM-NET study was conducted in the region of Västra Götaland (with about 1.6 million inhabitants) in 2010-2014. All the PCCs in the region, with a CBT psychotherapist on the team, were invited to participate in the study. Of those, sixteen PCCs (twelve urban and four rural, twelve publicly run and four privately) accepted, and were included. GPs and nurses at the PCCs were instructed to invite all patients aged eighteen years and older who had a probable diagnosis of mild to moderate depression to the study. Depression diagnosis was based on DSM-IV criteria and grading of depression was based on the MADRS-S score. Exclusion criteria were severe psychiatric disorder, suicidal ideation or anamnesis of suicidal attempt, cognitive disability, substance abuse or insufficient knowledge of the Swedish language (116, 117).

Included patients were randomised to ICBT or TAU. TAU patients received the treatment typically provided at the specific PCC. TAU could consist of visits to a GP, nurse, antidepressants, face-to-face psychotherapy, sick-leave certification or combinations thereof. Patients randomised to ICBT received access to a commercially available ICBT treatment program (Depressionshjälpen®) based on CBT techniques, consisting of seven modules accessible throughout the treatment period of twelve weeks. The modules were completely self-help. Contact with a psychotherapist was established once a week via secure email and concentrated on validating the patient, reinforcing progress and encouraging the patient to continue working in the programme. The ICBT patients could also receive components of TAU treatment, excepting non-ICBT psychotherapy (116, 117).

Paper I – Cost-effectiveness analysis of ICBT vs TAU

This study was conducted alongside the PRIM-NET pragmatic effectiveness trial (116, 117). Practice and participant recruitment is described above.

Health outcomes

Changes in health status were assessed in terms of QALYs and BDI-II scores. Data were available at baseline and at three, six and twelve months post-

baseline. QALYs were calculated based on EQ-5D-3L scores and the time spent in each health state, according to the Dolan tariff (112). Adjustments were made for differences in baseline EQ-5D-3L scores of the two groups (118). Statistical significance was set at $p < 0.05$.

Cost outcomes

Costs were identified and valued as follows:

Health care utilization. The amount of visits and phone-counselling events with GPs, nurses and psychotherapists were retrieved at the individual patient level from electronic patient records (EPR). Hourly wages were based on market prices from databases (119, 120).

Intervention. The costs of intervention included the ICBT software and the working hours of the psychotherapist. The cost of the ICBT software was defined as the market price of similar, commercially available programs.

Medication. Drug consumption was retrieved from EPR and patients' questionnaires. Drug costs were based on prices retrieved from the Dental and Pharmaceutical Benefits Agency (TLV) (121).

Productivity loss. The human capital approach (25) was used to measure and value the costs of productivity loss. Sick-leave data were patient-reported. Patients' hourly wages were calculated using individual income data from the Tax Directory 2013 and were multiplied by the total hours of sick leave to obtain a value for productivity loss.

Patient costs. Transportation time and transportation expenses were calculated using the postal codes of the PCCs and the patients' residential addresses.

Cost-effectiveness analysis

The economic evaluation was made from a health care – that is, the payer's – perspective, encompassing resource use of health care, intervention, and medication. From a societal perspective, it included the resource-use consequences of productivity loss and patient costs. No discounting was applied since all costs (and health outcomes) analysed were within a one-year period.

We estimated ICER and NMB for the cost-per-reduced score on the BDI-II scale and the cost per QALY at the twelve month follow-up. To assess uncertainty, deterministic sensitivity analyses were carried out using scenario analysis, (i.e. changing relevant assumptions in different analyses to assess how they affected cost-effectiveness). To assess sampling uncertainty, confidence intervals of the NMB were constructed using probabilistic sensitivity analysis (non-parametric bootstrapping with 1,000 bootstrap resamples) of the observed data (115). Data analysis was carried out in Microsoft Excel.

Paper II – Patients experiences of ICBT – qualitative analysis

Upon closing the PRIM-NET pragmatic effectiveness trial (116, 117) the ICBT patients were invited to participate in a focus group discussion about their experiences. Of the thirty-six contacted, seventeen were interested in participating and thirteen were included. We went through with one focus group of four patients and one of two (two cancelled immediately preceding the set appointment). Seven patients were individually interviewed. Data were collected by independent researchers who had not been involved in the patients' ICBT treatment. Time from end of treatment to interview varied between one and thirty-six months. A topic guide was developed for focus groups and interviews based on study objectives. An interview guide used in ICBT research at Linköping University was used as inspiration (122). A semi-structured interview guide (123) was developed for the individual interviews.

The focus group discussions were led by one moderator and one observer. Open-ended questions were used inviting the patients to talk about their own experiences of ICBT. Questions such as How would you describe ICBT? or, How did you perceive the Internet as a treatment context? or What did you experience at the end of your ICBT treatment? served to enrich and deepen data collection. Each meeting lasted no longer than 1.5 hours. All sessions were audiotaped and transcribed verbatim.

Data were analysed by systematic text condensation (STC) according to Malterud (124), as inspired by Giorgi's phenomenological approach (125), which is developing descriptions and concepts concerning ICBT experiences. STC was chosen because it aims to describe the experiences of informants, as they express them, rather than explore the possible underlying meaning of their statements. Before starting the analysis, the analysers identified their preconceptions about depression treatment and ICBT in order to bracket

previous ideas and knowledge. The process involved four steps: I. Reading all the material several times to obtain an overall impression. II. Identifying units of meaning, representing different aspects of the research question, and coding and sub-coding them. III. Condensing and summarising the contents of each of the coded groups. IV. Generalising descriptions and concepts reflecting the informants' most important experiences of ICBT. One of the focus group discussions was coded by two analysers separately to assure analysis quality, and the codes were set after thorough discussions between analysers. Analysis was data-driven, but in the last step the relevance of our findings was assessed by comparing them to existing studies (85, 126, 127).

The PRIM-CARE study

The first wave of implementation on collaborative care with a care manager (CCCM) was performed as a pragmatic cluster randomised controlled trial – PRIM-CARE – to obtain a thorough evaluation of CCCM in Swedish primary care. The RCT format was chosen to enable further adaptation of CCCM to patient and staff considerations and their perceptions of the organisational change. (See Figure 5.) The CCCM intervention was compared to CAU as a treatment in Swedish primary care for mild to moderate depression and evaluated depressive symptoms, quality of life and sick-leave results in a three, six and twelve-month evaluation (41).

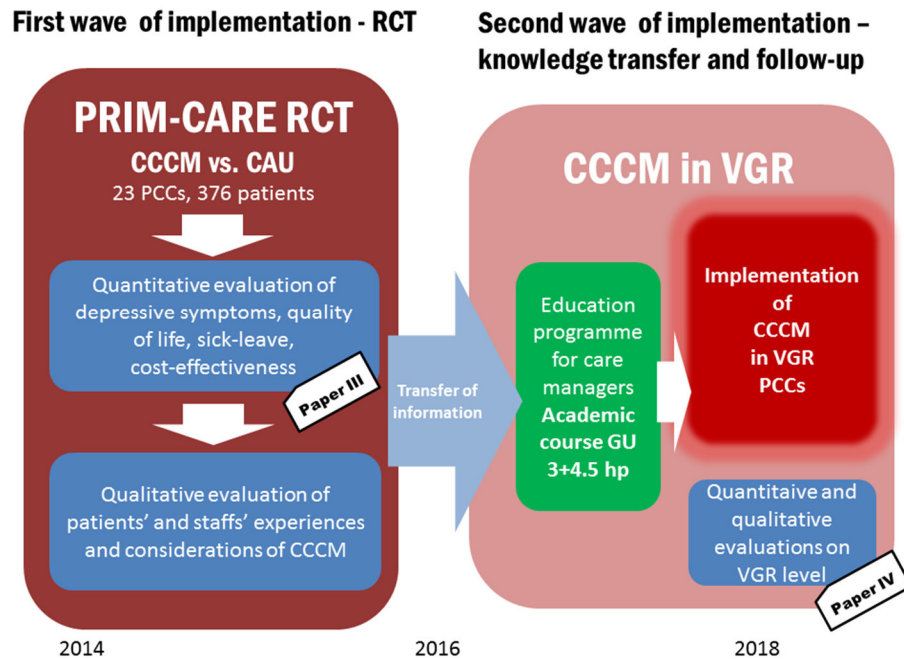


Figure 5. The two implementation waves of CCCM including the PRIM-CARE RCT in first wave. By Anna Holst, 2018. CAU, care as usual; CCCM, collaborative care with a care manager; GU, Gothenburg university; PCC, primary care centre; RCT, randomised controlled trial; VGR, Region Västra Götaland.

The PRIM-CARE study was conducted in Region Västra Götaland and Region Dalarna in 2014-2016. All the PCCs in Västra Götaland that did not have an on-site position comparable or equal to care manager were invited to participate in the implementation CCCM. In Västra Götaland, 160 PCCs expressed interest in participating in the implementation of a care manager and twenty-three urban and rural PCCs accepted to be included in the RCT as well. Four PCCs in Dalarna also were interested and included. Randomisation to CCCM or CAU was carried out at the PCC level.

The GPs and nurses at the PCCs were instructed to invite all patients aged eighteen years and older with a diagnosis of mild to moderate depression to the study. The depression diagnosis was based on ICD-10 and graded according to its MADRS-S score. Exclusion criteria were severe psychiatric disorder, suicidal ideation or anamnesis of suicidal attempt, cognitive disability, substance abuse or insufficient knowledge of the Swedish language (41).

PCCs randomised to CAU provided treatment – typically at the PCC – according to the Swedish National Guidelines for Depression and Anxiety Disorders, which recommend a stepped care model with easily accessible and continual care, short intervals between follow-up appointments, guided self-help, CBT, interpersonal therapy and/or antidepressants (71).

CCCM intervention PCCs each established a nurse as a care manager who used 20% – 25% of her/his working time to coordinate and manage the care and support of patients with depression. Before the study started, participating staff members were educated as to their tasks in the care manager programme (two days for GPs, five days for nurses/care managers and one day for PCC directors). Programme services for participating patients included an individual care plan (one hour session per patient with care manager), regular telephone contact between care manager and patients to assess self-rated depressive symptoms (at least six to eight times during the twelve-week intervention period) and the opportunity to contact the care manager at any point (unscheduled) if needed. Furthermore, care managers were in constant dialogue with GPs, psychotherapists and other health care personnel in following up patients. Thus, care managers did not perform any psychotherapeutic measures beyond behavioural activation; they were a supportive link between specialists and patients while improving accessibility and continuity of care, as well as treatment adherence. In addition, care managers had regular follow-up meetings (every second month) during the study, to discuss difficulties and successes with the research team and the region's implementation team (41).

Paper III – Cost-effectiveness analysis of collaborative care with a care manager vs CAU

The study was conducted alongside the PRIM-CARE RCT (41). Practice and participant recruitment is described above.

Health outcomes

Main health outcome measure were DFDs calculated from depressive symptoms expressed as change in MADRS-S, and QALYs based on EQ-5D-3L scores and the Dolan tariff (112). The number of DFDs was assessed by estimating the number of days each patient scored below 12 on the MADRS-S.

Cost outcomes

As in Paper I costs were estimated both from a health care perspective, considering health care costs, and from a societal perspective, which added productivity loss to health care costs. Costs were identified and valued as follows:

Health care utilization. The amount of visits and phone counselling events involving GPs, nurses and psychotherapists were retrieved at individual patient level from EPR and patient research interviews/questionnaires in PRIM-CARE. Health care costs included the costs of educating PCC personnel for the intervention group. Costs per health care contact and for staff education were calculated by means of time spent and gross wages (including social fees) of the respective professional groups (119).

Medication. Drug consumption was retrieved from EPR and patients' questionnaires. Drug costs were estimated based on prices retrieved from the Swedish Pharmaceutical Industry Association's Service (LIF) (128).

Productivity loss. The human capital approach (25) was used to measure and value the costs of productivity loss, which were calculated using EPR and patient-reported sick-leave data (percentagewise) during the follow-up period and the average gross wage (including social fees) of women in Sweden (since almost two-thirds of the study population were female).

Cost effectiveness analysis

The economic evaluation was made from both health-care and societal perspectives. No discounting was applied since all costs (and health outcomes) analysed occurred in less than one year.

The ICER was calculated as the ratio of differences in mean costs per patient and mean QALYs ($\Delta\text{Costs}/\Delta\text{QALYs}$) or mean DFDs per patient ($\Delta\text{Costs}/\Delta\text{DFD}$), respectively, between the intervention group and the CAU group at the six-month follow-up. Because the design was a cluster randomised study, the difference in effect and costs was analysed using a multi-level model of patients nested in the PCCs. Patients were included (342 of 376) if data were available for baseline and at least one follow-up assessment. Missing values at the three- or six- month follow-up were imputed from a linear regression analysis combining non-missing EQ-5D-3L data with individual characteristics (age, sex, education level, ethnicity, marital status) as predictors. Data analysis was carried out in Microsoft Excel and Stata v.15.

To assess sampling uncertainty non-parametric bootstrapping (25) was used to focus on the cost per QALY. ICERs for both health outcome measures were estimated based on 5,000 bootstrap resamples and summarised in a cost-effectiveness plane and a cost-effectiveness acceptability curve (CEAC). For the cost-effectiveness plane we showed confidence ellipses of the areas containing 95%, 75% and 50% of the bootstrapped ICERs, together with the point estimates from the main analysis. To eliminate the difficulty of interpreting negative ICERs, the net monetary benefit was estimated and used to construct the CEAC.

Paper IV – Director and clinician experiences of collaborative care with a care manager – descriptive and qualitative analysis

In July 2016 the second wave of implementation (see Figure 5.) was ongoing and 83 of the 200 PCCs operating in Region Västra Götaland had established a care manager for depression. A stepped strategic sampling of these 83 PCCs was made. The first division was geographical, the second was a subdivision into city/urban/rural and the third was subdivision into privately or publicly run PCCs in each area.

The study population were two groups of participants: clinicians (of any profession) and directors of the PCCs from the strategic sampling. The PCCs' care managers were not invited.

Two different questionnaires were used to capture experiences from the horizons of clinicians and directors, respectively. The questionnaires had been pilot tested.

The first part of both questionnaires consisted of questions about background characteristics. The statements in the second part were developed from questionnaires used in previous studies of the same context, evaluating the Swedish rehabilitation guarantee (129-131). Additional questions were related to the Consolidated Framework for Implementation Research (CFIR) guide (132, 133). The CFIR is an over-arching theoretical framework useful for implementation research. The CFIR includes 39 constructs known to be relevant for implementation organised into five domains: intervention, outer setting, inner setting, characteristics of individuals and process.

In the clinician questionnaire, the statements addressed factors potentiating care manager implementation as well as facilitators and barriers of cooperation with the care manager. Open-ended questions were included. In the director questionnaire, the statements addressed care manager implementation as well as facilitators and barriers of introducing the care manager position. The questionnaires were distributed to the participants by email (including several reminders) and data were gathered during two months in 2016.

Quantitative data were analysed in SPSS version 24.0. Descriptive statistics of the items, for directors and clinicians separately, were compiled for the following groups: I. The study population as a whole. II. The treating and administrative professionals (for the clinicians' result only). III. The staff working at small and large PCC units. IV. The staff working at city, urban and rural PCC units.

Qualitative analysis of the free text answers of the open-ended questions was made by inductive manifest content analysis according to Graneheim et al (134, 135). The process contained four steps: I. The free text in each question area was compiled separately for the PCC directors and the PCC clinicians. II. The material was read through several times, and with the objective in focus, meaning units were identified. III. The meaning units were compared to each other, abstracted and labelled with codes. IV. The codes were compared to each other based on differences and similarities and grouped into categories with subcategories representing similar meanings, which constituted the manifest content.

Data analysis was performed by one of the authors. For improved trustworthiness, the codes, categories and subcategories were discussed with the other members of the research team which represented different professions.

Ethical issues

Health care has a responsibility to maintain a balance between biomedical and humanistic approaches to health, illness and disease. Interventions of disputable benefit should be avoided. In reality, health care and society do not always live up to these central ethical principles, for example by – outside research environments – exposing individuals to non-evaluated interventions. The studies of this thesis have been conducted according to the Declaration of Helsinki. After being provided oral and written information about the studies prior to inclusion, participants signed written informed consent. They were informed that they at any time during the study could withdraw without reason and without consequences for future care. The participants were also assured that all information they provided would be handled confidentially. The researchers made an effort to be observant and respectful during the interviews. If a participant was in need of emotional support or healthcare, the researcher assisted with further guidance.

Papers I and II – PRIM-NET – Ethical approval was given by the Regional Ethical Review Board in Gothenburg, Sweden (Dnr 2010/696-09 and supplement 2014/T033-14).

Papers III and IV – PRIM-CARE – Ethical approval was given by the Regional Ethical Review Board in Gothenburg, Sweden (Dnr 2014/903-13 and supplements 2015/T963-15, 2015/T975-14, 2016/T403-15).



Tempellaukio kirkko, Helsinki

Photo: Chris Walton

Results

Paper I – Cost-effectiveness of ICBT vs TAU

The baseline characteristics of the 90 patients constituting the primary sample of PRIM-NET (117) are shown in Table 2. PRIM-NET was designed as an RCT in which all included patients were supposed to be randomised to TAU or ICBT. However, we had difficulties recruiting patients, because we only recruited those who were attending primary care with a new depression and also positive to ICBT. Therefore, eight patients randomised to TAU were transferred to the ICBT group at the end of the recruitment period to achieve a higher number ICBT-treated individuals at the twelve-month follow-up. That is, PRIM-NET could be categorised as an RCT only for the first three months of follow-up. For the twelve-month follow-up we categorised it as a controlled study without randomisation.

The ICBT and TAU-groups were closely comparable.



Better work outside than locked in a room

Photo: Nell's journey

Table 2. Baseline characteristics of the PRIM-NET patients.

	ICBT (n=52)	TAU (n=38)	p-value difference in means/propor- tions
Woman, n (%)	31 (60)	39 (75)	0.16
Age, mean (SD)	39 (13)	38 (10)	0.63
Living alone, n (%)	24 (46)	13 (38)	0.44
University level education, n (%)	19 (37)	9 (24)	0.19
High socioeconomic status,* n (%)	28 (65)	18 (60)	0.63
Employed, n (%)	38 (73)	29 (78)	0.59
On sick-leave during past year, n (%)	24 (46)	15 (39)	0.51
Income years (SEK), mean (SD)	290,885 (93,094)	268,496 (60,508)	0.20

*According to SEI (socioeconomic index). ICBT, internet-mediated cognitive behavioural therapy; TAU, treatment as usual; SEK, Swedish kronor (1 SEK~ €0.105).

For the cost-effectiveness analysis we only included patients with sufficient cost and outcome data which resulted in 40 ICBT patients and 33 TAU patients. In both the ICBT and the TAU groups, the excluded cases were relatively healthy patients with low levels of care consumption.

Health outcome

In both ICBT and TAU groups, the reduction of depressive symptoms was significant (117) with reduced BDI-II scores and increased EQ-5D-3L scores (see Table 3). The TAU group had slightly better results but the differences between the groups were not statistically significant.

The mean total QALYs was 0.74 for the ICBT group and 0.79 for TAU. We adjusted for the minimal difference in EQ-5D-3L scores at baseline (the ICBT group scored a little higher than the TAU group) with no statistical significance.

Table 3. Health outcomes. Means and 95% confidence intervals (in parentheses).

	BDI-II		EQ-5D-3L score	
	ICBT	TAU	ICBT	TAU
Baseline	24.38 (21.77;26.98)	25.66 (21.98;29.33)	0.66 (0.59;0.73)	0.61 (0.52;0.70)
12 months	10.97 (7.66;14.28)	11.83 (8.29;15.36)	0.79 (0.72;0.87)	0.81 (0.75;0.87)
Within-group change	-13.40 (-17.5;-10.5)	-13.83 (-17.90;-0.17)	0.13 (0.05;0.21)	0.19 (0.12;0.28)
Between-group change (ICBT-TAU)	-0.46 (-5.83;4.91)		-0.07 (-0.18;0.04)	
Total QALYs*	-	-	0.74 (0.75;0.84)	0.79 (0.70;0.78)

*Adjusted for baseline difference in the EQ-5D-3L score. No differences between ICBT and TAU were statistically significant. The within-group changes were statistically significant for both ICBT and TAU (for both BDI-II change and EQ-5D-3L score change). BDI-II, Beck depression inventory-II; EQ-5D-3L, EuroQol five-dimension; ICBT, internet-mediated cognitive behavioural therapy; TAU, treatment as usual; QALYs, quality-adjusted life years.

Cost outcome

A detailed overview of cost identification, valuation, and distribution is presented in Table 4. There were no statistically significant differences between the two groups concerning total health care costs, total non-health care costs or total societal costs per patient. No patients were referred to psychiatric care. All costs were expressed at the 2013 price level.

Table 4. Mean health care, non-health care and total costs during the twelve follow-up months.

Cost items	Cost/ unit (SEK)	ICBT n=40	TAU n=33	p- value
GP visits	333	782	1,098	0.15
Therapist, ICB support therapist and nurse	Varies	856	2,198	0.002
Phone counselling (15 min)	115	1,025	699	0.007
Medication (antidepressants+sedatives)	Varies	382	440	0.19
ICBT program	1,000	1,000	.	.
Mean health care cost per patient (SD)		4,044 (1,853)	4,434 (2,651)	0.73
Time cost (treatment + transportation)	Varies	1,598	1,421	0.39
Sick-leave	Varies	41,997	44,321	0.90
Transportation	Varies	39	167	0.001
Mean non-health care cost per patient (SD)		43,634 (77,394)	45,909 (85,951)	0.86
Mean total cost per patient (SD)		47,679 (77,641)	50,343 (87,176)	0.85

GP, general practitioner; ICBT, internet-mediated cognitive behavioural therapy; SEK, Swedish kronor (1 SEK ~€0.105). TAU, treatment as usual.

Cost-effectiveness

The main cost-effectiveness results are shown in Table 5. From a societal perspective (i.e. including all cost items), the cost per QALY with ICBT compared to TAU was 53,874 SEK, and the cost per reduced BDI-II score was 3,896 SEK.

As both the incremental cost and the incremental health outcome for ICBT vs TAU was negative (ICBT was less expensive and less beneficial) and thus ended up in the SW quadrant of the cost-effectiveness plane, the ICERs were positive (divided negative numbers give positive quota), which could be deceptively interpreted as ICBT being both more expensive and more effective (the NE quadrant of the cost-effectiveness plane) than TAU. However, in this case the result represented cost savings of 53,874 SEK per lost QALY and 3,896 SEK per increased BDI-II score.

From a health-care perspective, the results were relatively similar with savings per lost QALY of 5,371 SEK and a saving per increased BDI-II score at 388 SEK.

Table 5 also shows the results from the deterministic sensitivity analyses (scenario analyses). There is no substantial impact on the results, as the ICERs are all in the SW quadrant of savings per lost health, except for the scenario of no adjustment being made for the EQ-5D-3L difference at baseline. This result ends up in the dominant SE quadrant but, given its large variation, does not merit any further interpretation.



Buscando el sudeste

Photo: Fabian Kopetsckny

Table 5. Cost-effectiveness results of ICBT vs TAU. Costs per BDI-II point reduction and cost per QALY.

Scenario	Cost per QALY	Cost per BDI-II point
Main estimates (ICBT vs TAU)		
Societal perspective	53,874 SEK*	3,896 SEK*
Health care perspective	5,371 SEK*	388 SEK*
Sensitivity analyses (ICBT vs TAU from a societal perspective)		
With non-commercial ICBT program (i.e. freeware)	38,117 SEK*	2,756 SEK*
With multiple imputations for missing data	17,245 SEK*	1,247 SEK*
Without adjusting for baseline differences in health	118,753 SEK*	ICBT dominant

*Results indicate savings per lost QALY (BDI-II point) since ICBT was less expensive but also with less beneficial health outcomes. The 95% confidence interval was not defined because it included estimates in all four cost-effectiveness plane quadrants (and is thus not shown). Main estimates were based on QALYs and BDI-II changes adjusted for differences in baseline health status.

BDI-II, Beck depression inventory-II; ICBT, internet-mediated cognitive behavioural therapy; QALY, quality-adjusted life year; SEK, Swedish kronor (1 SEK ~€0.105). TAU, treatment as usual.

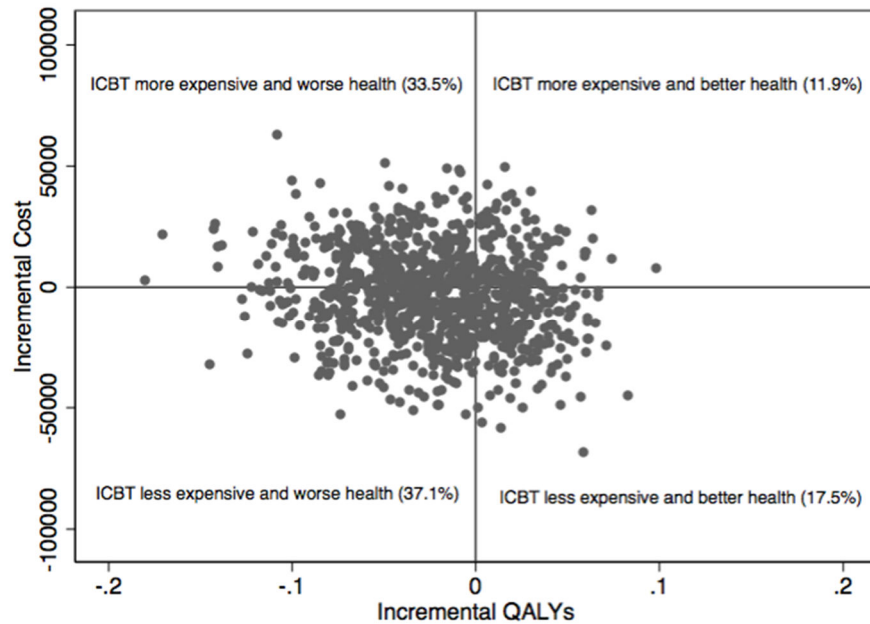


Figure 6. Cost-effectiveness plane of ICBT vs TAU based on 1,000 bootstrap replications.
 The percentage number in each quadrant identifies the proportion of replications obtained in the respective quadrant.
 ICBT, internet-mediated cognitive behavioural therapy; QALY, quality-adjusted life year.

Reproduced with permission from BMJ Open: Holst A, Björkelund C, Metsini A, Madsen JH, Hange D, Petersson EL, Eriksson MC, Kivi M, Andersson PA, Svensson M. Cost-effectiveness analysis of internet-mediated cognitive behavioural therapy for depression in the primary care setting: results based on a controlled trial. *BMJ Open* 2018;8(6):e019716.

The 1,000 bootstrapped ICER replications were scattered throughout all four quadrants of the cost-effectiveness plane (33.5% in the NW (dominated), 17.5% in the SE, 11.9% in the NE and 37.1% in the SW (dominant)) indicating uncertainty. See Figure 6.

Therefore NMB was calculated for a range of assumed WTP threshold values per QALY together with a 95% confidence interval (CI). The 95% CI, irrespective of the value per QALY, included both positive and negative NMB estimates showing no clear results. See Figure 7.

To sum up, we could show no evidence that ICBT was more or less cost-effective than TAU, because costs, health outcomes and cost-effectiveness were similar for ICBT and TAU, from health care and societal perspectives.

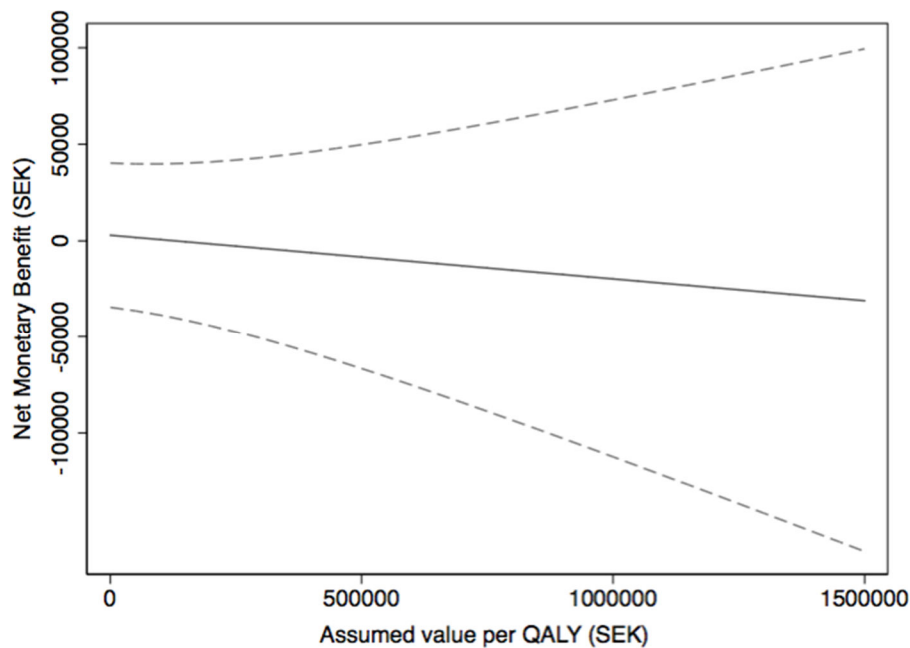


Figure 7. Net Monetary Benefit (NMB) of ICBT vs TAU with 95% confidence intervals.

Note: The NMB is shown for a range of assumed values for the willingness to pay per QALY (0 to 1.5 million SEK).

QALY, quality-adjusted life year; SEK, Swedish kronor (1 SEK ~€0.105). TAU, treatment as usual.

Reproduced with permission from BMJ Open: Holst A, Björkelund C, Metsini A, Madsen JH, Hange D, Petersson EL, Eriksson MC, Kivi M, Andersson PA, Svensson M. Cost-effectiveness analysis of internet-mediated cognitive behavioural therapy for depression in the primary care setting: results based on a controlled trial. *BMJ Open* 2018;8(6):e019716.

Paper II – Patient experiences of ICBT

Thirteen patients that received ICBT in PRIM-NET participated in the study. The sample was considered to be acceptably diversified in age, educational level and gender. However, a primary prerequisite for inclusion in the PRIM-NET trial was that the patient be positive to ICBT. Additional criteria excluded patients without sufficient knowledge of the Swedish language or computer skills. As the patients were asked to describe their experiences of ICBT, it was not entirely clear whether their experiences reflected the internet- or the CBT-part of ICBT. We conducted one focus group discussion with four patients and one with two patients. The latter was planned to include four patients but two of them cancelled right before the set appointment. However, the two remaining were eloquent and supported each other in sharing their experiences

freely and richly. Seven patients were individually interviewed. Detailed data on the patients are presented in Table 6.

Table 6. Characteristics of the study subjects.

Patient	Gender	Age	F/I*	Working status	Education
1	F	27	I	employed	secondary school
2	M	40	I	employed	university
3	F	42	I	employed	university
4	F	47	I	employed	university
5	M	58	I	employed	university
6	M	30	I	-	secondary school
7	F	28	I	employed	secondary school
8	F	43	F	employed	university
9	M	45	F	employed	secondary school
10	M	37	F	employed	university
11	M	37	F	employed	university
12	F	68	F	other	-
13	F	31	F	employed	primary school

*F,Focus group; I,individual interview

The patients were generous about sharing their experiences. Some described a need for face-to-face meetings with a psychotherapist and valued the check-ups and the support during the ICBT process. Some felt left alone in the treatment while others felt well and secure. The possibility of privacy and freedom with smoothly working technology was valued, but there was also a lack of confidence and a feeling of risk. The findings are presented as a word-cloud representing the most used words of the interviews (Figure 8), descriptions and concepts illustrated with selected quotations.



Figure 8. Word-cloud representing the most used words of the interviews. By Anna Holst, 2018.

Privacy and well-functioning technology

Most patients did not want it to be obvious that they suffered from – and got treated for – depression, as they were ashamed. They needed time alone at home to be able to do the ICBT, and that could be difficult to obtain. Others were open about their condition, and some even completed the ICBT during working hours. Most considered the Internet to be safe regarding their integrity. Most patients had some kind of technical problem with either the hardware or software. For others the technology worked smoothly, and this was important because depression involves low tolerance for adversity.

‘It was a bit difficult in practical terms, in that I did not want the whole world to know that I was on ICBT for depression.’

With freedom comes responsibility

ICBT was perceived as accessible and effective. The ICBT program was easy to access from their personal computer and they could choose when, to which extent and where to do the ICBT, such as at moments of alertness or outdoors. Some experienced difficulties finding suitable conditions to do the ICBT considering the location of the computer. Many experienced freedom and relaxation about not having scheduled appointments. Many patients felt stressed by the ICBT requiring too much from them. The perceived responsibility was too heavy for the progress of the treatment. Maintaining discipline could be difficult, and it was sometimes easier to avoid than to tackle the tasks. Some thought the tempo was too high to allow adaption to the new knowledge. On the other hand, some perceived the self-responsibility stimulating, since it signified the ability to influence one’s own health. The ICBT was experienced as meaningful and as an easy way to get into a better mood.

‘It felt like it was very, very smart to have it on the Internet. It is fast; it is easily accessible. You can get immediate help just when you feel like it. Just turn on the computer and go into the different exercises.’

‘I had a hard time, those days I felt bad, getting myself to sit at the computer and start.’

Inter-process feedback

The regular contact with the psychotherapist was considered positive. The impaired ability caused by the depression meant that they needed someone pushing them to continue the ICBT treatment. Some considered the contacts stressful and felt guilty or controlled upon being contacted.

'I got a bad conscience because I felt I betrayed her when I did not do what she asked me to do.'

Some patients perceived the contacts with the psychotherapist as an opportunity for venting and support; some felt they covered only technical problems and practical issues. Sometimes the contact was too sporadic and came to nothing as time passed. Most patients would have appreciated a more comprehensive introduction to – and evaluation during – the ICBT. They also wanted continuity during the process and a closing meeting.

'I had a therapist who called me and checked how I had proceeded and pushed me a bit and said, Come on, go through this chapter by tomorrow. I'll call you back then. I needed someone to push me because I had a problem sitting down and getting things done, pursuing things...'

Does it work without the face-to-face meeting?

Some patients appreciated ICBT and would have felt uncomfortable talking to a stranger in an unfamiliar place. They thought that writing down thoughts by the computer was a good alternative to a personal relationship. However, most informants missed the regular contact with a psychotherapist. They would have preferred to have the opportunity to speak out and dwell on experiences with someone listening.

'You can easily fool your computer. You get no eye contact, no body contact, you get no pat on the back.'

Many wished for real-time interaction with the psychotherapist for instant feedback and thus a possibility to make progress. Patients felt there was a large workload placed on the individual in ICBT treatment. Guidance and interpretation assistance were needed and a prerequisite for the treatment to work.

'Why do you do such a thing, replace the psychotherapist with software?'

Is ICBT a suitable treatment?

ICBT can be an effective treatment for the right patients. However, since determination is needed to pursue the ICBT process, ICBT is not suitable for deeply depressed patients. The patients need to feel confidence in the choice of ICBT. Some perceived ICBT as a superficial tool. Some felt offended by being offered ICBT, in that it had been a big step for them to seek health care, and when they finally did, they were offered a self-help treatment. The

perception of not being taken seriously led to low confidence in the ICBT. Some feared they might crash mentally on ICBT, without healthcare noticing.

'I think it may well have suited a great number of people, but not people like me, who dig down into their own thoughts and can't come out of it.'

'I strongly believe in this, and I definitely think this is a good option.'

'How dare they do this? They do not know how bad I feel. I could have thrown this book on the table and said, Damn health care, to hell with this!'

Paper III – Cost-effectiveness of collaborative care with a care manager vs CAU

The baseline characteristics of the 376 patients constituting the primary sample of PRIM-CARE (41) are shown in Table 7. There were no statistically significant differences between the groups.

Data on HRQoL and depression scores were available for 342 patients at baseline and at least one follow-up assessment. Analysing the 34 patients that dropped out just after randomisation showed that the only significant predictor was age (increasing in age by one year increased probability of missing by 0.4%). Analysis of cost-effectiveness was based on this sample.

Health outcome

The CCCM group had better health outcome at the six-month follow-up than the CAU group in terms of both QALYs (0.357 vs 0.333) and DFDs (79.43 vs 61.14). Both differences reached statistical significance ($p < 0.001$).

Cost outcome

A detailed overview of identification, valuation, and distribution of costs is presented in Table 8. All costs are expressed at the 2016 price level. No patients were referred to psychiatric care during the 6 months observation time in the intervention or in the control group.

Table 7. Baseline characteristics of the PRIM-CARE patients.

	CCCM n = 192	CAU n = 184	Total n = 376
Age, mean (SD)	40.8 (15.0)	41.6 (15.4)	41.2 (15.2)
Gender, n(%)			
Women	131 (68.2)	137 (74.5)	268 (71.3)
Men	61 (31.8)	47 (25.5)	108 (28.7)
Occupation, n(%)			
Working	137 (72.9)	122 (66.3)	259 (69.6)
Studying	18 (9.6)	19 (10.3)	37 (9.9)
In search of work/other	23 (17.6)	43 (23.4)	76 (20.5)
Working, n(%)			
Full-time	157 (87.7)	149 (87.6)	306 (87.7)
Other (25%-75%)	22 (12.3)	21 (12.4)	43 (12.3)
Marital status, n(%)			
Cohabiting	122 (67)	122 (68)	244 (67)
Single	61 (33)	58 (32)	119 (33)
Born outside of Nordic country, n(%)	18 (9.4)	21 (11.5)	39 (10.4)
Educational level, n(%)			
Primary education	17 (8.9)	27 (14.8)	44 (11.8)
Secondary education	103 (53.9)	90 (49.2)	193 (51.9)
University	71 (37.2)	66 (36.1)	137 (36.6)
Sick-leave at baseline, n(%)	93 (50.5)	94 (55.0)	187 (52.7)
MADRS-S m(SD)	20.8 (7.2)	21.9 (7.1)	21.4 (7.1)
BDI-II m(SD)	23.9 (8.7)	25.1 (8.5)	24.5 (8.7)
EQ-5D m(SD)	0.58 (0.24)	0.56 (0.25)	0.57 (0.24)

BDI-II, Beck Depression Inventory II; CAU, care as usual; CCCM, collaborative care with a care manager; EQ-5D, EuroQoL five-dimension; MADRS-S, Montgomery-Åsberg Depression Rating Scale-Self rating version

Table 8. Cost items, volumes used, costs per unit and average cost per patient.

Cost item	Volume		Cost/unit (SEK)		Cost/patient (SEK)	
	CCCM	CAU	CCCM	CAU	CCCM	CAU
Education physicians (per physician)	11	-	7,747.00	-	443.84	-
Education nurses (per nurse)	11	-	8,287.00	-	474.78	-
Nurse contacts (face to face)	384	203	103.59	103.59	207.18	114.28
Physician contacts (face to face)	447	413	363.14	363.14	845.44	815.09
Psychologist contacts (face to face)	370	421	262.97	262.97	506.77	601.69
Physiotherapist contacts (face to face)	29	79	145.23	145.23	21.94	62.36
Nurse contacts (phone)	1513	417	51.79	51.79	408.15	117.38
Physician contacts (phone)	298	284	121.05	121.05	187.87	186.83
Psychologist contacts (phone)	39	41	60.69	60.69	12.33	13.52
Medication	-	-	-	-	566.05	552.62
Total health care costs	-	-	-	-	3,674	2,464
Sick-leave (days)	5,756	7,076	1,824	1,824	58,500	71,241
Total costs	-	-	-	-	62,174	73,705

CCCM, collaborative care with a care manager; CAU, care as usual; SEK, Swedish kronor (1 SEK~ €0.1).

The distribution of health care costs was rather similar among groups. The greatest share of healthcare costs was related to contacts with healthcare professionals in both groups. Obvious differences were observed in visits to and phone contacts with the nurse (depending on the nature of the intervention) and education costs, which were likewise only related to the care manager programme. The difference in mean costs between the two groups was not statistically significant.

Cost-effectiveness

The main cost-effectiveness results are shown in Table 9. From a societal perspective, CCCM dominated CAU (SE quadrant), in that it produced larger health benefits at a lower cost. From a health care perspective, the cost per QALY was 67,731 SEK and the cost per depression free day was 71 SEK (NE quadrant).

Table 9. Cost-effectiveness results of CCCM vs CAU. Costs per QALY and DFD.

Incremental cost-effectiveness ratios	cost-effectiveness
Cost per QALY: Societal perspective	Care manager is dominant
Cost per QALY: Health care perspective	67,731 SEK
Cost per DFD: Societal perspective	Care manager is dominant
Cost per DFD: Health care perspective	71 SEK

CCCM, collaborative care with a care manager; CAU, care as usual; QALY, quality-adjusted life year; DFD, depression-free day; SEK, Swedish kronor (1 SEK~ €0.1).

Most of the bootstrapped ICERs ended up in the SE quadrant of the cost-effectiveness plane (dominant), indicating that CCCM is likely to be more effective and less costly than CAU. From a health care perspective, most ICERs were in the NE quadrant, indicating that CCCM increases costs but improves health. See Figure 9.

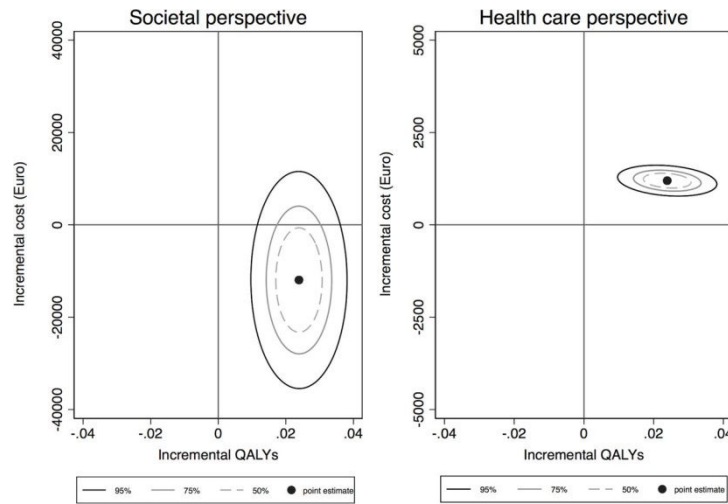


Figure 9. Cost-effectiveness planes with confidence ellipses. Left graph: societal perspective, right graph: health-care perspective. CAU, care as usual; QALYs, quality-adjusted life years.

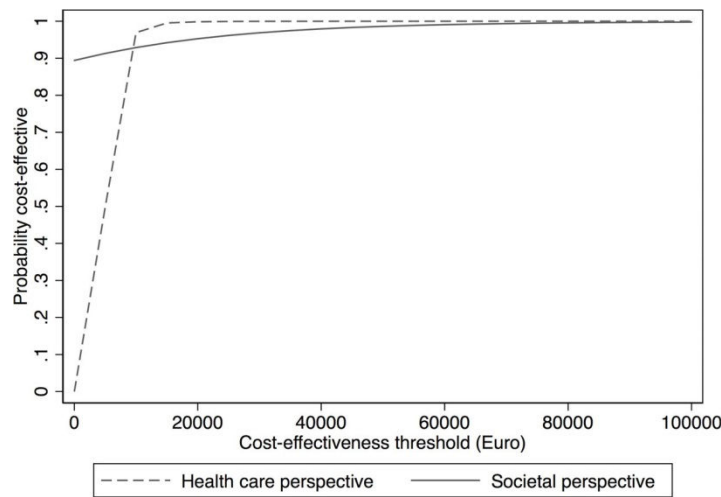


Figure 10. Cost-effectiveness acceptability curves for various willingness-to-pay thresholds for one quality-adjusted life year gained based on health-care and societal perspectives.

Figure 8 and 9 reproduced with permission from BMJ Open: Holst A, Ginter A, Björkelund C, Hange D, Petersson EL, Svenningsson I, Westman J, André M, Wikberg C, Wallin L, Möller C, Svensson M. Cost-effectiveness of a care manager collaborative care programme for patients with depression in primary care: economic evaluation of a pragmatic randomised controlled study. *BMJ Open* 2018;8:e024741.

The probability of CCCM being cost-effective for several WTP threshold values per QALY is shown in Figure 10. At a WTP threshold value of €10,000 (100,000 SEK) per QALY, there was a 93% probability of CCCM being cost-effective from a societal perspective and a 97% probability from a health care perspective (higher as a result of less variability).

To sum up, CCCM was highly cost-effective compared to CAU, particularly from the societal perspective, but also from a health care perspective.

Paper IV – Director and clinician experiences of collaborative care with a care manager

Of 83 PCCs with established care manager, 39 were included based on strategic sampling. Three declined participation. The remaining 36 PCCs employed 937 clinicians and 36 directors, all of which were sent an email containing a questionnaire and information.

Of a total of 784 clinicians, 465 consented to participation by submitting the questionnaire, and four were excluded, as they were no longer employed at the included PCCs. Finally, a total of 461 clinicians (59%) were included in the analysis.

The email to directors reached 36 directors, and all of them consented to participation by submitting the questionnaire, yielding a total of 36 directors included in the analysis (100%).

For both groups (clinicians and directors), 50% of the respondents were in the age range of 31-50 years, 86% were female and 70%-75% had a public employer. The most common profession was nurse followed by physician. The most common PCC size was >24 employees and the most common geographical location was urban.

Quantitative results

Clinician perceptions of the care manager implementation

Of the clinicians, around 10% were not at all familiar with the care manager's assignments and responded 'no opinion' to the other items of the questionnaire in 70%-95% of the cases. Most of them were administrative staff rather than care providers.

Fifty-two per cent of clinicians had the opportunity to cooperate with the care manager without problems. The majority were doubtful (neither agreed nor disagreed) whether they had received information about the care manager's assignment and 40% judged their knowledge of it as insufficient. However, 56% perceived that work routines for the care manager existed at their PCC. Approximately half of the clinicians reported their patients being generally positive to the care manager's efforts. Around two thirds thought that collaborating with the care manager was part of their duty as PCC staff.

Clinician perceptions of barriers and facilitating factors in cooperating with the care manager.

Forty per cent of the respondents prioritised working with the care manager. Around half of them perceived that the assignment of the care manager corresponded to the aims of the PCC, 42% perceived support from colleagues and 51% perceived support from their directors in collaborating with the care manager. Around 50% did not perceive conflicts with existing routines or uncertainties in the assignment of the care manager, and ~40% did not perceive any unclear division of responsibilities between the respondent as a clinician and the care manager. Most of the respondents had been informed about the care manager.

Most respondents reported that they were used to working with new methods and only ~10% perceived that it was difficult to make use of the care management.

PCC director perceptions of the care manager implementation

Almost 90% of the PCC directors considered that the assignment of the care manager had been clearly designed, ~70% considered the priority of the implementation to be high, and ~90% were positive to the implementation. More than half of the directors – more often at smaller than at larger PCCs – had reorganised in conjunction with the care manager implementation. Clinicians' attitudes to the implementation were rated as positive by most

directors, but the proportion of positive ratings was greater at small and urban PCCs than at large, city or rural PCCs.

In cases not mentioned above, the results showed no clear differences in terms of type of profession, size or geographical location of the PCC.

Qualitative results

Thirty-six directors and 135 clinicians answered the open-ended questions. The answering clinicians' professions were in the majority physician or nurse. Overall, the responses were short and concise, and as the responses from the directors and the clinicians did not differ in any essential way, they were analysed together in one group. The analysis resulted in the following categories:

Organisational changes – resourceful well-ordered caring

The implementation of a care manager was perceived positively by PCC directors and clinicians especially at PCCs lacking resources in the psychosocial area. The implementation had resulted in a clear organisation for patients with mental illness, and the directors experienced results of improved utilization of the PCCs resources. Organisational changes made at the PCCs to implement a care manager, such as forming psychosocial teams, provided opportunities to raise important issues and increased the interest in patients with mental illness. However, at PCCs with good access to psychosocial resources, the perception was that a care manager did not add anything further.

The size of the PCC could facilitate or hinder the possibility of getting in touch with the care manager. At smaller PCCs, the contact was facilitated by patients having easy access to the care manager. The implementation of a care manager, with its structured approach and designated time together with frequent and active contacts with the patients, led to new routines with early assessment resulting in improved patient flow. According to the clinicians, the care manager provided support in the medical follow-ups of patients. As a consequence, clinicians perceived themselves to be less isolated when giving care, and the patients received closer follow-ups.

Barriers – the art of finding the time in a tight work situation

It took time for the role of the care manager to be incorporated at the PCC, leaving the clinicians with a feeling of insufficient knowledge about the care manager function. Some concerns were raised that the high workload, lack of time for cooperation or the care manager being absent from the PCC could lead to the care manager position not being used as intended. This could result in

the care manager falling from awareness. Many concurrent demands and tasks at the PCC affected the ability to implement the care manager position.

Facilitators – soft values and structured roll-out

For collaborative care with a care manager to work, a good collaborative climate among the director and the clinicians at the PCC was crucial, and it was important to have a positive attitude towards new challenges. Personal characteristics of the care manager were valued as important, such as a willingness to interact with the other clinicians at the PCC, and an explicit interest in mental health.

The directors stated that financial compensation was crucial to be able to allocate resources for the implementation of the care manager. Directors also valued participating in part of the academic education of the care manager as the course was helpful towards implementation. The support from the implementation team was also valued.



It's all about the location

Photo: Ken Mattison

Discussion

Major findings

The PRIM-NET trial compared ICBT to TAU, and the PRIM-CARE trial compared CCCM to CAU as treatment and care for mild to moderate depression in Swedish primary care. Cost-effectiveness and how the intervention was experienced by patients and health care staff are important perspectives in the effectiveness approach, which should shed light on as many important aspects as possible, to increase the likelihood of creating value in the complex system of the real world (24).

ICBT is an acceptable and feasible treatment for depression

Our results suggested that ICBT is an acceptable alternative for treating depression from the perspectives of patient experience and cost-effectiveness. No firm conclusions could be drawn from our results as to whether ICBT or TAU was the most cost-effective use of health-care and societal resources. There was a great deal of uncertainty, as illustrated by the ICERs scattered over all the four quadrants of the cost-effectiveness plane. The mean cost per patient in our sample was modestly lower for ICBT than for TAU both from health care and societal perspectives, but the differences were not statistically significant. Even though the TAU group on average spent more on health care personnel resources, the cost of the ICBT software was significant. The largest cost in both groups was productivity loss related to sick leave. The health benefits measured as QALYs and reduction in BDI-II score were comparable for ICBT and TAU. Patient experience of ICBT pointed in the same direction, as the findings described ICBT as a good alternative to common depression treatment; however, the patients presented diverse experiences. Some patients appreciated the possibility of getting treatment without having to repeatedly meet with health personnel in real time, but many patients expressed a need for face-to-face contact with a psychotherapist and valued real-time interaction, human contact, guidance and dialogue. Many patients felt that healthcare placed a heavy responsibility on their shoulders by sending them away with ICBT, and some expressed indignation at being treated as one in a pile of depressed patients. However, all of the patients appreciated the freedom of being able to work with ICBT anytime, anywhere and to an extent they chose. This freedom may be a great advantage considering that most patients with depression are working and need the possibility of choosing when to have

treatment so as not to affect their work. They also stressed the importance of easily used and highly functioning technology.

Collaborative care with a care manager is an effective way of giving care for depression

CCCM was shown to be an effective way of providing care for depression from the perspectives of cost-effectiveness and PCC directors' and clinicians' experiences. The health benefits were significantly greater statistically in CCCM than CAU in terms of QALYs and DFDs. The mean health care cost per patient was modestly higher for CCCM than for CAU which was explained by the nature of the care manager programme. The mean total cost per patient was higher in CAU but with no statistical significance. From a societal perspective CCCM dominated CAU in that CCCM was both cheaper and more beneficial. From a health care perspective CCCM was cost-effective already at a modest willingness to pay per QALY (97% likelihood of cost-effectiveness at a WTP per QALY of 100,000 SEK).

The findings of the PCC directors' and clinicians' experiences of implementing and working within CCCM pointed in the same direction. We divided the results by size and geographical location of the PCC, but in most of the areas studied there were no important differences between the groups. Most of the clinicians reported that they had routines for the work in CCCM at their PCC and that they had support from colleagues and directors. The PCC directors were generally positive to the implementation of CCCM and rated their clinicians' attitudes towards the implementation as positive, to a greater extent at small and urban PCCs, than at large, city or rural PCCs. Most PCCs had reorganised working routines and educated existing staff in conjunction with the implementation. Regarding successful implementation the directors highlighted the overall positive attitudes of clinicians interacting with the care manager, and that CCCM be enhanced by guidelines and education. Important facilitators for the implementation of – and collaboration within – CCCM were support from colleagues and directors, cooperative skills and positive attitudes of clinicians. Barriers were high workload, shortage of staff and extensive requirements and demands from the health care organisation.

PRIM-CARE is one of the reports on implementing a care manager for depression treatment in primary care, in which the formation of collaborative care is generated *within* the primary care context and at the PCC, with the care manager as one of the ordinary personnel and working together with the PCC team (136).

General discussion

Differences in study design and health-care systems, including aspects such as professional roles, resources, access to health care or organisational levels of care, limited the comparison of patient and staff experience as well as costs, benefits and cost-effectiveness studies.

Cost-effectiveness of CCCM och ICBT

The evaluation of interventions that can facilitate the implementation of evidence-based care for patients with depression in primary care is of great importance, as there are identified knowledge gaps in this area (59, 75). It is crucial to assess the cost-effectiveness of an intervention, because societal and health care resources are limited, and decision makers need thorough documentation to be able to prioritise between the different options.

To assess the costs and benefits that are relevant to identify and measure in a study, clinical experts with knowledge of the medical conditions and resources that may be involved should cooperate with health economists who can identify what constitutes real resource consumption and what does not (e.g. transfers of resources from one point to another within the same system should not be characterized as costs). In both of our cost-effectiveness studies (Papers I and III) experts on both health economics and the regular clinics of primary care collaborated closely.

Several studies have suggested that ICBT is a cost-effective treatment option for depression (76-79), but until now (Paper I), no ICBT cost-effectiveness study had been conducted in the Swedish primary care context. McCrone et al. found that ICBT was more effective than TAU in UK primary care at a minimal additional cost and that reductions in levels of sick leave were greater in ICBT than TAU, but that study was not restricted to patients with depression (76). In the REEACT trial, also conducted in UK primary care, the cost-effectiveness analysis suggested that none of the ICBT programs studied were cost-effective compared with usual GP care alone (80). However, comparisons with our results should be made with caution, as study design, follow-up and methodology differ.

The cost-effectiveness study of CCCM was the first such study conducted in the Swedish primary care context (Paper III), and our results were in line with the majority of existing literature (92, 94, 97) showing CCCM to be cost-effective. The systematic review of Gilbody et al. showed that the majority of

the included economic evaluations from the US found positive health effects as well as increased health care costs associated with the intervention. ICERs were located in the NE quadrant of the cost-effectiveness plane, indicating that the intervention was more effective and more costly than CAU. However, none of the reviewed studies had included societal costs. Gilbody et al. noted that a societal perspective is more meaningful to policy makers and that there is evidence of collaborative care programmes having positive effects on sick leave (98). In our study, 70% of the population were in the work force, indicating that a societal perspective was of high relevance for this study. A recent systematic review showed CCCM being dominant, meaning that intervention was more effective and less costly. However, only five out of nineteen studies had used a societal perspective (137), making direct comparisons impossible. More recent evaluations have accounted for societal costs and are therefore more suitable for comparison. Aragonès et al. found in Spain that the collaborative care programme INDI was cost-effective. Nonetheless, the small differences in sick-leave days between the study groups kept the total costs in the intervention group higher than in the control group. This located the ICER in the NE quadrant of the cost-effectiveness plane (138). The results of a German study were similar to ours in that the total costs of the control group exceeded the total costs of the intervention group, when societal costs were included. However, our results were more favourable for CCCM mainly because of lower costs in nearly all cost categories. Effects regarding QALYs were almost identical to our study (139). Both of the studies identified, as we did, societal costs as the largest share of total costs.

Productivity loss may be underestimated

Productivity loss is the largest societal cost for depression (76), and *absenteeism* (i.e. sick leave) is the most common outcome measure. People with depression usually go to work, but their condition can substantially reduce their performance. This is known as *presenteeism* (140). Eighty-one per cent of the costs of lost productivity could be explained by reduced performance while at work during depression according to Stewart et al. (140). Most studies do not take into account presenteeism; thus, the costs of productivity loss during depression may be far higher than is commonly estimated and small improvements in depressive symptoms may have a great bearing on those costs. In future studies of the cost-effectiveness of treatments of depression, presenteeism would be an important factor to take into account.

Age and personality traits may matter, and depressive symptoms certainly do

In our study (Paper II), some patients experienced ICBT a heavy responsibility for their own recovery, and they could not maintain the discipline needed to carry out the treatment. Depression is known to affect motivation and executive abilities (68), which may partially explain these experiences. Wilhelmsen et al. showed that patient motivation to persist in ICBT is crucial to its completion and that motivation is closely linked to a feeling of relatedness which is enhanced by a social relationship with the therapist, suggesting that face-to-face support during ICBT is preferred (141). The age range in our study was 27 - 68 years. In one study, depressed elderly patients were suggested to be unsuitable for ICBT as they might lack skills to use web-based resources and computers (142). However, Karyotaki et al. showed that elderly people were more likely to respond to ICBT than younger ones (70). Many patients perceived themselves as too ill to benefit from ICBT, even though none had a more severe degree of depression than moderate according to MADRS-S (43). Patients also expressed a feeling that, in ICBT, they were left unguarded by health care compared to those treated by face-to-face therapy and that this could be hazardous for deeply depressed patients. However, a recent meta-analysis of self-guided ICBT showed that ICBT patients were less likely to deteriorate than the control group, and that ICBT cannot be judged as harmful (143).

Personality traits of the patients were not investigated in our ICBT studies (Papers I and II). A study by Bendelin et al. of advertisement-recruited patients' experiences of ICBT showed that ICBT was perceived in different ways depending on personality traits. Patients with a practical hands-on approach were more positive towards ICBT than those with more of an uncertain and doubtful personality (122). However, this phenomenon has been observed even in face-to-face CBT. Further studies of ICBT for depression could benefit from analysing potential differences in effect, costs and experiences for different personality profiles or other differences that may exist between groups of individuals. For CCCM a focus group study of patient experiences is under way.

The need for a helping hand

Since depression is known to affect executive abilities and tolerance for adversities, the need is great for support and guidance – in the health-care system and in treatment – as are the well-known factors of continuity and

accessibility. In our study (Paper II) feedback and help from the therapist during ICBT was appreciated by the patients, particularly as support and a push when needed, but as they had only met the therapist once at the start of the treatment, they perceived the feedback as not deep and personal enough. To make patients feel secure and not left alone seems to be important (144). Care managers, in a recent study of their experiences of CCCM felt they constituted a safety net for patients by following and supporting them. This increased continuity and accessibility to primary care for patients with depression (145).

Cyberspace and hardware considerations

Some patients believed that the feedback process in our ICBT study (Paper II) would have been more helpful in a real time chat- design rather than email; the immediate response seemed important. This ICBT mode has been successfully tested (126), but requires as much therapist time as face-to-face therapy. Well-functioning and accessible technology seems to be crucial, and both hardware and software options could be developed to make ICBT even more feasible. Bargh et al. (146) found that some people feel more able to express their true selves on the Internet than in face-to-face interaction. In our results we found few such opinions, but some patients valued getting treatment without talking to a person they were not familiar with. The opportunity ICBT offers of getting treatment in privacy, and the freedom of being able to choose a time and place for treatment, was stressed as positive. No one worried about online integrity.

Blending care

There is evidence that blending care, combining ICBT with face-to-face psychotherapist support, is more effective than ICBT without face-to-face support in community and secondary care (72, 83). In our study, many patients suggested that ICBT be a part of a therapeutic intervention. Some suggested that if CBT was initiated by face-to-face meetings to develop a relationship, ICBT treatment would be made more effective by the patient feeling more secure and individually treated. In line with this, psychotherapists of the PRIM-NET trial considered ICBT as a good treatment that should be introduced to primary care. Several adaptations of ICBT were suggested to optimise the procedure in primary care settings. Integrating and blending ICBT and face-to-face therapies, for example, would render primary care psychology more efficient (82).

Facilitators for implementing CCCM

Our results from studying clinician and director experiences of CCCM implementation (Paper IV) are in broad agreement with previous studies (94, 95, 97, 100-103). The care manager being on site at the PCC is seen as an asset facilitating collaboration with remaining staff (97, 100). Our and other studies highlight the importance of ensuring that the person employed for the care manager role is dedicated, and that the right training and support is supplied. Important facilitators are also the soft values of care managers and other staff; values such as cooperative skills and positive attitudes to the challenge (100, 101). In the present study, no respondent highlighted the well-known benefit of a standardised systematic clinical pathway, which the care manager intervention represents (41, 95, 100). In one review it was concluded that implementation requires a buy in from commissioners to ensure financial barriers are removed and that allowing sufficient training for staff is essential both at the planning stage and in the long term (100).

Barriers to implementing CCCM

Our results of time constraints and high workload being critical factors when implementing collaborative care are in agreement with other studies (101, 103). However, neither the barriers nor the facilitators identified are unique to collaborative care. A focus group study with care managers (145) showed that they perceived their function as helping to provide continuity – a main task of primary health care – and this enabled them to follow and support patients with depression and to maintain close contact during the illness. To provide a care manager from outside the ordinary PCC team as a collaborative care implementation, as described in a recent publication, does not seem to be as effective as CCCM in terms of constancy (103).

The CCCM study (Papers III and IV) indicates that the implementation of CCCM for depression in primary care was partly successful. Still, important factors remain concerning information sharing, knowledge about care management, and financial, organisational, administrative and professional structures. All these factors must be continually attended to, both at the PCC and the regional management levels.

Methodological considerations – strengths and limitations

Paper I

The design of the PRIM-NET study was a strength. It is generally acknowledged that pragmatic effectiveness studies are the most informative for economic and cost-effectiveness conclusions (25). A major strength was that the patients were exclusively primary care patients. Additionally, patients with somatic co-morbidity were not excluded, making the study population representative of primary care patients, who often suffer from mental and somatic co-morbidity. Another strength was the diversity of age and gender within the included population; there was a higher proportion of men in the study population than in previous studies. Thoroughly scrutinised EPR for care consumption throughout the entire period of follow-up provided legitimacy of health-care cost outcomes. Average standard costs are listed for several posts, such as GP visits. However, these are not only marginal costs but also rental and overhead costs. We considered it was more accurate to calculate actual costs, because we had the possibility of thorough data collection of care consumption.

We assessed cost-effectiveness for the period of twelve months from baseline. This captured most of the relevant consequences of the intervention. Discounting was not needed, as the time period did not exceed one year.

Absenteeism and sick leave

To get as complete data on absenteeism (140) as possible is central in cost-effectiveness analyses of depression interventions, because productivity loss from absenteeism constitutes the largest part of societal costs. Due to the trial exclusion criteria, patients with high risk of secondary care needs were not included, and consequently no costs for hospital care were generated. Our data on absenteeism were collected by patient reports of days on sick leave, with no consideration given to part- or full time, which was a weakness. However, returning to work following an absence, seems to be a more important improvement than to progress from part-time to full-time work. Complete data collection of sick leave events is a major challenge since there is no solid method. Firstly, a patient report of sick leave is the most accurate data collection method as patients can be absent from work without informing health care or the Social Insurance Agency (Försäkringskassan); however this is insecure given the human tendency to not remember actual circumstances. Secondly, data from the Social Insurance Agency, the authority that is notified of sickness (apart from the patient's employer), is not complete, because the two first weeks of sick pay are paid by the employer. Thirdly, the EPR of today

are not designed for data collection, so the EPR of every single patient needs to be explored to get sickness data.

The lack of sick-leave data for some patients was a weakness. However, missing sick-leave data occurred in both ICBT and TAU populations and the difference in mean sick-leave costs between the two groups was small and possibly random. However, a sensitivity analysis was made of a scenario using multiple imputations for missing sick-leave data. The ICER was affected minutely and did not change the interpretation.

The journey from RCT to controlled trial

A major limitation was that, at the end of inclusion to the PRIM-NET trial, the randomisation process was hampered as follows. PRIM-NET was designed as an RCT in which all included patients were randomised to TAU or ICBT. However, there were difficulties in recruiting patients, as only patients attending primary care with a new depression and positive attitudes towards ICBT were recruited. Other studies with these difficulties have used advertisement or Internet recruitment, yet been unable to reach the calculated power (147). Therefore, eight patients randomised to TAU were transferred to the ICBT group at the end of the recruitment period to obtain a higher number of ICBT-treated individuals at the twelve-month follow-up. That is, PRIM-NET can be categorised as an RCT only for the first three months of follow-up. At the twelve-month follow-up we categorised it as a controlled study without randomisation.

Paper II

A key strength of this study was – as in Papers I, III and IV – that the patients were exclusively primary care patients. Only a few similar studies been conducted (126, 127), which is astounding considering the amount of studies on the clinical effectiveness of ICBT in similar contexts. This study is also one of few reporting negative consequences of ICBT (88).

The study sample

All ICBT patients from PRIM-NET (n=52) were invited to the study, and seventeen patients initially agreed to participate. The ones who did not, gave lack of time as their reason. Gradually four persons withdrew and, finally, thirteen patients were included. There was thus no strategic sampling procedure which may be a limitation. In all research it is up to the individual to participate or not, and this may cause bias. However, STC does not claim its

results as being generalizable, but rather exploratory (124). The number of patients was considered sufficient and the included patients were acceptably diversified in age and gender, enabling a broad description of ICBT experiences. There was relative homogeneity with regard to cultural background; informants were with one exception native Swedes. Also, for some of the patients, quite a lot of time had passed between their treatment and this study. To sum up, our results cannot be regarded as generalizable for all people receiving ICBT, or even for all participants in the PRIM-NET study.

Focus groups and interviews

A strength was that moderators and interviewers had different occupations (GP, occupational therapist and nurse), creating wide analytic space, which increased the validity of the results. Additionally, none of the moderators/interviewers had in any way been part of the patients' ICBT treatment. Data were collected in neutral surroundings. The patients were very informative, had clear views of their experiences of ICBT, and presented them openly. Our impression was that they expressed themselves honestly and did not try to meet any expectations. One of the focus groups contained only two patients, which generally is too few to create a wide discussion, but since these two patients were very eloquent and helped each other to remember their experiences, the discussion became very informative.

Analysing in cooperation

Three of the authors cooperated in the analysis seeking to adhere strictly to the guidelines of the STC research method. Preconceptions were identified to the extent possible before conducting the focus groups, interviews and analysis. However, the risk of researcher bias, that is, a bracketing deficit affecting the results, could not be totally eliminated.

Psychotherapist continuity

Most patients had wished for a more comprehensive introduction to the ICBT from the psychotherapist; they lacked evaluation during ICBT and a closing meeting. Continuity was stressed by most informants as a very important factor. Circumstances of geography and lack of time meant that some patients were diagnosed and included in the PRIM-NET study by an external psychotherapist who was not the same one guiding the patients in their ICBT. This was a weakness, as it may have biased the results of these patients' treatment effects as well as their experiences. However, the aim in standard ICBT is to maintain psychotherapist continuity.

Paper III

This study has several strengths. Firstly, it is highly relevant both on a national health-care level and a societal level, as mental health problems today constitute a growing part of health-care costs, especially at the primary care level. Secondly, patient, care-consumption and sick-leave data obtained by examining EPR, in addition to patient and health-care personnel reports, were extensive. Thirdly, participation rates were robust for both PCCs (urban and rural scattered over the region with 10% of all PCCs participating) and patients (acceptably diversified in age and gender). The latter may partly have been a result of the support from the study group, which had thorough experience of primary care and accomplishing primary care clinical trials. Fourthly, we used both health-care costs as well as societal costs for our analyses, as societal costs widely exceed health-care costs in the form of sick-leave costs. Fifthly, randomisation was done at the PCC level instead of the patient level, because the intervention was supposed to imply a change in the PCC working system. This would have made it inappropriate to randomise at the patient level.

Last but not least, we used robust and accepted methods of health economic analyses and modelling. Discounting did not have to be done as the time period was less than one year. The results of this trial could consequently be generalizable to and representative of Swedish primary care.

What will happen around the corner?

The short follow-up time of six months was a limitation. Health economic consequences of health-care consumption, health status and sick leave should preferably be assessed over a longer time perspective. However, we feel most of the relevant consequences of the intervention are covered within the first six months, mainly because the intervention lasted for only three months. A long-term analysis of CCCM will be conducted shortly, as data from the twelve-month follow-up become available. It is likely that CCCM would be even more cost-effective with a longer follow-up time, considering that improved health was maintained at six months.

Absenteeism and sick leave

As mentioned in the method discussion section of Paper I, it is central to get as complete data as possible on absenteeism in cost-effectiveness analyses of depression interventions, as productivity loss from absenteeism constitutes the largest part of societal costs. However, there is no solid method for this. In PRIM-CARE, our data on absenteeism were collected by patient reports of part-time and full-time sick days. We also collected data on sick days from EPR to assure the quality of patient reported data. This was a strength

compared to the method used in the PRIM-NET study. However, presenteeism was not assessed (140). Due to the trial exclusion criteria, patients with high risk of secondary care needs were not included, and consequently no costs for hospital care were generated.

Paper IV

The strengths of this study are several. Firstly, a major strength is that at baseline, a collaborative care organisation with a care manager was implemented at 83 PCCs making it possible to apply a strategic sampling of PCCs by geographical location, funding and PCC size. Secondly, when we conducted the study the implementation of care managers at the PCCs had been going on for at least a year, and the organisational changes had had time to adapt to the individual PCC and its staff. Thirdly, the use of previously used items in the questionnaires (129-131) was a strength. Fourthly, the participation rate of the clinicians was acceptable and outstanding for PCC directors. The opportunity of open answering may have facilitated addressing both important research questions concerning implementation as well as capturing the real world. This resulted in a broad understanding of the implementation process. However, some of the open answers were short and sometimes difficult to interpret.

The questionnaires

Another limitation would be the lack of validated questionnaires in this research area. However, most of the items in the clinician questionnaire were tested for reliability. The other items in the questionnaires were previously used (129-131). A weakness was that the open-ended questions were limited and the answers short. A focus group study with physicians will be presented in a separate publication (manuscript under preparation).

No patients were included in the present study; however, patients' experiences were studied and will be presented in another publication (manuscript submitted).

Implications for healthcare

The high incidence of depression makes it important to evaluate and implement new evidence-based effective forms of treatment and care. Despite the high quality of medical and psychotherapeutic competence in Swedish primary care, cornerstones such as accessibility, coordination and continuity are not sufficient to meet the needs of patients with depression and anxiety. New forms of treatment and care should be evaluated not only in follow-ups, but also upstream or parallel to implementation, since interventions of disputable benefit should be avoided in observance of basic ethical principles. Studies on patient and staff experiences of interventions are scarce but very important from an effectiveness perspective. Both the PRIM-NET and PRIM-CARE trials are examples of pragmatic effectiveness research conducted in the real world, alongside implementation of ICBT and CCCM in Swedish primary health care. The knowledge gained from these studies is broad and representative and could preferably be used in decision making and prioritization in health care.

ICBT as safe and effective treatment for depression in primary care has been widely introduced in recent years as a solution to the problem of accessibility to psychotherapy. However, our results on cost-effectiveness and patient experiences highlights that TAU should not be replaced by ICBT; rather, both options should be available. Although there may be positive effects for society, the patient's preference must be ascertained in patient-centred consultation.

PRIM-CARE shows that CCCM is beneficial to patients and for the national economic system. However, the major benefits are obtained on a societal level, while the costs for increasing quality of care and effectiveness are generated on the (primary) health care level. If Swedish authorities decide on a nationwide implementation of CCCM the financing of the implementation should include transforming the societal health insurance gain to the primary health care level. Also, implementation would benefit from a bottom-up perspective so that the introduction and development of CCCM at the PCC includes the PCC team as a whole to secure sufficient knowledge and adaptation.

Conclusion

ICBT is a safe and effective treatment that seems to be an acceptable alternative to TAU for treating depression in Swedish primary care from the perspectives of the patient experience and cost-effectiveness. ICBT seems to be as cost-effective as TAU both from a health care and societal perspective. The largest cost is productivity loss related to sick leave. ICBT is an attractive alternative in primary care to some patients with depression, but not to all. The freedom of being able to work with ICBT anytime, anywhere and to a chosen extent is favourable but the responsibility placed on the patient in ICBT is considerable. Ease of use and smoothly functioning technology is crucial. Patients need different amounts of support from a psychotherapist. An individual treatment design seems to be preferred, and elements of ICBT could be included as a complement to face-to-face meetings. There is no evidence of ICBT or TAU being more advantageous than the other. This result is in line with the general practice idea that having a plethora of treatment options to choose between is a strength.

Collaborative care with a care manager is an effective way of providing care for depression in Swedish primary care from the perspectives of cost-effectiveness and PCC director and clinician experience. From a societal perspective, CCCM generates higher health benefits for the patient at lower costs compared to CAU. From a health care perspective, CCCM is cost-effective already at a modest WTP per QALY threshold. Both PCC clinicians and directors are generally positive to implementing and working in CCCM. Important facilitators are support from colleagues and directors, cooperative skills and positive clinician attitudes. Barriers are high workload, shortage of staff and extensive requirements and demands from the health care organisation. Guidelines and education are important. These results are of high relevance for decision makers on a national level.

Future perspectives

Our cost-effectiveness analysis of CCCM in PRIM-CARE was conducted at a six-month follow-up. Data from the twelve-month follow-up will be available and analysed from a cost-effectiveness perspective. Results on fidelity of the implementation as well as patient and GP experiences of CCCM will be published shortly.

In the future, effectiveness studies including cost questionnaires could be used to gather even more accurate data on productivity loss from absenteeism, and to estimate presenteeism. The societal costs of reduced daily functioning (e.g. less availability to support children and relatives) could also be assessed.

ICBT was perceived differently depending on personality. Further studies of ICBT for depression could benefit from analysing potential differences in effects, costs and experiences for different personality profiles or other differences between groups of individuals. Further studies on blending ICBT and other aspects of psychotherapeutic intervention for the most appropriate point of delivery in the depression episode according to the patient and the professional, would be valuable in this more person-centred model.

Further studies should investigate ICBT delivered via other forms of technology, such as tablet computers and smart phones. Psychotherapist support in chats or internet-mediated video calls is another development that could provide better outcomes and should be further investigated in the primary care setting.

Most important to keep in mind in future research is that study design and execution be based on the real world to create as much value as possible.

Acknowledgement

Jag vill tacka de *963 patienter och personal* som agerat studieobjekt i avhandlingens studier. Och alla de slitvargar *in the real world* som rekryterat patienter och samlat in data. Utan er – ingen forskning, ingen avhandling.

Cecilia Björkelund, min kära huvudhandledare och stora förebild. Tack för att du med själ och hjärta förädlar allmänmedicinen som handledare, forskare, opinionsbildare, lärare och kliniker. För att du för fram allmänläkarperspektivet överallt där det saknas. För att du tror på mig och för att du verkar ha lagt den där pensioneringen på hyllan så att vi kan fortsätta kampen för det rätta tillsammans.

Tack *Mikael Svensson* för att du räddade mig när jag höll på att sjunka i hälsoekonomins träsk, och med excellens och tålamod bytte träsket mot en spännande djungel. Tack övriga handledare: *Eva-Lisa Petersson*, min läromästare i kvalitativ metodik, *Dominique Hange*, *Jörgen Thorn* och inte minst *Jenny Kindblom* som inspirerade mig att börja forska och som alltid funnits där med strategiska råd, handfasta tips och varm omtanke. Tack medförfattare *Alexandra Metsini*, *Annika Ginter*, *Carl Wikberg*, *Christina Möller*, *Elisabeth Björk Brämberg*, *Jens-Henrik Madsen*, *Irene Svenningsson*, *Per-Åke Andersson*, *Pia Augustsson* och *Shabnam Nejati* för gott samarbete. Tack medarbetare på Enheten för allmänmedicin, GU. Tack Rehsam och Västra Götalandsregionen för ekonomiska bidrag till studierna.

Tack Nationella forskarskolan i allmänmedicin för fantastisk forskarutbildning: eldsjälar, lärare, grupp 6 och inte minst *Maria Boström*. Tack allmänläkar-vänner/-aktivister för styrka, inspiration och glädje i planeringen och genomförandet av ST-dagarna 2010 och Nordisk allmänmedicinsk kongress NCGP 2015: *Andy Maun*, *Bernd Sengpiel*, *Karin Asztely*, *Karolina Sandell*, *Malin Lagerberg*, *Niklas Lehtipalo*. *Cecilia*, igen.

Tack alla vänner och medarbetare på mitt andra hem Närhälsan Backa vårdcentral. Tack för att vi tillsammans, över stock och sten, håller den allmänmedicinska fanan stolt och högt, tack för värme, gemenskap, vilda fester och gapskratt. För att ni stått ut med en forsknings-frånvarande chef – aldrig en sur min – tack. Tack särskilt *Lisa Rogbrant*, min work-wife, och *Mats Olsson*, min work-husband.

Tack mina chefer och överordnade genom åren, som gett mig den frihet och bekräftelse som varit helt avgörande för min forskning: *Jane Nyman*, *Anna Larsson*, *Cathrine Thanner* och *Marie-Louise Gefvert*.

Tack *Barbro Edén* och mina vänner på SUs ST-utvecklingsprogram för den hjälp till utveckling som människa och ledare ni gav mig.

Tack vänner från studietiden på Medicinareberget, SU och Hvilla Medici. Tack särskilt mina "amigos para siempre" *Elisabeth Norder-Grusell* och *Lisa Ternström*. *Anna Öfverholm*, *Malin Andersson* och *Mia Skarström*, som också blev kollektivkamrater i "Lidköping kicking bitches" under AT-åren. Tack Chalmersvänner (VSH), sångarvänner (Espiro), seglarvänner (QB), lovsångs- och karriärvänner (KKfL), nyfikna vänner (DNS), nyårsvänner (SNOW) och alla övriga vänner.

Tack ni starka modiga kvinnor som kämpat för det rätta, ibland i tufft motstånd. Ni har banat väg och inspirerat. Jag vill, förutom dem som redan är nämnda, lyfta fram *Agnes Wold*, *Barbara Starfield*, *Iona Health*, *Karolina Widerström*, *Kirsten Persson*, *Linn Getz*, *Lisa Emelia Svensson*, *Marianne Olsson*, *Minna Johansson* och *Stina Åberg*.

Tack *mina föräldrar* för den plantskola i engagemang, patos, bildning, argumentationsteknik och retorik som våra dagliga hetsiga middagsbordsdebatter utgjorde. Tack för villkorslös kärlek, bekräftelse och ledning, och för er oupphörliga tilltro till mig och min förmåga. *Mamma Kerstin*: min stora inspiratör i rättframhet, drivkraft, jämställdhetskamp samt i att aldrig ge upp eller vara rädd för att ställa sig på barrikaderna. *Pappa Henrik*: min läromästare i helikopterperspektiv och strategiskt kreativt entreprenörskap. I vikten av nöjda kunder och rena bänkytor i köket. Jag är så ledsen att Alzheimer tog din hjärna så tidigt. Som nationalekonom och tidig förespråkare för telemedicin och nätverk hade du älskat detta.

Tack mina systrar *Lisa* och *Nina*, jag är bara en tredjedel utan er — då, nu och sen. Tack övriga fina släktingar och vänner. Och tack *mormor Ingeborg*, hos dig var min fristad.

Tack min älskade make *Peter*, och mina underbara, fantastiska söner *Hugo* och *August*. Ni är mitt allt.

Och till sist: tack *slumpen*. Tack för att jag fötts i ett land och i en tid som gett mig förutsättningar för att få utbilda mig till läkare, allmänläkare och forskare. För att jag får verka inom en grundad och rättvis välfärdssektor där vetenskap är en självklar bas. För att jag fritt får uttrycka min åsikt.

References

1. WHO. The Declaration of Alma Ata. Alma Ata; 1978.
2. Starfield B, Shi L, Macinko J. Contribution of primary care to health systems and health. *Milbank Q.* 2005;83(3):457-502.
3. Kringos DS, Boerma WG, Hutchinson A, van der Zee J, Groenewegen PP. The breadth of primary care: a systematic literature review of its core dimensions. *BMC Health Serv Res.* 2010;10:65.
4. Primary health care - main terminology. WHO. 2018. Accessed 2018 Oct 28. Available from: <http://www.euro.who.int/en/health-topics/Health-systems/primary-health-care/main-terminology>.
5. Starfield B. Primary care: concept, evaluation, and policy: Oxford University Press, USA; 1992.
6. Balint E. The possibilities of patient-centered medicine. *Br J Gen Pract.* 1969;17(82):269.
7. McWhinney I. The need for a transformed clinical method. *Communicating with medical patients.* 1989;9:25-40.
8. Baker A. Crossing the quality chasm: a new health system for the 21st century. *BMJ.* 2001;323(7322):1192.
9. Care AGSEPoPC, Brummel-Smith K, Butler D, Frieder M, Gibbs N, Henry M, et al. Person-centered care: A definition and essential elements. *J Am Geriatr Soc.* 2016;64(1):15-8.
10. McWhinney IR. Primary care: core values Core values in a changing world. *BMJ.* 1998;316(7147):1807-9.
11. Leopold N, Cooper J, Clancy C. Sustained partnership in primary care. *J Fam Pract.* 1996;42(2):129-37.
12. Maguire P, Pitceathly C. Key communication skills and how to acquire them. *BMJ.* 2002;325(7366):697-700.
13. Engström S. Quality, costs and the role of primary health care [dissertation]. Linköping: Linköping University; 2004.
14. Skarback S. Läkarna i gamla Göteborg [The doctors of ancient Gothenburg]. Göteborg: Tre Böcker Förlag AB; 1999.
15. Swartling P. Den svenska allmänmedicinens historia [The history of Swedish general medicine]. *Läkartidningen.* 2006;103:1950-3.
16. Socialstyrelsens föreskrifter och allmänna råd om läkarnas specialiseringstjänstgöring [Physician's specialist training]. Stockholm; 2015.
17. Schoen C, Osborn R, Doty MM, Squires D, Peugh J, Applebaum S. A survey of primary care physicians in eleven countries, 2009: perspectives on care, costs, and experiences. *Health Affairs.* 2009;28(6):w1171-w83.
18. Hälso-och sjukvårdslagen [The Swedish Health and Medical Services Act] SFS [Svensk författningssamling]. Stockholm; 1982.
19. Patientsäkerhetslagen [Patient Safety Act] SFS [Svensk författningssamling] (2010: 659). Stockholm; 2010.

20. Sweden's State Auditor. RiR 2014:22 Primärvårdens styrning - efter behov eller efterfrågan? [Primary care governance - according to need or demand?] Stockholm; 2014.
21. Anell A, Glengard AH, Merkur SM. Sweden: Health system review. Health systems in transition. 2012;14(5):1-159.
22. Act on System of Choice in the Public Sector [Lagen om valfrihetssystem, LOV] SFS [Svensk författningssamling] Stockholm; 2008.
23. OECD, European Observatory on Health Systems Policies. Sweden: Country Health Profile 2017. OECD Publishing; 2017.
24. Roy-Byrne PP, Sherbourne CD, Craske MG, Stein MB, Katon W, Sullivan G, et al. Moving treatment research from clinical trials to the real world. Psychiatr Serv. 2003;54(3):327-32.
25. Drummond M, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the economic evaluation of health care programmes. 4th ed. new York, United States: Oxford university press; 2015.
26. Van Lerberghe W. WHO, The world health report 2008: Primary health care: now more than ever. Geneva; 2008.
27. WHO. The World Health Report 2004. Geneva; 2004.
28. Greenhalgh T. WHO/WONCA report - Integrating Mental Health in Primary Care: A Global Perspective. London J Prim Care (Abingdon). 2009;2(1):81-2.
29. Olesen J, Gustavsson A, Svensson M, Wittchen HU, Jonsson B, group Cs, et al. The economic cost of brain disorders in Europe. Eur J Neurol. 2012;19(1):155-62.
30. Behandling av depressionssjukdomar. En systematisk litteraturoversikt. [Treatment of depression. A systematic review.]. Stockholm: Swedish Council on Technology Assessment in Health Care; 2004.
31. Nationell utvärdering 2013 - vård och insatser vid depression, ångest och schizofreni. Rekommendationer, bedömningar och sammanfattning. [National evaluation, 2013 - care and interventions for depression, anxiety and schizophrenia. Recommendations, estimates and summary]. Stockholm: Swedish National Board of Health and Welfare; 2013.
32. Bower P, Rowland N, Hardy R. The clinical effectiveness of counselling in primary care: a systematic review and meta-analysis. Psychol Med. 2003;33(2):203-15.
33. Nationella Riktlinjer för Vård vid Depression och Ångestsyndrom - stöd för styrning och ledning. [National Guidelines for Care in Cases of Depression and Anxiety Disorders]. Stockholm: Swedish National Board of Health and Welfare; 2016.
34. Maier W, Gänsicke M, Gater R, Rezaki M, Tiemens B, Urzúa RF. Gender differences in the prevalence of depression: a survey in primary care. J Affect Disord. 1999;53(3):241-52.

35. Pålsson SP, Östling S, Skoog I. The incidence of first-onset depression in a population followed from the age of 70 to 85. *Psychol Med.* 2001;31(7):1159-68.
36. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: WHO; 1992.
37. Diagnostic and statistical manual of mental disorders, 10th revision. Washington, DC, US: American Psychiatric Association; 2000.
38. Internationell statistisk klassifikation av sjukdomar och relaterade hälsoproblem (ICD-10-SE) [International statistic classification of diseases and related health problems – Swedish version]. Stockholm: Swedish National Board of Health and Welfare; 2010.
39. Kessler RC, Bromet EJ. The epidemiology of depression across cultures. *Annu Rev Public Health.* 2013;34:119-38.
40. Petersson EL, Wikberg C, Westman J, Ariai N, Nejati S, Bjorkelund C. Effects on work ability, job strain and quality of life of monitoring depression using a self-assessment instrument in recurrent general practitioner consultations: A randomized controlled study. *Work.* 2018;60(1):63-73.
41. Björkelund C, Svenningsson I, Hange D, Udo C, Petersson EL, Ariai N, et al. Clinical effectiveness of care managers in collaborative care for patients with depression in Swedish primary health care: a pragmatic cluster randomized controlled trial. *BMC Fam Pract.* 2018;19(1):28.
42. Sjukfrånvarons utveckling 2017. Försäkringskassan. [Development of sick-leave 2017. Social Insurance Agency]. Accessed 2018 nov 20. Available from: <https://www.forsakringskassan.se/wps/wcm/connect/1596d32b-7ff7-4811-8215-d90cb9c2f38d/socialforsakringsrapport-2017-13.pdf?MOD=AJPERES&CVID=>.
43. Svanborg P, Asberg M. A new self-rating scale for depression and anxiety states based on the Comprehensive Psychopathological Rating Scale. *Acta Psychiatr Scand.* 1994;89(1):21-8.
44. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16(9):606-13.
45. Beck AT, Steer RA, Brown GK. Beck depression inventory-II. San Antonio. 1996;78(2):490-8.
46. Wikberg C, Westman J, Petersson EL, Larsson ME, Andre M, Eggertsen R, et al. Use of a self-rating scale to monitor depression severity in recurrent GP consultations in primary care - does it really make a difference? A randomised controlled study. *BMC Fam Pract.* 2017;18(1):6.
47. Gilbody S, House A, Sheldon T. Screening and case finding instruments for depression. *Cochrane Database of Systematic Reviews.* 2005(4).
48. Wikberg C, Pettersson A, Westman J, Bjorkelund C, Petersson EL. Patients' perspectives on the use of the Montgomery-Asberg depression

- rating scale self-assessment version in primary care. *Scand J Prim Health Care*. 2016;34(4):434-42.
49. Wikberg C, Nejati S, Larsson ME, Petersson EL, Westman J, Ariai N, et al. Comparison Between the Montgomery-Asberg Depression Rating Scale-Self and the Beck Depression Inventory II in Primary Care. *Prim Care Companion CNS Disord*. 2015;17(3).
50. Wiles N, Thomas L, Abel A, Ridgway N, Turner N, Campbell J, et al. Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: results of the CoBaIT randomised controlled trial. *Lancet*. 2013;381(9864):375-84.
51. Priest RG, Vize C, Roberts A, Roberts M, Tylee A. Lay people's attitudes to treatment of depression: results of opinion poll for Defeat Depression Campaign just before its launch. *BMJ*. 1996;313(7061):858-9.
52. Solberg LI, Crain AL, Sperl-Hillen JM, Hroschikoski MC, Engebretson KI, O'Connor PJ. Effect of improved primary care access on quality of depression care. *The Ann Fam Med*. 2006;4(1):69-74.
53. Palmer W, Hemmings N, Rosen R, Keeble E, Williams S and Imison C. Improving access and continuity in general practice. UK: Nuffield Trust; 2018.
54. Malt UF, Robak OH, Madsbu H, Bakke O, Loeb M. The Norwegian naturalistic treatment study of depression in general practice (NORDEP)—I: randomised double blind study. *BMJ*. 1999;318(7192):1180-4.
55. Björkelund C, Maun A, Murante AM, Hoffmann K, De Maeseneer J, Farkas-Pall Z. Impact of continuity on quality of primary care: from the perspective of citizens' preferences and multimorbidity - position paper of the European Forum for Primary Care. *Qual Prim Care*. 2013;21(3):193-204.
56. de Graaf LE, Gerhards SA, Evers SM, Arntz A, Riper H, Severens JL, et al. Clinical and cost-effectiveness of computerised cognitive behavioural therapy for depression in primary care: design of a randomised trial. *BMC Public Health*. 2008;8:224.
57. Steinert C, Stadter K, Stark R, Leichsenring F. The Effects of Waiting for Treatment: A Meta-Analysis of Waitlist Control Groups in Randomized Controlled Trials for Social Anxiety Disorder. *Clin Psychol Psychother*. 2016.
58. Young KS. An empirical examination of client attitudes towards online counseling. *Cyberpsychol Behav*. 2005;8(2):172-7.
59. Implementeringsstöd för psykiatrisk evidens i primärvården. En systematisk litteraturoversikt. [Implementation support for the psychiatric evidence in primary care. A systematic review.]. Stockholm: Swedish Council on Health Technology Assessment; 2012.

60. Gilbody S, Whitty P, Grimshaw J, Thomas R. Educational and organizational interventions to improve the management of depression in primary care: a systematic review. *JAMA*. 2003;289(23):3145-51.
61. Andersson G. Using the Internet to provide cognitive behaviour therapy. *Behav Res Ther*. 2009;47(3):175-80.
62. Andersson G, Titov N. Advantages and limitations of Internet-based interventions for common mental disorders. *World Psychiatry*. 2014;13(1):4-11.
63. Cuijpers P, Donker T, van Straten A, Li J, Andersson G. Is guided self-help as effective as face-to-face psychotherapy for depression and anxiety disorders? A systematic review and meta-analysis of comparative outcome studies. *Psychol Med*. 2010;40(12):1943-57.
64. Arnberg FK, Linton SJ, Hulcrantz M, Heintz E, Jonsson U. Internet-delivered psychological treatments for mood and anxiety disorders: a systematic review of their efficacy, safety, and cost-effectiveness. *PLoS One*. 2014;9(5):e98118.
65. Hedman E, Ljotsson B, Lindefors N. Cognitive behavior therapy via the Internet: a systematic review of applications, clinical efficacy and cost-effectiveness. *Expert Rev Pharmacoecon Outcomes Res*. 2012;12(6):745-64.
66. Wagner B, Horn AB, Maercker A. Internet-based versus face-to-face cognitive-behavioral intervention for depression: a randomized controlled non-inferiority trial. *J Affect Disord*. 2014;152-154:113-21.
67. Andersson G, Hesser H, Hummerdal D, Bergman-Nordgren L, Carlbring P. A 3.5-year follow-up of Internet-delivered cognitive behavior therapy for major depression. *J Ment Health*. 2013;22(2):155-64.
68. Kessler D, Lewis G, Kaur S, Wiles N, King M, Weich S, et al. Therapist-delivered Internet psychotherapy for depression in primary care: a randomised controlled trial. *Lancet*. 2009;374(9690):628-34.
69. Proudfoot J, Ryden C, Everitt B, Shapiro DA, Goldberg D, Mann A, et al. Clinical efficacy of computerised cognitive-behavioural therapy for anxiety and depression in primary care: randomised controlled trial. *Br J Psychiatry*. 2004;185:46-54.
70. Karyotaki E, Ebert DD, Donkin L, Riper H, Twisk J, Burger S, et al. Does guided internet-based interventions result in clinically relevant changes for patients with depression? An individual participant data meta-analysis. *Clin Psychol Rev*. 2018.
71. Nationella riktlinjer för vård vid depression och ångestsyndrom 2010 - stöd för styrning och ledning [National guidelines for treatment of depression and anxiety 2010 - Support for governance and management]. Stockholm: Swedish National Board of Health and Welfare; 2010.
72. Richards D, Richardson T. Computer-based psychological treatments for depression: a systematic review and meta-analysis. *Clin Psychol Rev*. 2012;32(4):329-42.

73. Löbner M, Pabst A, Stein J, Dorow M, Matschinger H, Lupp M, et al. Computerized cognitive behavior therapy for patients with mild to moderately severe depression in primary care: a pragmatic cluster randomized controlled trial (@ktiv). *J Affect Disord.* 2018;238:317-326
74. Gilbody S, Littlewood E, Hewitt C, Brierley G, Tharmanathan P, Araya R, et al. Computerised cognitive behaviour therapy (cCBT) as treatment for depression in primary care (REEACT trial): large scale pragmatic randomised controlled trial. *BMJ.* 2015;351:h5627.
75. Internetförmad psykologisk behandling vid ångest- och förstämningssyndrom. [Internet mediated psychological treatment to anxiety and mood disorders] Stockholm: The Swedish Council of Technology Assessment in Health Care; 2013 [
76. McCrone P, Knapp M, Proudfoot J, Ryden C, Cavanagh K, Shapiro DA, et al. Cost-effectiveness of computerised cognitive-behavioural therapy for anxiety and depression in primary care: randomised controlled trial. *Br J Psychiatry.* 2004;185:55-62.
77. Warmerdam L, Smit F, van Straten A, Riper H, Cuijpers P. Cost-utility and cost-effectiveness of internet-based treatment for adults with depressive symptoms: randomized trial. *J Med Internet Res.* 2010;12(5):e53.
78. Titov N, Dear BF, Ali S, Zou JB, Lorian CN, Johnston L, et al. Clinical and cost-effectiveness of therapist-guided Internet-delivered cognitive behavior therapy for older adults with symptoms of depression: a randomized controlled trial. *Behav Ther.* 2015;46(2):193-205.
79. Geraedts AS, van Dongen JM, Kleiboer AM, Wiezer NM, van Mechelen W, Cuijpers P, et al. Economic Evaluation of a Web-Based Guided Self-Help Intervention for Employees With Depressive Symptoms: Results of a Randomized Controlled Trial. *J Occup Environ Med.* 2015;57(6):666-75.
80. Littlewood E, Duarte A, Hewitt C, Knowles S, Palmer S, Walker S, et al. A randomised controlled trial of computerised cognitive behaviour therapy for the treatment of depression in primary care: the Randomised Evaluation of the Effectiveness and Acceptability of Computerised Therapy (REEACT) trial. *Health Technol Assess.* 2015;19(101):viii, xxi-171.
81. Waller R, Gilbody S. Barriers to the uptake of computerized cognitive behavioural therapy: a systematic review of the quantitative and qualitative evidence. *Psychol Med.* 2009;39(5):705-12.
82. Kivi M, Eriksson MC, Hange D, Petersson E-L, Björkelund C, Johansson B. Experiences and attitudes of Primary Care Therapists' in the Implementation and Use of Internet-Based Treatment in Swedish Primary Care Settings. *Internet Interv.* 2015;2(3):248-56.
83. Johansson R, Sjöberg E, Sjögren M, Johnsson E, Carlbring P, Andersson T, et al. Tailored vs. standardized internet-based cognitive behavior therapy for depression and comorbid symptoms: a randomized controlled trial. *PLoS One.* 2012;7(5):e36905.

84. Khan N, Bower P, Rogers A. Guided self-help in primary care mental health: meta-synthesis of qualitative studies of patient experience. *Br J Psychiatry*. 2007;191:206-11.
85. Gerhards SA, Abma TA, Arntz A, de Graaf LE, Evers SM, Huibers MJ, et al. Improving adherence and effectiveness of computerised cognitive behavioural therapy without support for depression: a qualitative study on patient experiences. *J Affect Disord*. 2011;129(1-3):117-25.
86. Holländare F, Gustafsson SA, Berglind M, Grape F, Carlbring P, Andersson G, et al. Therapist behaviours in internet-based cognitive behaviour therapy (ICBT) for depressive symptoms. *Internet Interv*. 2016;3:1-7.
87. Svartvatten N, Segerlund M, Denhag I, Andersson G, Carlbring P. A content analysis of client e-mails in guided internet-based cognitive behavior therapy for depression. *Internet Interv*. 2015;2(2):121-7.
88. Rozental A, Boettcher J, Andersson G, Schmidt B, Carlbring P. Negative effects of internet interventions: a qualitative content analysis of patients' experiences with treatments delivered online. *Cogn Behav Ther*. 2015;44(3):223-36.
89. Cohen DJ, Davis M, Balasubramanian BA, Gunn R, Hall J, Peek C, et al. Integrating behavioral health and primary care: consulting, coordinating and collaborating among professionals. *Am Board Family Med*. 2015;28(Supplement 1):S21-S31.
90. Green LA, Cifuentes M. Advancing care together by integrating primary care and behavioral health. *Am Board Family Med*; 2015.
91. Wagner EH, Austin BT, Von Korff M. Organizing care for patients with chronic illness. *Milbank Q*. 1996;511-44.1.
92. Jacob V, Chattopadhyay SK, Sipe TA, Thota AB, Byard GJ, Chapman DP, et al. Economics of collaborative care for management of depressive disorders: a community guide systematic review. *Am J Prev Med*. 2012;42(5):539-49.
93. Taylor EF, Machta RM, Meyers DS, et al. Enhancing the primary care team to provide redesigned care: The roles of team facilitators and care managers. *Ann Fam Med* 2013;11:80-3.
94. Richards DA, Bower P, Chew-Graham C, Gask L, Lovell K, Cape J, et al. Clinical effectiveness and cost-effectiveness of collaborative care for depression in UK primary care (CADET): a cluster randomised controlled trial. *Health Technol Assess*. 2016;20(14):1-192.
95. Coventry P, Lovell K, Dickens C, Bower P, Chew-Graham C, McElvenny D, et al. Integrated primary care for patients with mental and physical multimorbidity: cluster randomised controlled trial of collaborative care for patients with depression comorbid with diabetes or cardiovascular disease. *BMJ*. 2015;350:h638.
96. Walshe K. Understanding what works—and why—in quality improvement: the need for theory-driven evaluation. *Int J Qual Health Care*. 2007;19(2):57-9.

97. Whitebird RR, Solberg LI, Jaeckels NA, Pietruszewski PB, Hadzic S, Unutzer J, et al. Effective Implementation of collaborative care for depression: what is needed? *Am J Manag Care*. 2014;20(9):699-707.
98. Gilbody S, Bower P, Whitty P. Costs and consequences of enhanced primary care for depression: systematic review of randomised economic evaluations. *Br J Psychiatry*. 2006;189:297-308.
99. Moise N, Shah RN, Essock S, Jones A, Carruthers J, Handley MA, et al. Sustainability of collaborative care management for depression in primary care settings with academic affiliations across New York State. *Implement Sci*. 2018;13(1):128.
100. Wood E, Ohlsen S, Ricketts T. What are the barriers and facilitators to implementing Collaborative Care for depression? A systematic review. *J Affect Disord*. 2017;214:26-43.
101. Overbeck G, Davidsen AS, Kousgaard MB. Enablers and barriers to implementing collaborative care for anxiety and depression: a systematic qualitative review. *Implement Sci*. 2016;11(1):165.
102. Holm AL, Severinsson E. Chronic care model for the management of depression: synthesis of barriers to, and facilitators of, success. *Int J Ment Health Nurs*. 2012;21(6):513-23.
103. Moller MCR, Mygind A, Bro F. Who needs collaborative care treatment? A qualitative study exploring attitudes towards and experiences with mental healthcare among general practitioners and care managers. *BMC Fam Pract*. 2018;19(1):78.
104. Johannesson M, Karlsson G. The friction cost method: a comment. *J Health Econ*. 1997;16(2):249-55.
105. Mallick R, Chen J, Entsuaeh AR, Schatzberg AF. Depression-free days as a summary measure of the temporal pattern of response and remission in the treatment of major depression: a comparison of venlafaxine, selective serotonin reuptake inhibitors, and placebo. *J Clin Psychiatry*. 2003;64(3):321-330.
106. Vannoy SD, Arean P, Unutzer J. Advantages of using estimated depression-free days for evaluating treatment efficacy. *Psychiatr Serv*. 2010;61(2):160-3.
107. Pharmacoeconomic guidelines around the world. Lawrenceville: International Society for Pharmacoeconomics and Outcomes Research; 2016.
108. Hälsoekonomiska utvärderingar. SBU. [Health economic evaluations. The Swedish Council of Technology Assessment in Health Care]. Accessed 2018 Nov 5. Available from: https://www.sbu.se/globalassets/ebm/metodbok/sbushandbok_kapitel11.pdf.
109. MacKillop E, Sheard S. Quantifying life: Understanding the history of Quality-Adjusted Life-Years (QALYs). *Soc Sci Med*. 2018;211:359-66.
110. User guide: Basic information on how to use EQ-5D: EuroQol Group; 2009. Accessed 2018 Nov 5. Available from:

www.euroqol.org/fileadmin/user_upload/Documenten/PDF/User_Guide_v2_March_2009.pdf.

111. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy: The EuroQol Group; 1990.

112. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997;35(11):1095-108.

113. Nationella riktlinjer för sjukdomsförebyggande metoder. Socialstyrelsen. 2011. [National guidelines for methods of preventing disease. Swedish National Board of Health and Welfare]. Accessed 2018 Nov 7. Available from:

<http://www.socialstyrelsen.se/nationellariktlinjerforsjukdomsforebyggandemetoder/Documents/nr-sjukdomsforebyggande-halsoekonomisktunderlag.pdf>.

114. Svensson M, Nilsson FO, Arnberg K. Reimbursement decisions for pharmaceuticals in Sweden: the impact of disease severity and cost effectiveness. Pharmacoeconomics. 2015;33(11):1229-36.

115. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves - facts, fallacies and frequently asked questions. Health Econ. 2004;13.

116. Kivi M, Eriksson MC, Hange D, Petersson EL, Vernmark K, Johansson B, et al. Internet-based therapy for mild to moderate depression in Swedish primary care: short term results from the PRIM-NET randomized controlled trial. Cogn Behav Ther. 2014;43(4):289-98.

117. Eriksson MC, Kivi M, Hange D, Petersson E-L, Ariai N, Häggblad P, Ågren H, Spak F, Lindblad U, Johansson B, Björkelund C. Long-term effects of internet cognitive behavioural therapy for depression in primary care – the PRIM-NET controlled trial. Scand J Prim Health Care. 2017;35(2):126-36

118. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health Econ. 2005;14(5):487-96.

119. Löner inom hälso- och sjukvård. SCB. 2017. [Salaries in Health Care. Statistics Sweden]. Accessed 2018 Nov 6. Available from: http://www.statistikdatabasen.scb.se/pxweb/sv/ssd/START_AM_AM0110_AM0110A/.

120. Lön. Läkarförbundet. 2013. [Salaries. Swedish Medical Association] Accessed 2013 March. Available from: <http://www.slf.se/Forbundet/2013>.

121. Läkemedel. Tandvårds- och läkemedelsförmånsverket. 2013 [Drugs. The Dental and Pharmaceutical Benefits Agency] Accessed 2013 March. Available from: <http://www.tlv.se/beslut/sok/lakemedel/>.

122. Bendelin N, Hesser H, Dahl J, Carlbring P, Nelson KZ, Andersson G. Experiences of guided Internet-based cognitive-behavioural treatment for depression: a qualitative study. BMC Psychiatry. 2011;11:107.

123. Kvale S. *InterViews. An introduction to qualitative research writing*. Sage Publications, Thousand Oaks, CA; 1996.
124. Malterud K. Qualitative research: standards, challenges, and guidelines. *Lancet*. 2001;358(9280):483-8.
125. Giorgi A. Sketch of a psychological phenomenological method. *Phenomenology and psychological research: essays*. Pittsburg, PA: Duquesne University Press; 1985.
126. Beattie A, Shaw A, Kaur S, Kessler D. Primary-care patients' expectations and experiences of online cognitive behavioural therapy for depression: a qualitative study. *Health Expect*. 2009;12(1):45-59.
127. Montero-Marin J, Prado-Abril J, Botella C, Mayoral-Cleries F, Banos R, Herrera-Mercadal P, et al. Expectations among patients and health professionals regarding Web-based interventions for depression in primary care: a qualitative study. *J Med Internet Res*. 2015;17(3):e67.
128. FASS, Allmänhet. Läkemedelsindustriföreningen. 2017. [Pharmaceutical Specialties in Sweden, public version. Swedish Association of the Pharmaceutical Industry]. Accessed 2018 Dec 7. Available from: <http://www.fass.se/LIF/startpage>.
129. Hellman T, Jensen I, Bergstrom G, Brämberg EB. Essential features influencing collaboration in team-based non-specific back pain rehabilitation: Findings from a mixed methods study. *J Interprof Care*. 2016;30(3):309-15.
130. Björk Brämberg E, Klinga C, Jensen I, Busch H, Bergstrom G, Brommels M, et al. Implementation of evidence-based rehabilitation for non-specific back pain and common mental health problems: a process evaluation of a nationwide initiative. *BMC Health Serv Res*. 2015;15:79.
131. Björk Brämberg E, Jensen I, Kwak L. Nationwide implementation of a national policy for evidence-based rehabilitation with focus on facilitating return to work: a survey of perceived use, facilitators, and barriers. *Disabil Rehabil*. 2018:1-9.
132. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implement Sci*. 2009;4:50.
133. Kirk MA, Kelley C, Yankey N, Birken SA, Abadie B, Damschroder L. A systematic review of the use of the Consolidated Framework for Implementation Research. *Implement Sci*. 2016;11:72.
134. Graneheim UH, Lindgren BM, Lundman B. Methodological challenges in qualitative content analysis: A discussion paper. *Nurse Educ Today*. 2017;56:29-34.
135. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse Educ Today*. 2004;24(2):105-12.

136. Taylor EF, Machta RM, Meyers DS, Genevro J, Peikes DN. Enhancing the primary care team to provide redesigned care: the roles of practice facilitators and care managers. *Ann Fam Med*. 2013;11(1):80-3.
137. Grochtdreis T, Brettschneider C, Wegener A, Watzke B, Riedel-Heller S, Harter M, et al. Cost-effectiveness of collaborative care for the treatment of depressive disorders in primary care: a systematic review. *PLoS One*. 2015;10(5):e0123078.
138. Aragones E, Lopez-Cortacans G, Sanchez-Iriso E, Pinol JL, Caballero A, Salvador-Carulla L, et al. Cost-effectiveness analysis of a collaborative care programme for depression in primary care. *J Affect Disord*. 2014;159:85-93.
139. Gensichen J, von Korff M, Peitz M, Muth C, Beyer M, Guthlin C, et al. Case management for depression by health care assistants in small primary care practices: a cluster randomized trial. *Ann Intern Med*. 2009;151(6):369-78.
140. Stewart WF, Ricci JA, Chee E, Hahn SR, Morganstein D. Cost of lost productive work time among us workers with depression. *JAMA*. 2003;289(23):3135-44.
141. Wilhelmsen M, Lillevoll K, Risor MB, Hoifodt R, Johansen ML, Waterloo K, et al. Motivation to persist with internet-based cognitive behavioural treatment using blended care: a qualitative study. *BMC Psychiatry*. 2013;13:296.
142. Aakhus E, Oxman AD, Flottorp SA. Determinants of adherence to recommendations for depressed elderly patients in primary care: a multi-methods study. *Scand J Prim Health Care*. 2014;32(4):170-9.
143. Karyotaki E, Kemmeren L, Riper H, Twisk J, Hoogendoorn A, Kleiboer A, et al. Is self-guided internet-based cognitive behavioural therapy (iCBT) harmful? An individual participant data meta-analysis. *Psychol Med*. 2018:1-11.
144. Hange D, Björkelund C, Svenningsson I, Kivi M, Eriksson MC, Petersson EL. Experiences of staff members participating in primary care research activities: a qualitative study. *Int J Gen Med*. 2015;8:143-8.
145. Svenningsson I, Udo C, Westman J, Nejati S, Hange D, Björkelund C, et al. Creating a safety net for patients with depression in primary care; a qualitative study of care managers' experiences. *Scand J Prim Health Care*. 2018;36(4):355-362.
146. Bargh JA, McKenna KYA, Fitzsimons GM. Can You See the Real Me? Activation and Expression of the "True Self" on the Internet. *J Soc Issues*. 2002;58(1):33-48.
147. Andersson G, Hesser H, Veilord A, Svedling L, Andersson F, Sleman O, et al. Randomised controlled non-inferiority trial with 3-year follow-up of internet-delivered versus face-to-face group cognitive behavioural therapy for depression. *J Affect Disord*. 2013;151(3):986-94