Internet-based Treatment of Depression in Primary Care

Effectiveness and Feasibility

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To Saga & Per

Abstract

Internet-delivered psychological treatments emanate from a long tradition of psychological methods and should be seen as a natural effect of the evolution within psychology, society, and technology. Psychological treatments via Internet have been shown to be effective, however the vast majority of research has been conducted outside of health care, and corresponding research in primary care settings is sparse.

Psychological illness, such as depression, is common and most often treated within primary care, where therapist availability varies. One way to increase availability and provide effective and high quality psychological treatments could be to offer Internet-delivered therapy with minimal therapist support. This raises questions, however, such as: Is Internet treatment as effective as treatment as usual (TAU) in primary care? Which patients would benefit the most? And, is Internet treatment feasible within primary care?

This thesis reports findings from four studies based on the PRIM-NET project that implemented Internet-delivered cognitive behavior therapy (ICBT) at 16 primary care centers in the Västra Götaland region in Sweden. Patients thought to be suffering from mild-to-moderate depression were assessed. 90 patients were included and randomized to either ICBT or TAU.

Study I & II – Effectiveness: No significant differences in the reduction in depression scores were found between the ICBT and TAU groups during treatment, after twelve weeks of treatment (post) or at follow-up three and nine months after treatment. The mean between-group effect size (Cohens' *d*) was in effect zero, while there was a large within-group effect size for both ICBT and TAU at post and at follow-ups.

Study III – Effectiveness and latent classes: Analysis of the ICBT patients' depression trajectories by person-oriented methods corroborated the findings of an overall effect of the ICBT treatment. A large heterogeneity among the patients was also found. Three latent classes were identified: two classes (in total 50% of the patients) responding well to the treatment, while one class (50% of the patients) effectively did not respond. No distinguishing factors were identified for the non-responding class, but initial rapid response, or lack of response, as well as level of adherence to the ICBT, could give an indication of treatment outcome.

Study IV – Feasibility: Qualitative methods revealed the primary care therapists' attitudes and experiences as positive; they viewed ICBT as an asset, would like to use ICBT programs in the future, and also introduce elements from ICBT into their face-to-face treatments. Some adaptations of the ICBT to better suit primary care circumstances were suggested.

Conclusion: Internet-delivered treatments seem to be both effective and feasible within primary care and can be introduced as a complement to other treatments.

Keywords: *Internet, ICBT, Depression, Primary care, Randomized controlled trial, Person-oriented*

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Svensk populärvetenskaplig sammanfattning

En vanlig bild av *psykologisk behandling* är att den sker i ett terapirum, bakom stängd dörr. Men så ser det ofta inte ut. Psykologisk behandling är så mycket mer.

I takt med att samhället har utvecklats, och nya behov har uppstått, har också nya behandlingar och sätt att förmedla dem tagits fram. Psykologin är en del av det omgivande samhället, och i psykologiska behandlingar har man i alla tider använt sig av de möjligheter som tekniken gett. Den form av behandling som den här avhandlingen undersöker, Internet-baserad psykologisk behandling, ses ofta som något revolutionerande och helt nytt. Jag ser i stället Internetbehandling som ett naturligt steg i en lång utvecklingstradition.

Att läsa har alltid setts som en väg till ett bättre mående i både kropp och själ. Självhjälpslitteratur inom de mest skilda ämnen har funnits länge, men sedan ett tag tillbaka har också ett antal väl undersökta och fungerande psykologiska behandlingar publicerats som självhjälpsböcker. Genom dem har allmänheten enkelt kunna ta del av psykologisk kunskap och behandling, och på så sätt hjälpa sig själva. Så kallad *biblioterapi* har alltså använts länge, och forskning har också visat att den ger goda resultat. Men att ställa korrekt diagnos, och genom det välja rätt behandling, kan vara svårt. Bäst blir det oftast när patient och psykolog tillsammans definierar problemet. Även då är det många gånger rationellt att sen låta patienten själv arbeta med ett väl genomtänkt, pedagogiskt och beprövat material, men med stöd från psykologen. Många psykologer har använt sig av detta arbetssätt, även jag själv.

Fastän drömmen om den intelligenta maskinen är gammal var det först med 1900-tals-uppfinningar som radioröret, transistorn och den integrerade kretsen som den moderna *datorn* blev möjlig. Teknikutvecklingen har sedan gått mycket fort. Den mångfalt ökade datorkraften och i samma takt minskade datorstorleken gör att dagens unga växer upp i ett helt annat samhälle än vad min generation gjorde. Då, på 1970- och 80-talen när vi var unga, var "dator" en väldigt stor låda med en mycket liten skärm, och som man egentligen inte hade så mycket nytta av i det vanliga livet. Idag är datorer i olika former integrerade i vår vardag. Nästan alla unga i Sverige är dagligen "uppkopplade" och använder också Internet som sin primära källa för in-

formation, kunskap, underhållning, shopping och sociala kontakter. I takt med att dagens unga åldras kommer deras förhållningssätt med allra största sannolikhet att följa dem. Detta påverkar naturligtvis samhället i stort, och i och med det även sjukvården.

På 1990-talet började man experimentera med att flytta det psykologiska självhjälpsmaterialet in i datorn. Patienter kunde då erbjudas att arbeta med *datorbaserad självhjälpsbehandling*, oftast på plats hos sjukvården och på en av sjukvårdens datorer. Försöken slog väl ut och när Internet så småningom slog igenom stort så utvecklades den datorbaserade självhjälpsbehandlingen till *Internet-baserad självhjälpsbehandling*, tillgänglig på den plats och tid som passade patienten bäst. Med flytten till Internet blev också den stödjande kontakten med behandlaren enkel och integrerad i behandlingen.

Att behöva hjälp för själen är inte helt ovanligt. Man brukar uppskatta att ungefär en tredjedel av alla besök i primärvården är kopplade till psykologiska problem eller psykiska sjukdomar. *Depression* är ett ord många av oss rätt ofta använder i dagligt tal, kanske för att beskriva hur vi blivit lite ledsna eller nedstämda en stund. Men depression är också något annat, en definierad sjukdom. Omkring var femte svensk kommer att uppleva åtminstone en depressionsepisod under sin livstid och för varje depression man upplevt så ökar risken att få en ny. Depression kan också få allvarliga konsekvenser, inte bara pga den ökade risken för självmord, utan också för den ökade risken för att få somatiska sjukdomar, och att därigenom dö i förtid. Detta gäller även om depressionssjukdomen i sig inte är särskilt djup.

Det finns idag flera olika effektiva behandlingar mot depression. Statens beredning för medicinsk utvärdering (SBU) rekommenderar för mildare depressioner psykologiska behandlingar som t ex kognitiv beteendeterapi (KBT), och för lite allvarligare depressioner, sk måttlig depression, psykologisk behandling eller antidepressiv medicin. De flesta depressioner som upptäcks behandlas i primärvården. På många håll har primärvården också sedan en tid erbjudit psykologisk behandling, men *primärvårdspsykologin* är relativt ny och långt ifrån heltäckande. Det råder också brist på psykologer utbildade och kunniga i sk evidensbaserade metoder, dvs metoder med bevisat stöd i forskningen.

Ett sätt att gå runt bristen på behandlare är att erbjuda Internet-baserade behandlingar med behandlarstöd. En Internet-behandling innebär för patienten lika mycket arbete som i en behandling där man möter psykologen ansikte mot ansikte, medan psykologen däremot lägger ner en bråkdel av den tid som behövs för en traditionell behandling. Det har redan forskats relativt mycket på Internet-behandling för olika diagnoser, även mot depression, och resultaten är goda. Internet-behandling fungerar i stort sett lika bra som annan behandling. Men, hittills har nästan all forskning

utförts utanför sjukvården, på specialrekryterade patienter. För att verkligen veta att en metod fungerar i vården och på verkliga patienter så måste vi också testa den på plats i vården. Att forska på plats i t ex primärvården är alltså mycket viktigt.

PRIM-NET projektet har finansierats av Västra Götalandsregionen och REHSAM för att undersöka om Internet-behandling mot depression är effektivt och fungerar ute på vårdcentraler. Mellan 2010 och 2013 har 18 vårdcentraler från regionen varit involverade i projektet. Patienter på vårdcentralerna, 18 år eller äldre, med misstänkt depression har fått frågan om de vill delta. De har sedan fått träffa primärvårdens psykolog eller psykoterapeut som har diagnosticerat dem i en sk strukturerad intervju under ca en timma. De patienter som har diagnosticerats med depression, men inte med andra problem som skulle kunna störa behandlingen, har slumpats till antingen Internet-behandling, eller till den behandling de skulle ha fått om projektet inte funnits, sk sedvanlig behandling. Totalt blev 90 patienter inkluderade i projektet. Alla patienter har fått fylla i mätningar av bl a depressionsdjup före, under och efter behandlingen. De har sen också följts i uppföljande mätningar tre och nio månader efter behandlingen avslutats.

Den Internet-behandling patienterna fick var Depressionshjälpen®, en kognitiv beteendeterapeutisk behandling utvecklad av Psykologpartners W&W AB. Under som mest tolv veckor kunde patienten logga in till sju moduler med text, film, mm, via Internet. De fick också en tryckt arbetsbok som de arbetade med parallellt. Behandlingen gick ut på att lära sig hur depressioner fungerar, och hur man kan påverka sitt mående genom det man gör. Varje vecka hade patienterna telefon- eller säker e-mail kontakt med den behandlare som gjorde den inledande bedömningen.

Behandlingsresultaten, direkt efter tolv veckors behandlingsperiod, och under uppföljningar tre och nio månader efter avslutad behandling, skiljer sig inte signifikant mellan Internet-behandlingen och den sedvanliga behandlingen. Detta ligger i linje med tidigare forskning, och tyder på att Internet-behandling är effektiv även i primärvården. Både Internet-behandlingen och den sedvanliga behandlingen visade en stor effektstyrka, vilket tyder på att båda alternativen är verksamma.

Av de patienter som fått Internet-behandling har också en hög andel, lite drygt hälften, gått igenom alla sju Internetmodulerna. Detta är relativt högt jämfört med tidigare studier på liknande Internet-behandlingar. Här är det viktigt att komma ihåg att det i alla behandlingsformer, även i mera traditionell psykologisk behandling, är långt ifrån alla patienter som går igenom hela behandlingen med alla erbjudna sessioner.

Men dessa resultat säger egentligen inte så mycket om den enskilda patientens utvecklingskurva. För att få en mera komplett bild av vad som händer kan man komplettera de statistiska beräkningarna av medelvärden på gruppnivå med sk personorienterade metoder. I dem är det den enskilda personens utvecklingskurva som analyseras. Man försöker också här att hitta sk latenta klasser bland patienterna där utvecklingskurvorna inom en klass liknar varandra mer, än mellan olika klasser.

Den person-orienterade analysen av depressionsutvecklingen hos Internet-patienterna visar att Internet-behandlingen har en god effekt, på gruppnivå. Men den visar också att det är en stor spridning i hur patienternas depression utvecklas. Tre olika mönster, latenta klasser, avtecknar sig. En tredjedel av Internet-patienterna startar med mild depression, svarar bra och snabbt på behandlingen, och effekten kvarstår i princip vid uppföljningarna. En femtedel startar med måttlig depression, svarar bra och snabbt på behandlingen, och effekten kvarstår också här vid uppföljningarna. Hälften av Internet-patienterna startar med mild depression, svarar inte på behandlingen, och ligger kvar på ungefär samma nivå vid uppföljningarna. Detta betyder att för hälften av patienterna fungerade behandlingen, depressionen minskade, men för den andra hälften hade behandlingen ingen egentlig effekt.

Vi kan inte hitta någon faktor som särskiljer de patienter som *inte* svarar på behandlingen från de som gör det. Däremot så jobbar de patienter som svarar på behandlingen mera med Internetpaketet. Vi ser också en snabb initial effekt hos de patienter som svarar på behandlingen. Denna tidiga effekt saknas i den grupp som inte svarar på behandlingen. Liknande mönster har man också sett i tidigare forskning kring kognitiv beteendeterapi som bedrivs ansikte mot ansikte. Det kan alltså vara så att om den enskilda patientens depression inte minskar tidigt i Internet-behandlingen, så bör man överväga att byta till annan behandling, alternativt anpassa eller komplettera behandlingen.

Totalt 14 psykologer eller psykoterapeuter (som härefter tillsammans benämns "terapeuter") deltog i PRIM-NET. Under vården 2012 fick de 12 terapeuter som deltagit i projektet fram till dess en enkät om upplevelser av Internet-behandling och av forskning i primärvården. Elva av dem svarade på enkäten. Under hösten 2012 till våren 2013 berättade också fyra av dem, i ungefär en timma långa intervjuer, om sina erfarenheter av forskningsprojektet och Internet-behandling.

Sammanfattningsvis ser terapeuterna Internet-behandling som ett värdefullt tillägg till annan behandling och de vill också fortsätta att använda Internet-behandling, men gärna mera fritt än vad de tillåts göra i PRIM-NET. De vill också gärna integrera delar från Internet i den traditionella behandlingen där man möter patienten ansikte mot ansikte, särskilt när det gäller deprimerade som ses som extra sköra och i behov av

mera traditionell kontakt med behandlaren. Det verkar också som att patienter med mild eller måttlig depression idag är en grupp som sällan möter primärvårdspsykologin. Detta innebär att PRIM-NET inte, som tänkt, har blivit någon avlastning för behandlarna, utan snarare ökat arbetsbördan i och med att projektet identifierat "nya" patienter.

Terapeuternas syn på forskning inom primärvården är positiv, men de upplever att det idag är svårt att få resurser, som t ex tid, till det. Primärvården upplevs också som centrerad kring läkare och den somatiska sidan av patienterna, och där primärvårdspsykologin ännu inte har integrerats.

Min slutsats, med utgångspunkt från tidigare forskning och de studier som vi genomfört, är att Internet-behandling kan och bör införas i primärvården som ett komplement till den behandling som redan erbjuds. Internet-behandling uppvisar stor effekt och kan hjälpa många patienter, men kommer med säkerhet inte att passa alla. Internet-behandling kan också frigöra terapeutresurser så att fler patienter kan få kontakt med, och hjälp av primärvårdspsykologin. På så sätt får även de patienter som av olika skäl inte är aktuella för Internet-behandling nytta av den.

Jag tror också att Internet-behandling i framtiden inte kommer att ses eller användas som något helt separerat från och annorlunda än "vanlig" traditionell psykologisk behandling. Internet-moduler med information, hemuppgifter, mm som kan nås via t ex smarta telefoner har stor potential och skulle kunna integreras med det traditionella arbetet så att Internet blir ett verktyg bland många i terapeutens verktygslåda.

De psykologiska metoder vi använder måste grundas i vetenskap och vara evidensbaserade. Samtidigt har ny teknik alltid inneburit nya möjligheter som måste undersökas och utvärderas. På så vis skapas ny kunskap, evidens, där ibland gamla sanningar får stryka på foten. Genom historien har alltså teknikens, och med den också samhällets, utveckling påverkat psykologin. Idag är informationsteknologin en naturlig och integrerad del av våra liv. För att fortsätta vara relevant måste även psykologin ta steget in i informationsåldern och undersöka de möjligheter som den nya tekniken ger.

Contents

Figures & tables

Abbreviations & Thesaurus

BAI	Beck Anxiety Inventory.
BDI	Beck Depression Inventory.
BDI-II	Beck Depression Inventory, 2nd edition.
CBT	Cognitive behavior therapy.
CCBT	Computerized Cognitive behavior therapy, a subtype of Computer-based treatments.
CD-ROM	Compact Disc – Read Only Memory; CD which contains data intended for use by a computer.
Computer-based treatment	Psychological treatment delivered via computer. Internet-delivered treatments are one subtype. Can be based on different theoretical foundations.
DALY	Disability Adjusted Life Years; One DALY can be thought of as one lost year of "healthy" life. DALY is a measurement of the gap between current health status and an ideal health situation. DALY = YLL + YLD.
Depressions-hjälpen®	The Depression-help, a commercially available Internet-delivered CBT program in Swedish, developed by Psykologpartners W&W AB, and based on Behavioral Activation, with elements from Acceptance and Commitment Therapy and Mindfulness.
DSM-IV	Diagnostic and Statistical Manual for Mental Disorders, 4th edition.
EBP	Evidence based practice.
Face-to-face therapy	"Traditional" therapy in which the patient and therapist meet face to face, sometimes abbreviated as f2f.

GMM	Growth mixture modeling, a person-oriented statistical method allowing differences in growth parameters across unobserved sub-populations (i.e., individual growth trajectories are allowed to vary around different means, with the same or different forms), resulting in separate growth models for each latent class.
GP	General practitioner.
ICBT	Internet-delivered Cognitive Behavior Therapy, a subtype of CCBT, and also a subtype of Computer-based treatments.
ICD-10	International Classification of Diseases, 10th edition.
Incidence	The number of new cases in a given time period.
Internet-based therapy	See Internet-delivered therapy
Internet-delivered therapy	For extended definition see page 20. Sometimes called "Internet-based" or "Internet therapy" for short. Can be based on different theoretical foundations, such as CBT, thus ICBT is a subtype of Internet-delivered treatment.
IPT	Interpersonal therapy.
IPU	Internetpsykiatri; the Internet Psychiatry Unit, an outpatient psychiatric clinic in Stockholm, Sweden, developing, researching, and also providing Internet-based treatments to patients.
Internet therapy	See Internet-delivered therapy
LCGM	Latent class growth models, can be seen as an expansion of LGCM where differences in growth parameters across unobserved sub-populations is allowed, see also GMM.
LGCM	Latent growth curve modeling, see also LCGM and GMM.
LOCF	Last observation carried forward. A statistical method where missing data will be replaced by the last known value.
MADRS-S	Montgomery Åsberg Depression Rating Scale – Self rating version.

MINI	Mini International Neuropsychiatric Interview, a structured interview developed to determine the presence of Axis-I disorders using DSM-IV diagnostic criteria.
MVK	Mina Vårdkontakter; My Health care Contacts. An e-mail-like communication system used in Swedish health care for secure communication between patient and health care staff.
PC	Primary care.
PDT	Psychodynamic Therapy.
Person-oriented	Statistical model based on a holistic-interactionistic paradigm focusing on patterns in individual developmental data. Analysis is often focused on developmental trajectories. In a population, some trajectories will resemble each other more, forming latent sub classes, where trajectories within a class are more similar than between classes.
Prevalence	The proportion of a population found to have a condition at any given time point or period.
PRIM-NET	The primary care Internet research project.
Psychologist	A licensed Swedish psychologist has studied five years (full time) at university (ground- and advanced-) level at the special psychologist education "Psykologprogrammet". The education program includes clinical psychotherapy training usually at special educational clinics at the various psychology departments. To become licensed, in addition to graduating from psykologprogrammet, one year of clinical work under supervision of a licensed psychologist is required. This means that in Sweden a degree of MSc or PhD in psychology does not make you eligible to become a licensed psychologist, but is rather a separate educational path.
Psychotherapist	A licensed Swedish psychotherapist has studied three years (half time) at university (advanced) level at the special psychotherapist education "Psykoterapeutprogrammet". Students at psykoterapeutprogrammet can come from a number of primary professions such as nurse, physiotherapist, medical doctor or psychologists. In order to be eligible for the education the students must also have acquired basic

	knowledge and training in psychotherapy. The students are required to work, practicing psychotherapy, parallel to the education. This means that some Swedish licensed psychotherapists are also licensed psychologists, but far from all.
RCT	Randomized controlled trial.
REHSAM	The REHSAM project is a cooperation between the Swedish Ministry of Health and Social Affairs, Vårdalstiftelsen, Försäkringskassan, and the Swedish Association of Local Authorities and Regions (SKL), funding research focusing on helping people regain their capacity to work.
RN	Registered nurse.
SBU	Statens beredning för medicinsk utvärdering; the Swedish Council on Health Technology Assessment.
SCB	Statistiska centralbyrån; Statistics Sweden.
Study-nurse	RN engaged to handle the study protocol, such as administering surveys, and perform follow-ups, at the primary care center.
TAU	Treatment as usual.
Therapist	Used in this thesis as a collective term for licensed psychologists and licensed psychotherapists.
Transmogrify	To change in appearance or form; transform. Used in this thesis as a tribute to my favorite historian, author, former permanent secretary of the Swedish Academy, and great linguistic model Peter Englund, who introduced this word into the Swedish language.
Variable-oriented	Statistical models that study relations between variables across individuals at group level.
WHO	World Health Organization.
YLD	Years Lived with Disability for people living with the health condition or its consequences.
YLL	Years of Life Lost due to premature mortality in the population.

Original Papers

This thesis is based on the following scientific papers, which from now on will be referred to in the text by their corresponding Roman numbers

I.   Kivi, M., Eriksson, M. C. M., Hange, D., Petersson, E-L., Vernmark, K., Johansson, B., & Björkelund, C. (2014). 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, 43*(4), 289-298. doi: 10.1080/16506073.2014.921834.

II. Eriksson, M. C. M., Kivi, M., Hange, D., Petersson, E-L., Ariai, N., Häggblad, P., Ågren, H., Spak, F., Lindblad, U., Johansson, B., & Björkelund, C. (2015). Long-term effects of Internet Cognitive Behavioural Therapy for mild/moderate depression in primary care – the PRIM-NET randomised controlled trial. (Submitted manuscript).

III. Kivi, M., Eriksson, M. C. M., Björkelund, C., Johansson, B., & Lindwall, M. (2015). Internet-delivered Cognitive Behavioral Therapy for Depression in Primary Care: A person-oriented analysis of depression trajectories. (Submitted manuscript).

IV. Kivi, M., Eriksson, M. C. M., 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. (2015). *Internet Interventions, 2*(3), 248-256. doi: 10.1016/j.invent.2015.06.001.

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1 Preface

Internet-delivered psychological treatments are often perceived as something revolutionary and new, turning established notions of psychological treatment upside down. This, I will argue, is not the case. Alternatively, Internet-delivered psychological treatments rest firmly in a long tradition of psychological methods, and must be seen as a natural effect of the evolution within society and technology, as well as psychology.

However, Internet-delivered psychological treatments have only recently moved into regular health care. As a primary care psychologist facing this new tool, I ask myself: How will it perform in primary care? For starters, is it effective? Will Internet-delivered cognitive behavior therapy (ICBT) measure up to treatment as usual (TAU)? Which of my patients would benefit the most from it? Is it feasible? And if so, how can we put it to best use?

This thesis briefly explains the background of Internet-delivered psychological treatments as we know them today. It places them in the contexts of history and society, primary care, primary care psychology, and the concept of depression. It also relates the circumstances of the research project PRIM-NET, where ICBT for depression was implemented in routine primary care settings, and reports some of the findings from research on this project.

By adding piece by piece of research findings, sometimes concordant and sometimes not, any new phenomena or application will someday become "ordinary" and "well-known". This thesis represents one small contribution to the body of knowledge concerning Internet-delivered psychological treatments in a primary care context.

2 Introduction

2.1 Depression

Depression is a word commonly used in our daily conversations. You have almost certainly heard someone use it to describe a state of low mental vitality, of feeling sad, or just being less active than usual (SBU, 2004a). However, in addition to this everyday usage, "depression" is also the name of an illness. The main symptoms of the illness depression are depressed mood, loss of interest and pleasure in all or almost all activities, and reduced energy. Often involuntary weight loss/gain, sleeping problems, reduced ability to concentrate, feelings of worthlessness, guilt, and recurrent thoughts of death, are also present. Depression as an illness was the second leading cause of Years Lived with Disability (YLD) in 2010, and "major depression" accounts for about 8% of YLDs worldwide (Ferrari et al., 2013). Depressive disorders were also a leading cause of Disability Adjusted Life Years (DALY; Ferrari et al., 2013). It is estimated that in 2030 depression will contribute the highest disease burden in high-income countries (Mathers & Loncar, 2006).

Depression as an illness is also a serious mental health condition. Most of us recognize the elevated risk of suicide associated with depression, but beyond this, depression also increases the risk of morbidity and mortality by somatic diseases, such as cardiovascular disease and stroke (Musselman, Evans, & Nemeroff, 1998; Pan, Sun, Okereke, Rexrode, & Hu, 2011; Wulsin, Vaillant, & Wells, 1999). An increased mortality rate does not only exist for diagnosed major depression, but also in subclinical forms (Cuijpers & Smit, 2002). This means that even if your depression is not as pronounced, it can still affect your life in a major way. In fact, the mortality rate for subthreshold depression is on par with the mortality rate for major depression (Cuijpers, Vogelzangs, et al., 2013).

2.1.1 The emergence and standardization of depression

Depending on the prevailing zeitgeist, the ways we choose to cluster and demarcate symptoms differ, as do the ways in which we understand and name them. What is seen as natural during one era might be unnatural during another (Englund, 1991).

As long as the existence of humanity, there has been illness and mental suffering, and throughout history there have been reports of symptoms and behavior we would to-day understand as depression. During different ages it has been interpreted and named differently, and sometimes it has been seen as melancholia. As can be ex-pected, the meaning and symptoms of melancholia have changed quite a lot through-out history (Johannisson, 2009). However, it seems that one of the many aspects of melancholia has often been the absence of something, and the feeling of being "low," of being "*de-pressed.*"

In recent times our urge for order, control, and statistics has led to the development of standardized diagnostic systems that delimit different illnesses. To be diagnosed this way, you have to fulfill a number of predetermined symptoms and conditions. This has, to some degree, standardized our illnesses, as the vague and shifting quality of the suffering has been harnessed.

2.1.2 Diagnostic systems

The most widely used diagnostic systems in research as well as health care are the International Classification of Diseases (ICD; World Health Organization, 2014), and the Diagnostic and Statistical Manual (DSM; American Psychiatric Association, 2014), covering psychiatric disorders.

From the researchers' point of view, the major advantage of using a standardized diagnosis is a clearly defined illness, and also continuity. However, the new version of the DSM (the DSM-5) has recently been published, which has meant some changes in the diagnoses and criteria of various depressive variants. But, regarding the core di-agnosis *major depression*, only minor changes have been made[1] (Rodríguez-Testal, Cristina, & Perona-Garcelán, 2014). The fact that the changes have been kept at a minimum is a relief to many researchers, as major depression is a widely used diag-nosis in research. The implemented changes are of a magnitude that still allows easy comparisons to earlier versions of the DSM, and thus also still renders already per-formed research, using earlier versions of the criteria, useful and clinically relevant.

The diagnostic systems are used not only for research purposes, but within regular health care. This means that research cannot operate in a parallel universe, but must also be relevant in the real world. Thus, constructs used in research should always reflect real world phenomena. It is important to be aware of the critique that has

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[1] DSM-5 has added two new specifiers to Major Depressive Disorder; "anxious distress" used to specify anxiety symp-toms beyond the diagnostic criteria for depression, and "with mixed features" that allows manic features in unipolar depression. Also, the previously applied "bereavement exclusion" that prevented simultaneously diagnosing grief and depression has now been removed.

been put forth concerning the diagnostic systems in general, and the DSM-5 in particular. Cautionary voices have been raised of a diagnostic "creep" and inflation, turning normal reactions into psychiatric disorders (Frances, 2013). It has also been pointed out that health care systems, as well as the pharmaceutical industry, have many incentives to give as many individuals as possible diagnoses. According to this critique, the "major depression" diagnosis is often not so major. This standardization of illnesses can also be seen as a manifestation of the Western culture it emanates from, and thereby not always transferable to other cultures (Kirmayer & Groleau, 2001). The diagnostic systems have been criticized as a way for the Western world and the pharmaceutical industry to "export" illnesses to other cultures (Watters, 2010).

2.1.3 Diagnostic criteria

Although the ICD and the DSM are, to a large extent, compatible, they are not identical (SBU, 2004a). Concerning depression, their classifications are also slightly different. For a comparison of (somewhat abbreviated) DSM-IV and ICD-10 criteria for depression, see page 6, Table 1 and page 7, Table 2.

Depression is usually divided into mild, moderate, and severe. According to ICD-10:

> *Individuals with mild depressive episodes are common in primary care and general medical settings, whereas psychiatric inpatient units deal largely with patients suffering from the severe grades* (World Health Organization, 1992, p. 100).

One research project using DSM-IV criteria is PRIM-NET, which is the basis for this thesis. The focus of the thesis is primary care and mild-to-moderate depression.

2.1.4 Screening, questionnaires, and structured interviews

Since depression is a common and serious condition, it is desirable to, in a relatively easy way, be able to identify individuals within a population who are at risk of suffering from this condition. A number of different screening instruments, comprised of short fill-in forms, have been developed and can be used as a first step toward diagnosis (SBU, 2012). During the next phase, when an individual is suspected to suffer from depression, questionnaires are often used to rule out or confirm the possibility of depression (SBU, 2012). Questionnaires are also frequently used to assess the depth of the depression when diagnosing. During treatment, questionnaires will often be used in repeated measures to assess the course of the depression and thus, also as an attempt to assess the possible effect of the treatment.

Table 1   Criteria for depression diagnosis, DSM-IV vs. ICD-10

Note: To enhance readability the text has been abbreviated and edited.
For complete criteria, please consult American Psychiatric Association (2014)
and World Health Organization (2014).

DSM-IV	ICD-10
A. At least five of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either 1) depressed mood or 2) loss of interest or pleasure.	In typical depressive episodes of all three varieties (mild, moderate and severe), the individual usually suffers from
1. Depressed mood most of the day, nearly every day, as indicated either by subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)	I. depressed mood, II. loss of interest and enjoyment, III. reduced energy leading to increased fatiguability and diminished activity.
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated either by subjective account or observation made by others)	Marked tiredness after only slight effort is common. Other common symptoms are:
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day	a) reduced concentration and attention; b) reduced self-esteem and self-confidence; c) ideas of guilt and unworthiness (even in a mild type of episode);
4. Insomnia or hypersomnia nearly every day	d) bleak and pessimistic views of the future; e) ideas or acts of self-harm or suicide;
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)	f) disturbed sleep g) diminished appetite.
6. Fatigue or loss of energy nearly every day	The lowered mood varies little from day to day, and is often unresponsive to circumstances, yet may show a characteristic diurnal variation as the day goes on.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)	… the clinical presentation shows marked individual variations, … In some cases, anxiety, distress, and motor agitation may be more prominent at times than the depression, and the mood change may also be masked by added features such as irritability, excessive consumption of alcohol, histrionic behaviour, and exacerbation of pre-existing phobic or obsessional symptoms, or by hypochondriacal preoccupations.
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)	For depressive episodes of all three grades of severity, a duration of at least 2 weeks is usually required for diagnosis, but shorter periods may be reasonable if symptoms are unusually severe and of rapid onset.
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide	
B. The symptoms do not meet criteria for a mixed episode.	Some of the above symptoms may be marked and develop characteristic features that are widely regarded as having special clinical significance. The most typical examples of these "somatic" symptoms … are: loss of interest or pleasure in activities that are normally enjoyable; lack of emotional reactivity to normally pleasurable surroundings and events; waking in the morning 2 hours or more before the usual time; depression worse in the morning; objective evidence of definite psychomotor retardation or agitation (remarked on or reported by other people); marked loss of appetite; weight loss (often defined as 5% or more of body weight in the past month); marked loss of libido. Usually, this somatic syndrome is not regarded as present unless about four of these symptoms are definitely present.
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.	
D. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).	
E. The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.	

Table 2   Mild, moderate, and severe depression according to ICD-10

Note: To enhance readability the text has been abbreviated and edited.
For complete criteria, please consult World Health Organization (2014).

See also page 6, table 1, column 2: ICD-10.

ICD-10: Mild – Moderate – Severe Depression	
[…] *Differentiation between mild, moderate, and severe depressive episodes rests upon a complicated clinical judgment that involves the number, type, and severity of symptoms present.* *[…]*	
Mild	*Depressed mood, loss of interest and enjoyment, and increased fatiguability [symptoms I, II and III] are usually regarded as the most typical symptoms of depression, and at least two of these, plus at least two of the other symptoms [a – g] … should usually be present for a definite diagnosis. None of the symptoms should be present to an intense degree. Minimum duration of the whole episode is about 2 weeks.* *An individual with a mild depressive episode is usually distressed by the symptoms and has some difficulty in continuing with ordinary work and social activities, but will probably not cease to function completely.* *[…]*
Moderate	*At least two of the three most typical symptoms [I, II and III] noted for mild depressive episode should be present, plus at least three (and preferably four) of the other symptoms [a – g]. Several symptoms are likely to be present to a marked degree, but this is not essential if a particularly wide variety of symptoms is present overall. Minimum duration of the whole episode is about 2 weeks.* *An individual with a moderately severe depressive episode will usually have considerable difficulty in continuing with social, work or domestic activities.* *[…]*
Severe (without psychotic symptoms)	*In a severe depressive episode, the sufferer usually shows considerable distress or agitation, unless retardation is a marked feature. Loss of self-esteem or feelings of uselessness or guilt are likely to be prominent, and suicide is a distinct danger in particularly severe cases. …* *All three of the typical symptoms [I, II and III] noted for mild and moderate depressive episodes should be present, plus at least four other symptoms [a – g], some of which should be of severe intensity. … The depressive episode should usually last at least 2 weeks, but if the symptoms are particularly severe and of very rapid onset, it may be justified to make this diagnosis after less than 2 weeks.* *During a severe depressive episode it is very unlikely that the sufferer will be able to continue with social, work, or domestic activities, except to a very limited extent.* *[…]*

Screening tools and questionnaires can be of great help, but as always, the user must understand the strengths and weaknesses of the tool, and what they can and cannot be used for. It is important to note that screening instruments and questionnaires alone are never sufficient to diagnose depression (SBU, 2012). In diagnosing depression, the patient must be interviewed by a professional, although sometimes the professional can be assisted by a structured or semi-structured interview.

The Swedish Council on Health Technology Assessment (SBU; SBU, 2012) names Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) as one of the structured interviews having sufficient scientific support for diagnostic reliability

Questionnaires often used for assessing the depths of the depression include the Beck Depression Inventory – II (BDI-II; Beck, Steer, & Brown, 1996) and the Montgomery Åsberg Depression Rating Scale – Self Administered version (MADRS-S; Montgomery & Åsberg, 1979). MADRS-S was initially developed to be sensitive to change and is often used in Swedish primary care. According to SBU it is, however, not yet possible to determine the reliability of the BDI-II and the MADRS-S instruments in assessing the depth of depression, due to a lack of high quality research on this matter (SBU, 2012).

2.1.5 Prevalence and incidence

Western European countries show one-year prevalence rates of depression, of about 5% of the population (Paykel, Brugha, & Fryers, 2005). The Swedish Lundby Study found a cumulative probability of developing a depression of 22.5% for men and 30.7% for women during the period 1972–1997 (Mattisson, Bogren, Nettelbladt, Munk-Jorgensen, & Bhugra, 2005). According to SBU, about every fifth person in Sweden will experience at least one major depression episode during their lifetime, but the risk of experiencing depression is almost twice as high for women (20%, compared to men, 11%; SBU, 2004a). In a survey distributed to randomly selected adults in Sweden, 17.2% were experiencing clinically significant depression (Johansson, Carlbring, Heedman, Paxling, & Andersson, 2013). Older adults often suffer from "atypical," somewhat milder, but longer lasting depressions. Other illnesses, such as dementia, are also common in older adults, and this fact often skews the prevalence numbers. When this skewness is adjusted for, prevalence among older adults seems to be on par with prevalence among the rest of the adult population (Skoog, 2004). Most people experiencing one depression episode will experience at least one more during their lives (SBU, 2004a). This risk of depression relapse is higher the more episodes you have experienced (SBU, 2004a).

Most cases of depression are identified and treated at the primary care level (Bijl & Ravelli, 2000; Kallioinen, Bernhardsson, Groph, Lisspers, & Sundin, 2010; SBU, 2004b), and the prevalence of depression among Swedish primary care patients has been estimated at about 4% (Bodlund, Andersson, & Mallon, 1999). However, Lejtzén, Sundquist, Sundquist, and Li (2014) more recently found a prevalence of 1.1% in primary care, and an incidence rate per 1,000 persons per year of 6.9 (9.0 women, 4.8 men).

The lower prevalence numbers within primary care, compared to the population, seem to reflect the fact that many suffering from depression are hesitant to seek help (Andrews, Issakidis, & Carter, 2001; Priest, Vize, Roberts, Roberts, & Tylee, 1996). There are also signs that General Practitioners (GPs) are rather unsuccessful in diagnosing depression (Cameron, Lawton, & Reid, 2011; Craven & Bland, 2013; Mitchell, Vaze, & Rao, 2009), and that many depressed patients could go unnoticed (Åsbring, Dal, Ohrling, & Dalman, 2014). It is, however, predominantly milder forms of depression that go undetected (SBU, 2004a).

So, despite high prevalence and incidence rates of depression, there are several indications that many cases actually remain untreated. Kohn, Saxena, Levav, and Saraceno (2004) found that the treatment gap for major depression in the WHO European Region was 45.4%, and for the Americas 56.9%. According to Ebmeier, Donaghey, and Steele (2006), only half or less of all individuals with depression actually establish contact with the health services for their problem. This substantial gap between illness and treatment also seems to be the case in Sweden, where available data shows a considerably lower frequency of depressions diagnosed in health care compared to prevalence numbers (SBU, 2004b).

2.1.6 Treating depression

In a systematic survey of treatments for depression, SBU concluded that there are a number of medicines and psychological treatments shown to be effective in treating depression in adults up to 75 years of age. SBU also states that, everything considered, the goal of all treatments for depression should be recovery, not only from depressive symptoms, but recovered social ability, as well as the ability to work (SBU, 2004a).

The National Board of Health and Welfare issues recommendations on a group basis that are intended to guide Swedish health care providers in the allocation of resources. Interventions with documented effect or effect proven by experience are ranked 1-10, according to degree of priority. Priority 1 is the most recommended intervention, while 10 indicates poor value relative to cost. According to the latest issue

(National Board of Health and Welfare, 2010), health care providers should offer patients with mild depression psychological treatment with Internet-delivered cognitive behavior therapy (ICBT; priority 3), individual face-to-face cognitive behavior therapy (CBT; priority 4) or interpersonal therapy (IPT; priority 4), while psychological treatment with short-term psychodynamic therapy (PDT; priority 5) or antidepressant medication (priority 10) are secondhand choices. For moderate depression, psychological treatment with CBT (priority 2) or IPT (priority 2), antidepressant medication (priority 2), or psychological treatment with short-term PDT (priority 3), is recommended. A second-hand choice is antidepressant medication combined with psychological treatment. Severe depression should, according to The National Board, be treated with antidepressant medication and electroconvulsive treatment (ECT).

This means that in most cases of mild-to-moderate depression, psychological treatments are seen as the first-hand treatment choice. It also means that for mild depression, ICBT is the recommended treatment. It is noteworthy that this recommendation is based almost entirely on research performed outside of the health care system, primarily in what are known as "efficacy studies" (see section 2.2.1, page 11).

Concerning psychological treatments, several forms of psychotherapy have been shown to be effective in the treatment of depression (Cuijpers, van Straten, Andersson, & van Oppen, 2008), but less so in cases of chronic depression or dysthymia (Cuijpers, van Straten, et al., 2010). Structured, manual-based and time-limited psychological treatments seem to work better than unstructured, nondirective approaches. Among these structured therapies, CBT has strong support in research when it comes to treating depression. Studies concerning the effectiveness of psychological treatments performed within primary care are relatively rare, but psychological treatment of depression has also been found to be effective in this setting (Cuijpers, van Straten, van Schaik, & Andersson, 2009). Additionally, it seems that the effect of psychological treatment is higher when GPs refer patients, compared to patients found and referred by screening (Cuijpers et al., 2009).

2.2 Science and practice

Scratch the surface of any straightforward concept, and you will most probably find that it is no longer so clear-cut. Once a treatment method is accepted and in use, it might seem like a natural thing, but the road from research and statistics to practice is often long and complicated.

2.2.1 From research and evidence to usual care practice

Evidence based practice (EBP) has become an important objective for health care. EBP aims at delivering the right care, to the right person, at the right time. What is "right" is determined by using all types of research-based evidence, and then turning this body of evidence into effective quality care.

When developing a new treatment, the natural first question is, does it perform better than a comparison condition, the so-called control? This is known as the treatment's *efficacy* (Roy-Byrne et al., 2003). In efficacy trials, the treatment is tested under controlled conditions, which allows quite rigorous influence over a number of variables. Efficacy trials are also usually performed under ideal or best-practice conditions, using resources not typically available in routine health care, and perhaps with participants recruited outside of the normal health care system, sometimes through advertising (Wells, 1999). The focus in this type of research is on internal validity, that is, if the results are true for the population and setting used in the study.

But, results from efficacy trials do not really say much about the effect of the treatment when delivered within health care. Efficacy does not always equal *effectiveness,* and the effectiveness of the treatment should therefore be evaluated under typical conditions in usual care and treatment settings, using representative patients and providers (Wells, 1999). In this move to test effectiveness, the researcher has to let go of the high level of control possible in efficacy research and also accept that there now are a number of things, apart from the treatment, that must also be functional. The daily routines in a "live" health care environment are not as easily altered as in a lab. This means that a treatment showing efficacy can fail in effectiveness in a number of ways. If, for example, the staff or patients find the treatment impractical, they will not use it as recommended, and hence the treatment will not be as effective. Thus, effectiveness research tests the feasibility of the treatment, that is, if the treatment can be used and be effective in live health care (Andersson et al., 2008). In effectiveness research, the focus is, to a greater extent, on external validity, that is, the generalizability of the results to other populations and settings. The aim of this is to find results that will be generally applicable to patients and health care providers.

One important factor in effectiveness is the degree to which patients correctly follow the treatment, the so-called level of *adherence*. Typically, adherence rates in research are high in efficacy-trials settings, but when moving treatments into the "real world" and regular primary care for effectiveness-trials, this rate becomes much lower (Cuijpers et al., 2009; Newby et al., 2013). One suggested explanation is that patients in primary care have usually only been screened and thus have not been properly diagnosed, meaning they possibly received the wrong treatment. However, when

first studying one ICBT treatment's efficacy, and then its effectiveness, Newby et al. (2013) found that adherence dropped from 89% in the efficacy to 41% in the effectiveness trial, despite patients in the effectiveness trial being referred by medically trained staff. Using a treatment within usual care seems to be a completely different matter, and it is far from certain that an efficacious treatment will be effective or disseminated successfully.

Inherent in the movement for evidence-based practice is a transference line between research (the evidence) and health care (the practice). This transference is, however, often not as direct as one might hope (Green, 2012). In fact, dissemination and implementation of evidence-based methods have turned into a research area in itself, *implementation science*, which is the study of methods to promote the uptake of research findings into routine practice (Bhattacharyya, Reeves, & Zwarenstein, 2009). Implementation science tries to ensure that research knowledge correctly reaches the population it is intended for. In many ways Implementation science deals with

> *…human behavior and organizational inertia, infrastructure and resources constraints, and the messiness of providing the effectiveness of 'moving targets' under conditions that investigators cannot fully control* (Woolf, 2008, p. 212).

This side of the translation of knowledge is often neglected. Instead we tend to focus on the laboratory side, and not give so much thought to how we can transfer our findings into highly complex environments, such as the health care system (Woolf, 2008).

Several frameworks to help understand and guide implementations have been suggested. One example is the seven barriers to optimal care by Cochrane et al. (2007) (table 3, page 13), condensed from a systematic review of studies, in which factors that limited or restricted health care providers from adhering to an implementation of evidence-based clinical practice were identified.

2.2.2 Different perspectives – the variable and the person

When trying to capture a complex reality, we simplify and tend to concentrate on one perspective at a time. Imagine a photographer taking two-dimensional photographs of a three-dimensional world. Depending on the position of the camera, the photos can give completely different outlooks of the same reality. One way to deal with this is to move the camera around and let different perspectives complement each other. The combined result will then present a more comprehensive, and in one sense truer, picture of the complex reality.

Table 3   Categories of Barriers to Optimal Care by Cochrane et al (2007)

Barrier category	Barrier descriptive
I Cognitive-behavioral barriers	*Lack of knowledge, awareness, professional skills, or appraisal skills*
II Attitudinal or rational-emotional barriers	*Lack of efficacy, lack of confidence, lack of sense of authority, lack of outcome expectancy, lack of accurate self-assessment*
III Health care professional/physician barriers	*Influence of invariants such as age, experience, gender, lack of motivation, influence of individual characteristics, concern for legal issues, rigidity of professional boundaries, lack of appropriate peer influences or models*
IV Clinical practice guidelines/evidence barriers	*Lack of practical access, lack of comprehensible structure, lack of utility, lack of local applicability, lack of convincing evidence*
V Patient barriers	*Conflicting culture; educational, cognitive, attitudinal behaviors; lack of adherent or concordant behavior*
VI Support or resources	*Lack of support, lack of human and material resources, lack of financial resources or funding, lack of time*
VII System and process barriers	*Lack of organization and structure, lack of harmony with health and oversight systems, lack of referral process, lack of workload-outcome balance, lack of teamwork structure and ethic*

In a way statistics is like photography. Choosing which statistical method to use implies choosing a position, and thus also from which perspective too look at reality. Statistical methods always makes assumptions and thus creates a somewhat one-dimensional statistical model that then can be applied to a multidimensional reality. Research, and the evidence produced, will always be somewhat reductionist.

Currently the statistical methods used to study development are mostly *variable-oriented*. That is, what is studied are statistical relationships between variables across individuals at group level (Bergman, Magnusson, & El-Khouri, 2003). However, development tends to diverge between individuals. Variable-oriented methods and analysis target mean changes and thus do not really take into account the individual variation (Duncan & Duncan, 2004). Using traditional statistical variable based methods, the individual person will not really emerge. In order to see the person you need a different perspective.

The *person-oriented* approach is based on a holistic-interactionistic paradigm. That is, the approach is contextual and views the individual as an intentional and active agent interacting with the environment (Bergman et al., 2003). Using this approach, change

or development is seen as a process, and the focus is put on patterns in individual developmental data (Bergman & Andersson, 2010; Bergman & Lundh, 2015). When treating depression, each individual can be expected to display a unique depression development trajectory. Some of these trajectories will resemble each other more than others, and in a population we can therefore expect latent subclasses, where trajectories within a class are more similar than between classes (Nagin, 2005).

Group-based modeling techniques such as Growth Mixture Modeling (GMM; Muthen & Muthen, 2000) and latent class growth models (LCGM; Nagin, 2005; Nagin & Land, 1993) focus on individual change and make it possible to explore the shape of the individual development, and to identify latent classes in a heterogeneous group of patients.

Thus, to complement more traditional statistical methods with GMM and LCGM adds new perspectives and allows us to produce a more comprehensive picture of reality.

2.3 A bit of history

As long as humans have existed, the ways and means of communication and processing information have continuously evolved. In order to better understand society and psychology of today, we need to widen our perspective and look back into our history.

2.3.1 The computing (r)evolution and the era of Information

The pre-history of the computer runs far into ancient times and really starts with the abacus. In the 1600s, "*computer*" denoted a person whose job it was to, by hand, perform all the tedious calculations necessary in science. One example is the mind-bogglingly time consuming process of calculating the orbit of the comet subsequently known as Halley's (Grier, 2005). This process of performing calculus by hand was also prone to numerous errors (Gleick, 2011), a fact that left many innovators dreaming of creating a mechanical, and thus more reliable, computer.

In 1822, mathematician and engineer Charles Babbage, in a paper to the Royal Society, presented the "Difference engine", that is, a *mechanical computer*. Some years later Ada Lovelace complemented the computer with the first modern *computer software*, a computer program. This mechanical computer and software had pretty much the same basic architecture as modern computers. It was for various reasons not built until recently, but today one complete and working Babbage computer is on display at the Museum of Science in London. It is the size of a small room and can, at least in today's perspective, perform a very limited set of operations.

With this, the groundwork of the modern computer was laid, and with the invention of the *vacuum tube,* a non-human, electronic computer suddenly became a reality. Computers built with vacuum tubes are, of course, also huge, prone to frequent vacuum tube malfunctions, and have a very limited set of uses. However, in 1948, Bell Telephone Laboratories invented the *semiconductor*, a.k.a. the transistor, and the modern computer was born. Development from then on has been fast and accelerating. In 1958 the *integrated circuit* combined a set of transistors on a small chip. The size of the integrated circuit has, with advancements in technology, been reduced over and over. Today we can pack amazingly large numbers of transistors onto very small chips, which is reflected in the increased capacity and the reduced size of today's computers.

As recently as in the late 1980s, when I studied Computer Programming at the university, a "computer" was an easily identifiable, large box with a very small screen, and in order to be able to use it and complete your assignments, you had to pre-book timeslots, go to the department and work there. Very few, if any, of the students had anything like it at home. In many ways computers then were not very user-friendly, and almost not at all integrated into daily life.

Since then information technology has exploded. Today, computers are often integrated into our environment in a way that makes them almost completely unremarkable. Computing power is just there at our fingertips and we take it for granted.

The wonderful device called "Internet" was introduced among the initiated as early as in the 1960s, but it was not until Tim Berners-Lee created the World Wide Web in the 1990s (Berners-Lee, 1992) that it was turned into the popular tool we so frequently use today. In this day and age the Internet has made information accessible in a hitherto unimaginable way. This gives generations growing up with this technology quite a different view of the world.

Swedes are famous for quickly adopting new technology, and Sweden is one of the countries with the highest rate of Internet use (Findahl, 2014). According to Statistics Sweden, in 2014, 83% of youth, ages 16-24 years, used personal computers nearly every day, 94% used the Internet nearly every day, while 99% had Internet access in their homes, and 84% had used their mobile phones to access Internet away from home or work (SCB, 2014). This tells us that for a vast majority of the younger generations, computers, and especially Internet, have become an everyday, natural commodity. Internet is now the primary source of information. For the young, Internet means, among other things, information, knowledge, entertainment, shopping, and being social. (Findahl, 2014; SCB, 2014).

The ways of the young of today will most likely be the ways of the adult tomorrow. It seems that the *Information era* truly has arrived, made its mark on society and, I believe, on psychology as well.

2.3.2 From Alphabet to Bibliotherapy…

Usually we think of *psychological therapy* as taking place within a closed room, where a therapist and a patient meet face-to-face. The popular view as presented in movies and on TV almost always involves this closed room, more often than not a couch, and sometimes an elderly man with a cigar, closely directing what is happening. But this is far from being the norm, and as we will see, psychological therapy and treatments can take many forms.

The alphabet and the art of writing were invented ca 1500 B.C. (Gleick, 2011). The wonder of letters that make up a text is that it can contain and transfer information and knowledge between persons without the writer and reader ever meeting each other. The advent of industrial printing of books, which were previously a true sign of wealth, also meant that books could be bought by the average person. Today, reading is such a common skill, at least to most Westerners, that we hardly even think about it anymore. Try *not* reading a text put in front of you and see what happens.

Since the first scribe, reading has also been used as a means to improve ourselves and our health. In 1270 A.D. patients at the Al-Mansur hospital in Cairo were prescribed reading the Quran as a part of their treatment (Jack & Ronan, 2008). Bibliotherapy, in a very broad sense, then refers to any reading that is thought to help the reader with physical or emotional problems (Alston, 1962). The term has, however, increasingly, and especially when used by psychologists, turned into referring to the use of do-it-yourself, or "self-help", texts in treatment of psychological problems.

Using *treatment manuals* as a part of the treatment has a long tradition within, for example, behavioral therapy (Glasgow & Rosen, 1978). Most forms of CBT also contain elements like psychoeducation, information leaflets, and homework as a part of the treatment process, all of them easily lending themselves to the written format. This makes it natural to integrate and use written material as a part of therapy, and many psychologists have been doing so for a long time (Starker, 1988). These texts can be used in a number of different ways: as a preparation, giving increased understanding of the treatment; as information or as assignments and worksheets during treatment; as reminders to maintain the treatments' effect after treatment; or as the main treatment in which the patients work with self-help texts mostly on their own, with only limited contact with the therapist.

From therapists using manuals and texts in treatment, there is only a small step to using the manuals for self-help and publishing them for the public to use. Starting in the 1970s, many experts and leading therapists in the field, predominantly behavior therapists, followed the American Psychological Association's president George A. Miller's (1969, p. 1071) call to psychologists to "*give psychology away*" and to start learning how to help people help themselves, for example by publishing treatments and manuals in a do-it-yourself manner. These treatments were also often scientifically evaluated (Rosen, 2003). The content of the treatments was not new; they followed the same principle that had been used for a long time within the therapy room, instead the novelty was the means to deliver the treatment, namely by *self-help texts* (Cuijpers, 1997) in a *bibliotherapy* treatment.

2.3.3 Bibliotherapy in practice

Pure self-help bibliotherapy, although perhaps a good alternative for many, also has a number of drawbacks. For example, it is the patient who determines the diagnosis, and naturally most patients have limited knowledge of psychology. This may result in the patient choosing the wrong treatment altogether, which of course limits the effect. Even if the patient arrives at a correct diagnosis and hence chooses the correct treatment, a basically sound and functional treatment can become ineffective, or even harmful, if administered only by a layman (Rosen, 1987). Because of this, compared to other treatments, pure self-help has not shown very promising results (Rosen, 2003).

One way to circumvent these flaws is to introduce some amount of therapist assistance into the self-help. This "minimal therapist contact" reduces many of the drawbacks inherent in pure self-help, and significantly improves the effect (Gellatly et al., 2007). What is important to recognize is that, although the time put in by the therapist is markedly reduced in all self-help variants, compared to face-to-face therapy, the time and effort required from the patient are the same, or in some cases even larger (Andersson et al., 2008).

When discussing manuals and self-help it is also important to distinguish between the varying degrees of therapist contact. At one end of this continuum we have "*self-administered,*" a pure self-help in which the patient administers the entire treatment without the aid of a therapist, through "*minimal therapist contact*" or "*guided self-help*". On the other end of this continuum is "*therapist administered*" self-help, in which the patient has regular, and perhaps even quite comprehensive, contact with a therapist (Glasgow & Rosen, 1978; Newman, Erickson, Przeworski, & Dzus, 2003).

Research on bibliotherapy across a large number of diagnoses has shown that this type of treatment can be a serious alternative to other treatments. In his meta-analysis, Marrs (1995) found that bibliotherapy was moderately effective, $d = 0.565$, but that the effectiveness differed for different problems, and that it is possible that bibliotherapy is most effective in reducing anxiety, and less so in helping with problems that require patients to delay gratification. Depression was among the diagnoses for which bibliotherapy seemed to be moderately effective, with $d = 0.567$ (Marrs, 1995). A meta-analysis focusing on assisted, or guided, self-help for depression has indicated results on par with individual face-to-face therapy (Cuijpers, 1997). These results have been supported by a more recent meta-analysis on cognitive bibliotherapy (Gregory, Schwer Canning, Lee, & Wise, 2004).

Concerning bibliotherapy in primary care, Naylor et al. (2010) compared reading a self-help book to usual care treatment for depression in primary care (which for most patients meant antidepressant medications), and found that the effects of the treatments did not differ.

It seems that bibliotherapy is a practical psychological treatment, successfully used for a long time, with research to support it (at least the type supported by a therapist). However, in spite of bibliotherapy being an effective treatment, it has not become commonplace within health care (Den Boer, Wiersma, & Van Den Bosch, 2004). For some reason, it simply has not caught on.

2.3.4 …from Bibliotherapy to Internet and apps

The obvious, but mostly unused, potential of bibliotherapy, combined with the evolution of computing technology, made it only a matter of time before some of the already existing self-help material, on paper, was digitized and thus transferred to a computer.

The resulting *computer-based treatment* initially rested in standalone computers, often placed within health care, and where the patients had to book a timeslot and work with the material on the premises. Noteworthy is the study by Selmi, Klein, Greist, Sorrell, and Erdman (1990) demonstrating a large effect size for computer based cognitive behavioral therapy (CCBT) for depression. At this point, the tradition of bibliotherapy was simply adapted to fit a new medium. As the Internet slowly went from "nerd-heaven" to world wide web and every person's tool, and from the mid-1990s could be accessed from a computer near you, computer-based treatments transmogrified into *Internet-delivered treatments.* This Internet-delivered treatment could be conveniently accessed, where and when the patient decided, making self-

help more readily accessible to a larger group of people (Andersson & Carlbring, 2003).

Though printed texts and standalone computers allow the user to interact with the text, the Internet also allows the user to also interact with others. To complement self-help treatments with some amount of therapist contact suddenly became very natural. Via the Internet, therapist advice can be given on a continuous basis and without delay (Andersson & Carlbring, 2003).

The early computer- and Internet-delivered treatments were mainly text-based (Andersson, 2009), given that their first incarnations were simply printed material transferred to the computer, or in some cases to the more portable CD-ROM. As time went by, psychologists developing treatments learned to utilize the many possibilities of the Internet and computing. Modern technology provides a lot of exciting opportunities to administer a user-friendly, pedagogical, and working treatment. Today, there are often pictures, films, animations, cartoons (in some cases even manga), and/or sound integrated into the treatment (Carlbring et al., 2013; Imamura et al., 2014; Podell, Mychailyszyn, Edmunds, Connor, & Kendall, 2010; Whittaker et al., 2012).

As most of us nowadays constantly carry around a very powerful computer in our pockets (i.e., the smartphone) Internet-based treatments have also evolved into apps (Dagoo et al., 2014; K.H. Ly et al., 2014; Proudfoot et al., 2013; Roepke et al., 2015; Watanabe et al., 2015; Watts et al., 2013). In 2014, 73% of Swedes older than 12 years owned a smartphone and among the youngest, 12-15 year olds, almost everyone, 98%, had a smartphone (Findahl, 2014). Of course, smartphones and apps provide new possibilities to integrate treatment into our daily lives with features such as reminders and instant logging of events. With Internet treatment available in our pockets, psychological treatment is definitely no longer limited to a one-hour event once a week, rather it can become a constant companion and quest.

2.4 Psychological treatments in the Information era

As society has evolved, new needs have emerged, and new treatments and ways of delivering them have been developed, using the latest technology. Computers and advanced technology have, for some time, been abundant within most aspects of health care. Now that social life and communicating with others is, to a large extent, mediated by computers, there is no reason for technology to linger on the threshold any longer, the time has come for technology to enter the therapy room as well.

2.4.1 Defining Internet-delivered therapy

Among other uses, the Internet can be used to communicate (via e-mail, social media and video/voice communication), present and access information, and as a platform for interactive programs. This means that using the Internet as a tool in psychological treatment can take many forms (Andersson, 2009).

One obvious use of the Internet is online therapy, in which the therapist and the patient use e-mail, chat, or even video conferencing software, such as Skype®, to perform essentially the same function as a regular face-to-face therapy session. This form of *online therapy* has its advantages, especially when dealing with great geographical distances between patient and therapist, but some concerns have been raised over ethical issues, as well as the risk of unauthorized persons accessing and eavesdropping on the sessions (Hilgart, Thorndike, Pardo, & Ritterband, 2012). Computer technology and the Internet also lends itself to methods such as Virtual Reality exposure to feared objects. Another possibility is augmented reality, a wearable technology with an optical head-mounted camera and display. Augmented reality could, for example, be used so that the therapist, live but remotely, could guide the patient through assignments such as exposures. Only imagination restricts the uses of technology in psychological treatments, but mostly these types of Internet treatment must be seen as something essentially different from the *Internet-delivered self-help* (i.e., bibliotherapy via Internet), with or without some amount of therapist contact, which is usually implied when we talk about Internet-delivered therapy, or "Internet therapy" for short (Andersson & Carlbring, 2003). For example, Internet-delivered therapy (guided self-help) focuses on helping the patient find and explore tools that then can be utilized by the patient, on her own, in real-life. This guidance + real life exposure then results in behavioral and emotional change for the patient (Andersson et al., 2008).

One definition of Internet-delivered therapy, and the one I will abide by in this thesis, is

> *…a therapy that is based on self-help books, guided by an identified therapist who gives feedback and answers to questions, with a scheduling that mirrors face-to-face treatment, and which also can include interactive online features…* (Andersson et al., 2008, p. 164)*.

"Books" in this context should be interpreted as the treatment mainly being text-based, but sometimes with other elements included.

Looking at the more typical Internet therapies, there is a continuum, with comprehensive treatments targeting defined and ascertained diagnoses (such as depression)

at one end, and treatments that are briefer, and aimed at a more general population at the other (Andersson & Cuijpers, 2009). The latter are usually unguided, and therefore cheaper, but also typically less effective (Spek, Cuijpers, et al., 2007).

There is nothing about Internet-delivered treatments that restricts the theoretical foundation of the treatments. So far, most Internet-delivered treatments have been based on CBT (Andersson & Cuijpers, 2009), although other theoretical approaches, such as problem-solving focused therapy (van Straten, Cuijpers, & Smits, 2008; Warmerdam, van Straten, Twisk, Riper, & Cuijpers, 2008), IPT (Donker et al., 2013), and PDT (Johansson, Ekbladh, et al., 2012) have also been developed and researched. Just as there are small differences in effectiveness between different face-to-face therapies for depression based on different theories (Cuijpers et al., 2008), there seem to be comparable effectiveness differences among Internet-delivered treatments for depression of different theoretical schools (Johansson & Andersson, 2012).

2.4.2 What makes Internet-delivered treatments work?

In 2009, Andersson, Carlbring, Berger, Almlov, and Cuijpers (2009) summarized the evidence on Internet therapy thus far, and made four suggestions on how to design Internet-delivered psychological treatments for best effect. They advised to 1) target specific conditions and make sure patients are properly diagnosed, 2) design comprehensive and pedagogical treatments, 3) design user-friendly and accessible treatments for both patients and staff, and 4) include some form of minimal therapist support.

Since then, transdiagnostic Internet treatments have been tested with good results (Titov et al., 2011), and this kind of more generic recipe, in which one treatment is used to treat more than one diagnosis, can be beneficial in the case that a thorough assessment cannot be performed (Johansson & Andersson, 2012). There has also been research on individually tailored treatments for depression (Johansson, Sjöberg, et al., 2012) that, instead of providing a one-size-fits-all solution, tailors the individual treatment from a pool of different treatment modules, according to what the initial assessment tells about the patient. There are indications that this type of treatment is a better choice for patients with more severe forms of depression (Johansson, Sjöberg, et al., 2012).

Evidence points towards the importance of the patient being assessed in some way and receiving a diagnosis before commencing therapy. A pre-treatment contact, via telephone or face-to-face, often in the form of a structured diagnostic interview, enhances the results of guided treatments. Actually, it could be that the effectiveness of guided self-help is moderated by pre-treatment contact being available or not

(Johansson & Andersson, 2012). Moreover, without a proper diagnosis, there is no assurance that the patient receives treatment for the actual problem (Johansson & Andersson, 2012). If the patient receives treatment not for the problem at hand, but for some other, it does not matter if the treatment is previously proven to be effective. In cases like this, the treatment will most probably not help the patient with the problem.

In order for the treatment to be effective, the patient must be able to access and use it without having advanced computer knowledge. It is therefore a good idea to avoid using the most avant-garde technology, and instead stick to more commonly understood and user-friendly features (Andersson et al., 2008). This can, of course, be seen as a limitation, but with the rapid development and dissemination of technology, this limitation will be diminished over time.

Unguided Internet-delivered self-help treatments have proven themselves effective to some degree; however, although they are cheaper than guided self-help (Johansson & Andersson, 2012), they are also generally less effective (Andersson & Cuijpers, 2008; Spek, Cuijpers, et al., 2007) and drop-out rates are high (Cuijpers et al., 2011; Meyer et al., 2009). Fortunately, these effects can be mediated with some level of support. How this support should be tailored and how much support is needed is not altogether clear (Andersson et al., 2009). This is, at least in part, because the concept of support has not yet been fully investigated (Andersson & Cuijpers, 2009). In ICBT, the role of the therapist is to provide support, encouragement, and now and then direct the patient (Andersson, 2009; Sanchez-Ortiz, Munro, Startup, Treasure, & Schmidt, 2011). That is, it is the Internet package that constitutes the treatment and the therapist's role is merely to support this. When it comes to ICBT, it is clear that there is a strong correlation between the degree of support and the outcome of the treatment (Johansson & Andersson, 2012). Not only the amount of time, but also what the therapist does while supporting patients is important. Therapist behaviors have been found to be associated with treatment results, and behaviors such as "task reinforcement", "task prompting", "self-efficacy shaping", and "empathetic utterance" reinforces patients' module completion. "Task reinforcement" also had a significant positive correlation to treatment outcome, while "deadline flexibility" had a significant negative effect (Paxling et al., 2013). That is, research seems to suggest that the prime function of the therapist in ICBT is to help the patient focus on, work with and complete tasks according to schedule.

The comparably easy access to the therapist in Internet-delivered treatments is important. In a metaregression analysis of psychotherapy for depression, Cuijpers,

Huibers, Ebert, Koole, and Andersson (2013) found that intensity, rather than quantity, determines the therapeutic effect. Often the therapist is more accessible in Internet-delivered treatments than in face-to-face treatments, and this could be one reason why Internet-delivered treatments have been found to be as effective as face-to-face treatments.

Concerning who the therapist should be, this is still somewhat unclear. In a study on Social Anxiety Disorder, it was shown that experienced therapists may require less time to guide patients, but therapist experience did not seem to make any difference concerning the effect of the treatment. It should be noted, however, that all therapists participating in the cited study were well-trained in the method used (CBT), and that they were using a highly structured protocol (Andersson, Carlbring, & Furmark, 2012). A less structured protocol might give more room for experience to play a role, but the findings of Vernmark et al. (2010) seem to contradict this. In any case, it is recommended that the therapist is knowledgeable in the principles behind the treatment in question (e.g. CBT, IPT, PDT, …; Andersson et al., 2008), which makes sense since a therapist who is not knowledgeable could unknowingly counteract the treatment, and thus cause diminished effect. Since therapist-patient contact is very condensed and often in a written format, therapists need to be good communicators and have sufficient writing skills (Andersson et al., 2008). Interestingly, a study comparing clinician-assisted treatment to technician-assisted for depressed patients found high within-group effect sizes for both groups, 1.27 and 1.20 respectively. The technicians provided encouragement and support, whereas the clinicians also provided clinical advice. Both technician and clinician were instructed to spend no more than 10 minutes per patient per week (Titov et al., 2010). It seems, at least in this study, that a lower level of clinical knowledge in the "therapist" might be sufficient. On the other hand, a meta-analysis has revealed more completers among CCBT patients receiving therapist support, than among those receiving administrative support (Richards & Richardson, 2012).

Providing therapist contact thus improves adherence (Hilvert-Bruce, Rossouw, Wong, Sunderland, & Andrews, 2012), as does a clear treatment deadline (Andersson et al., 2009). It is believed that a deadline, in conjunction with a scheduled follow-up interview, might also enhance the effect of less-supported treatments (Andersson & Cuijpers, 2009). The supervising aspect of the support thus being transferred to the follow-up interview.

Often Internet treatments are seen as a treatment for the young, since they are believed to be accustomed to the technology to a higher degree. However, the level of Internet literacy has not been found to be an important factor in treatment outcome,

while stable life circumstances (such as working full-time and having children, which often equates to not being so young anymore) predict better treatment outcome (Hedman, Andersson, et al., 2012).

Acceptability of Internet treatment has been good (Cavanagh et al., 2009). There have however been recent reports of initially low acceptance among depressed primary care patients, prior to being offered Internet-delivered treatment. The level of acceptance was however substantially increased by patients receiving a short information on the treatment (Ebert et al., 2015). Thus, the novelty and lack of knowledge of the treatment can be a disadvantage, and sometimes lead people to hasty and unfounded conclusions. Patients also usually experience a good working alliance towards the therapist, even if the contact is minimal, and in some cases patient and therapist have never even met in person (Andersson et al., 2009; Knaevelsrud & Maercker, 2007; Preschl, Maercker, & Wagner, 2011). Interestingly, there has not to date been any study where the working alliance has been rated as low, which means that we cannot yet say if a low working alliance might influence the outcome of the Internet treatment (Andersson & Hedman, 2013).

2.4.3 The Pros and/or Cons of Internet treatments

A general advantage of Internet-delivered treatment is that the patient can use it at home or any place that is convenient, without travelling to a clinic, and at times that suit the patient.

Depending on personality and learning styles, Internet-delivered therapy can also suit some patients better than other treatment alternatives. As noted earlier, Internet-therapy is not restricted to any one theoretical foundation. Still, Internet-delivered treatments so far have often concentrated almost entirely on what DeRubeis and Feeley (1990) called "concrete adherence", that is, the Internet-materials have focused on cognitive-behavioral tools, such as behavioral techniques and worksheets. Much less attention has been paid to "abstract adherence", such as a focus on discussing other therapy-relevant issues like understanding the patients' situation and beliefs, or the patients' wellbeing and progress. This might be seen as a disadvantage, but can be an advantage to some patients (Wagner, Horn, & Maercker, 2014), depending on personal preferences. Sometimes patients wanting abstract adherence might also initiate, and find at least some outlet for, this more personal side in their contact with the supporting therapist.

Face-to-face therapy, in group format or in one-on-one situations, can be a stressful experience, and stress can, to some degree, prevent the patient from understanding

the message (Andersson et al., 2013). Because of this, for some patients, the Internet format might enhance effectiveness by reducing stress for some patients.

One problem with psychological treatments is that patients can misunderstand or forget important aspects of the treatment. Therefore, another possible advantage of Internet-delivered treatments is that they are almost always delivered in a format that allows the patient to repeat parts of the treatment, often even after the actual treatment period is over (Andersson et al., 2013).

Internet-delivered treatments can, of course, be tailored and adapted for very specific populations, such as specific ages or combinations of problems, for example depression and diabetes (van Bastelaar, Pouwer, Cuijpers, Riper, & Snoek, 2011). This can make very specific and specialized treatments available to patients who, for some reason, cannot attend specialized clinics.

Internet-delivered psychological treatments are not only standalone treatments; they can also be used in conjunction with, and as an enhancement of more traditional care (Krieger et al., 2014). Studying patients who had previously received treatment for major depression, and who had experienced partial remission, Holländare et al. (2011) found that significantly fewer patients who received ICBT experienced relapse compared to a control group.

One possible disadvantage of Internet treatments is the fear of patients dropping out of the treatment, meaning patients that for some reason discontinue the treatment. To minimize drop-out, unguided self-help treatments should be avoided (Cuijpers et al., 2011). Concerning guided self-help, the risk of dropping out has been found to be somewhat higher, but not significantly, compared to face-to-face treatment (Cuijpers, Donker, van Straten, Li, & Andersson, 2010). This is, however, hard to ascertain because the definition of drop-out is unclear and varies between studies (Melville, Casey, & Kavanagh, 2010). While on the subject of drop-outs, it is important to note that some amount of drop-out always occurs in all treatment forms, and that drop-outs do not always mean that a treatment has failed. As many as 25-30% of drop-outs have been found to have experienced significant benefit from the treatment (Hadjistavropoulos et al., 2014; Newby et al., 2013), and many of the non-completers could have attained sufficient help to justify dropping out (Hilvert-Bruce et al., 2012). Adherence to ICBT appears to be adequate and probably equal to face-to-face CBT, but the pattern of drop-out seems to differ between the two. In face-to-face CBT patients mostly discontinue treatment early, while in ICBT patients tend to drop-out more gradually (van Ballegooijen et al., 2014). As mentioned earlier, one reason for dropping out, particularly later on, could be that the patient feels a high sense of improvement and is satisfied with the outcome.

When discussing treatments, we tend to focus on positive effects. Psychotherapy research in general has also focused on examining efficacy and effectiveness, and often neglects the possible negative effects of the treatment (Barlow, 2010; Nutt & Sharpe, 2008). Reports from Internet treatments have thus followed the beaten path (Boettcher, Rozental, Andersson, & Carlbring, 2014). A recent consensus document from ten leading experts on Internet interventions concluded that negative effects are also to be expected from Internet treatments, and thus need to be acknowledged to a greater extent than has been the case so far (Rozental et al., 2014). In a recently published study, 61 (11%) of the 558 included patients indicated that they had experienced at least one adverse event that might be related to the ICBT treatment (Rozental, Boettcher, Andersson, Schmidt, & Carlbring, 2015). Deterioration and experiencing novel symptoms were common, as in face-to-face therapies, as well as negative experiences that the patients related to the Internet-format. Often a need for more flexibility and therapist contact than the trial protocol allowed was expressed. In response to this, adjustments in treatment design, such as increased flexibility in therapist-patient contact, can be suggested. Design should also focus on user-friendly interfaces.

As always, we must consider ethical issues and implications of the treatments we offer. It is also important to recognize the need for therapists to keep pace with new technologies and methods within this field (Dever Fitzgerald, Hunter, Hadjistavropoulos, & Koocher, 2010).

2.4.4 The Efficacy and Effectiveness of ICBT for depression

Internet-delivered therapy has shown good results for a number of different disorders, including depression (Hedman, Ljótsson, & Lindefors, 2012). The bulk of research conducted so far has however been in the form of efficacy-studies.

In addition to the previously mentioned study on CCBT by Selmi et al. (1990), another example of an early study the ODIN trial that offered unguided ICBT or control to severely depressed persons, with no feedback or reminders given during treatment (Clarke et al., 2002). The effect across the sample was low, but among persons with a low level of depression at inclusion, the effect was moderate. For the follow-up study, ODIN-2, adding postcard and telephone reminders resulted in a small between-group effect (Clarke et al., 2005). Interestingly, in this study the effect was more pronounced among persons who were more severely depressed at inclusion. Another early study where participants were randomized to either unguided ICBT, information via Internet, or control, demonstrated a significant moderate within-group effect (Christensen, Griffiths, & Jorm, 2004). At 12-month follow-up, the effect

size had been somewhat reduced (Mackinnon, Griffiths, & Christensen, 2008). However, both at post and follow-up, the effect of the "information via Internet" condition was on par with the effect of ICBT.

In a study of subthreshold depression in persons 50 years of age or older, participants were randomized to either unguided ICBT, CBT (face-to-face) group treatment, or control. The ICBT demonstrated a moderate between-group effect size compared to control, and the CBT group treatment a small (Spek, Nyklicek, et al., 2007). One year after the start of treatment the effect of the ICBT was maintained, but not so for the effect of the CBT group treatment (Spek et al., 2008).

More importantly, using the Swedish DAVID-program, Andersson et al. (2005) compared *guided* ICBT (including participation in a discussion group) to activity in a discussion group only (waitlist control), and reported a large between-group effect size. When comparing guided ICBT, and guided problem solving therapy, to control, Warmerdam et al. (2008) reported moderate between-group effect sizes for both treatment conditions. More recently, large effect sizes have been reported from a number of studies on guided ICBT, for example, Perini, Titov, and Andrews (2009) and Ruwaard et al. (2009).

A meta-analysis on Internet- and computer-based psychological treatments for adult depression shows an overall effect size of $d = 0.41$ (Andersson & Cuijpers, 2009). Even more interestingly, treatments with support had an average between-group effect of $d = 0.61$, while unsupported treatments had a much smaller average effect of $d = 0.25$ (Andersson & Cuijpers, 2009). This is in line with the findings of other meta-analyses (Richards & Richardson, 2012; Spek, Cuijpers, et al., 2007), although one meta-analysis have found larger effects, average $d = 0.94$ (Hedman, Ljótsson, et al., 2012).

Concentrating on studies specifically comparing Internet-delivered, guided self-help to face-to-face therapy, a meta-analysis indicates that the effect of Internet-delivered, guided self-help for depression and anxiety is comparable to face-to-face therapy. This remains the case at a one-year follow-up (Cuijpers, Donker, et al., 2010). More recently, a randomized controlled trial (RCT) using patients recruited via advertising, and comparing ICBT to group-based face-to-face CBT with the same components as the ICBT (i.e., comparing the same treatment but in different formats), found moderate to large within-group effect sizes and non-inferiority for ICBT (Andersson et al., 2013). The three year follow-up actually showed a tendency for ICBT to be superior to group treatment (Andersson et al., 2013). Comparing ICBT to a face-to-face intervention with the same treatment modules, delivered in the same chronological order and time-frame, no significant between-group differences were found (Wagner

et al., 2014). Wagner et al. concludes, although further research is necessary, that ICBT can be a cost-effective way to meet the growing demand for treating depression.

All this (mainly efficacy, but also some effectiveness) research makes it easy to join Cuijpers, Donker, et al. (2010, p. 1943) in their statement "It is time to start thinking about implementation in routine care".

This is exactly what has been done at the Internet Psychiatry Unit (IPU), a research and routine care setting at an outpatient psychiatric clinic providing Internet-based treatment in Stockholm, Sweden. The IPU has evaluated the effectiveness of guided ICBT for depression among all patients that were treated between 2007 and 2013 (Hedman et al., 2014), and found an effect size on the MADRS-S of d = 1.27, 99% (CI, 1.14-1.39), and that the improvements were sustained at 6-month follow-up. Seventy-five percent of the patients completed at least half (five of ten modules) of the treatment and were considered completers.

However, studies of the effectiveness of ICBT for depression outside of specialized wards, and especially in primary care are, as mentioned before, scarce, and randomized controlled trials are even rarer. Both CCBT (Proudfoot et al., 2004) and ICBT (Newby, Mewton, Williams, & Andrews, 2014; Ruwaard, Lange, Schrieken, Dolan, & Emmelkamp, 2012; Watts, Newby, Mewton, & Andrews, 2012; Williams & Andrews, 2013) have been evaluated with good results, but clearly, more research is needed (Andersson & Hedman, 2013).

2.5 Primary care & psychology

The Swedish Law on Health and Care §5 states:

> *Primary care … shall without demarcations concerning the disease, age, or patient populations, cater to people's need for such basic medical treatment, care, prevention, and rehabilitation that do not require hospital medical and technical resources, or other special skill* [author's translation] (Government Offices of Sweden, 1982).

Primary care is often the point of entry into the health care system. It is also comprehensive in the sense that it encompasses all major disciplines and caters to all kinds of different health issues (Bray, Frank, McDaniel, & Heldring, 2004). This means that primary care plays a key role in preventing, diagnosing, and treating most health problems and diseases, and, as a consequence, primary care staff will have to deal with almost any somatic or psychiatric disorder. No matter what your problem is, big or small, body or mind, you turn to your primary care center, and most of the time

your problem will be treated within primary care. Most depressive disorders, for example, are treated within primary care (National Board of Health and Welfare, 2010; SBU, 2004a).

It has been estimated that about a third of all visits in Swedish primary care are, in some way, connected to psychological suffering/mental illnesses (Carlsson, 2001). In a waiting room survey in the Swedish region of Västernorrland of adults visiting primary care centers (Kallioinen et al., 2010), about 18% named psychological problems as "the reason" or "one of the reasons" for the visit. Additionally, 27% of the women and 16% of the men rated their psychological health as low. All accounted for, about 36% of the women and 22.5% of the men rated their psychological health at levels warranting attention from the health care system (Kallioinen et al, 2010).

The American Psychological Association defines primary care psychology as

> …the application of psychological knowledge and principles to common physical and mental health problems experienced by patients and families throughout the lifespan and presented in PC (APA Interorganizational Work Group on Competencies for Primary Care Psychology Practice, 2013, p. 5).

There is an obvious need for psychological treatment in primary care. This makes primary care psychology seem only natural, but, surprisingly, it has been only recently introduced, and is in no way comprehensive. According to the Swedish Psychological Association survey in 2011, only 52% of Swedish primary care centers had a psychologist among their staff (Sveriges Psykologförbund, 2011). In a survey by the Swedish National Board of Health and Welfare (National Board of Health and Welfare, 2007), only 22% of primary care center managers described access to psychological treatment at their primary care center as "satisfactory." The managers named lack of resources and/or shortage of skilled personnel as the reason for this deficiency. Psychologists and therapists trained in evidence-based treatments, such as CBT, are also still in short supply (National Board of Health and Welfare, 2013), and poor access to primary care psychology leads to long waiting times for patients.

2.6 The PRIM-NET project

In 2009 the Västra Götaland region was facing the problem of a substantial number of depressed patients in primary care, the recommended treatment for depression being CBT, and a shortage of psychologists or psychotherapists knowledgeable and experienced in CBT. It was then recognized that ICBT might be an answer. Acknowledging that the research on ICBT in clinical settings, especially in primary care, was

very sparse, and that no one really knew how to implement ICBT in primary care, the *PRIMary care InterNET* research project (*PRIM-NET*) was initiated.

The main objective of the project was to help primary care centers implement ICBT for depression, using the psychologists and psychotherapists (henceforth collectively called "therapists") already employed at the primary care centers, and also to evaluate different aspects of the implementation and effectiveness of the ICBT treatment in the process. A total of 18 primary care centers throughout the region, situated in urban and rural areas, were involved, and 16 of these provided patients. The project operated at primary care centers from the spring of 2010 through the spring of 2013, and has been a cooperation between the Department of Public Health and Community Medicine/Primary Health Care, the Department of Psychology, the Section of Social Medicine, and the Department of Psychiatry and Neurochemistry, all at the University of Gothenburg; the Research and Development Board for Primary Care; and the Primary care of the Västra Götaland region. The project has received additional funding from REHSAM.

The Regional medical ethics review board in Gothenburg, Sweden approved the protocol. Written informed consent was obtained from all patients.

2.6.1 The taskforce and package

Professor Cecilia Björkelund at the Department of Public Health and Community Medicine/Primary Health Care was appointed project leader, and the main workgroup has been drawn from the Department of Public Health and Community Medicine/Primary Health Care, the Department of Psychology, and the Research and Development Board for Primary Care. The ICBT treatment used was Depressionshjälpen®, a commercially available ICBT package in Swedish, developed by Psykologpartners W&W AB. The communication system Mina Vårdkontakter (MVK), used nationwide for secure communication between patient and health care provider, was used as the secure e-mail system for communication between therapists and patients.

The PRIM-NET workgroup assembled and supplied the primary care centers with a package consisting of:

- − a comprehensive and user-friendly therapist and study-nurse manual
- − all materials needed, such as patient forms and documents
- − access to the ICBT treatment Depressionshjälpen®
- − access to the secure e-mail system, MVK
- − a thorough introduction to all components and protocol, for therapists and study-nurses
- − regular supervision of therapists and study-nurses

- telephone support during all office hours
- repeated information meetings and demonstrations of the ICBT for all staff at the primary care centers
- a payment to the primary care center per enrolled patient, or in some cases a fixed percentage of the study-nurse or therapist's pay, intended as reimbursement for extra time spent due to PRIM-NET.
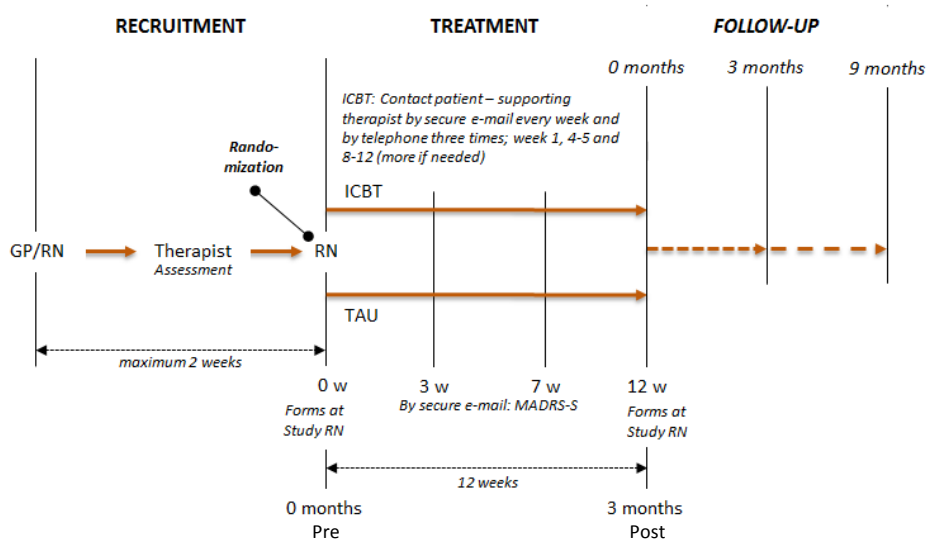
Figure 1   Schematic overview of the design of PRIM-NET

2.6.2 The primary care centers

To participate in the project, primary care centers had to have access to a licensed psychologist or licensed psychotherapist (henceforth collectively called "therapists"), educated and experienced in working with CBT, and who wanted to use and integrate ICBT into their work. They also needed a registered nurse (RN), acting as study-nurse at the primary care center.

The main idea of the project was that GPs and RNs in the primary care centers would approach all patients aged 18 years or older, who they perceived as being depressed, and offer them the possibility to enroll in PRIM-NET. This meant that in order for the implementation to be successful, there had to be some acceptance among the GPs

and RNs towards ICBT, and of research being performed within their primary care center.

The enrolled patients first met the therapist for an assessment, and, if they were deemed eligible for PRIM-NET, they then met the study-nurse for randomization to either ICBT or TAU.

TAU meant the patient would receive the treatment normally offered to this type of patient at the particular primary care center, had there been no PRIM-NET. TAU, therefore, could consist of a diverse mix of antidepressants, scheduled contacts with personnel at the primary care center, referral to regular psychotherapy (often preceded by a non-negligible waiting period), or some combination of these options, depending on routines and available resources at each primary care center.

Randomization to ICBT on the other hand meant that the patient received (from the study-nurse) a short explanation of the ICBT package, a workbook on paper, and a code for accessing the ICBT.

During the treatment, all patients in PRIM-NET, ICBT and TAU, were given a questionnaire measuring their depression (MADRS-S) twice (week three and seven), in order to follow their wellbeing and observe any aggravation of their depression. This questionnaire was sent out via MVK. Any signals, via the questionnaires or via other channels, to the study-nurse or therapist, indicating the patient deteriorating, led to them making contact with the patient for assessment and the possibility to substitute the care.

12 weeks after inclusion (i.e., at post-treatment), the patient once more visited the study-nurse to fill out forms.

2.6.3 The recruitment rates – Intensified efforts and Adjustments in study setup

Due to the fact that PRIM-NET was being performed within regular live primary care, all demands of the study protocol on participating primary care staff had to be carefully considered, and any intrusion on their time limited to a minimum. This, of course, severely restricted the possibilities to keep an accurate account of the number of invitations and assessments made at the primary care centers, as well as reasons for exclusion of patients.

It did, however, soon become evident that recruitment rates in PRIM-NET were lower and much slower than anticipated. Difficulties in recruiting patients to depression trials have also been reported in other studies (Hughes-Morley, Young, Waheed, Small, & Bower, 2014).

The evident low recruitment rate lead to extended efforts by the PRIM-NET taskforce in recruiting additional primary care centers, intensified campaigns toward staff at new and already enrolled primary care centers in order to market the project, educating and reminding staff, and also assisting and simplifying the primary care staff's work as much as possible. Additional material was developed and distributed, for example:

− quick reference guides for GPs and RNs
− posters and other informational material aimed at the patients

PRIM-NET also recruited CBT knowledgeable psychologists to perform assessments and ICBT support at participating primary care centers wanting to join PRIM-NET but lacking this resource.

In an effort to enhance enrollment by relieving the primary care centers of extra work and administration, a centralized primary care ICBT unit was set up and also run by PRIM-NET personnel in the municipality of Uddevalla. All primary care centers in Uddevalla municipality were invited to participate and remit patients to this unit. The centralized ICBT unit served the seven participating primary care centers in Uddevalla with all parts of the study protocol after the GP consultation. Since remitting patients to a centralized unit would not impact the primary care centers limited psychosocial resources, this was believed to possibly enhance the interest in remitting patients. For referral reinforcement reasons, all included patients randomized to TAU at the centralized unit were also offered ICBT *after* the treatment period. See Figure 3, page 39.

Note that these TAU+ICBT patients have been analyzed as TAU in Study I, (figure 4, page 42) but as ICBT in Study II and III (figure 5, page 43).

2.6.4 The assessment

The semi-structured therapist assessment lasted approximately one hour, and was based on the Mini International Neuropsychiatric Interview (MINI), with adjustments in section I (alcohol, relaxed criteria), and additions from MINI plus concerning depression and dysthymia, a procedure diagnosing Burn-out according to suggested Swedish criteria (National Board of Health and Welfare, 2003), and questions asserting that the patient was not cognitively disabled, see also section 4.1.2, page 46.

Exclusion criteria concerning previously attempted suicide, and current suicidal ideation and/or plans were set rather conservatively, mostly due to ethical considerations and according to medical ethics review board requirements. Exclusion of patients with recently introduced or changed medication was also done in order to minimize the impact of medication on the reduction of depression during the study.

The full therapist guide, in Swedish, used to assess eligibility can be found at http://psy.gu.se/digitalAssets/1535/1535088_manual_prim-net.pdf

2.6.5 The patients

In order to participate, patients had to be diagnosed with mild-to-moderate ongoing depression according to DSM-IV. Diagnosed anxiety was allowed, if it was considered secondary to depression. The patients also had to have access to a computer, with speakers or headphones, connected to the Internet.

Initially, the goal was, over the course of one year, to recruit a minimum of 142 patients, at four to six participating primary care centers. It soon became apparent that this plan was not realistic.

In total, 92 patients were randomized, although the post study review of interview protocols identified two patients who had been incorrectly included. They were consequently removed from the analyses (one in ICBT and one in TAU), leaving 90 included patients. These reviews were carried out post-study, with the intent that this would inconvenience the patients and the primary care centers the least.

In an effort to enhance enrollment a centralized unit was set up (see section 2.6.3, page 32). Eight patients at the centralized unit were randomized to TAU+ICBT. These patients have been analyzed as TAU in Study I, (figure 4, page 42) but as ICBT in Study II and III (figure 5, page 43).

2.6.6 The ICBT treatment

Within the first week after randomization, the ICBT patients were contacted via telephone by the same therapist they had met during assessment. The goal of this call was to help the patients start the treatment. The patients then worked on the Internet-package by themselves, at home or where it was convenient for them, but also had regular contact via MVK and/or phone every week with their therapist.

Depressionshjälpen® is based on CBT, and more specifically Behavioral Activation, a method shown to be effective for depression in previous research (Dimidjian et al., 2006), with components from Acceptance and Commitment Therapy (ACT) and mindfulness (Zettle, 2007).

The treatment consisted of seven information modules accessed through the Internet and a workbook on paper, to be used in conjunction with the online material. PRIM-NET recommended to the patients that they work on and finish one module per week, and thus finish the whole treatment in eight weeks. Previous research has found improved effectiveness if a clear deadline for the treatment is used (Andersson et al., 2009; Paxling et al., 2013), and thus the patients were informed that their access code

would expire after 12 weeks. The 8-12 week setup was used to allow patients' ordinary life to interfere with their treatment.

Each treatment module consisted of eight to ten slides and followed the same structure: The first few slides addressed the assignments from the last module, followed by a short survey on the current level of wellbeing in four different dimensions (sadness, fatigue, hope for the future, and quality of life). The main part of the slides then presented the patient with new information in the form of short texts, films, pictures, and/or animations. The last few slides introduced new assignments to be carried out and also directed the patients to the workbook and the fill-in exercises and diaries. All texts were narrated and the patients could therefore listen to them, if preferred, instead of just reading.

Undvikandebeteenden

Vi människor har en tendens att låta oss styras av de kortsiktiga konsekvenserna av våra beteenden. Det är helt normalt och något alla människor gör. Men när man är deprimerad och så mycket i tillvaron känns jobbigt är det vanligt att man ökar antalet beteenden som ger den kortsiktiga konsekvensen av att slippa mer av det jobbiga. Man börjar undvika för att slippa ytterligare obehag. Det kan handla om att slippa det jobbiga med att skriva en handlingslista när man är helt orkeslös eller det kan vara att inte orka möta den ångest det innebär att ringa en vän som man lovat ringa för länge sedan. När livet börjar styras av fler och fler av dessa beteenden så kan man likna det med att fastna i "onda cirklar" som kan vara svårare och svårare att ta sig ur ju längre de får snurra. Vi använder undvikandebeteenden mer ofta i sammanhang där vi stöter på "igångsättare". Vilka undvikandebeteenden har du?

Slå upp sidan 11 i din arbetsbok. Titta på exemplen och skriv sedan på nästa sida ner beteenden som du gör för att undvika jobbiga känslor och tankar och vad du tycker att du får ut av det i stunden, samt vilken effekt de får på sikt. Titta även på det du tidigare skrev ner på sidan 5 i arbetsboken (strategier/anpassningar) och se om några av dessa beteenden kan klassas som undvikanden.

Figure 2   Text-slide example from Depressionshjälpen®

Every module contains eight to ten slides of text, pictures, films etc. The slide shown above is from module two and explains Avoidance ("Undvikande"). The squares below the text show how many slides there are in this module (eight), and where you are within this particular module (indicated by the yellow arrow head under the sixth slide).

In short, Depressionshjälpen® explained depression (according to behavior activation theory), showed the patients how their behavior influenced their wellbeing, and aimed to help them find a better balance in their activities, and thus break the negative spiral of depression.

The themes of the modules were:

1. Psychoeducation on depression
2. The link between activity and wellbeing (avoidance and activities)
3. Understanding different activities and the role of reinforcement
4. Make a difference in your life (focusing on behavioral change)
5. Thoughts and emotions (defusion and acceptance)
6. Repetition and continued practice
7. Relapse prevention

2.6.7 The therapist support – Minimal therapist contact

Internet treatments that include therapist contact have, in previous research, shown better results than pure self-help Internet treatments (Andersson et al., 2009). In the PRIM-NET project, therapist contact was to be provided by therapists already employed at the primary care center. In order to facilitate the working alliance between patient and therapist, the patient was always assisted by the same therapist as in the initial assessment.

Therapist and patient engaged in at least three telephone calls during treatment. In week one, the therapist called to check if everything was going well, and to help the patient get started. The therapist also checked in on the patient in the middle of the treatment (week four or five) and at the end of the treatment (between weeks eight and twelve). More calls could be made if deemed necessary. Every week patient and therapist also communicated via MVK, in short written messages.

In case of any signs of patients not engaging in their treatment or their wellbeing deteriorating, the therapists should contact the patient and evaluate the situation. All patients also received written information on where to turn in case of an emergency, such as their depression turning worse or if they experienced any suicidal tendencies.

The therapist could, throughout the treatment, oversee the patient's progress via login times and information on which modules were accessed. As mentioned earlier, the therapist also had access to the patient's weekly reports on wellbeing, and MADRS-S at weeks three and seven.

In PRIM-NET, the therapist met the patient only during the initial assessment. After the treatment period, the patient was scheduled to once again meet the study-nurse to fill in forms.

2.6.8 The therapists

All therapists participating in PRIM-NET were required to be educated and experienced in CBT and in treating depression prior to participation. They also had to be licensed psychologists and/or psychotherapists, or graduated psychologists working under supervision pending their license. 14 therapists participated in PRIM-NET, and of these, one therapist had diplomas as both psychologist and psychotherapist. Among the other 13 therapists, ten were psychologists and three were psychotherapists. Of the ten psychologists, two had pending licenses. The gender distribution among the therapists was equal, with seven women and seven men.

The requirements of license (or degree pending license), CBT experience, and depression experience were set to ensure that 1) the patients and their problems would be properly assessed and correctly diagnosed, and 2) that the therapists would understand the theory and methods in the ICBT, minimizing the risk of them performing any action contradictory to the treatment.

Assisting patients in Internet-delivered therapies differs from working as a therapist in face-to-face therapy. The task is here to *support* the Internet package, that is, it is the Internet package that constitutes the treatment. The therapist should not introduce anything new, but rather explain, help, and support the patient in their work with the Internet package. If the supporting therapist would, for example, introduce themes that are not included in the Internet package, or perhaps even counteract the Internet treatment, there would be an impending risk that the treatment would not work. As a supporting therapist, it is therefore important to understand the theory and method, in this case CBT, and more specifically Behavioral Activation.

One of the therapists in the project did not perform any assessment at all within PRIM-NET, while a few of the therapists performed many, some as many as 30. This number is somewhat uncertain since PRIM-NET was performed as an effectiveness study within live primary care, and some assessments not leading to the patient being included in the project might have been performed under the radar. On the other hand, we do know the number of ICBT patients the therapists were responsible for in PRIM-NET: four therapists did not support any ICBT treatments at all, while others supported as many as sixteen; the mean number of supported patients among the therapists that did support patients was five. It should be noted that some of the therapists had experience working with Internet treatments outside of the PRIM-NET project, and in some cases this experience has been rather extensive.

The original plan for PRIM-NET was to use therapists already working at the participating primary care centers. For various reasons, this did not always work out, and

PRIM-NET therefore also provided and used qualified therapists normally not working in primary care, and who only made special appearances at the primary care centers to perform assessments and act as support for ICBT treatments within PRIM-NET. The therapists' experiences of primary care therefore varied from none, among some of these specially provided therapists, to very extensive, among a few of them.

Quite naturally, the initial attitude among all recruited and participating therapists towards Internet-delivered treatment and towards CBT was positive.
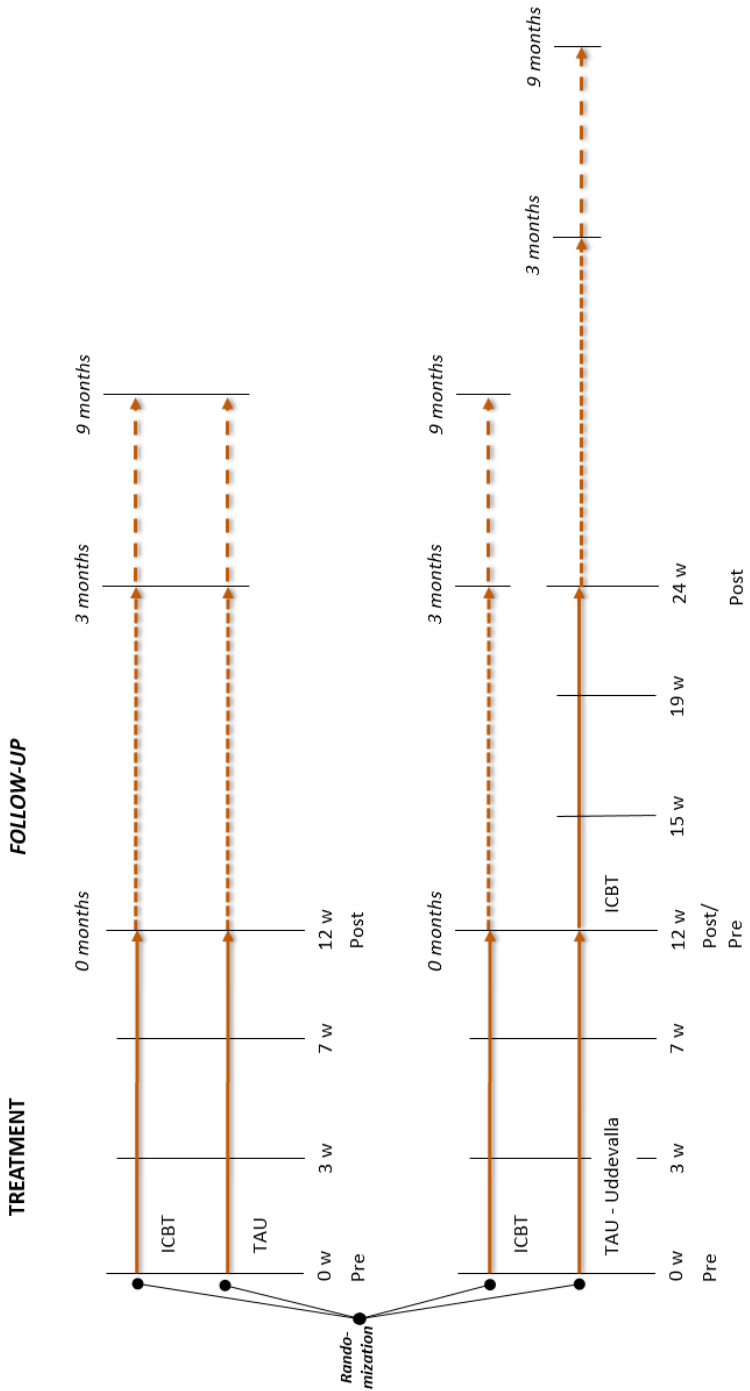
Figure 3   Schematic overview of PRIM-NET and the two different setups

The original design with randomization to either ICBT or TAU at the top. Below the adjusted design used in Uddevalla where TAU was followed by ICBT. Randomization was carried out consecutively across all primary care centers irrespective of setup.

3 Aims

The overall aim of this thesis is to investigate aspects of Internet-delivered psychological therapy, as implemented in primary care. More specifically:

I. *Is the effectiveness of ICBT for depression in a primary care context, in both short and long term perspective, comparable to TAU?*

Introducing new treatments in health care should always signify progress. Thus, new treatments should be at least as effective as what is already being offered to the patients, with effectiveness typically examined in RCT designs. If ICBT is found to be at least as effective as TAU, patients receiving ICBT will not be at a disadvantage. ICBT can then also become a treatment alternative in primary care. Previous research has indicated that ICBT would be at least as effective as TAU in reducing depression, and that ICBT might very well outperform TAU.

II. *For which patients is ICBT for depression most effective in the primary care context?*

Health care such as primary care operates on limited resources. Matching a treatment to those who are most likely to benefit from it optimizes treatment outcome, and also saves resources. Knowledge of factors that predict outcome thus gives the therapist the ability to help patients to a greater extent, and also help more patients.

III. *What are the primary care therapists' experiences of and attitudes towards ICBT?*

Without acceptance from the staff that ultimately will have to use it, an otherwise effective treatment will not disseminate. Consequently, acceptance among primary care therapists is crucial for successful implementation of ICBT in primary care, and thus ultimately an effective treatment. Without acceptance, ICBT will not be feasible. A qualitative investigation of therapists' experiences and attitudes could then set the direction of future implementations. This could also give important insights into how to best adapt and implement ICBT in primary care, as well as into how ICBT might evolve once implemented.
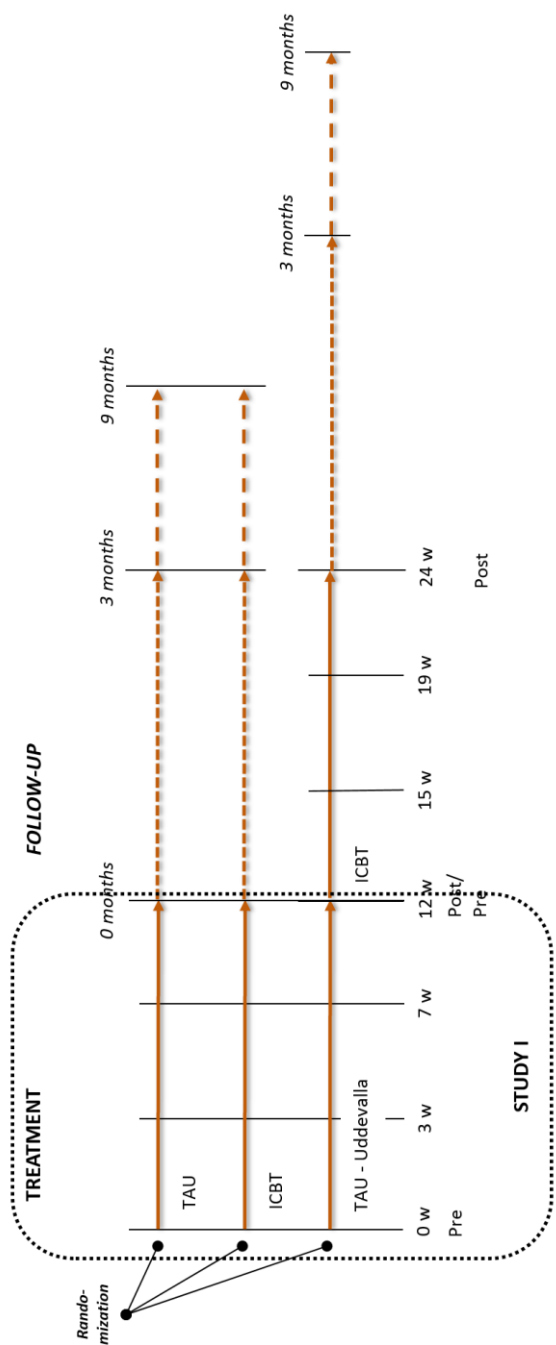
Figure 4   Schematic oververview of Study I

Where the Uddevalla TAU+ICBT-patients were seen as TAU-patients and included in this group in the analysis.
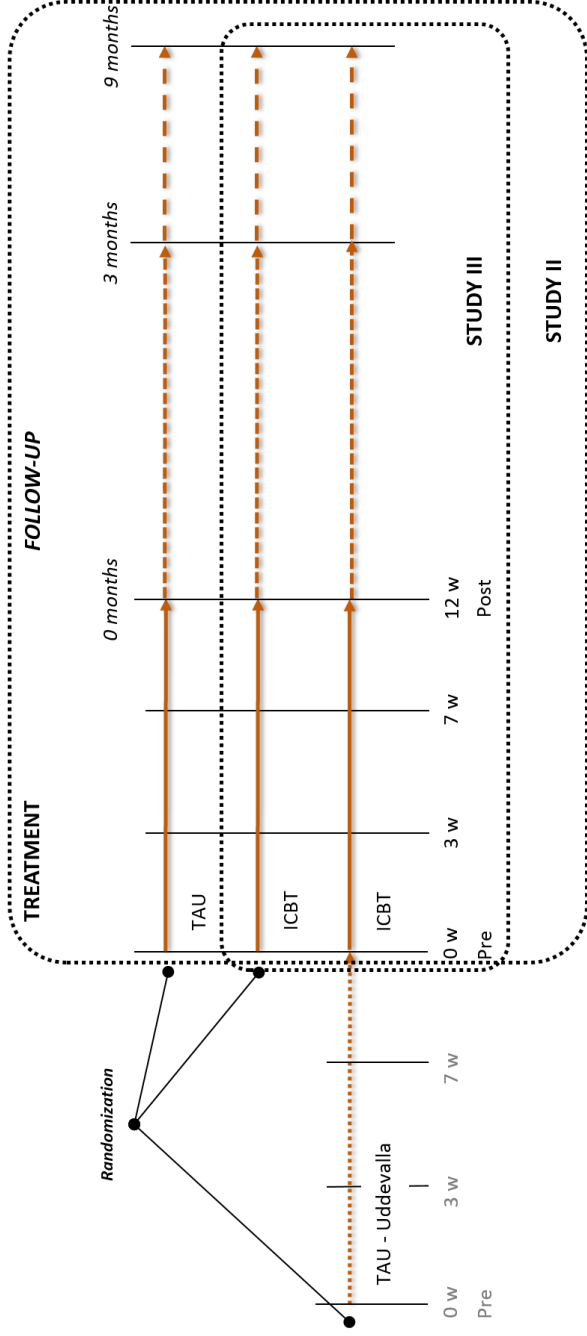
Figure 5   Schematic overview of Study II & III

Where the Uddevalla TAU+ICBT-patients were seen as ICBT-patients and included in this group in the analysis.

4 Procedures & Methods

4.1 Study I

Study I compared the effects, during and post treatment, of ICBT to TAU in terms of reduction of the degree of depression in patients.

4.1.1 Participants

At primary care centers participating in the PRIM-NET project, patients thought to be suffering from depression were invited to be assessed by a therapist, to determine if they suffered from mild-to-moderate depression (according to MADRS-S score) and were thus eligible for the study.

Ninety-two patients were randomized into either ICBT or TAU. The post-study review of assessment protocols identified two patients who had, due to human error, been incorrectly included. They were consequently excluded and removed from the analyses (one in ICBT and one in TAU).

Of the remaining 90 patients, eleven later withdrew from participation and have therefore been excluded from the analyses

Figure 6   Study I: Included patients and drop-out

in Study I. Sixty-five of the 79 patients (82%) completed the post-treatment forms: 30 (83%) in the ICBT and 35 (81%), in the TAU condition (see Figure 4, page 42, and Figure 6, page 45).

4.1.2 Method

4.1.2.1 Assessment and randomization

Naturally, all patients accepting participation in the study were, at least to some degree, positive to ICBT. To be *included* in the study, patients had to meet the following criteria: (a) aged 18 or older; (b) access to a computer with speakers or headphones; (c) diagnosed with depression according to the MINI, Swedish version 6.0.0b (Lecrubier et al., 1997; Sheehan et al., 1998); and (d) a MADRS-S (Montgomery & Åsberg, 1979) score < 35. If the patient was on antidepressant medication, the dosage had to be constant for the 4 weeks prior to inclusion[2].

The *exclusion* criteria were: (e) any prior suicide attempt (no boundary of time) or (f) currently found to be at a medium to high risk of suicide (operationalized by PRIM-NET as MADRS-S, Question 9 > 3 points and/or MINI Part B – Suicide > 9)[3], or were diagnosed according to the MINI with (g) substance dependence, (h) alcohol abuse, (i) bipolar disorder (manic and hypomanic episodes), (j) psychotic disorders, or (k) any other severe psychiatric disorder, or during the interview demonstrated (l) cognitive disability, or (m) insufficient knowledge of the Swedish language.

Diagnosed anxiety disorders were allowed if deemed to be secondary to depression.

It is important to note that at inclusion depression was diagnosed according to DSM-IV criteria (see (c) above), while the depth of the depression (i.e., mild-to-moderate) was ascertained by a MADRS-S score < 35 (see (d) above). The MADRS-S cut-off point for severe depression being a score of 35. In this sense all included patients suffered from mild-to-moderate depression (according to MADRS-S).

All *assessments* were performed by a therapist (i.e., a licensed psychologist or licensed psychotherapist) and were based on the MINI, developed to determine the presence of Axis-I disorders using DSM-IV diagnostic criteria (Sheehan et al., 1998).

In order to establish the validity of the initial assessment and diagnosis, the interview protocols were also reviewed by the project management. For practical reasons this review was carried out after the patients had completed the study. The results of the randomization and the outcome after treatment were not known to the reviewers at that time.

Included patients were then randomized to either ICBT or TAU by an independent randomization service. The randomization procedure occurred consecutively for all

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[2] Exclusion of patients with recently introduced or changed medication was made in order to minimize the impact of medication on the reduction of depression during the study.

[3] Exclusion criteria (e) and (f) were set conservatively due to ethical considerations and according to medical ethics review board requirements.

patients across primary care centers which made it impossible, at a specific primary care center, to predict the allocation of patients.

There were 13 therapists involved in the study, assessing patients; ten of those were also engaged in the support of patients[4].

4.1.2.2 Outcome measures

The primary outcome measure of depression was the BDI-II (Beck et al., 1996), administered at pre- and post-treatment. A secondary outcome measure was the MADRS-S, administered at pre-treatment, weeks three and seven, and at post-treatment. The Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988) for comorbid anxiety was used at pre- and post-treatment. All inventories were administered in paper format, except the MADRS-S at weeks three and seven, which, for practical reasons, had to be administered via the MVK to both TAU and ICBT patients. Carlbring et al. (2007) identified significant effects between Internet- and paper administration of BDI-II and BAI. However, no significant version-, order-, or interaction effects were found for MADRS-S.

4.1.2.3 Statistical analyses

Analysis was restricted to complete cases, rather than employing available imputation methods. Missing individual items were set to zero, since this assumption may underestimate, but never overestimate illness. For BDI-II, this was the case for two patients (both patients TAU, in total three items) in pre-measurement. For BAI, this was the case for four patients (in total four items) pre-, and two patients (in total two items) post-.

Means of change in questionnaire scores were analyzed using univariate ANCOVAs, assigning pre-treatment depression scores as the covariate. Effect sizes (Cohen's d) were calculated for between- and within-group changes.

We also identified the proportion of patients who, after the treatment, reached a score of 13 or below on the BDI-II, which according to norms is the cut-off for defining recovery from depression (Beck, Steer, & Brown, 2006). The difference in recovery rate between groups was evaluated by the χ^2 test. For ICBT-patients, adherence and correlation of reduction of depression to adherence, were also reported.

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[4] Numbers stated in Paper I are unfortunately erroneous, these are the correct numbers.

When examining possible waiting effects of the subsequent ICBT for the group of TAU+ICBT patients in Uddevalla, we also compared the mean values of intra-individual changes of this group to all other patients using ANCOVAs[5].

As a comparison, we also calculated ANCOVAs and Cohen's *d* for all included patients (n=90), with missing individual items set to zero, and with last observation carried forward (LOCF) for missing values[6].

4.1.2.4 Baseline comparisons

The mean age of participants pre-treatment (n=79) was 36.6 years (SD = 11.3); 52 (66%) were women. At inclusion, five (6%) patients suffered from minimal, 15 (19%) from mild, 27 (34%) from moderate, and 32 (41%) from severe depression, according to BDI-II cut-off scores. That is, according to BDI-II, 59% of the included patients suffered from mild-to-moderate depression, while 41% suffered from severe depression.

A comparison of baseline scores revealed no significant difference between treatment groups. χ^2 tests failed to reveal any significant between-group differences in demographic characteristics.

Independent t-tests revealed no significant differences in degree of depression (BDI-II or MADRS-S) at pre-treatment between drop-outs (including patients that withdrew), compared to all other patients[7].

4.2 Study II

Study II compared the effects, post-treatment and at three-month and nine-month follow-ups, of ICBT to TAU in terms of the degree of depression in patients.

4.2.1 Participants

Concerning adjustments to study setup, see section 2.6.3, page 32. See also Participants, Study I (first and second paragraph Section 4.1.1, page 45).

Study II used all available ICBT data. This means that for patients in Uddevalla, randomized to TAU (twelve weeks), who then received ICBT, the data from the ICBT treatment and the subsequent follow-ups were used (see also Figure 5, page 43).

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[5] Supplementary information. Analyses of TAU+ICBT vs all other patients at pre-treatment are not reported in Paper I. However, this information extends the understanding of the complete PRIM-NET project.

[6] Supplementary information. Alternative LOCF analyses are not reported in Paper I.

[7] Supplementary information. Baseline analyses of drop-outs are not reported in Paper I.

This setup gives a total of 52 ICBT-patients, including eight patients that received the ICBT treatment after an initial period of twelve weeks receiving TAU.

It should be noted that drop-out numbers vary between different measurements and also instruments, sometimes due to patients not answering all instruments, and sometimes due to patients not answering individual items in an instrument (see also section 4.2.2.3). This means that the number of patients responding in each step/measurement as a whole, does not always correspond to the number of patients answering individual instruments, such as BDI-II, in that measurement. For numbers pertaining to the BDI-II measurement only, see Figure 7, page 49[8].

4.2.2 Method

4.2.2.1 Assessment and randomization

See also Study I (Section 4.1.2.1, page 46)

The randomization procedure occurred consecutively for all patients across all primary care centers, including the centralized Uddevalla unit.

4.2.2.2 Outcome measures

The primary outcome measure was the BDI-II, administered at pre-treatment, post-treatment, three-month follow-up, nine-month follow-up.

Secondary outcome measures were the Quality of Life instrument EQ-5D (EuroQol Group, 1990), and the 12-item General Health Questionnaire (GHQ-12; Schmitz, Kruse, Heckrath, Alberti, & Tress, 1999);
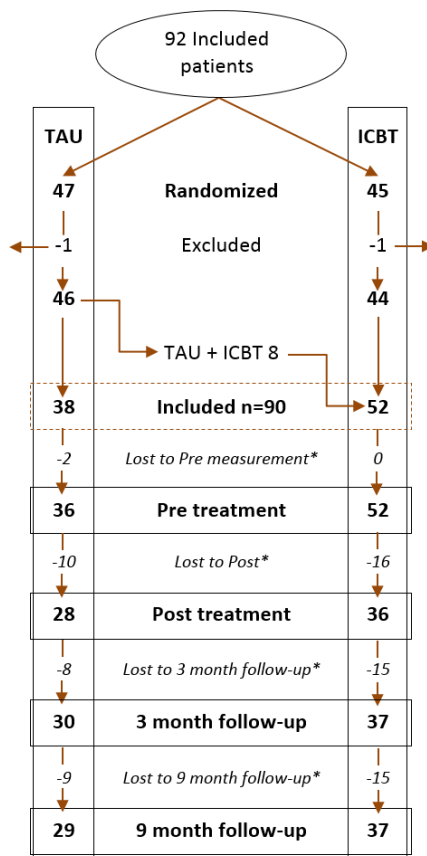
Figure 7   Study II: Included patients and lost to follow-up (BDI-II)

Note: Numbers in this flowchart pertain to BDI-II measurements only.

* "Lost to…" refers to patients whose data have not been included in the analysis (for details see also section 4.2.1 and 4.2.2.3). Numbers given as "Lost to…" should also be subtracted from the "Included n=90" level throughout the flowchart.

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[8] Supplementary information. Flowchart presented in Paper II states number of patients responding to any of the instruments included in each measurement. In this thesis only results from BDI-II is presented, thus the flowchart presented here states numbers pertaining to BDI-II only. For numbers concerning general response rate, please consult Paper II.

use of antidepressants (yes/no) and sedatives (yes/no); sick leave (yes/no) and number of days of sick leave; number of contacts with GPs, therapists, and nurses; number of therapist-patient telephone calls.

4.2.2.3 Statistical analyses

Analysis was restricted to complete cases. Missing individual items were not imputed, thus missing individual items lead to exclusion of that whole instance of the instrument. Concerning BDI-II, this was the case for two patients (both TAU) in pre-treatment, one patient (TAU) at three-month follow-up, and two patients at nine-month follow-up (one TAU, one ICBT). In analyses of change in BDI-II, pre – post two patients (TAU), pre – three-month follow-up five patients (four TAU and one ICBT) and pre – nine-month follow-up four patients (three TAU and one ICBT) were lost due to missing individual items[9].

Means of change in scores were compared using independent t-test. Frequencies were compared using χ^2-test or Mann Whitney U-test. Mean values for intra-individual changes in BDI-II, GHQ-12 and EQ-5D scores was calculated as pre – post, pre – three-month follow-up, and pre – nine-month follow-up. Medication was compared at pre- and post-treatment, three-month follow-up, and nine-month follow-up. Sick-leave was compared as pre – post, post – three-month follow-up, and three-month follow-up – nine-month follow-up.

Effect sizes (Cohen's *d*) were calculated for between- and within-group changes for pre – post, pre – three-month follow-up, and pre – nine-month follow-up.

For ICBT-patients, adherence is also reported[10].

As a comparison, means of change in scores were compared using independent t-tests and Cohens *d* calculated using LOCF (n=90; with missing individual items set to zero)[11].

4.2.2.4 Baseline comparisons

The mean age of all included participants (n=90) was 37.1 years (SD = 12.8); 63 (70%) were women. At inclusion, five (6%) patients suffered from minimal, 17 (19%) from mild, 31 (34%) from moderate, and 35 (39%) from severe depression according to BDI-II cut-off scores.

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[9] Supplementary information. Numbers of missing individual items are not given in Paper II. However, this information expands the understanding of data loss.

[10] Supplementary information. Adherence to ICBT is not reported in Paper II. However, due to the inclusion of additional patients (TAU+ICBT) in the ICBT treatment group, adherence statistics will differ from what has been reported in Paper I. It is thus of importance to report adherence for the complete ICBT treatment group as well.

[11] Supplementary information. Alternative LOCF analyses are not reported in Paper II.

There were no significant differences between ICBT and TAU patient characteristics, except concerning the number of patients using sedatives. There were significantly more patients using sedatives in the ICBT group, five patients (10%), compared to none among TAU.

Independent t-tests revealed no significant difference in degree of depression (BDI-II) at pre-treatment between drop-outs (at post-treatment, three-month follow-up, or nine-month follow-up) and all other patients.

4.3 Study III

Study III applied person-oriented methods to data on ICBT-patients' development during treatment and follow-up, in order to identify latent classes and explore distinguishing and possibly predicting factors.

4.3.1 Participants

See also Study I (Section 4.1.1, first paragraph, page 45) and Study II (Section 4.2.1, page 48).

Study III used all available ICBT treatment data, with the exclusion of patients that had withdrawn their participation. This number will however not correspond to Study I, since two patients (one TAU and one ICBT) later changed their mind and retracted their withdrawal, and thus have been included in the analysis in Study III.

This setup gives a total of 44 ICBT-patients, including seven patients that received the ICBT treatment after an initial period of twelve weeks receiving TAU. (See Figure 8)

4.3.2 Method

4.3.2.1 Assessment and randomization

See also Study I (Section 4.1.2.1, page 46) and Study II (Section 4.2.2.1, page 49).

4.3.2.2 Outcome measures

The primary outcome measure was the

Figure 8   Study III: Included patients and drop-out

Note: All MADRS-S measures were used (i.e. for weeks 0, 3, 7, 12, 24 and 48).

MADRS-S, administered at pre-treatment, weeks three and seven, at post-treatment, and at three-month and nine-month follow-up (Figure 5, page 43).

For practical reasons, and in order to create accurate longitudinal trajectories and statistical analyses in Study III, all time-points were translated into the unit of weeks. Time-points given in Paper III can be translated as 0 weeks = pre-, 12 weeks = post-, 24 weeks = three-month follow-up, and 48 weeks = nine-month follow-up.

4.3.2.3 Statistical analyses

Missing individual items were replaced by mean substitution (this was the case for one patient/three items at the three-month follow-up).

Latent growth curve models (LGCM) and latent class growth models (LCGM) were fitted to data using Mplus software (version 7.1; Muthén & Muthén, 1998-2012). First, LGCM were run to examine the overall patterns of change in depression for the whole sample. Then LCGM were used to identify possible latent subgroups/classes in data.

A number of fit-indices were used to compare model fit between the models with different number of classes. Following the recommendations of previous work (e.g., (Jung & Wickrama, 2008), we also used other criteria, aside from the fit-indices, such as parsimony, theoretical justification, and interpretability, when deciding which model and how many latent classes would be most appropriate to choose given the data.

Subsequent analysis of possible predicting factors was performed using ANOVA, χ^2-test or Fisher's exact test.

4.3.2.4 Baseline comparisons

Independent t-tests and χ^2-test, revealed no significant between-group differences in demographics for the seven TAU+ICBT patients compared to all other ICBT patients. However, patients randomized to TAU+ICBT showed significantly lower anxiety (BAI) and depression scores (MADRS-S) at the start of the ICBT treatment, compared to all other ICBT patients.

4.4 Study IV

Study IV explored primary care therapists' attitudes and experiences of ICBT and the implementation of ICBT within PRIM-NET, using qualitative methods from grounded theory and the seven barriers to implementation identified by Cochrane et al. (2007) (Table 3, page 13).

4.4.1 Participants

During the spring of 2012, all therapists (licensed psychologists or psychotherapists) at primary care centers participating in the PRIM-NET were invited to answer a survey. Twelve therapists had been participating up to that point, eleven of them replied. Focusing on the experienced primary care therapists' view, four therapists with long-term experience working both within primary care and with CBT were subsequently interviewed (two female and two male). Therapists with little or no experience in primary care were thus excluded from the interviews. All interviewed therapists had also answered the previous survey. The interviewed therapists rated themselves as having a rather balanced approach to CBT, with no clear focus on either cognitive or behavior therapy.

4.4.2 Method

4.4.2.1 Survey

The survey consisted of one section with 39 multiple-choice questions, and one section containing five open questions, whereby the therapists could write their opinions and thoughts in their own words.

Results focusing on the multiple-choice questions in the survey have previously been presented in a local report (Kivi, 2012). Study IV focused on the data emanating from the open questions.

4.4.2.2 Interviews

The four therapists were interviewed at length between November 2012 and February 2013. At the time of the interviews, all interviewed therapists had concluded their participation in PRIM-NET. All interviews were conducted by the author of this thesis.

Three interviews were performed via telephone, and one face-to-face at the primary care center. The interviews lasted 46-75 minutes. Each interview was introduced as an opportunity to give feedback to PRIM-NET. It was also stressed that the purpose of the interviews was to learn from experience and from any mistakes that may have been made. The importance of disclosing all criticism and anything that had not been optimal, had not worked, and that could have been better, was stressed. The interviews then started with the prompt "Please tell me about your experience of participating in PRIM-NET." The goal of the interview was to cover two main areas: *I. Thoughts and attitudes on performing research within primary care*, and *II. Thoughts and attitudes on ICBT*. If the interviewed therapist did not spontaneously cover these two topics, the interviewer would prompt the therapist. All interviews were taped and transcribed verbatim; one interview by the author of this thesis, and three by an independent professional transcription service.

4.4.2.3 Data analysis – General Themes

As a first step, inductive analysis using methods from grounded theory (Birks & Mills, 2010) was commenced. All transcribed data from the interviews, as well as the open ended questions in the survey, were read several times, focusing on both manifest and latent content. Open codes were then created for each paragraph.

The second step involved inductive analysis grouping data into themes. The open codes from the first step were grouped, re-read, and re-grouped into broader categories emerging from the data. These categories were then grouped into six general themes.

4.4.2.4 Data analysis – Barriers to Implementation

The open codes emerging from the data in the first step, section 4.2.2.3 above, were analyzed and grouped using the seven possible behavioral and system barriers against successful implementation defined by Cochrane et al. (2007) (see Table 3, page 13) as a guide, but not as a forced grid.

4.4.2.5 Credibility of analysis and findings

The credibility of the findings was ascertained by co-author Maria Eriksson reading the transcripts of the interviews, the results of the analysis, and the supporting quotations, and comparing them to, and finding them to be in line with, what the therapists had expressed during meetings, supervision, and tutoring, earlier in the project.

5 Findings

5.1 Study I

5.1.1 Post-treatment outcomes in depression

No significant differences were found between the reduction in scores for the ICBT and TAU groups, on MADRS-S scores during treatment, or on post-treatment for BDI-II, MADRS-S, and BAI scores (Table 4, page 55; Figure 9, page 56).

For the TAU+ICBT patients in Uddevalla, no significant differences in the reduction in scores (BDI-II and MADRS-S) were found compared to all other patients[12].

On the primary outcome measure (BDI-II), the mean between-group effect size post-treatment was d = 0, with within-group effect size (pre- vs. post-) for the ICBT group d = 1.09, and for the TAU group d = 1.27. There was no difference between treatment groups concerning the proportion of recovered patients, with a score of < 14 on the BDI-II at post-treatment (i.e., minimal depression). In the TAU group, this was the case for 35% (15 out of 43), and in ICBT for 42% (15 out of 36), (χ^2 (1) = .38, ns).

For the ICBT patients, the correlation of the reduction of depressive symptoms, measured by reduction of BDI-II, to the number of accessed modules was r = -.328, p = .072 (ns).

Table 4   Study I: Improvement in depression TAU vs ICBT

ANCOVA. Negative values indicate improvement. Covariate pre-treatment score for the same scale

Period of time	TAU				ICBT				Statistical significance
	n	M	SD	95% CI	n	M	SD	95% CI	
BDI-II pre-post	35	-11.63	9.88	-8.24, -15.02	30	-12.27	10.94	-8.18, -16.35	F(1,62) = .02, NS
MADRS-S w 0-3	29	-2.12	5.56	-0.18, -4.06	29	-0.91	6.12	1.30, -3.11	F(1,63) = .84, NS
MADRS-S w 0-7	34	-6.24	8.16	-3.14, -9.35	32	-4.31	7.96	-1.28, -7.34	F(1,55) = .85, NS
MADRS-S pre-post	35	-8.46	7.64	-5.83, -11.08	30	-7.67	9.79	-4.01, -11.32	F(1,62) = .16, NS

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[12] Supplementary information. Findings from analysis of TAU+ICBT vs all other patients are not reported in Paper I

Figure 9   Study I: Development of depression TAU vs ICBT
Mean depression scores for TAU- and ICBT-patients.
BDI-II: Pre- (0) and Post-treatment (12).
MADRS-S: Pre- (0), week 3, week 7, and Post-treatment (12).

5.1.2 Adherence to ICBT

Twenty (56%) of the ICBT participants completed the seven modules within the 12-week treatment period (Figure 10, page 57). The average number of completed modules was 5.1 (range 0–7, SD = 2.6, median = 7). The login time ranged from 0 to 864 minutes with a mean time of 249 minutes (median 188 minutes).

5.1.3 Negative effects

We also examined possible negative treatment effects, as recommended by Rozental et al. (2014). Measured by BDI-II, among the 65 patients who responded at post-treatment, we found that four patients (6%) deteriorated during treatment, one in TAU (3%) and three in ICBT (10%).

Number of ICBT patients

Number of treatment modules
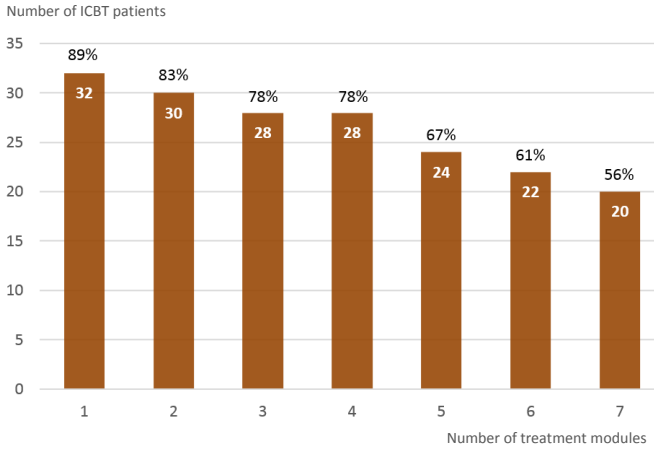
Figure 10   Study I: Adherence among ICBT patients

*Number of entered treatment modules (1-7) by number
and proportion of ICBT patients. (n=36)*

5.1.4 Alternative analysis

The LOCF-ANCOVA analysis revealed no significant differences between the reduc-
tion in scores for the ICBT and TAU groups, on MADRS-S scores during treatment, or
on post-treatment for BDI-II, MADRS-S and BAI scores (Table 5)[13].

Table 5   Study I: Improvement in depression TAU vs ICBT: LOCF

ANCOVA, last observation carried forward analysis.

*Change in mean scores for TAU and ICBT patients. Negative values indicate
improvement. Covariate pre-treatment score for the same scale*

Note: Supplemental info, these findings are not reported in Paper I.

Period of time		TAU			ICBT			Statistical significance
		M	SD	95% CI	M	SD	95% CI	
BDI-II pre-post	n=90	-8.61	10.02	-5.63, -11.59	-8.36	10.68	-5.12, -11.61	F(1,87) = .03, NS
MADRS-S week 0-3	n=90	-1.63	4.84	-0.19, -3.07	-.73	5.23	.86, -2.32	F(1,87) = .80, NS
MADRS-S week 0-7	n=90	-4.22	7.12	-2.10, -6.33	-2.68	6.89	-.59, -4.78	F(1,87) = 1.33, NS
MADRS-S pre-post	n=90	-7.35	7.52	-5.11, -9.58	-5.07	8.98	-2.34, -7.80	F(1,87) = 2.04, NS

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[13] Supplementary information. Findings from LOCF-ANCOVA analysis are not reported in Paper I.

On the primary outcome measure (BDI-II), using LOCF, the mean between-group effect size post-treatment was d = 0.08 in favor of TAU, with within-group effect size (pre- vs. post-) for the ICBT group d = 0.78, and for the TAU group d = 0.86[14].

5.2 Study II

5.2.1 Post-treatment and follow-up outcomes in depression

No significant differences were found in change in depression between the ICBT and TAU groups on BDI-II scores pre – post, pre – three-month follow-up, and pre – nine-month follow-up. (Table 6, page 58). Both ICBT and TAU experienced significant reduction of depressive symptoms during the treatment period, which remained in the follow-ups (Figure 11, page 59).

Table 6   Study II: Improvement in depression TAU vs ICBT

Paired samples t-test. Change in BDI-II mean scores for TAU and ICBT. Negative values indicate improvement.

Note: Supplemental info given, only abbreviated version of table is presented in Paper II

Period of time	TAU				ICBT				Statistical significance
	n	M	SD	95% CI	n	M	SD	95% CI	
Pre-post	27	-13.26	10.64	-9.05, -17.47	36	-11.25	10.63	-7.65, -14.85	t(61) = -.74, NS
Pre-3m follow-up	30	-14.80	10.82	-10.76, -18.84	37	-12.11	10.69	-8.54, -15.67	t(65) = -1.02, NS
Pre-9m follow-up	28	-13.54	11.27	-9.17, -17.90	37	-14.00	10.50	-10.50, -17,50	t(63) = .17, NS

On the primary outcome measure (BDI-II), the mean between-group effect sizes were d = 0.09, d = 0.18, d = 0.09 (for pre – post, pre – three-month follow-up, and pre – nine-month follow-up respectively). The within-group effect size for the TAU group d = 1.31, d = 1.43, d = 1.29, and for the ICBT group d = 1.17, d = 1.23, d = 1.42 (for pre – post, pre – three-month follow-up, and pre – nine-month follow-up respectively).

5.2.2 Antidepressant use

At post-treatment, there were significantly fewer patients in the ICBT group still on antidepressants, eight ICBT-patients (22%) compared to 14 TAU-patients (50%). During treatment, the number of patients using antidepressants increased in the TAU group, and decreased in the ICBT group. However, at three- and nine-month follow-

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[14] Supplementary information. Findings from LOCF analysis of Cohens d are not reported in Paper I.

ups, there were no significant differences between the ICBT and the TAU group concerning medication.
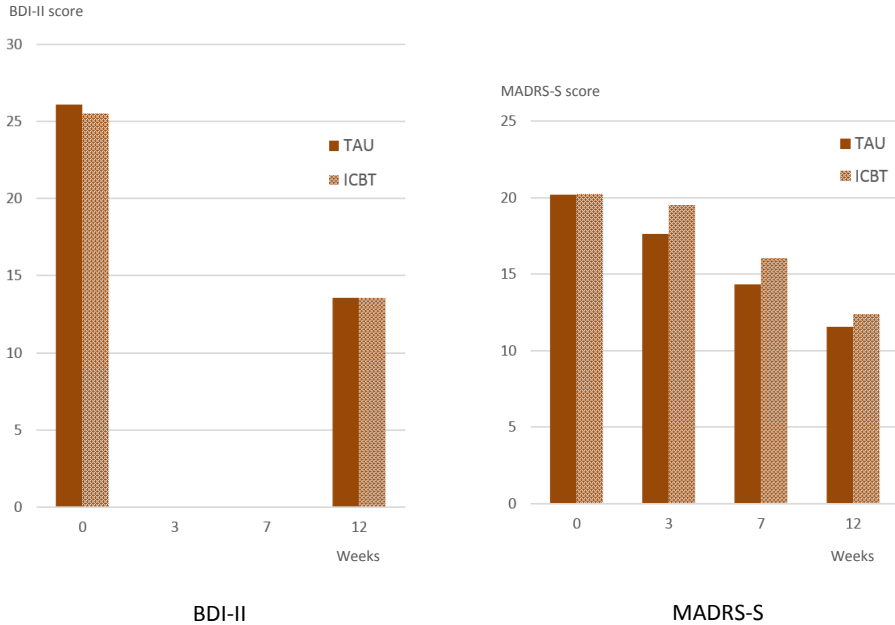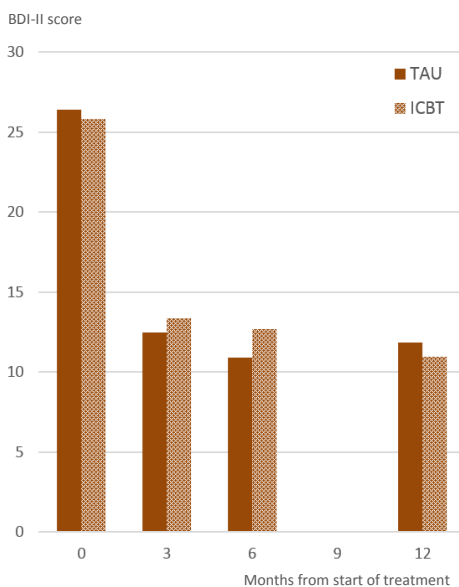

Figure 11 Study II: Development of depression TAU vs ICBT

Mean depression scores for TAU- and ICBT-patients.
BDI-II: Pre- (0), Post-treatment (3), Three month follow-up (6) and Nine month follow-up (12)

5.2.3 Therapist contact during treatment

Registered contacts with primary care centers during treatment, excluding PRIM-NET activities, showed that the TAU group had significantly more visits to therapists compared to the ICBT group. There was, however, no difference between treatment groups in number of visits to GPs, nor to nurses.

No significant differences were found between the TAU and ICBT group concerning therapist-patient telephone calls. On average, ICBT-patients made/received 0.4 calls (SD=1.6, range 0-10) and TAU-patients 0.4 calls (SD=0.9, range 0-4). (See also Table 7, page 60).

Table 7   Study II: Therapist contacts during the treatment period

Number of occasions for individuals in each treatment group (number of patients (percent of the group)).
Data from research records. Note that these number excludes scheduled PRIM-NET activities (i.e. the initial assessment visit, and three scheduled telephone calls).

Number of occasions	Visits		Telephone calls	
	TAU	ICBT	TAU	ICBT
0	23 (61%)	48 (92%)	30 (79%)	47 (90%)
1 to 2	2 (5%)	2 (4%)	6 (16%)	3 (6%)
More than 3	13 (34%)	2 (4%)	2 (5%)	2 (4%)

5.2.4 Adherence to ICBT

Ten (19%) of the 52 patients receiving ICBT did not log on to the ICBT treatment. Twenty-four (46%) completed the seven modules within the 12-week treatment period, and 32 (62%) completed at least four modules (i.e., more than half of the treatment) (See figure 12, page 61). Including the ten patients that did not start the ICBT treatment, the average number of completed modules was 4.3 (range 0–7, SD = 2.9, median = 5). The login time ranged from 0 to 864 minutes, with a mean time of 179 minutes (median 99 minutes)[15].

5.2.5 Negative effects

Among the responding patients, and measured by BDI-II, the number of patients identified as deteriorating were: for TAU one patient (4%) at post-treatment, two patients (7%) at three-month follow-up, and three patients (10%) at nine-month follow-up; for ICBT four patients (11%) at all three time-points[16].

5.2.6 Alternative analysis

No significant differences were found in LOCF-independent t-test analysis (replacing individual missing items with zero), of the reduction in BDI-II scores between the ICBT and TAU groups (pre – post, pre – three-month follow-up, or pre – nine-month follow-up) (Table 8, page 61)[17].

On the primary outcome measure (BDI-II), using LOCF, the mean between-group effect size at nine-month follow-up was d = 0.11 in favor of TAU, with within-group

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[15] Supplementary information. Findings concerning adherence are not reported in Paper II.

[16] Supplementary information. Negative effects are not reported in this way in Paper II.

[17] Supplementary information. Findings from LOCF t-test analysis are not reported in Paper II.

effect size (pre- vs. nine-month follow-up) for the ICBT group d = 0.86, and for the TAU group d = 1.08[18].

Number of ICBT patients

Number of treatment modules
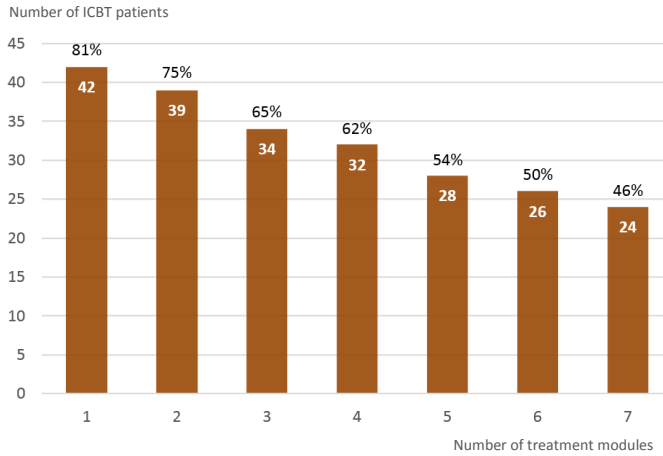
Figure 12   Study II: Adherence among ICBT patients

Number of entered treatment modules (1-7) by number and proportion of ICBT patients. (n=52)

Note: Supplemental info, findings concerning adherence not stated in Paper II.

Table 8   Study II: Improvement in depression TAU vs ICBT: LOCF

LOCF-Independent t-test analysis.
Negative values indicate improvement.

Note: Supplemental info, these findings are not reported in Paper II.

Period of time		TAU			ICBT			Statistical significance
		M	SD	95% CI	M	SD	95% CI	
Pre-post	n=90	-9.61	10.70	-6.09, -13.12	-7.79	10.25	-4.94, -10.64	t(88) = -.82, NS
Pre-3m follow-up	n=90	-11.89	11.20	-8.21, -15.58	-8.58	10.60	-5.63, -11.53	t(88) = -1.43, NS
Pre-9m follow-up	n=90	-11.79	10.92	-8.20, -15.38	-9.69	11.28	-6.55, -12.83	t(88) = -.88, NS

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[18] Supplementary information. Findings from LOCF analysis of Cohens *d* are not reported in Paper II.

5.3 Study III

5.3.1 Overall effect of the ICBT treatment

The result of the one-class LGCM model demonstrated that the average starting point (mean intercept) was 19.54 on the MADRS-S scale (i.e., at the cut-off-point between mild and moderate depression). The mean slope (average change) was significant and negative (-0.613), indicating a decreased MADRS-S score, with an average of 0.61 points per week. Also, the mean quadratic effect was significant, but positive (0.031), demonstrating a curvilinear trend where the average decrease levels out across time, in particular after three-month follow-up.

There was also a significant heterogeneity in the sample in terms of both baseline value (intercept variance: σ^2 = 26.86, p<.001) and change (slope variance: σ^2 = 0.031, p<.01). (See also Figure 13, page 63.)

5.3.2 Latent classes among ICBT patients

To examine the existence of multiple classes, we ran multiple LCGM with 2, 3, 4, and 5 class solutions. Weighing statistical and clinical meaningfulness, and parsimonious-related arguments, we decided to move forward with our analyses based on the 3 class solution.

The 3 class solution is illustrated in Figure 14 (page 63), and the characteristics (in terms of mean estimates for baseline value, change, and curvilinear change) of the classes are described in Table 9 (page 62).

Table 9   Study III: Three latent class – specifics

Mean estimates for baseline value (intercept) change (slope) and curvilinear (quadratic) change in the three latent classes

Latent classes	Mean intercept (S.E.)	Mean slope (S.E)	Mean quadratic slope (S.E.)
Class 1 (n=13, 29.6%)[a]	16.10 (1.23)	-0.81 (0.13)*	0.011 (0.002)*
Class 2 (n=22, 50.0%)[b]	17.24 (1.56)	-0.20 (0.13)	0.003 (0.002)
Class 3 (n=9, 20.4%)[c]	29.12 (1.30)	-1.09 (0.29)*	0.018 (0.006)*

[a]*mild baseline depression, response, retains;*
[b]*mild baseline depression, no response, retains;*
[c]*moderate baseline depression, response, slighty rebounds.*
*p<.001
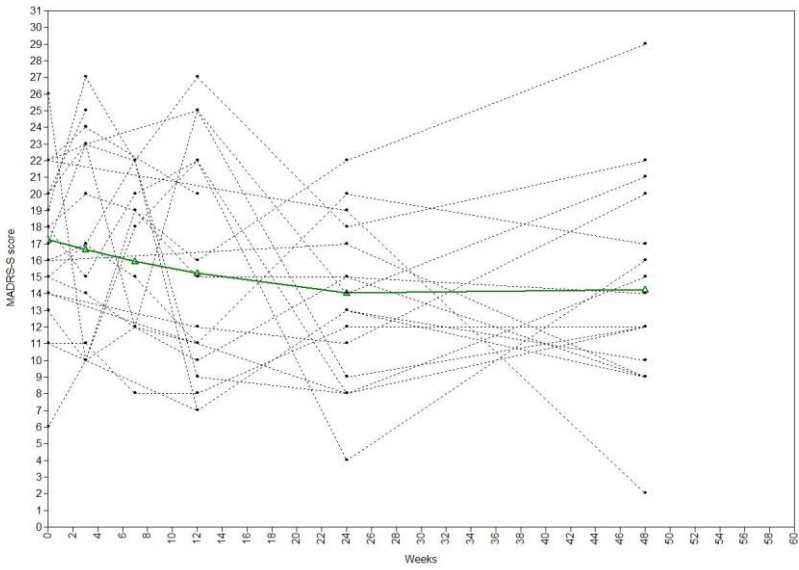
Figure 13   Study III: LGCM one class model

MADRS-S trajectories of ICBT patients.
The solid line indicates the one class LGCM model.
Note: not all patients' trajectories are shown.
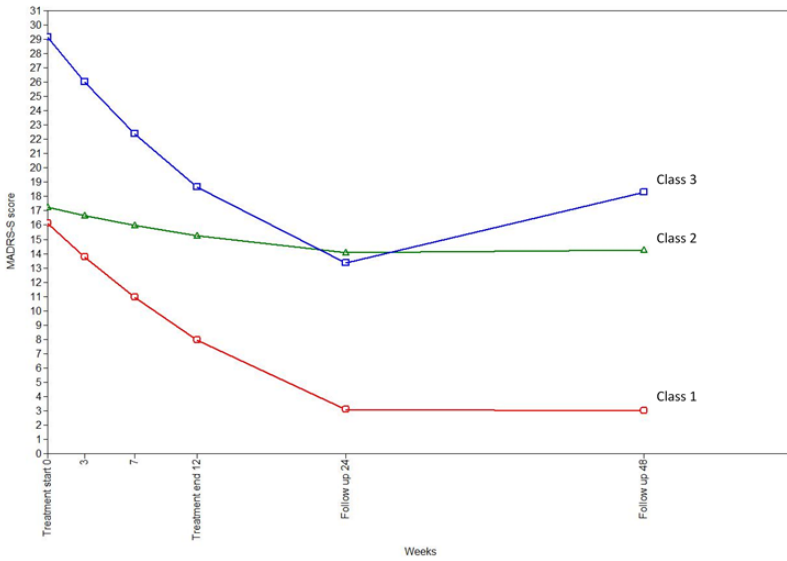
Figure 14   Study III: LCGM three latent class solution

The three identified latent classes can be described as responders (class 1 and 3), and non-responders (class 2), where each class is characterized by; Class 1) Mild depression at baseline, rapid response to the treatment, slightly declining improvement at three-month follow-up, retaining effect at nine-month follow-up (13 patients, 30%); Class 2) Mild depression at baseline, no response to treatment, retaining (no) effect at follow-up three and nine months (22 patients, 50%); and Class 3) Moderate depression at baseline, rapid response to the treatment, slightly declining improvement at three-month follow-up, a slight rebound at nine-month follow-up (9 patients, 20%).

As can be seen in figure 14, the mean trajectories of the responders (class 1 and 3) are very similar with a rapid response and improvement until follow-up at week 24, while the non-responders (class 2) stand out with a much lesser slope throughout treatment and follow-up.

5.3.3 Predicting and distinguishing factors

With two exceptions, no significant baseline differences in characteristics were revealed in analysis of possible predictors of latent classes, using ANOVA across all three classes, or χ^2-test or in some cases Fisher's exact test comparing responders (i.e., class 1 & 3) vs. non-responders (i.e., class 2).

The two exceptions were:

- At baseline there were significant differences between the classes in degree of depression (see also figure 14) (F = 33.74, p = .00) and anxiety scores. Class 1 had twice as high mean BAI compared with class 2 and 3, (F = 9.95, p = .00).
- Six (85.7%) of the seven TAU+ICBT patients (first receiving TAU, and then ICBT) were identified as belonging to the non-responders, constituting 27.3% of this latent class. The one remaining TAU+ICBT was identified as belonging to class 1.

Post hoc analyses of possible distinguishing factors showed a high mean level of adherence (i.e., above 50% of the treatment) during the ICBT treatment among both responders (class 1 & 3; M = 5.8, SD = 2.1) and non-responders (class 2; M = 4.2, SD = 2.9). Also, independent t-tests revealed a significant difference in adherence between responders (class 1 & 3) and non-responders (class 2) t(42) = 2.06, p = .045.

5.3.4 Initial response – slope

The mean trajectories of the two classes of responders, despite their initial difference in intercept, are similar to an early and rapid response to the treatment. The non-

responders on the other hand stand out with a much lesser slope throughout treatment and follow-up.

5.4 Study IV

5.4.1 General Themes

Six general themes were identified (for supporting quotations, see Paper IV).

5.4.1.1 ICBT – a good alternative

More generally, ICBT was seen as a feasible treatment option and an asset for the primary care therapists, which expands their repertoire, saves resources, and makes quality psychological treatment available to more patients. The therapists thought ICBT should be introduced into primary care. Some believed that a central unit would be a good alternative, but most of them also saw advantages in distributing ICBT to all primary care centers. The latter alternative was seen as preferable.

5.4.1.2 ICBT – in a primary care context

The primary care therapists mostly viewed ICBT as another tool in their toolbox, and something not completely separate from face-to-face therapy. They wanted to keep using ICBT treatments, but some concerns were vented about sending depressed patients home with "just" an Internet package. Especially when treating depressed persons, the therapists would have liked to use the Internet package more freely than the research protocol allowed; as a resource, perhaps first seeing the patient a couple of times, and then integrating the Internet resources into face-to-face therapy. Elements from ICBT, such as online diaries, can also, according to the therapists, advantageously be integrated into regular face-to-face treatment. There was also a belief that ICBT fit younger patients best.

Concerning possible negative attitudes towards ICBT among other primary care professions and patients, the therapists had encountered some, but they reported that this was not a problem, nor a dominant view. The therapists did not feel that the introduction of ICBT had been opposed by others.

5.4.1.3 Attitudes and experiences towards the PRIM-NET project

The PRIM-NET project was seen as a rewarding experience, but the low recruitment rate meant that the routines never became automated, but remained hard to master. It was thought that offering Internet treatments for more than one diagnosis would widen the base for recruitment, and make it easier for the therapists to master and automate Internet treatment routines. The offered package of Depressionshjälpen®

was seen as good, but perhaps lacking cognitive content. Patients with milder depressions (i.e., the targeted patients) were seen as wanting cognitive elements to be included in their treatment. The secure communication program, MVK, was perceived as too technically demanding.

There were also thoughts expressed that because patients with mild-to-moderate depression are rarely seen by primary care therapists, rather than relieving some of the burden of existing patients, PRIM-NET instead brought in new patients and thus increased the workload.

5.4.1.4 Research and implementation within primary care

Attitudes towards performing research within primary care were very positive, and it was seen as both natural and necessary to perform. At the same time, there was very little time to perform the extra tasks inherent in research. It was seen as important that management supports research and that the staff is informed, feels engaged in, and responsible for, the process. Today, research is the exception within primary care, and the necessary infrastructure to perform it seems to be lacking.

5.4.1.5 Primary care psychology

The focus on somatic health within primary care limits the scope for therapists who felt that there is a general lack of knowledge on psychological matters among the non-therapist staff, with psychological treatments still being seen as the "alternative" approach. This made it hard to reach a common ground concerning the patients' needs. It seems as though psychology has not fully been integrated into primary care.

5.4.1.6 Primary care culture

The therapists believed that primary care focuses on somatic health, and revolves around the GP. The GP role also seemed to make it difficult to abstain from prescribing antidepressants and instead remit to psychological treatments. Primary care of today has a clear focus on finances and production, which was also seen as limiting the possibilities of preventative work and putting patients' needs in focus.

5.4.2 Barriers to implementation

Using the framework by Cochrane at al. (2007), five of the seven barriers were identified: I. Cognitive/behavioral barriers – *Lack of knowledge and skill*, III. Health care professional/physician barriers – *Boundaries and peer influence*, IV. Clinical practice guideline/evidence barriers – *The nature of the treatment*, VI. Support/resource barriers – *Lack of resources or time*, and VII. System/process barriers – *Lack of organizational/system structures or processes*. These findings are presented further in Table 10, page 67 - 69.

Table 10   Study IV: Identified barriers according to Cochrane et al (2007)

Barrier Category	Barrier Descriptive	Condensed therapists views	Supporting quotations
I. Cognitive/behavioral barriers	Lack of knowledge and skill	Most GPs and RNs are not trained in detecting psychological problems. The situation is also worsened by the pressured schedule of both GPs and RNs leading to difficulties in accurately detecting mild-to-moderate depression among patients.	*"There is no deeper knowledge and education [among non-psychological staff, concerning psychological problems]."*
II. Attitudinal or rational-emotional barriers		--- None identified ---	
III. Health Care professional/physician barriers	Boundaries and peer influence	Inherent in the role of the GP seems to be a notion that the doctor should keep responsibility over the patient and that the GPs should fix the problem themselves as often as possible. Often the GPs prescribe antidepressants. Referring the patient to ICBT (and not prescribing medication) might be perceived by the GP as not keeping to the GP role.	*"... the [GP] has to do something, , has to offer a solution..."* *"GPs are taught to write prescriptions, establish diagnoses and sick leave, use their instruments, ...or else the GPs don't feel at ease..."*
		The autonomy inherent in the professions allows GPs and RN:s control over the methods they choose and this autonomy permits them to keep to the old ways if they prefer. Many members of staff also display an unwillingness to change practice.	*"We know very little about what happens behind the red busy lamp."* *"...it's not a learning environment, it's not an environment where you want to expose your ignorance."*

Table 10   Continued

Barrier Category	Barrier Descriptive	Condensed therapists views	Supporting quotations
IV. Clinical practice guideline/evidence barriers	The nature of the treatment	Although ICBT is an interesting and feasible new treatment it is perceived as not being particularly suited to treatment of depression and many therapists would rather have used ICBT aimed at some other diagnosis. This might have created a certain degree of hesitancy towards the treatment.	"… there is something special with depressed patients … treating depression you are more cautious… [i.e., not completely comfortable using ICBT]."
		A perceived and unwanted rigidity in the treatment left many therapists feeling they would like to apply the treatment more freely than PRIM-NET permitted. Regardless of the treated diagnosis many of the therapists would rather use ICBT in conjunction with face to face therapy and not as a standalone treatment. This could have lowered the acceptance towards the treatment.	"It would be exciting to integrate ICBT elements into face-to-face therapy in the form of homework or reminders … to intensify treatment, helping patients to integrate it into their daily lives."
V. Patient barriers		--- None identified ---	
VI. Support/resource barriers	Lack of resources or time	A pressured schedule and a general sense of lack of time among RNs and GPs makes them hesitant to add any new procedures or interventions to their patient interviews and could lower their interest in investing time to probe and invite patients to PRIM-NET.	"It has been hard to make the new procedure stick with the GPs … the information ends up at the bottom of the pile … we remind and inform again … and then it disappears anyhow."

Table 10   Continued

Barrier Category	Barrier Descriptive	Condensed therapists views	Supporting quotations
VII. System/process barriers	Lack of organizational/system structures or processes	The financial incentives are always paramount in primary care, which leads to a culture of focusing on efficiency and productivity, mostly defined as processing as many patients as possible. This leads to not fully supporting the introduction of new methods and left PRIM-NET competing for attention among primary care staff.	*"It is so much like an assembly line [...] to make a lot of money and get a good budget. It is the only measure today."*
		Primary care psychology being a rather new concept and not fully integrated into the daily routines at primary care centers makes it natural for non-psychological staff to focus on the somatic and more medical ways of understanding and treating patients.	*"Many primary care centers lack routines for their therapists, [...] it is still a very new profession in primary care."*

6 Discussion

This thesis emanates from the PRIM-NET project implementing ICBT at primary care centers in the Västra Götaland region in Sweden, and assumes a primary care perspective on ICBT. The overall aim was to investigate aspects of Internet-delivered psychological therapy as implemented in primary care settings.

6.1 Using ICBT in primary care

To be considered a serious alternative in primary care, ICBT has to be at least as effective as TAU. The main question and touchstone of this thesis, therefore, was; Can ICBT measure up to TAU? In other words, is the effectiveness of ICBT at least on par with TAU? And, can ICBT be a contender not only in a short-term, post-treatment, perspective, but also when it comes to long term effects?

Beyond this basic question of effectiveness, we also wanted to examine two other important aspects of the performance and use of ICBT in primary care; Which patients benefit the most? And, is ICBT feasible in primary care settings? Also, in order to correctly understand the results and draw the right conclusions, it is important to evaluate possible negative effects, and to put the results in context and perspective.

6.1.1 Effectiveness – Can ICBT measure up to TAU?

Study I showed no significant differences between ICBT and TAU in effectiveness (i.e., ability to reduce symptoms of depression) during the three-month treatment period. In addition, Study II showed that this result was sustained at follow-up, nine months after treatment was completed. That is, ICBT for depression as implemented in PRIM-NET was as effective in reducing depression as the treatments usually offered (TAU) to depressed primary care patients, both in a short- and long-term perspective. The between-group effect size was in effect zero, however, the within-group effect sizes for both ICBT and TAU must, across all time-periods and analyses, be considered large. (However, we should note that the LOCF analysis in Study I resulted in an effect size of $d = 0.78$, somewhat on the low side of "large".)

TAU-patients made significantly more visits to the therapist during the treatment period, and used significantly more antidepressants at post-treatment. This difference, compared to the ICBT-patients, must, however, be seen as natural. After all, TAU could be expected to include psychological face-to-face treatments, as well as prescriptions of antidepressant medications. The difference in use of medication disappeared, however, at follow-up.

ICBT performing on par with TAU might, to some, seem like a disappointing result. From a primary care perspective, however, this is not the case. In order to consider introducing a new treatment in health care, the treatment must not be detrimental to patients. Since the effect of ICBT was as good as that of TAU, the patients offered ICBT were not at a disadvantage. Thus, at least in measures of effectiveness, this thesis supports the introduction of ICBT as a treatment option in primary care.

6.1.2 Predicting factors – Which patients benefits the most?

An overall view, like the one applied in Study I and II, does, however, only reveal one facet of a multifaceted reality. At group level the ICBT treatment is effective. But looking at the ICBT patients from a different perspective Study III revealed individual differences in the response to the ICBT. Three different latent classes were identified among the ICBT patients, where one class of patients in essence did not respond to the treatment.

To the primary care therapist, being able to predict which patients might benefit from a treatment is valuable, as is the ability to predict which patients will most likely not benefit from it. If we can offer a treatment almost exclusively to those patients that will respond, the overall effectiveness will be much higher. This would also be very much to the benefit of the patients.

Analyses of possible predicting factors among PRIM-NET ICBT-patients did, however, not reveal anything that could explain the different response patterns of the responders and non-responders.

Yet, the trajectories of the latent classes that *did* respond to treatment demonstrated an early and rather rapid effect. Similar patterns have been found in earlier research on CBT (Lewis, Simons, & Kim, 2012; Schibbye et al., 2014), as well as ICBT (Sunderland, Wong, Hilvert-Bruce, & Andrews, 2012). Also, even though the mean adherence must be considered high for both responders and non-responders (i.e., above 50% of the treatment modules), there was a significant difference between the groups, with a lower level of mean adherence among the non-responders.

Although we cannot today predict for whom ICBT will be most effective, PRIM-NET data indicates some possible distinguishing factors important to monitor once the

ICBT has been started. It is essential to keep a keen eye on the adherence and the development of the patients. If the patients, early in the treatment, do not exhibit reduced levels of depression, it is advisable to review the situation and to, if possible, adapt the ICBT to better fit the patients' needs, or consider other treatments. The absence of early response to the ICBT might indicate a situation of non-response to treatment. Further research on this possible effect in ICBT is, however, necessary in order to reach any definite conclusions.

6.1.3 From a primary care therapist point of view – Is ICBT feasible?

On the whole, the primary care therapists expressed a positive attitude towards ICBT and believed ICBT ought to be introduced at primary care centers. Giving therapists access to ICBT could render primary care psychology more efficient.

Naturally, the experienced primary care therapist's focus is to find the optimal way to use any new tool within the primary care context. It is to be expected that the therapists would suggest adaptations and improvements. From their perspective, to integrate ICBT into their daily work is a natural next step. ICBT as a mixed intervention, blended into face-to-face treatments, has been tried and evaluated with positive results (Kooistra et al., 2014; K. H. Ly et al., 2015; Månsson, Skagius Ruiz, Gervind, Dahlin, & Andersson, 2013). As ICBT develops and becomes customary within regular care, this mode of using Internet-delivered psychological treatments ought to increase. The therapists stressed the need for user-friendly programs. The technology used should be intuitive and mainstream enough to allow access also to patients with low levels of technological knowledge.

There was a sentiment among the therapists that the depressed patients they meet are often too frail to fully benefit from ICBT. Other diagnoses, such as anxiety, were seen as a better fit for ICBT. The therapists also pointed to the necessity of a steady flow of patients. If ICBT-patients are rarely treated, with intermissions in between, the therapists will experience problems mastering the method. This circumstance will then probably lead to suboptimal treatment outcomes. One suggested solution to this was to complement the depression treatment with additional programs for other diagnoses. This would increase the flow through of ICBT patients and thus drastically increase the potential for the therapist to master the Internet-delivered method.

A centralized unit handling Internet-delivered psychological treatments where patients could be remitted was discussed. This was seen as a possibility to relieve some of the heavy burden of patients in primary care psychology. But, the opportunity and possibility to integrate ICBT into primary care psychology and face-to-face treatments was seen as important, which rendered the centralized solution less attractive.

Therapists participating in PRIM-NET all regarded ICBT as a feasible and potent new tool. Their general view was that they looked forward to using it in their future work within primary care.

6.1.4 Possible risks and negative effects

Not all patients benefit from ICBT. Study I found that 10% of ICBT-patients deteriorated during treatment, compared to 3% of TAU-patients. In study III, 50% of the ICBT-patients were identified as belonging to the latent class of non-responders.

One possible indicator of patients who will respond or not respond to ICBT seems to be their response during the first crucial weeks of treatment. Responders demonstrated an early and rapid response in this time frame. This pattern has also been found in previous research (Lewis et al., 2012).

Interestingly, six out of seven of the TAU+ICBT patients who waited three months before commencing ICBT, ended up as non-responders to the treatment. This might indicate that waiting times should be avoided, but further research on this will be needed.

6.1.5 PRIM-NET in context

6.1.5.1 Other ICBT implementations in health care

When PRIM-NET was initiated in 2009, implementation of Internet treatments in regular health care was scarce, and mostly efficacy studies on Internet-delivered treatments had been performed. After all, the lack of evidence was the PRIM-NET raison d'être.

Since then, implementation of Internet treatments in regular health care has become, if not ordinary, at least more common. A Swedish example of ICBT used within health care is a specialized outpatient psychiatric clinic, the Internet Psychiatry Unit (IPU) in Stockholm. At the IPU, Internet treatments for a number of different diagnoses, among them depression, have been developed, implemented, and researched, as they are routinely offered to patients. This unit specializes in Internet treatment only. Any other problems or needs (such as concurrent diagnoses, prescriptions, or sick leave) have to be handled by the patients' GP or regular doctor. A large number of patients (1203 patients during 2007-2013), have received guided ICBT for depression; effect sizes have been large, and improvement sustained at six-month follow-up (Hedman et al., 2014). This raises the question of what new knowledge PRIM-NET, and this thesis, can possibly bring.

However, most of the effectiveness research thus far, including at the IPU, has been performed within specialized (and centralized) care, and often at dedicated research

units. Health care is a broad concept, including a diverse set of branches, operating under differing conditions. Research performed outside of health care, or within health care but not within primary care, cannot automatically be generalized as also pertaining to the primary care context. Moving from psychological treatments performed at specialized, second level care, to routine primary care psychology, is no small step (Roy-Byrne et al., 2003). Primary care seldom treats one defined and isolated diagnosis, but must treat the whole person, including different concurrent diagnoses, as well as the prescription of medications (influencing each other), sick leave, rehabilitation. Primary care therefore involves interaction and cooperation among many different professions such as GPs, RNs, physiotherapists, and psychologists. Implementing new treatments at dedicated research units is always essentially a different matter than implementing them at routine (primary) care units.

Different modes of recruitment have also been found to result in differences in demographics and degree of symptoms in the recruited patients (Lindner, Nyström, Hassmén, Andersson, & Carlbring, 2015). Patients recruited to second level care might not be representative of the ordinary primary care patient.

In order to create a better understanding of ICBT in primary care, we need to assume many different perspectives. The unique strength of PRIM-NET, and its contribution to the knowledge-base, is that it has been operating within routine primary care, and has also implemented ICBT at a large number of primary care centers, in different areas, and under different conditions. PRIM-NET has thus been deeply embedded in real life primary care psychology, distributed at routine primary care centers, allowing a good insight into ICBT at work.

6.1.5.2 Why did ICBT not outperform TAU?

Based on previous effectiveness findings, mainly the Proudfoot et al. (2004) study of CCBT in British primary care, there were expectations of ICBT performing better than TAU in PRIM-NET. After all, efficacy, and more recently also effectiveness, of ICBT has been established, often with large effect sizes (Richards & Richardson, 2012).

However, Proudfoot et al. (2004) targeted a slightly different population consisting of patients diagnosed with depression, mixed depression and anxiety, or only anxiety. They also excluded patients medicating for more than six months, thereby possibly avoiding the inclusion of patients with more chronic cases. Further, the effectiveness of TAU in the Proudfoot trial can be questioned, since the mean score for the TAU group did not reach remission (i.e., BDI-II score < 14), whereas the patients receiving the CCBT did. In PRIM-NET, the mean score for both the TAU and ICBT group did reach remission and both groups demonstrated large within-group effect sizes, with the effect size for ICBT being comparable to other findings (Hoifodt et al., 2013; Williams &

Andrews, 2013). Thus it seems like TAU in the Proudfoot study was, for some reason, less effective, while the PRIM-NET TAU performed well.

6.1.6 PRIM-NET in perspective

6.1.6.1 Study design

The optimal design (Cuijpers, Donker, et al., 2010) and recruitment strategy of RCT studies conducted within primary care is debatable. But we do know that performing research within regular primary care places extra demands on the researcher that must adapt to existing routines and practices, while trying to maintain as much control as possible. Consequently, the level of control in effectiveness research will always be lower than in efficacy research.

In clinical trials the gold standard to strive for has, for some time, been the randomized controlled trial (RCT). The RCT minimizes the risks of selection and confounding, and allows inference of causality (El-Masri, 2014). At the same time, performing a RCT requires quite rigorous control over the trial.

Alternatives to the RCT could be a controlled or open trial requiring less resources, but would also offer a more limited knowledge-base. Knowing this, the PRIM-NET steering group decided to use the RCT setup rather than any alternative. This was in an attempt to provide the best possible data as a basis for future decisions, and also feeling that the standards of RCT were possible to achieve.

6.1.6.2 What was compared?

It could be argued that since we did not restrict patients' access to other care during the ICBT treatment, PRIM-NET really compared TAU to ICBT *and* TAU. This practice is however not uncommon (Proudfoot et al., 2004). It would, for example, not be considered ethical to prevent regular health care patients from receiving parallel treatments; recruitment rates have also probably been even lower if these conditions had been enforced, while drop-out would have increased. One solution to this conundrum is to monitor parallel treatments if and when they occur. It should be noted that PRIM-NET had access to electronic patient records and has evaluated the patients' contacts with the primary care center and what parallel treatments the patients received.

6.1.6.3 Patient recruitment

There is also the question of the sample. Patients not willing to enter ICBT treatments will, of course, turn down an offer to participate, thus leaving only patient's positive toward Internet-delivered treatment participating in PRIM-NET. This trend has also been shown to be the case in previous research (Cuijpers, Donker, et al., 2010). What

can be said is that Internet-delivered treatments are as effective as other treatments, for some patients.

It is, however, important to note that the patient always has a right to decline offered treatments. This means that all patients within regular primary care that enter Internet-delivered treatments will be, at least to some degree, positive toward it. Thus, these results are applicable also under regular primary care circumstances.

Recruiting patients to clinical trials is a common problem (Clarke et al., 2005; de Graaf et al., 2009; Mead et al., 2005) and this has also been a problem in PRIM-NET. We also have reason to believe that the recruitment of patients was biased, and thus select. Throughout the course of the PRIM-NET project, 3,603 patients were diagnosed with depression at the participating primary care centers. At the same time, only 90 patients were included in the project. This means that compared to the group of patients diagnosed with depression, only 2.5% were recruited to the PRIM-NET project. Given that the groups of "patients diagnosed with depression" and "patients eligible for PRIM-NET" are only overlapping, but not completely matching, 2.5% is still a low number, indicating recruitment difficulties.

Interestingly, it seems that GPs tend to underdiagnose depression (Mitchell et al., 2009), but at the same time widely prescribe antidepressants (National Board of Health and Welfare, 2009). Thus it seems that when depressed patients are identified, doctors tend to not remit them to other treatments (Åsbring et al., 2014). Established behaviors like this might take some time to break. In study IV, the therapists also expressed beliefs of a lack of knowledge concerning psychological problems among the non-psychological professions, which makes them less likely to remit suitable patients to ICBT.

6.1.6.4 Power

Despite great efforts and an extended study period, PRIM-NET did not achieve the initial goal concerning the number of recruited patients. It can therefore be argued that the results would have been different, had there been more patients included. Naturally, adding more patients, thus increasing power, might enable detection of a significant difference in Study I & II. However, the difference in effect between the two treatments was negligible throughout. There is reason to believe that the insignificant and relatively small difference between the two treatments would have remained of the same order, even if a greater number of patients had been included.

Study III examined the outcome of ICBT-patients exclusively. The number of included patients were thus reduced even further. A low number of patients can, of course, influence the model and the outcome. However, the statistical method used, and the

longitudinal design with six points of measurement, compensates for the relatively low number of individual patients. Considering this, it seems likely that the results presented are rather robust. Using a quite new approach to analyzing ICBT-data, our results, although tentatively, point to interesting new areas of research.

6.1.6.5 Degree of depression

The patients recruited to PRIM-NET were, according to BDI-II, more severely depressed than the mild-to-moderate depression intended[19]. Patients with milder depression seem to be less likely to actively seek treatment (Kessler et al., 2003). Perhaps the symptoms of depression need to become more pronounced before patients seek help and/or are properly diagnosed in primary care. It has been said that about half of the cases of depression go undetected, and that it is predominantly the severe cases that are detected and diagnosed (SBU, 2004c). According to previous research, the treatment gap for depression is large, with approximately only half of depressed patients being treated (Ebmeier et al., 2006; Kohn et al., 2004; SBU, 2004b). This corroborates the therapists' views, expressed in Study IV, that patients with mild-to-moderate depression today are seldom seen within primary care psychology.

6.1.6.6 Age and Internet use

Study IV revealed a possible sentiment among the therapists that Internet-delivered treatments primarily fit younger patients. This bias might have limited the offers to join PRIM-NET to patients perceived as more Internet-literate, especially if this notion also influenced the rest of the primary care centers' staff. Previous research points to Internet literacy not being a factor in the effectiveness of ICBT, while it is possible that a less stable life, and thus often a younger age, might influence the outcome negatively (Hedman, Andersson, et al., 2012). A post hoc analysis revealed no differences in the effectiveness of the ICBT across age groups in PRIM-NET. It seems that, at least in PRIM-NET, the notion of ICBT as a treatment primarily for the young does not hold up. This bias among therapists, and possibly other categories of staff as well, will hopefully diminish over time as Internet use rises in older age groups.

There have been indications in previous research that the interest among the population for Internet-delivered treatments is lower than for face-to-face treatments (Woodford, Farrand, Bessant, & Williams, 2011), and that the level of acceptance of Internet-delivered depression treatments could be low (Ebert et al., 2015). The level of Internet usage in Sweden is high, but the young are still more ardent Internet users compared to older adults (Statistics Sweden, 2013). The trend is, however, increased

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[19] Exclusion of patients with severe depression was based on MADRS-S scores.

use of computers/Internet in everyday life for a growing proportion of the population. With the rapid rise of Internet-literacy within the population, including within older age groups, the presumably lower interest for Internet treatments compared to other alternatives will likely increase.

6.1.6.7 External validity

Available information on number of invited, assessed and excluded patients, as well as reasons for exclusion of patients, at the primary care centers must be regarded as, at best, uncertain. Also, mainly due to ethical considerations, the inclusion criteria restricted participation in a way that few primary care therapists do in their daily work. For example, the study excluded patients with recently introduced or changed medication[20], as well as patients with mild suicidal ideation and thoughts[21].

The generalizability of the findings can therefore be questioned, but we believe that the results are still important and lay a foundation for the introduction of ICBT for depression, as well as for further research within the primary care setting.

6.1.6.8 The primary care therapists

Study IV focused exclusively on the primary care therapist perspective in an effort to explore the possibilities to successfully implement ICBT in primary care psychology. Naturally, the viewpoint of these therapists differs from the viewpoint of therapists in other settings, such as secondary level care. But, this is also why these views can be valuable when planning future implementations of ICBT within primary care.

However, only a small sample of therapists were interviewed. The views expressed did, nevertheless, generally correspond to the views put forth in the survey, as well as earlier during the project. This study also aimed to capture the views of experienced primary care therapists, and not the views of therapists at large. Thus, the choice to exclude the therapists within PRIM-NET who were not as experienced in primary care seemed reasonable. The interviewed therapists were familiar with the interviewer in her role as project coordinator and supervisor of the therapists, but this might not have been entirely negative. For example, this familiarity could have made it easier for the therapists to reveal sensitive thoughts and honest opinions.

The problems in recruiting patients meant that ICBT-patients were few and included at long intervals. This lead to the ICBT method not being automated by the therapists. It also seems that some aspects of the treatment, such as the secure e-mail program

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[20] Exclusion of patients with recently introduced or changed medication was made in order to minimize the impact of medication on the reduction of depression during the study.

[21] Exclusion criteria concerning previously attempted suicide, and current suicidal ideation and/or plans were set rather conservatively, mostly due to ethical considerations and according to medical ethics review board requirements.

used for patient-therapist communications, were not optimal, and in some respects constituted somewhat of a hindrance. Some therapists would have also liked more cognitive content in the ICBT. Circumstances such as these could, of course, have influenced the results. It is always hard to know how different treatment and research setups influence user acceptability and outcome. The results presented in this thesis can strictly speaking only be said to pertain to the setup used in PRIM-NET.

6.2 Implementing ICBT in primary care

But, there is more to the introduction of new methods, such as ICBT, than effectiveness and feasibility. Any new method must also be implemented successfully. It has been said that implementation in health care is always a challenge (McFlynn et al., 2003; Seddon, Marshall, Campbell, & Roland, 2001). The PRIM-NET task force has put a lot of resources into implementing, maintaining, and "marketing" the ICBT method at participating primary care centers. In spite of this massive effort, problems with recruitment have been obvious.

Study IV revealed a number of issues within current primary care and primary care psychology that could potentially negatively influence the introduction of psychological treatments like ICBT. One factor mentioned was primary care staff experiencing a constant stress to perform tasks within a limited time frame. The staffs' adherence to guidelines and suggested procedures have previously been found to decline when under time constraints (Tsiga, Panagopoulou, Sevdalis, Montgomery, & Benos, 2013). The analysis resulted in a number of additional possible barriers to implementation: the therapists' own views of the ICBT treatment as perhaps not being optimal for depressed patients; psychology not being truly integrated into primary care; and, according to the therapists in this study, a primary care culture in which the somatic knowledge and thinking are principal, and with a perceived lack of psychological knowledge among the non-psychological staff.

In short, it seems that primary care has not yet fully integrated psychology. Primary care psychology is also a fairly new concept (APA Interorganizational Work Group on Competencies for Primary Care Psychology Practice, 2013), and it is thus not surprising that the therapists feel they have not yet truly become a part of mainstream primary care.

The implementation experiences revealed in PRIM-NET can be summarized as; A successful implementation of ICBT in primary care will require planning, resources and perseverance; ICBT will, however, in addition to being an effective treatment for

many patients, also bring an increased access and flexibility to therapists and patients. This can warrant the effort.

6.3 Conclusions

The combined results from Studies I-IV support the introduction of Internet-delivered treatment for depression in primary care. ICBT can have a large effect on depressive symptoms in primary care patients with mild-to-moderate depression. ICBT is as effective as TAU, and can be seen as a good complement to the treatments already in use. Many patients can benefit from ICBT, but ICBT will certainly not fit all. In order to identify non-responders, it is important to monitor ICBT-patients regularly and frequently. If a patient has not responded to the ICBT within the first weeks, other treatment options might be more appropriate, or, if possible, the ICBT should be adapted to better fit the patients' needs. There are also some indications of the advantage of a speedy introduction of ICBT. No solid conclusions can be drawn, but it is possible that waiting for ICBT lessens the effect when the treatment is administered. Further research into these questions is, however, necessary.

Internet-delivered treatments can free up limited therapist resources, and give more patients access to primary care psychology, including patients for whom Internet treatment is not an option. From a primary care therapist perspective, in addition to using complete ICBT treatments, integrating elements of ICBT into regular face-to-face therapies would be an attractive option that could render primary care psychology more efficient.

One major lesson learned from the implementation of PRIM-NET is that it takes time and patience to successfully introduce ICBT, as any new method, into regular primary care. However, considering the advantages of Internet-delivered treatments, the potential gains seem to be worth the effort.

6.4 Future directions

Internet-delivered treatment is evolving fast. In Sweden, a newly developed national platform for Internet-based Support and Treatment (Internetbaserat stöd och behandling (SOB); Swedish Association of Local Authorities and Regions, 2015) is about to be launched. This is a great initiative, and will undoubtedly facilitate implementation of Internet-delivered psychological treatments throughout Swedish health care. At the same time, treatment apps for smartphones are becoming increasingly common. Both are, however, resources to be used after some consideration. Since

the area of Internet-delivered psychological treatments is fairly new, many questions still need to be answered.

For example, future research should address if different setups and designs of the primary care ICBT will influence outcome and acceptability, how Internet-delivered elements best can be mixed into primary care psychology, if smartphone or tablet-apps are as effective as Internet-delivered treatments accessed from a personal computer, if the absence of rapid response should be seen as a sign of non-response, and how a larger part of depressed patients in primary care can be identified.

It is not surprising that psychological treatments have not yet been entirely integrated into the primary care context. To fully understand and embrace any new concept is a laborious process. When implementing and researching new methods in primary care, such as Internet-delivered treatments, it is paramount that all parties have a sufficient understanding of the intervention. It takes time and resources to get acquainted with and embrace any new method. Not to mention that presenting it to prospective patients in a "selling" way requires quite a bit of knowledge. Perhaps this is most easily achieved in small and targeted steps, concentrating implementing resources, possibly targeting one or a few primary care centers at a time, educating and supervising staff closely.

I believe that time will make primary care psychology and Internet tools more mainstream. The current, somewhat sharp, division between "Internet-delivered" and "traditional" psychological treatments will most likely be lessened. Mixed solutions with Internet resources such as psychoeducation or assignments, accessible via computers and smartphones, have great potential and can easily be blended and integrated into everyday treatments.

Psychological methods must always emanate from science and also be evidence-based. However, new technologies have always influenced psychology, as they have brought new opportunities for psychology to explore and evaluate. Information technology of today is seamlessly woven into our daily lives. Our society is built around information accessible through computers. This also invites and urges us to use and explore these new tools in psychology and psychological treatments. Some of these new ways will prove their value through research, improve psychological practice, and thus, in time, complement and/or replace more traditional methods.

The Internet and new technology can potentially facilitate psychological treatments for the benefit of patients, therapists, and health care. As always, we must seek evidence, reflect on possible risks, and on procedures to safeguard patient privacy at an optimal level. Nevertheless, in the interest of societal relevance, psychologists and

health care must explore the opportunities within the society in which they exist: the information society.

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