Common Conditions in Primary Care and Minimal Clinically Important Differences on Depression Scales

by

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ABSTRACT

Primary care has the highest patient volume and the greatest complexity of illness compared to other specialties and levels of health care. Although local data are available, a global perspective on the most common reasons for consulting primary care is lacking. Identifying these conditions would be helpful for directing primary care research towards patient-important priorities. Once these common conditions are determined, attention can be turned to identifying interventions that will impact patients with the conditions, as measured by patient-oriented outcomes. When describing patient-reported outcomes, it is important to report treatment effects with respect to clinical significance rather than reliance on statistical significance alone. Among conditions which are measured in scales (such as pain or depression), the minimal clinically important difference (MCID) is frequently considered to be a measure of clinical significance.

The first objective of this research program was to identify what the most commonly presenting conditions in primary care are. I was also interested in whether there were differences in common reasons for visits (RFV) as reported by clinicians compared to patients, and between countries of differing economic classifications (i.e. developed compared to developing countries). A systematic review of 12 scientific databases was carried out and dual independent review was performed to select primary care studies. Studies were included if they contained ≥20,000 visits (or equivalent volume by patient-clinician interactions) and listed ≥10 RFV. Eighteen studies from 11 countries on five continents met the inclusion criteria. The 10 most common clinician-reported RFV were upper respiratory tract infection (URTI), hypertension (HTN), routine health maintenance, arthritis, diabetes, depression/anxiety, pneumonia, otitis media, back pain and dermatitis. The 10 most common patient-reported RFV were cough, back pain, abdominal symptoms, pharyngitis, dermatitis, fever, headache, leg symptoms, unspecified

respiratory, and fatigue. Globally, URTI and HTN were the most common clinician-reported RFV. In developed countries, the next most common RFV were depression/anxiety and back pain, and in developing countries were pneumonia and tuberculosis.

Having identified depression as the most common condition in primary care in developing countries for which MCIDs could readily be determined, the second objective of this research program was to determine the MCIDs for depression scales, and how they are derived. In particular, I aimed to develop a summary resource that provides information on depression scales and their MCIDs, for use by both researchers and those attempting to interpret the depression literature. A systematic search of the Cochrane Database of Systematic Reviews was carried out, which retrieved 80 reviews on depression. From those reviews, 1540 unique studies were identified, which contained 34 different depression scales. Estimates of MCIDs were found for 10 of the scales: Hamilton Depression Rating Scale, Montgomery Asbergs Depression Rating Scale, Beck Depression Inventory, Centre for Epidemiologic Studies Depression Scale, Zung Depression Scale, Hospital Anxiety and Depression Scale, Patient Health Questionnaire-9, Profile of Mood States, Edinburgh Postnatal Depression Scale, and Quick Inventory of Depressive Symptoms. Data were also collected on how MCIDs were determined, i.e. by using anchor-based, distribution-based, or Delphi methods.

In conclusion, I found that there are differences in RFV to primary care between clinician-reported and patient-reported RFV, as well as differences in RFV between developed and developing countries. These results have utility for primary care guideline development, resource allocation, and training programs and curricula. Next steps arising from these results are for more research to be conducted on assessing common conditions, especially in developing countries.

I also identified MCIDs for 10 depression scales, and their methods of derivation. These results will be helpful for clinicians to monitor depression symptoms over time and assess the effects of treatment. Suggestions arising from my findings on MCID include improved reporting of the MCID in clinical trials, and increased consistency in using depression scales.

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LIST OF ABBREVIATIONS

BDI: Beck Depression Inventory

CES-D: Center for Epidemiologic Studies Depression Scale

EPDS: Edinburgh Postnatal Depression Scale

HADS: Hospital Anxiety and Depression Scale

HAM-D: Hamilton Depression Rating Scale

HTN: hypertension

ICD: International Classification of Diseases

ICPC: International Classification of Primary Care

MADRS: Montgomery Asbergs Depression Rating Scale

MCID: minimal clinically important difference

MID: minimal important difference

MOOSE: Meta-analysis Of Observational Studies in Epidemiology

PHQ-9: Patient Health Questionnaire-9

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

POMS: Profile of Mood States

QIDS: Quick Inventory of Depressive Symptoms

RFV: reasons for visits

SMD: standardized mean difference

URTI: upper respiratory tract infection

WHO: World Health Organization

ZDS: Zung Depression Scale

1 CHAPTER 1: INTRODUCTION

1.1 STATEMENT OF THE PROBLEM

To provide patient-centered and evidence-based healthcare, clinicians rely on patient-oriented research. Patient-oriented research involves patients' perspectives at all stages of research, and is translated into information that is usable by clinicians when caring for patients.[1] In primary care, clinicians directly and actively involve patients in making decisions about a huge variety of conditions and treatment options, so including patient perspectives in research is critical. Given the breadth of disease states managed by primary care clinicians, it would be helpful to know what the most common conditions patients present with in primary care are. This would encourage directing research priorities towards conditions that are important to patients and potentially positively impact the care of large numbers of patients.

Once the most common conditions in primary care have been identified, it is further important that research on them is patient-oriented. One way of incorporating patient values into clinical research is to interpret results from the perspective of clinical significance, rather than reliance on statistical significance. The minimal clinically important difference (MCID) is one method of determining what level of change is significant to patients. The MCID should be used in research on conditions where patients and clinicians report changes in signs or symptoms (i.e. pain, depressive symptoms, ability to perform daily activities, and so on). This includes many conditions that are common to primary care. However, finding literature on the MCID for some conditions can be difficult, hindering the use of MCID in primary care research. When information on MCIDs is found, the presence of many different scales, some with multiple MCID estimates, can make using this information challenging.

1.2 PRIMARY CARE COMMON CONDITIONS

1.2.1 Role of primary care in health care

Primary care, as the name suggests, is often the first point of access to health care systems patients encounter.[2-4] When patients seek medical care, the majority are visiting primary care professionals as compared to specialists, alternative care providers, emergency departments, or outpatient clinics.[2] For example, in Canada there are approximately 238 contacts to family physicians out of 1000 people in a month, compared to about 70 contacts to other physicians.[3] Looking at the ratio of number of contacts to number of physicians, a family physician sees approximately three times the volume of contacts that a specialist does.[3]

However, this vast number of visits to primary care is not composed of mostly simple, easy-to-manage cases. In fact, primary care sees the greatest variety of patients and complexity of illness.[5] The majority of patients visit primary care physicians for management of comorbidities or multi-morbidities, which increases the complexity of delivering care.[5]

Primary care clinicians seem to do a good job of managing these complex cases; it has been demonstrated that a strong primary care workforce results in decreased mortality and fewer hospitalisations.[6] Family medicine is consistently associated with reductions in mortality, more than other areas of primary care in the US, or specialties.[7] A stronger primary care infrastructure and greater number of primary care workers is also associated with lower health care costs.[6,8]

1.2.2 Time demands on primary care

Given the large numbers of visits and the complexity of patients presenting to primary care, it is perhaps not surprising that time demands on primary care have become excessive. It has been estimated that a primary care clinician with an average practice would need over 10 hours per

day just to provide guideline-based care for 10 chronic diseases.[9] Another seven hours per day would be required to provide preventive care according to guidelines.[10] These estimates do not include the hours necessary to provide management of acute, urgent care or short-term issues, which are an integral part of primary care. Despite these unattainable time demands, the workload of primary care continues to increase.[11]

1.2.3 Common conditions in primary care

Since primary care is responsible for managing the health care needs of much of the population at any given time, it is important to determine which conditions present most commonly in primary care settings. Some countries regularly publish updated reports of visits to primary care, including information such as the reasons for visits, the problems managed, and demographic characteristics of patients and healthcare providers. For example, General Practice Activity[12] and the National Ambulatory Medical Care Survey[13] are annually published reports that describe the state of primary care in Australia and the United States, respectively. Understanding this information can assist clinicians and primary care teams with planning and allocating scarce resources. Knowing common conditions can also guide training of primary care professionals, to ensure that training and evaluation have a focus on relevant conditions. As well, this information can identify priorities for researchers, administrators, and policy makers. However, to date there has been no systematic review of this type of primary care data undertaken from a global perspective.

1.3 MINIMAL CLINICALLY IMPORTANT DIFFERENCE

1.3.1 What is the minimal clinically important difference?

The concept of the minimal clinically important difference (MCID) was proposed by Jaeschke et al. in 1989 as "the smallest difference in score in the domain of interest which patients perceive

as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management".[14] Since the original definition was introduced there have been various iterations of similar concepts, but core elements of Jaeschke's MCID have remained unchanged. Perhaps the most critical part of the MCID is that it brings the patient perspective to the forefront of decision-making by placing the emphasis on the patient's perceptions of change. Thus, the MCID focuses on clinically significant changes in outcomes, rather than statistically significant changes.

1.3.2 Clinical vs. statistical significance

In discussing the relevance of the MCID, it is important to draw distinctions between statistical and clinical significance. Statistical significance refers to the likelihood that the results obtained in a study are due to chance. Whether or not statistical significance is achieved relies on the predetermined α level of the analysis, which is typically set at 0.05, meaning that the chance of type I error we are willing to accept is less than 5%. If the calculated p-value is less than 0.05, the chance of our analysis finding a spurious difference between the groups being studied, when in reality no difference exists, is less than 5%, and we would deem this difference statistically significant. There are several factors that can contribute to finding statistically significant results, including having a large difference in effect size between groups, a small amount of variability in the data, and having a large sample size. It is important to note that while the 0.05 cut-off is generally agreed upon for determining statistical significance, it does not have any clinical relevance.

Statistical significance does not necessitate clinical importance, and in many instances a treatment effect may be significant from a statistical point of view but not from a clinical

perspective. To be considered clinically significant, an outcome must be important and of interest to patients and/or physicians.[15] For example, outcomes like death or stroke are of clinical importance because they directly impact patients. Conversely, surrogate markers such as blood pressure or cholesterol can be markers for clinical outcomes, but are not necessarily of interest or importance to patients. As clinical significance depends on importance to patients, what is considered relevant can vary between patients or groups of patients (cultural groups, different ages). Effect size must also be considered when determining clinical importance, because patients may not feel that a 1% reduction in their risk of disease is important, but a 30% reduction is.

The opposite situation also occurs frequently in the literature, when an observed treatment effect does not reach statistical significance, but may include clinically important results. In these circumstances, it is important to consider the range of possible treatment effects as shown by the confidence intervals around the point estimate of effects. Instead of using p-values to interpret the results as a dichotomy (i.e. significant or not), examining confidence intervals provides more useful information regarding the maximum and minimum possible treatment effects, which could include potentially clinically meaningful results.[16]

The MCID can be used as a measure of clinical importance, by bringing in the perspective of patients to determine the smallest change on an outcome that matters to them. Using measures of clinical importance rather than relying on statistical significance can improve interpretability and usefulness of results for clinicians.

1.3.3 Methods for determining MCID

The methods used to determine the MCID for a certain scale can be broadly categorized into three main types: anchor-based approaches, distribution-based approaches, and the Delphi method. Several different ways to calculate the MCID using an anchor-based approach have been identified, including within-patients score change, between-patients score change, receiver operating characteristic curve approach, and social comparison approach.[17] In general, the anchor-based approach links changes on an outcome measure score to changes on global rating of change score.[17] For example, the scale of interest is filled out for the patient, and then compared to the patient's rating of change (i.e. did they feel the same, better or worse?). The scores on the scale of interest can then be "anchored" to the patient's assessment of change. Criticism of this approach has focussed on the potential for recall bias when patients are asked to compare how they feel currently, after treatment, with how they felt prior to treatment.[18] However, the anchor-based approach is the only method which directly incorporates patient assessment of change, which is a critical component of the MCID definition.

The distribution-based approach also encompasses several specific methods, such as standard error of the mean, reliable change index, 0.5 standard deviation (SD), effect size, and standardized response mean.[17] These methods use statistical properties of the distribution of scores to determine the MCID, rather than patient input. For example, using the 0.5 SD method, the MCID is calculated as half of the standard deviation of the score change. Recently, a new distribution-based method for determining MCID was proposed by Hedayat and colleagues, which includes a population-based method to determine an MCID for all patients, as well as an individualized approach which can personalize the MCID for a specific patient.[19] A benefit of using distribution-based methods is that they can account for random variability in patient

change.[17] A key weakness of this approach is the reliance on statistical methods, which requires using cut-offs to determine significance, similar to p-values.[17]

Finally, in the Delphi method (also known as the consensus method) an MCID value is determined via consensus among a panel of people who are stakeholders in the specific field.[18] A group of experts, patients, or other representatives for the topic of interest individually decide what value for the MCID would be relevant for patients, and then review the other experts' decisions and revise their assessments until one value is agreed upon. This approach can be useful because it takes less time to come up with an MCID estimate than the other methods, but a downfall is that it is subjective to the members of the panel. If patients are not consulted, then the MCID value agreed upon may not actually be relevant to patients.

As there are many different approaches that can be taken to determine the MCID, it is recommended to triangulate using several methods, with an emphasis on anchor-based methods.[20,21] This is consistent with using patient assessment as the primary measure of important change, while also accepting that under some circumstances it may be appropriate to include the MCID estimates given by distribution-based or Delphi methods.

1.3.4 Recommendations for using and reporting MCIDs

The MCID has many useful applications in clinical trials, systematic reviews, and clinical practice, and increasingly there have been recommendations regarding the use and reporting of MCIDs. In clinical trials the MCID is useful for determining the power and sample size of the study, as it provides a meaningful value for the effect size, which is required to make these calculations.[17] The MCID can also be used to assess the effectiveness of interventions being studied in clinical trials, as well as in the pilot test phase.[22] It has been suggested that in order to

conclude a benefit in clinical trials, the minimum treatment effect should be at least as large as the MCID.[23] When deciding whether an intervention makes a meaningful difference, speculation has arisen regarding whether to compare the overall mean change obtained by patients to the MCID, or to use the proportion of patients that reached the MCID. The latter approach, termed the responder analysis, has been recommended as it provides an estimate of the proportion of patients who would be expected to benefit from a treatment rather than an overall estimate of change based on both patients who respond to treatment and patients who do not.[24,25]

Recommendations for including the MCID are also included in guidelines regarding reporting of trials and systematic reviews. The 2013 Statistical Analyses and Methods in the Published Literature (SAMPL) Guidelines for reporting in biomedical journals recommends that authors "identify the smallest difference considered to be clinically important", in both the primary analyses and in reporting hypothesis tests.[26] The Cochrane Systematic Review Handbook states that regarding single patient-reported outcomes, it is "most useful to include estimate of MID [minimal important difference]".[27] Additionally, reporting the MCID may enhance interpretability of results in systematic reviews compared to commonly used methods of combining results, such as the standardized mean difference (SMD). The meaning of SMD is poorly understood by physicians, despite how often it is used, and it has been recommended that systematic reviews report the MID rather than the SMD.[28,29] Using measures of MID are more intuitive to interpret and also avoid the equal variance assumption when combining data from different sources.[29] Due to the issue which arises in meta-analyses when combining different measures, Johnston et al., 2012 has provided a method of calculating the MID for studies that do not give an MID, by using the "standard deviation ratio" which can be determined from studies using an anchor-based MID.[30]

In clinical practice, the MCID has potential for use in setting treatment goals.[17,25] Clinicians can use the MCID to monitor changes in depression symptoms over time and determine whether their patients are responding to treatment. In addition to providing a measure of meaningful difference in clinical research, the MCID can be used in clinical practice to interpret whether a treatment may have a meaningful effect on patients.

1.3.5 Gaps in literature

As previously discussed, there are many different methods which can be used to determine an MCID value. This has led to inconsistency in the literature because there has not been a clear consensus on which method is the most appropriate to use, and each of the methods have different strengths and weaknesses. Anchor-based approaches are the only ones that explicitly tie clinical importance to patient-reported outcomes, but this can be affected by recall bias. Distribution-based approaches account for random variability in patient responses, but still encounter problems similar to using a p-value for statistical significance. Delphi methods may be quicker to come up with an estimate of MCID, but are only as good as the panel selected.

Another reason why MCID uptake is challenging is because using different methods to determine the MCID on the same groups of patients results in different estimates of the MCID.[31] Variability in patient characteristics and baseline scores has created even less agreement on MCID values, as using the same method of determining MCID on different groups of patients results in different estimates.[31,32]

Much of the research utilizing MCIDs has been in certain specialty areas such as rheumatology and physical therapy, and as such there is a lack of knowledge of MCID in primary care literature. The infrequent reporting of MCIDs, combined with inconsistent methods of

determining MCIDs has made interpreting and using MCIDs difficult in practice. While a single MCID value will not be the MCID for every patient, using context-specific MCIDs in clinical trials and systematic reviews can be more useful and relevant than the traditional reliance on statistical significance alone.

1.4 SUMMARY

The first point of contact most patients have with the healthcare system is in primary care. Clinicians in primary care have the most contacts with patients, and these patients often present with complex cases and comorbidities. Identifying the most common reasons patients visit primary care is of use for professionals in all aspects of primary care, from researchers and administrators to clinicians and policy makers. The end goal of using information on common conditions is to provide better care to patients, and ensure that all aspects of care are patient-oriented, beginning with research.

The MCID is one way of incorporating patient values into clinical research. Using the MCID puts an emphasis on clinically significant changes, which are important to patients, rather than on statistical significance. One of the most common conditions in primary care is depression. There is a vast amount of research on depression, but many different scales exist to evaluate symptoms of this disorder. As such, it would be of use for both clinicians and researchers to have a readily available resource that provides information on common depression scales, and their MCIDs.

1.5 OBJECTIVES

The proposed research aimed to answer the following questions:

(1) What are the most commonly presenting conditions in primary care?

(2) What are the minimal clinically important differences on scales for depression, a common primary care condition, and how are they determined?

To achieve the stated objectives of this research program, two studies were undertaken. The first objective was addressed in a systematic review of the literature (Chapter 2), where I identified the most common reasons for visiting primary care globally. I also compared reasons for visits as reported by clinicians and patients, and between developed and developing countries.

The second objective was also addressed by systematically searching the literature (Chapter 3). I identified MCIDs for 10 depression scales, as well as the methods used to derive MCID estimates.

1.6 REFERENCES

1) Canadian Institutes of Health Research. Strategy for patient-oriented research. Government of Canada. 2016. Available at: http://www.cihr-irsc.gc.ca/e/41204.html
2) Green LA, Fryer GE, Yawn BP, Lanier D, Dovey SM. The ecology of medical care revisited. N Engl J Med. 2001;344:2021-5.
3) Stewart M, Ryan B. Ecology of health care in Canada. Can Fam Physician. 2015;61:449-53.
4) Roland M, Guthrie B, Thomé DC. Primary medical care in the United Kingdom. J Am Board Fam Med. 2012;25(S1):S6-11.
5) Starfield B, Lemke KW, Bernhardt T, Foldes SS, Forrest CB, Weiner JP. Comorbidity: implications for the importance of primary care in 'case' management. Ann Fam Med. 2003;1:8-14.
6) Chang CH, Stukel TA, Flood AB, Goodman DC. Primary care physician workforce and medicare beneficiaries' health outcomes. JAMA. 2011;305:2096-105.
7) Shi L, Macinko J, Starfield B, Wulu J, Regan J, Politzer R. The relationship between primary care, income inequality, and mortality in US States, 1980-1995. J Am Board Fam Pract. 2003;16:412-22.
8) Starfield B, Shi L. Policy relevant determinants of health: an international perspective. Health Policy. 2002 Jun;60(3):201-18.
9) Østbye T, Yarnall KS, Krause KM, Pollak KI, Gradison M, Michener JL. Is there time for management of patients with chronic diseases in primary care? Ann Fam Med. 2005;3:209-14.

10) Yarnall KS, Pollak KI, Østbye T, Krause KM, Michener JL. Primary care: is there enough time for prevention? Am J Public Health. 2003;93:635-41.

11) Hobbs FDR, Bankhead C, Mukhtar T, Stevens S, Perera-Salazar R, Holt T, et al. Clinical workload in UK primary care: a retrospective analysis of 100 million consultations in England, 2007-14. Lancet. 2016 Jun 4;387(10035):2323-30.

12) Britt H, Miller GC, Henderson J, Bayram C, Harrison C, Valenti L, et al. General practice activity in Australia 2014-15. General practice series no. 38. Sydney: Sydney University Press. 2015. Available at: <purl.library.usyd.edu.au/sup/9781743324523>

13) Centers for Disease Control and Prevention, National Center for Health Statistics. NAMCS 2014 most frequent reasons for visits to primary care practitioners [online]. Personal communication with Akintunde Akinseye (viu7@cdc.gov) 2017 Apr 25.

14) Jaeschke R, Singer J, Guyatt GH. Measurement of health status: ascertaining the minimal clinically important difference. Control Clin Trials. 1989;10:407-15.

15) Brignardello-Petersen R, Carrasco-Labra A, Shah P, Azarpazhooh A. A practitioner's guide to developing critical appraisal skills: what is the difference between clinical and statistical significance? JADA. 2013;144(7):780-6.

16) Allan GM, Finley C, McCormack J, Kumar V, Kwong S, Braschi E, … Garrison S. Are potentially clinically meaningful benefits misinterpreted in cardiovascular randomized trials? A systematic Examination of statistical significance, clinical significance and authors' conclusions. BMC Med. 2017; 15:58.

17) Wright A, Hannon J, Hegedus EJ, Emerson Kavchak A. Clinimetrics corner: a closer look at the minimal clinically important difference (MCID). J Man Manip Ther. 2012;20(3):160-6.

18) McGlothin AE, Lewis RJ. Minimal clinically important difference: defining what really matters to patients. JAMA. 2014;312(13):1342-3.

19) Hedayat AS, Wang J, Xu T. Minimal clinically important difference in medical studies. Biometrics. 2015;71:33-41.

20) Leidy NK, Wyrwich KW. Bridging the gap: using triangulation methodology to estimate minimal clinically important differences (MCIDs). COPD. 2005;2(1):157-65.

21) Revicki DA, Cella D, Hays RD, Sloan JA, Lenderking WR, Aaronson NK. Responsiveness and minimal important differences for patient reported outcomes. Health Qual Life Outcomes. 2006;4(70).

22) Lee EC, Whitehead AL, Jacques RM, Julious SA. The statistical interpretation of pilot trials: should significance thresholds be reconsidered? BMC Med Res Methodol. 2014;14(41).

23) Chuang-Stein C, Kirby S, Hirsch I, Atkinson G. The role of the minimum clinically important difference and its impact on designing a trial. Pharmaceut Statist. 2011;10:250–6.

24) Jones PW, Beeh KM, Chapman KR, Decramer M, Mahler DA, Wedzicha JA. Minimal clinically important differences in pharmacological trials. Am J Respir Crit Care Med. 2014;189(3):250-5.

25) Copay AG, Subach BR, Glassman SD, Polly Jr DW, Schuler TC. Understanding the minimal clinically important difference: a review of concepts and methods. Spine J. 2007;7(5):541-546.

26) Lang T, Altman D. Basic statistical reporting for articles published in clinical medical journals: the SAMPL Guidelines. In: Smart P, Maisonneuve H, Polderman A, editors. Science Editors' Handbook, European Association of Science Editors, 2013.

27) Patrick DL, Guyatt GH, Acquadro C. Chapter 17: patient-reported outcomes. In: Higgins JPT, Green S, (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available at: www.cochrane-handbook.org.

28) Johnston BC, Alonso-Coello P, Friedrich JO, Mustafa RA, Tikkinen KAO, Neumann I, Vandvik PO, Akl EA, da Costa BR, Adhikari NK, Mas Dalmau G, Kosunen E, Mustonen J, Crawford MW, Thanbane L, Guyatt GH. Do clinicians understand the size of treatment effects? A randomized survey across 8 countries. CMAJ. 2015. Early release published at www.cmaj.ca on Oct 26, 2015.

29) Johnston BC, Thorlund K, Schunemann HJ, Xie F, Hassan Murad M, Montori VM, Guyatt GH, Improving the interpretation of quality of life evidence in meta-analyses: the application of minimal important difference units. Health Qual Life Outcomes. 2010;8:116.

30) Johnston BC, Thorlund K, da Costa BR, Furukawa TA, Guyatt GH. New methods can extend the use of minimal important difference units in meta-analyses of continuous outcomes measures. J Clin Epidemiol. 2012;65:817-26.

31) Terwee CB, Roorda LD, Dekker J, Bierma-Zeinstra SM, Peat G, Jordan KP, Croft P, de Vet HCW. Mind the MIC: large variation among populations and methods. J Clin Epidemiol. 2010;63:524-34.

32) Wang YC, Hart DL, Stratford PW, Mioduski JE. Baseline dependency of minimal clinically important improvement. Phys Ther. 2011;91:675-88.

2 CHAPTER 2: WHAT ARE THE MOST COMMON CONDITIONS IN PRIMARY CARE? A SYSTEMATIC REVIEW

2.1 INTRODUCTION

Primary care is the major point of access to health care systems.[1-3] Primary care also provides care to the greatest variety of patients and complexity of illness.[4] The strength of a country's primary care infrastructure has been demonstrated to be positively associated with better health outcomes[5,6] and reduced health care costs.[7] However, the time demands on primary care have become excessive. It has been estimated that a primary care clinician with an average practice would need 18 hours per day to provide guideline-based care for chronic disease and preventive care.[8,9] This estimate does not include time necessary for acute, urgent care or short-term issues. Furthermore, the workload of primary care continues to increase.[10] Given the considerable demands on primary care clinicians, it is essential to understand which conditions present most commonly in primary care settings. This information can assist clinicians and primary care teams with planning and allocation of resources, and guide training of primary care professionals. As well, this information can identify priorities for researchers, administrators, and policy makers.[11]

While some studies present the most common reasons for visiting primary care in a particular country or region of a country,[12,13] there is currently no systematic review of common conditions in primary care globally. Our primary objective was to systematically identify the reasons un-referred patients visit their primary care practitioners. Our secondary objectives were to compare common reasons for visits (RFV) as reported by clinicians and patients, and between countries of differing economic classifications. We hypothesized that there would be similarities in the

reasons patients visit primary care globally, with potential differences between regions due to conditions affected by climate and/or socioeconomic reasons.

2.2 METHODS

This systematic review was performed and reported according to MOOSE guidelines,[14] augmented by the more updated PRISMA.[15]

In January 2016 a medical librarian (SC) searched databases using both controlled vocabulary (e.g. MeSH and EMTREE) and text-words describing the concepts of "primary health care" and "reasons for consulting." Twelve databases were searched with no limits applied. A complete list of databases and search strategies are provided in data supplement 2-1. Google was searched on January 21, 2016 and the first ten pages reviewed. References were exported to RefWorks bibliographic management software. Reference lists of included studies were hand-searched.

Title/abstract screening and full-text review of articles was performed by three independent reviewers (DC, CF, AL). Inclusion criteria were: 1) Study setting was general practice and/or primary care (defined as the first point of contact for providing general health care); 2) Study reported a minimum of 10 reasons for visits (RFV); 3) Population used included a minimum 20,000 visits, or 5 clinicians over 1 year, or 7,500 patients over 1 year. The rationale for the minimum number of visits was based on a practice with 5 clinicians each seeing 20 patients per day, with 200 working days per year, which would result in 20 000 visits. Equivalencies were determined based on 1500 patient practice panels per physician, which among 5 physicians would result in 7500 patients. Studies were observational in design.

Studies were excluded if they: 1) Focused on a specific type of visit or presentation (e.g. periodic health exam visits); 2) Focused on specific conditions or problems (e.g. acute conditions only);

3) Selected specific populations (e.g. adolescents); 4) Indicated that visits were the result of referrals to primary care physicians (e.g. to pediatrics or internal medicine); or 5) Were published before 1996. When there were multiple publications using data from the same source or database, priority was given to the most recent data and to complete data sets with the most specific information. Multiple publications using the same source were only included if they analyzed the data differently (e.g. subgroup analysis). Disagreement was resolved by consensus or third party review (GMA). Attempts were made to contact authors of studies if additional data were required (e.g. unpublished data). Articles published in languages other than English were translated using Google Translate.

Two reviewers extracted data independently (DC, CF). The primary outcome of interest was reported RFV. RFV were defined as reasons patients presented to primary care, and/or problems managed by physicians. For each RFV up to 20, the number, percent, and/or rate of visits associated with each condition were recorded. Descriptive characteristics of each study were also collected, including whether RFV were patient- or clinician-reported, total number of visits, number of clinicians or practices sampled, location and duration of data collection, percent of female patients, percent of patients over age 65, and coding system used (e.g. ICPC, ICD-9/10).

To assess the risk of bias, each study was given a score of 0 or 1 on five characteristics, with 0 indicating a high risk of bias, and 1 indicating a low risk of bias. No risk of bias tool exists for this type of study. The characteristics used were: 1) Representative sample of clinicians (had to meet 2/3 of: both male/female clinicians, not limited to specific number of years in practice, not limited to specific practice size); 2) Representative sample of patients (had to meet 2/3 of: both male/female patients, mixture of urban/rural, not limited to specific age group); 3) Prospective

(data collected for purposes of RFV data, score of 1) or retrospective (data collected previously for other purposes, score of 0) data collection; 4) Coding system specified (1 if yes, 0 if no); 5) Duration of data collection (1 if ≥1 year, 0 if <1 year). Discrepancies were resolved by consensus or third party review (GMA).

Data were separated into "general" and "specific" reported RFV. General categories were broad descriptive groupings (e.g. respiratory), while specific categories were more exact diagnoses (e.g. pneumonia). Within each category (general or specific), a standardized coding scheme was applied. For example, using our coding scheme for specific RFV, "back complaint", "dorsopathies", "back symptoms", "dorsalgia", "low back symptoms", and "neck pain" were all coded as "back pain/spinal pain" (data supplements 2-2 and 2-3). Applying this method of coding enabled us to combine data which were recorded with different existing codes (i.e. ICD, ICPC).

To analyze the primary outcome, we categorized RFV as clinician-reported or patient-reported, then pooled rankings for each RFV across studies within each category. In order to pool the rankings, we first determined the rank of each RFV in each study. The reporting of frequency of visits for particular RFV was inconsistent between studies (variably using number of visits, percent of visits, rate of visits, and others). Thus, the rank of each reported RFV was used as our measure of relative frequency. Using the top 20 ranked RFV, the first most common condition in each study was assigned the number 20, the second was 19 and so on. Therefore, RFV not in the top 20 in a particular study would be assigned a zero ranking from that study. An additive approach was used to combine these rank scores between studies. The mean rank score for each RFV was calculated by totaling the rank score and dividing by the total number of studies

included in that analysis. The most commonly seen conditions were those with the highest mean rank scores. RFV were included in the overall list if they appeared in at least two studies. In addition to mean rank score, the number of studies each RFV appeared in was counted.

To analyze the secondary outcome, countries were categorized by economic classification as either developed or developing, using the United Nations classification system,[17] and the mean rank scores of clinician-reported RFV were compared between categories. As well, when subgroup analyses from included studies were available (e.g. clinician or patient gender, practice setting), data from each study were combined using the same additive approach (providing that more than one study used that subgroup).

2.3 RESULTS

We identified 18 studies[11-13,16, 18-31] for inclusion from a total of 3501 original articles retrieved in our search (Figure 2-1). Agreement was 99% for study selection and 95% for data extraction.

Included articles represented 11 countries: Australia, England and Wales, India, Ireland, Malta, Netherlands, New Zealand, Serbia, South Africa, Sweden, and the United States. Seven studies provided the size of the included population, ranging from 9,896 to 2,780,270 (median: 250,000) (data supplement 2-4). Sixteen studies provided the total number of included visits, ranging from 4,383 to 3,810,843 (median: 83,161) (Table 2-1; data supplement 2-4). Overall the risk of bias was low, with 72% (13/18) of articles scoring at least 4 out of 5 on our assessment (data supplement 2-5).

Of the 18 included studies, six reported general categories of RFV.[11,19,22,23,25,30] Three of these studies[11,19,22] also reported specific RFV, as did an additional seven studies.[12,13,16,20,24,29,31] The remaining five studies[18,21,26-28] could not be included in either the general or specific analysis (as

they reported older or less complete sets of data) but were kept in the review as they provided additional subgroups for analysis.

Six studies were analyzed for general categories of RFV in primary care.[11,19,22,23,25,30] The most common categories of RFV in descending order were respiratory, nervous system/sense organs, cardiovascular/circulatory, skin/subcutaneous, and musculoskeletal (data supplement 2-8). Each of these categories were included in the top 20 reported RFV in all six included studies, providing high consistency with the ranking.

Fourteen rank lists from 10 studies were analyzed for specific RFV to primary care.[11-13,16,19,20,22,24,30,31] Nine data sets provided RFV as reported by clinicians, and five provided RFV as reported by patients. Two studies reported data from both clinician and patient perspectives.[12,22] One study provided data from three countries, which were analyzed as distinct sets of data.[31] The most common clinician-reported RFV were upper respiratory tract infections (URTI), hypertension (HTN), routine health maintenance, arthritis (not back), and diabetes (Table 2-2). None of the most common RFV were found in all nine included studies, but the top two (URTI and HTN) were found in eight studies. The most common patient-reported RFV were cough, back pain/spinal pain, abdominal unspecified, pharyngitis, and dermatitis (Table 2-2). Of the top 18 patient-reported RFV, 10 appeared in all five data sets.

Further analysis of clinician-reported RFV according to country classification showed specific differences. Patient-reported RFV were not further analyzed by economic classification due to the small number of studies providing these data. Five studies with information on clinician-reported RFV were classified as developed countries (Australia, England and Wales, Sweden, and the United States; Table 2-3),[11-13,16,20] and four were classified as developing (India and South

Africa; Table 2-3).[19,22,24,29] For both developed and developing countries, the top two most common reported RFV were URTI and HTN, consistent with the overall rankings. In developed countries the third and fourth most common RFV were depression/anxiety and back pain, neither of which appeared in the developing countries lists. In developing countries, the third and fourth most common RFV were pneumonia and tuberculosis, neither of which appeared in the developed countries list.

Subgroup analyses were provided in nine studies.[18,21,23,25-30] Subgroups included seasonality,[23,26] physician[18,21] and patient gender,[20,25,27,30] urban/rural,[28] methods of reimbursement/payment,[23,25] and practice setting.[19,29] The methods of reimbursement/payment and practice settings were frequently not well-described and inconsistent between studies. As a result, they are not pooled or included in this paper. Summaries of the remaining subgroup data are provided in data supplement 2-7.

2.4 DISCUSSION

This review includes primary care visit data from 18 studies with median 250,000 patients and/or 83,161 visits per study. Eleven countries provided data from five of six populated continents (missing only South America). Data on specific RFV were robust and provided a number of important results.

The 10 most common clinician-reported RFV were URTI, HTN, routine health maintenance, arthritis, diabetes, depression/anxiety, pneumonia, otitis media, back pain and dermatitis. Even this abbreviated list encapsulates the breadth of medical management provided by primary care, including acute symptomatic conditions like URTI and back pain, chronic medical conditions like hypertension and diabetes, and preventive care like routine health maintenance.

Given that primary care accounts for the majority of all office visits to physicians,[32] it is pertinent to examine which conditions present most often in order to improve allocation of limited resources. Understanding these core conditions can help policy makers and administrators in addressing the increasing demand for primary care services. For example, while routine health maintenance exams are the third most common clinician-reported RFV, there is considerable debate as to the merit of these appointments and some groups advise they be eliminated.[33] Our results are helpful for researchers in setting priorities for primary care research and reminding guideline developers of priorities in primary care. Future research could examine whether the number of guidelines, guideline recommendations, and associated opportunity costs correspond to how commonly the condition presents in primary care. Additionally, training and evaluating clinicians on their clinical abilities should reflect the relative frequency of conditions that they will see in practice. Our results can help inform the content of training programs and competency-based exams for primary care trainees. For example, many primary care clinicians report feeling unprepared to manage mental health problems[34] yet depression/anxiety is the sixth most common clinician-rated RFV. By focusing training and evaluations on common conditions, clinicians may be better prepared to provide care to patients, and examinations will better reflect clinical performance.

The 10 most common patient-reported RFV were cough, back pain, abdominal symptoms, pharyngitis, dermatitis, fever, headache, leg symptoms, unspecified respiratory, and fatigue. The patient-derived list is dominated by symptomatic conditions with no RFV related to preventive care or management of asymptomatic chronic conditions. This intuitively makes sense, as patients are often seeking a diagnosis or treatment for symptoms, but it may also suggest a difference in clinician and patient care priorities. Regardless, the differences between the lists

remind us that interpretation of RFV data requires examination of both clinician-and patient-reported data.

Comparing clinician-reported RFV in developed and developing countries, URTI and HTN remain the two most common RFV, confirming their prevalence in primary care regardless of economic conditions or health system. Other RFV that ranked similarly between developed and developing countries included arthritis, urinary tract infections, and diabetes. However, some RFV ranked highly in one grouping of countries but were absent from the other. Notably, depression/anxiety and back pain ranked as the third and fourth most common RFV in developed countries, but did not appear in the rankings for developing countries. There are several potential explanations for these differences between groups of countries. There is a paucity of data from developing countries and it is possible that the four studies from two countries do not reflect the situation for all developing countries. Still, these data are the best available and some of the differences noted are likely valid for many developing countries. Clinician-reported RFV may not reflect the prevalence of conditions such as depression/anxiety and back pain if patients do not report to medical care for these conditions or if conditions are reported differently between clinicians. Thus, depression/anxiety and back pain may be more common in developing countries than identified in these studies. The WHO estimates that over 75% of people with mental illness are untreated in developing countries.[35] Furthermore, certain cultures are more likely to report somatic symptoms than emotional symptoms, which can affect how mental illness presents to and is diagnosed by physicians.[36] Back pain is also likely underrepresented in these studies, as one-month prevalence estimates of back pain in South Africa and India are 39%.[37] RFV including acute otitis media, dermatitis, abdominal unspecified, medication, cough, lipids, and routine health maintenance also appeared only on the developed country list. A number of these

conditions are involved in system-wide health screening and prevention activities (i.e. lipids, routine health maintenance, and likely to some extent, medication). This may suggest a difference in healthcare priorities, resources, and the social determinants of health in developed countries compared to developing countries. Additionally, several infectious diseases such as pneumonia, tuberculosis, parasites, and HIV are considerably more prevalent in primary care in developing nations, which was reflected in our results.

This study is the first to systematically investigate RFV to primary care on a global scale and includes studies from a variety of countries and health care models. Although we conducted an exhaustive search for literature and carried out our systematic review in accordance to the highest reporting standards, our review is not without limitations. The use of different coding systems (i.e. ICPC, ICD, and Read) by each study presented challenges for combining data while retaining adequate detail. As well, studies recorded data with varying levels of specificity, which limited the number of data sets that could be combined. The biggest limit to our study was the paucity of published literature meeting our inclusion criteria; there were notable omissions from Canada, Europe, and South America, and only two countries classified as developing provided data. Thus, it is difficult to generalize results to all developing countries, and the representativeness of our results would be strengthened with additional data.

Examining large-scale studies encompassing 11 countries on five continents, we found that globally primary care clinicians manage a broad range of clinical presentations. Despite the differences between individual countries, there was a high degree of consistency in the 10 most common RFV to primary care. However, we identified that important differences exist depending on whether RFV are reported by clinicians or patients, which should be taken into

consideration when interpreting future RFV data. Differences were also apparent between countries of differing economic status, but our findings demonstrate the need for more large-scale primary care studies and serve as a call for primary care researchers around the globe to investigate common conditions in their regions.

Table 2-1: Characteristics of included studies.

Citation	Overall (OA) and/or subgroup (SG) data	Years of data collection	Total sampling duration (number of weeks)	Country	Total patient population served	Total number of visits included	General (Gen) and/or specific (Sp) level of coding	Patient reported (PT) and/or clinician reported (CR)	Quality Score (out of 5, higher better)
Binns, 2007	OA	2002	32 (continuous)	USA	N/A	597,176	Gen, Sp	CR	4
Britt, 1996	SG (physician gender)	1990-1991	2 (per physician, over 12 months)	Australia	N/A	113,468	Gen	PT, CR	5
Britt, 2015	OA	2014-2015	n/a (up to 100 encounters)	Australia	N/A	98,728	Sp	PT, CR	5
Brueton, 2010	OA (SG – practice setting)	2001-2002	26	South Africa	250,000	4,383	Gen, Sp	PT, CR	3
Fleming, 2005	OA (SG – patient gender)	2001	52 (continuous)	England, Wales	325,850	N/A	Sp	CR	3
Harrison, 2011	SG (physician gender)	2009-2010	n/a (up to 100 encounters)	Australia	N/A	101,349	Gen	PT, CR	5
Mash, 2012	OA (SG – patient age)	2010	1 (5 days over 1 year)	South Africa	2,780,270	18,856	Gen, Sp	PT, CR	4
Ministry of Health, 2004	OA (SG – practice type, season)	2001-2002	2 (per physician, over 18 months)	New Zealand	N/A	8258	Gen	CR	5
Mohan, 2003	OA	2000	52 (continuous)	India	N/A	N/A	Sp	CR	1
Murphy, 2015	OA (SG – patient gender, public/ private)	2008-2010	n/a (up to 100 encounters)	Ireland	503,823	16,899	Gen	PT	3
National Center for Health Statistics, 2014	OA	2014	52 (1 week per physician)	USA	N/A	6,386	Sp	CR	5
Pace, 2004	OA (SG – season)	1995-1998	208 (continuous)	USA	N/A	13,149	Sp	CR	5
Pearson, 1996	SG (patient gender)	1994-1995	52 (continuous)	England	65,000	4,685	Gen	CR	5
Probst, 2002	SG (urban/ rural)	1996-1997	104 (continuous)	USA	N/A	19,409	Sp	PT	5
Salvi, 2015	OA (SG – practice setting)	2011	1 day	India	N/A	204,912	Sp	CR	2
Sayer, 1996	SG (patient gender) OA	1990-1991	2 (per physician, over 12 months)	Australia	N/A	96,144	Gen	PT, CR	5
Soler, 2012	OA	1995-2005 (Netherlands), 2001-2005 (Malta), 2003 (Serbia)	132 (Netherlands), 60 (Malta), 12 (Serbia) (all continuous)	Netherlands, Malta, Serbia	15,318 (Netherlands), 9896 (Malta), 72,673 (Serbia)	838,896 (Netherlands), 70,177 (Malta), 207,323 (Serbia)	Sp	PT	4
Wandell, 2013	OA	2009-2011	104 (continuous)	Sweden	1,987,827	3,810,843	Sp	CR	4

Table 2-2: Ranking of reasons for visits to primary care as reported by clinicians and patients.

	Clinician Reported†			Patient Reported‡		
Rank	*Condition*	*Rank Score* (maximum score 20)*	*Number of Analyses Included in (out of 9)*	*Condition*	*Rank Score* (maximum score 20)*	*Number of Analyses Included in (out of 5)*
1	**Upper Respiratory Tract Infection, Unspecified**	16.7	8	**Cough**	19	5
2	**Hypertension**	16.1	8	**Back Pain/ Spinal Pain**	16.8	5
3	**Routine Health Maintenance**	8.7	4	**Abdominal unspecified**	16.6	5
4	**Arthritis (not back)**	8.6	6	**Pharyngitis**	14.4	5
5	**Diabetes**	8.4	5	**Dermatitis**	13.4	5
6	**Depression or Anxiety**	7.7	6	**Fever**	12.6	5
7	**Pneumonia**	7.2	6	**Headache**	12.4	5
8	**Acute Otitis Media**	6.8	6	**Leg Symptoms**	9.4	5
9	**Back Pain/ Spinal Pain**	6.7	4	**Respiratory unspecified**	8.8	4
10	**Dermatitis**	6.4	5	**Fatigue**	8.4	5
11	**Cough**	5.6	3	**Depression or Anxiety**	8	4
12	**Urinary Tract Infection**	5.4	5	**Arthritis (not back)**	6.8	5
13	**Tuberculosis**	4.4	3	**Sinusitis**	6.2	3
14	**Dyspepsia**	4.3	4	**Cardiovascular**	6	4
15	**Tonsillitis**	4.2	3	**Acute Otitis Media**	5.8	4
16	**Parasites**	4	2	**Urinary Tract Infection**	5.4	4
17	**Asthma**	4	4	**Vertigo/dizziness**	5.4	4
18	**Abdominal unspecified**	4	5	**Skin unspecified**	4.8	4

*Higher scores mean the condition was reported as a more common reason for visit in more studies.

†Studies included in this analysis were Binns et al. 2007, Britt et al 2015, Brueton et al. 2010, Fleming et al 2005, Mash et al. 2012, Mohan et al 2003, National Center for Health Statistics 2014, Salvi et al 2015, Wandell et al 2013.

‡Studies included in this analysis were Britt et al. 2015, Mash et al. 2012, Soler et al. 2012 (3 datasets).

Table 2-3: Ranking of reasons for visits presenting to primary care comparing developed and developing countries.

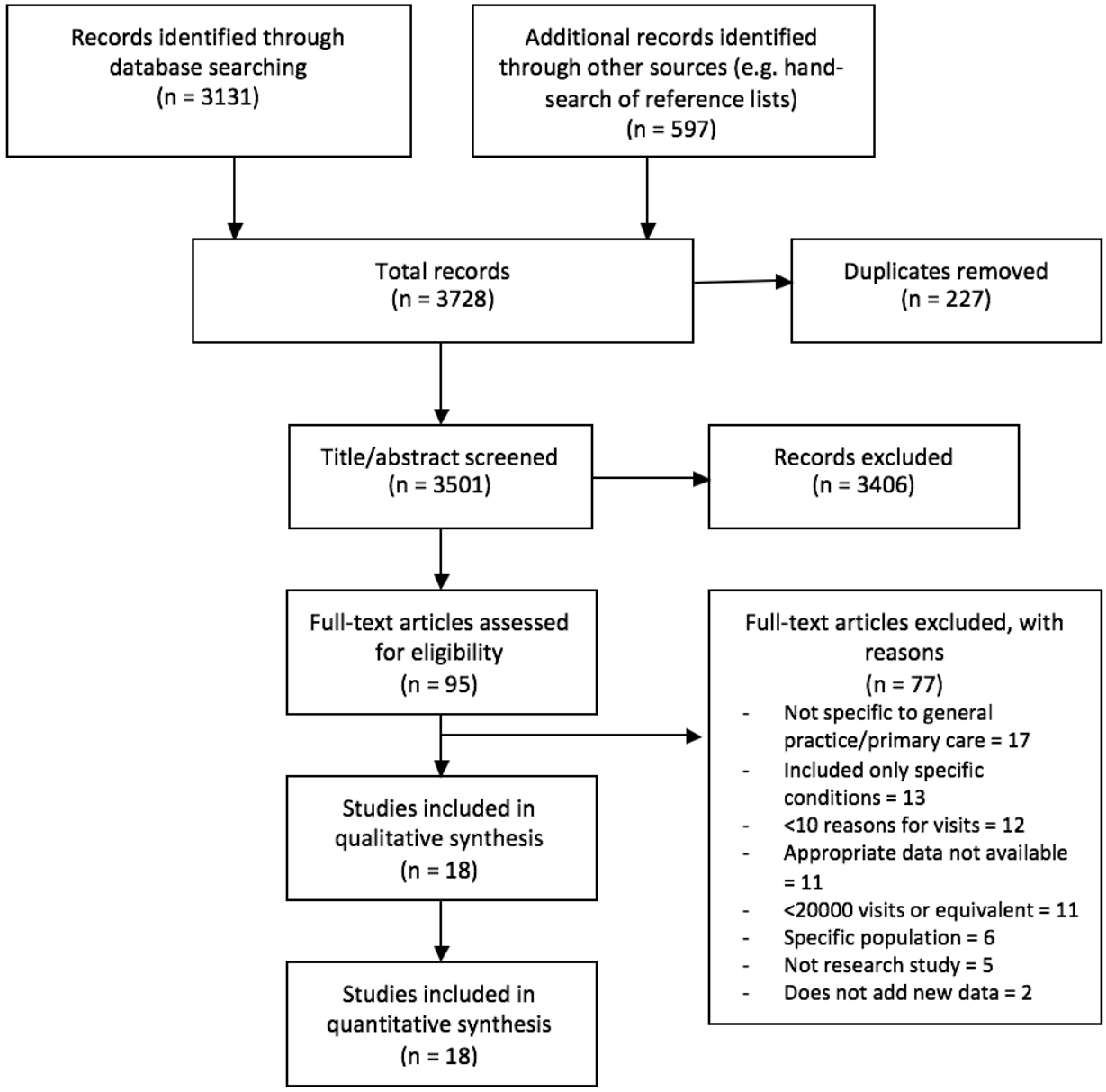
	Developed Countries†			Developing Countries‡		
Rank	*Condition*	*Rank Score* (maximum score 20)*	*Number of Analyses Included in (out of 5)*	*Condition*	*Rank Score* (maximum score 20)*	*Number of Analyses Included in (out of 4)*
1	**Hypertension**	17.4	5	**Upper Respiratory Tract Infection, Unspecified**	18.5	4
2	**Upper Respiratory Tract Infection, Unspecified**	15.2	4	**Hypertension**	14.5	3
3	**Depression or Anxiety**	12	5	**Pneumonia**	11.5	4
4	**Back Pain**	12	4	**Tuberculosis**	10	3
5	**Routine Health Maintenance**	11.6	3	**Parasites**	9	2
6	**Arthritis (not back)**	10	4	**Anemia**	8.3	2
7	**Dermatitis**	8.6	4	**Diabetes**	8.3	2
8	**Acute Otitis Media**	8.6	4	**Arthritis (not back)**	6.5	2
9	**Diabetes**	8.6	3	**Bronchitis/ bronchiolitis**	6.3	2
10	**Cough**	7	2	**Epilepsy**	6	2
11	**Medication**	5.8	2	**Urinary Tract Infection**	5.5	2
12	**Urinary Tract Infection**	5.4	3	**Tonsillitis**	5.5	2

*Higher scores mean the condition was reported as a more common reason for visit in more studies.

†Studies included in this analysis were Binns et al. 2007, Britt et al. 2015, Fleming et al. 2005, National Center for Health Statistics 2014, Wandell et al. 2013.

‡Studies included in this analysis were Brueton et al. 2010, Mash et al. 2012, Mohan et al. 2003, Salvi et al. 2015.

Figure 2-1: Study flow diagram.



2.5 REFERENCES

1) Green LA, Fryer GE, Yawn BP, Lanier D, Dovey SM. The ecology of medical care revisited. N Engl J Med. 2001;344:2021-5.
2) Stewart M, Ryan B. Ecology of health care in Canada. Can Fam Physician. 2015;61:449-53.
3) Roland M, Guthrie B, Thomé DC. Primary medical care in the United Kingdom. J Am Board Fam Med. 2012;25(S1):S6-11.
4) Starfield B, Lemke KW, Bernhardt T, Foldes SS, Forrest CB, Weiner JP. Comorbidity: implications for the importance of primary care in 'case' management. Ann Fam Med. 2003;1:8-14.
5) Chang CH, Stukel TA, Flood AB, Goodman DC. Primary care physician workforce and medicare beneficiaries' health outcomes. JAMA. 2011;305:2096-105.
6) Shi L, Macinko J, Starfield B, Wulu J, Regan J, Politzer R. The relationship between primary care, income inequality, and mortality in US States, 1980-1995. J Am Board Fam Pract. 2003;16:412-22.
7) Starfield B, Shi L. Policy relevant determinants of health: an international perspective. Health Policy. 2002 Jun;60(3):201-18.
8) Østbye T, Yarnall KS, Krause KM, Pollak KI, Gradison M, Michener JL. Is there time for management of patients with chronic diseases in primary care? Ann Fam Med. 2005;3:209-14.
9) Yarnall KS, Pollak KI, Østbye T, Krause KM, Michener JL. Primary care: is there enough time for prevention? Am J Public Health. 2003;93:635-41.

10) Hobbs FDR, Bankhead C, Mukhtar T, Stevens S, Perera-Salazar R, Holt T, et al. Clinical workload in UK primary care: a retrospective analysis of 100 million consultations in England, 2007-14. Lancet. 2016 Jun 4;387(10035):2323-30.

11) Binns HJ, Lanier D, Pace WD, Galliher JM, Ganiats TG, Grey M, et al. Describing primary care encounters: the primary care network survey and the national ambulatory medical care survey. Ann Fam Med. 2007 Jan/Feb;5(1):39-47.

12) Britt H, Miller GC, Henderson J, Bayram C, Harrison C, Valenti L, et al. General practice activity in Australia 2014-15. General practice series no. 38. Sydney: Sydney University Press. 2015. Available at: <purl.library.usyd.edu.au/sup/9781743324523>

13) Wandell P, Carlsson AC, Wettermark B, Lord G, Cars T, Ljunggren G. Most common diseases diagnosed in primary care in Stockholm, Sweden, in 2011. Fam Pract. 2013;30(5):506-13.

14) Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al; Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA. 2000;283:2008-12.

15) Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009 Jul 21;6(7):e1000100.

16) Centers for Disease Control and Prevention, National Center for Health Statistics. NAMCS 2014 most frequent reasons for visits to primary care practitioners [online]. Personal communication with Akintunde Akinseye (viu7@cdc.gov) 2017 Apr 25.

17) United Nations. Country classification. In: World economic situation and prospects 2012. New York: United Nations, 2012. p. 131-40.

18) Britt H, Bhasale A, Miles DA, Meza A, Sayer GP, Angelis M. The sex of the general practitioner: a comparison of characteristics, patients, and medical conditions managed. Med Care. 1996;34(5):403-15.

19) Brueton V, Yogeswaran P, Chandia J, Mfenyana K, Modell B, Modell M, et al. Primary care morbidity in Eastern Cape province. S Afr Med J. 2010;100:309-12.

20) Fleming DM, Cross KW, Barley MA. Recent changes in the prevalence of diseases presenting for health care. Brit J Gen Pract. 2005;55(517):589-95.

21) Harrison CM, Britt HC, Charles J. Sex of the GP - 20 years on. Med J Aust. 2011;195(4):192–6.

22) Mash B, Fairall L, Adejayan O, Ikpefan O, Kumari J, Mathee S, et al. A morbidity survey of South African primary care. PLoS One. 2012;7:e32358.

23) Ministry of Health. Family doctors: methodology and description of the activity of private GPs: the national primary medical care survey (NatMedCa): 2001/02. Report 1. Wellington: Ministry of Health. 2004.

24) Mohan N, Nagavi BG. Development of standard therapeutic guidelines for selected common diseases for the primary health care centres of a south Indian district. Int J Pharm Pract. 2003;11(3):169-74.

25) Murphy M, Brodie G, Byrne S, Bradley C. An observational study of public and private general practitioner consultations in the Republic of Ireland. Ir J Med Sci. 2015 Mar;184(1):147-52.

26) Pace WD, Dickinson LM, Staton EW. Seasonal variation in diagnoses and visits to family physicians. Ann Fam Med. 2004;2(5):411-17.

27) Pearson N, O'Brien J, Thomas H, Ewings P, Gallier L, Bussey A. Collecting morbidity data in general practice: the Somerset morbidity project. BMJ. 1996;312:1517-20.

28) Probst JC, Moore CG, Baxley EG. Lammie JJ. Rural-urban differences in visits to primary care physicians. Fam Med. 2002;34(8):609-15.

29) Salvi S, Apte K, Madas S, Barne M, Chhowala S, Sethi T, et al. Symptoms and medical conditions in 204 912 patients visiting primary health-care practitioners in India: a 1-day point prevalence study (the POSEIDON study). Lancet Glob Health. 2015;3(12):e776-84.

30) Sayer GP, Britt H. Sex differences in morbidity: a case of discrimination in general practice. Soc Sci Med. 1996;42(2):257-64.

31) Soler JK, Okkes I, Oskam S, van Boven K, Zivotic P, Jevtic M, et al. An international comparative family medicine study of the Transition Project data from the Netherlands, Malta and Serbia. Is family medicine an international discipline? Comparing incidence and prevalence rates of reasons for encounter and diagnostic titles of episodes of care across populations. Fam Pract. 2012; 29:283-98.

32) National Center for Health Statistics (US). Health, United States, 2010: With Special Feature on Death and Dying. Hyattsville (MD): National Center for Health Statistics (US); 2011 Feb.

33) Society of General Internal Medicine. Five things physicians and patients should question. Choosing Wisely. 2013 Sept 12. Available at: http://www.choosingwisely.org/wp-content/uploads/2015/02/SGIM-Choosing-Wisely-List.pdf

34) Osborn R, Moulds D, Schneider EC, Doty MM, Squires D, Sarnak DO. Primary care physicians in ten countries report challenges caring for patients with complex health needs. Health Aff. 2015;34(12):2104-12.

35) World Health Organization. Millions with mental disorders deprived of treatment and care. [updated 2008 Oct 9; cited 2016 Aug 11]. Available at: http://www.who.int/mediacentre/news/releases/2008/pr37/en/

36) Office of the Surgeon General (US); Center for Mental Health Services (US); National Institute of Mental Health (US). Mental Health: Culture, Race, and Ethnicity: A Supplement to Mental Health: A Report of the Surgeon General. Rockville (MD): Substance Abuse and Mental Health Services Administration (US); 2001 Aug. Available at: http://www.ncbi.nlm.nih.gov/books/NBK44249/

37) Willams JS, Ng N, Peltzer K, Yawson A, Biritwum R, Maximova T, et al. Risk factors and disability associated with low back pain in older adults in low- and middle-income countries: results from the WHO study on global AGEing and and adult health (SAGE). PLoS One. 2015;10(6):e0127880.

Supplement 2-1. Search strategy.

Databases searched:

OVID Medline (1946 to January 25, 2016), OVID EMBASE (1974 to January 25, 2016), SCOPUS, CINAHL (EBSCO, January 26, 2016), OVID EBM Reviews - Cochrane Database of Systematic Reviews (2005 to January 13, 2016), EBM Reviews - ACP Journal Club (1991 to February 2015), EBM Reviews - Database of Abstracts of Reviews of Effects (1st Quarter 2015), EBM Reviews - Cochrane Central Register of Controlled Trials (January 2015), EBM Reviews - Cochrane Methodology Register (3rd Quarter 2012), EBM Reviews - Health Technology Assessment (1st Quarter 2015), EBM Reviews - NHS Economic Evaluation Database (1st Quarter 2015) and Sociological Abstracts

Medline

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to 2016 January 25 Present>

Search Strategy:

1 (office visit* or general practi* or primary care or primary health care or family medicine or family doctor* or family physician* or family practice* or medical office or medical clinic or primary medical care).ti,ab. (172818)

2 exp *Primary Health Care/ or *"Office Visits"/ (68696)

3 exp *Physicians, Family/ (10285)

4 exp *Family Practice/ or *"Ambulatory Care"/ (56144)

5 1 or 2 or 3 or 4 (239479)

6 ((reason* or why or causes or common or complaints or conditions or diseases or disorders or problems) adj2 (attend* or present* or visit* or consult* or using)).ti,ab. (65952)

7 (Statistics & Numerical Data or Utilization).fs. or utiliz*.ti,ab. [mp=title, abstract, original title, name of
substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1032867)

8 5 and 6 and 7 (998)

9 ((common or prevalent or frequent*) adj1 (diagnoses or complaints or conditions or diseases or disorders or problems)).ti. (1110)

10 5 and 9 (82)

11 National Ambulatory Medical Care Survey.ti. or (Poseidon study not marrow).ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (139)

12 ((reason* or why or cause or causes or common or complaint* or condition or conditions or disease* or disorder* or problem*) adj2 (attend* or visit* or consult* or see) adj2 (doctor* or physician*)).ti. (15)

13 8 or 10 or 11 or 12 (1222)

14 remove duplicates from 13 (1201)

EMBASE

Database: Embase <1974 to 2016 January 25>

Search Strategy:

1 (office visit* or primary care or primary health care or family medicine or family doctor* or family physician* or family practice* or medical office or medical clinic).ti,ab. (151133)

2 exp primary health care/ or exp primary medical care/ or exp general practice/ or exp family medicine/ (189802)

3 *general practitioner/ (16704)

4 *"Ambulatory Care"/ (12167)

5 1 or 2 or 3 or 4 (267141)

6 ((reason* or why or cause or causes or common or complaint* or condition or conditions or disease* or disorder* or problem*) adj2 (attend* or present* or visit* or consult* or using)).ti,ab. (169419)

7 health care utilization/ or exp statistics/ or "utilization review"/ or utiliz*.ti,ab. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (868029)

8 5 and 6 and 7 (725)

9 ((common or prevalent or frequent*) adj1 (diagnoses or complaints or conditions or diseases or disorders or problems)).ti. (1277)

10 5 and 9 (90)

11 National Ambulatory Medical Care Survey.ti. or (Poseidon study not marrow).ti,ab. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (165)

12 ((reason* or why or cause or causes or common or complaint* or condition or conditions or disease* or disorder* or problem*) adj3 (attend* or visit* or consult* or see) adj3 (doctor* or physician*)).ti. (46)

13 8 or 10 or 11 or 12 (1010)

EBM Reviews

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 13, 2016>, EBM Reviews - ACP Journal Club <1991 to December 2015>, EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2015>, EBM Reviews - Cochrane Central Register of Controlled Trials <December 2015>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <4th Quarter 2015>, EBM Reviews - NHS Economic Evaluation Database <2nd Quarter 2015>

Search Strategy:

1 (office visit* or general practi* or primary care or primary health care or family medicine or family doctor* or family physician* or family practice* or medical office or medical clinic or primary medical care).ti,ab. (15600)

2 exp *Primary Health Care/ or *"Office Visits"/ (1154)

3 exp *Physicians, Family/ (1)

4 exp *Family Practice/ or *"Ambulatory Care"/ (2)

5 1 or 2 or 3 or 4 (15818)

6 ((reason* or why or causes or common or complaints or conditions or diseases or disorders

or problems) adj2 (attend* or present* or visit* or consult* or using)).ti,ab. (1826)
7 (Statistics & Numerical Data or Utilization).fs. or utiliz*.ti,ab. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (14103)
8 5 and 6 and 7 (12)
9 ((common or prevalent or frequent*) adj1 (diagnoses or complaints or conditions or diseases or disorders or problems)).ti. (23)
10 5 and 9 (8)
11 National Ambulatory Medical Care Survey.ti. or (Poseidon study not marrow).ti,ab. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (1)
12 ((reason* or why or cause or causes or common or complaint* or condition or conditions or disease* or disorder* or problem*) adj2 (attend* or visit* or consult* or see) adj2 (doctor* or physician*)).ti. (1)
13 8 or 10 or 11 or 12 (21)

CINAHL Searched January 26, 2016

Select / deselect all | **Search with AND** | **Search with OR** | **Delete Searches**

	Search ID#	Search Terms	Search Options	Actions
	S15	(S10 OR S11 OR S13) AND (S9 AND S14)	**Search modes** - Find all my search terms	View Results (264)
	S14	S10 OR S11 OR S13	**Search modes** - Find all my search terms	View Results (2,028)
	S13	((reason* or why or cause or causes or common or complaint* or condition or conditions or disease* or disorder* or problem*) N2 (attend* or visit* or consult* or see) N2 (doctor* or physician*))	**Search modes** - Find all my search terms	View Results (130)
	S12	"Poseidon study" NOT marrow	**Search modes** - Find all my search terms	View Results (0)
	S11	National Ambulatory Medical Care Survey	**Search modes** - Find all my search terms	View Results (610)
	S10	TI ((reason* or why or causes or common or complaints or conditions or diseases or disorders or problems) N2 (attend* or present* or visit* or consult* or using))	**Search modes** - Find all my search terms	View Results (1,305)
	S9	S2 OR S3 OR S4 OR S5 OR S6 OR S8	**Search modes** - Find all my search terms	View Results (26,930)
	S8	S1 AND S7	**Search modes** - Find all my search terms	View Results (26,122)
	S7	utiliz* or statistic*	**Search modes** - Find all my search terms	View Results (759,983)
	S6	(MH "Office Visits/UT/SN")	**Search modes** - Find all my search terms	View Results (493)
	S5	(MH "Ambulatory Care/UT/SN")	**Search modes** - Find all my search terms	View Results (911)
	S4	(MH "Family Practice/UT/SN")	**Search modes** - Find all my search terms	View Results (939)
	S3	(MH "Physicians, Family/UT/SN")	**Search modes** - Find all my search terms	View Results (519)
	S2	(MH "Primary Health Care/SN/UT")	**Search modes** - Find all my search terms	View Results (1,735)
	S1	"office visit*" or "general practi*" or "primary care" or "primary health care" or "family medicine" or "family doctor*" or "family physician*" or "family practice*" or "medical office" or "medical clinic" or "primary medical care"	**Search modes** - Find all my search terms	View Results (95,630)

Sociological Abstracts
ti(reason* OR why OR cause OR causes OR common OR complaint* OR condition OR conditions OR disease* OR disorder* OR problem) AND ti(attend* OR present* OR visit* OR consult* OR see OR utiliz*) AND ("primary care" OR "primary health care" OR "family physician" OR "family practi*" OR "family doctor*" OR "general practi*" OR "medical clinic*" OR "office visits" OR "primary medical care") = 22

SCOPUS
(TITLE("primary care" OR "primary health care" OR "family physician" OR "family practi*" OR "family doctor*" OR "general practi*" OR "medical clinic*" OR "office visits" OR "primary medical care")) and (TITLE(attend* OR present* OR visit* OR consult* OR see OR utiliz*)) and (TITLE(reason* OR why OR cause OR causes OR common OR complaint* OR condition OR conditions OR disease* OR disorder* OR problem*))

Google (Searched January 21, 2016)
(reasons or causes) (visit* or attend*) (doctor* or physician* or "primary care")

Supplement 2-2. Diagnostic coding legend for general conditions.

General Diagnostic Code Given for Systematic Review	Diagnostic Codes Used in Individual Studies
Blood/blood-forming organs	blood, blood forming organs and immune system blood, blood forming organs and immune mechanism blood blood/blood-forming organs
Breast	breast
Cancer	cancer cancers/neoplasms neoplasm
Cardiovascular/circulatory	cardiovascular/circulatory cardiovascular circulatory systems circulatory
Nervous system/sense organs	central nervous system nervous system/sense organs nervous system and sense organs neurological ear eye
Congenital	congenital
Dental	dental
Digestive	digestive gastrointestinal digestive system
Endocrine	endocrine, nutritional, metabolic diseases immunity disorders endocrine, metabolic, nutritional endocrine endocrine/nutritional/metabolic/immunity
General/unspecified	general and unspecified general unspecified general unspecified conditions

	all other diagnosis/unknown symptoms, signs, and ill-defined conditions symptoms non-specific
Hepatic	hepatic
Infectious/parasitic	infectious and parasitic diseases infectious/parasitic
Injury/poisoning	injury/poisoning injury and poisoning
Psychological	mental disorders psychological mental
Musculoskeletal	musculoskeletal musculoskeletal/connective tissue musculoskeletal and connective tissue muscular
Pregnancy/perinatal	pregnancy, child bearing, family planning pregnancy/childbirth/puerperium perinatal
Genitourinary	urological urinary urinary tract genito-urinary genitourinary genital tract gynaecology/infertility male genital female genital
Renal	renal
Respiratory	respiratory respiratory system
Skin/subcutaneous tissue	skin skin/subcutaneous tissue skin and subcutaneous tissue
Social problems	social social problems

Supplementary classification	actions (“therapeutic procedures”, “preventive procedures”, “operations”, “administration”) supplementary classification (ICD-9 - “Factors Influencing Health Status and Contact with Health Services”) check-up investigations (“examination”, “history”, “diagnostic procedures/lab test/radiology”)
Vaccines	vaccines

Supplement 2-3. Diagnostic coding legend for specific conditions.

Specific Diagnostic Code Given for Systematic Review	Diagnostic Codes Used in Individual Studies
Abdominal unspecified	Gastroenteritis/diarrhea Stomach pain, cramps Pain in the abdomen Intestines and peritoneum disease other Gastroenteritis Intestinal infectious disease Other localized abdominal pain Abdominal pain/cramps general Abdominal pain epigastric Diarrhoea Vomiting Nausea Abdominal complain/cramps
Acute MSK injury	Sprains strains joints and adjacent muscles
Acute otitis media	Ear and mastoid process diseases Otitis media Acute sup. otitis media Earache or ear infection Acute otitis media Ear pain/earache
Admin	Administrative procedure
Administrative medical	Physical for school or employment
Anemia	Anaemias Anaemia
Arthritis (not back)	Rheumatism excluding the back Arthritis Arthropathies and related disorders Pain in joint Osteoarthritis Arthritis/joint Swelling Knee symptoms Degenerative joint disease Knee symptoms/complaints Joint pain or symptoms Hand and finger pain or symptom
Asthma	Asthma
Back pain/spinal pain	Back complaint Dorsopathies Back symptoms Dorsalgia

	Low back symptoms Low back complaint excl radiation Neck pain Neck symptom/neck complaint excl headache Shoulder symptoms/complaints Shoulder pain or symptom
Bronchitis/bronchiolitis	Bronchitis Bronchiolitis Acute bronchitis/bronchiolitis
Cardiovascular	Ischaemic heart diseases Congestive heart failure Stroke/cerebrovascular accidents Coronary artery disease Chest pain and related symptoms Veins, lymphatic, and other circulatory diseases Pressure/tightness of heart Chest symptoms/complaints
Cellulitis	Skin and subcutaneous tissue infections Nonfungal skin infection
COPD	Obstructive airway diseases Pulmonary disease chronic obstructive and allied conditions
Cough	Coughing Cough
Depression/anxiety	Depression or anxiety Depression Anxiety Anxiety and nervousness Neurotic personality and other mental disorders Psychological disturbances Counselling Feeling anxious/nervous/tense
Dermatitis	Contact dermatitis Skin and subcutaneous tissues other inflammatory conditions Skin itch/eczema Skin rash Eczema Pruritus Rash generalized Local redness/erythema/rash
Diabetes	Type 2 diabetes Diabetes mellitus

	Diabetes
Dyspepsia	Gastro-esophageal reflux disease Peptic disease Dyspepsia/ulcers Esophagus stomach duodenal disease
Epilepsy	Epilepsy
Eye	Eye and adnexa disorders Red eye Eye pain
Fatigue	Malaise and fatigue General weakness/tiredness
Fever	Fever
Gynecology	Genital disease, other Female genital tract disorders, other Vaginal discharge
Headache	Headache, pain in head Headache
Hepatitis	Hepatitis
HIV	HIV/AIDS
Hypertension	Hypertension Hypertension/high blood pressure Essential hypertension Hypertensive disease Blood pressure test Hypertension, complicated Hypertension, uncomplicated
Hypothyroidism/endocrine	Hypothyroidism Endocrine gland disease, other
Immunization	Immunization/vaccination
Impacted cerumen	Impacted cerumen Hearing complaints excl H84
Infection unspecified	Virosis Infectious disease, other Mycoses
Influenza	Influenza
Leg symptoms	Leg symptoms Leg/thigh symptoms/complaints Foot and toe symptoms/complaints
Lipid	Lipid Disorder Hyperlipidemia Obesity/lipid disorders Dyslipidemia

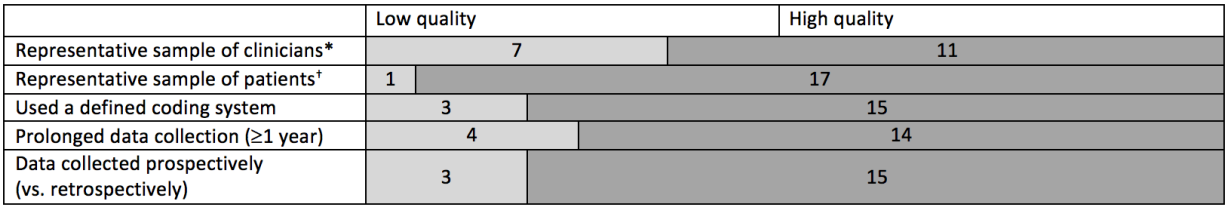
Medication	Medication Prescription
Metabolic immunity disorders	Metabolic immunity disorders
Myalgia	Myalgia Muscle pain
Nutritional deficiency	Vitamin/nutritional deficiency
Pain not specified	Generalised body pain Pain, not specified Generalized aches and pains
Parasites	Helminthiasis Worms, other parasites Scabies and other acariases
Pharyngitis	Throat symptoms Acute sore throat Pharyngitis Symptom/complaint throat Swallowing problems
Pneumonia	Lower respiratory tract infections/pneumonia Lower respiratory infection Pneumonia Acute lower respiratory infection Resp infection other
Pregnancy	Pregnancy-related
Progress visit	Progress visit
Respiratory unspecified	Pain in respiratory system Shortness of breath/dyspnea Respiratory/pleuritic pain
Routine health maintenance	Health maintenance and prevention General medical examination Check up Routine health maintenance Well-baby examination Observation/health education/advice/diet
Sinusitis	Sinusitis Sinus problems Rhinitis Sneezing/nasal congestion
Skin unspecified	Skin lesion, not specified Skin and subcutaneous tissue diseases other Local swelling/papule/lump/mass Skin symptom/complaint, other
Sleep disturbance	Sleep disturbance

Social problems	Social problems
Symptoms unspecified	Symptoms, signs and illdefined Feeling ill Loss of appetite Other referrals not elsewhere classified Weight loss
Tuberculosis	TB Tuberculosis
Test follow-up	Other and unspecified test results Test results Blood test
Tonsillitis	Acute tonsillitis Recurrent tonsillitis
Upper respiratory tract infection, unspecified	Common cold, rhinosinusitis Acute upper respiratory infection Upper respiratory infection Upper respiratory tract infections Upper respiratory tract infection URTI acute Upper respiratory tract diseases other Respiratory infections acute
Urinary tract infection	Urinary tract infection Cystitis Urinary system diseases, other Acute cystitis Recurrent UTI Acute urethritis Pyelonephritis Fungal UTI Catheter-associated UTI Urinary frequency/urgency Dysuria/painful urination Dysuria
Vertigo/dizziness	Vertigo/dizziness

Supplement 2-4. Characteristics of included studies.

Citation	Years of data collection	Total sampling duration (number of weeks)	Country	Specific area	Total patient population served	Total number of visits included	General system (SY) or specific (DX)	Patient reported (PT) or clinician reported (DR)	Name of coding system used	Results as number (N), percent (P), or rate (R)	Quality Score (out of 5)
Binns, 2007	2002	32 (continuous)	USA	national	N/A	597,176	SY, DX	DR	ICD-9-CM, PRINS	P	4
Britt, 1996	1990-1991	2 (per physician, over 12 months)	Australia	national	N/A	113,468	SY	PT, DR	ICPC	R	5
Britt, 2015	2014-2015	n/a (up to 100 encounters)	Australia	national	N/A	98,728	DX	PT, DR	ICPC-2	N, P, R	5
Brueton, 2010	2001-2002	26	South Africa	Eastern Cape	250,000	4,383	SY, DX	PT, DR	ICPC-2	N, P	3
Fleming, 2005	2001	52 (continuous)	England, Wales	national	325,850	N/A	DX	DR	ICD-9	R	3
Harrison, 2011	2009-2010	n/a (up to 100 encounters)	Australia	national	N/A	101,349	SY	PT, DR	ICPC-2	R	5
Mash, 2012	2010	1 (5 days over 1 year)	South Africa	national	2,780,270	18,856	SY, DX	PT, DR	ICPC-2	N, P	4
Ministry of Health, 2004	2001-2002	2 (per physician, over 18 months)	New Zealand	national	N/A	8258	SY	PT, DR	READ2	P (not practice subgroups), R (not season subgroups)	5
Mohan, 2003	2000	52 (continuous)	India	Mysore	N/A	N/A	DX	DR	N/A	P	1
Murphy, 2015	2008-2010	n/a (up to 100 encounters)	Ireland	national	503,823	16,899	SY	PT	N/A	N, P (not subgroups)	3
National Center for Health Statistics, 2014	2014	52 (1 week per physician)	USA	national	N/A	6,386	DX	DR	ICD-9-CM	N, P	5
Pace, 2004	1995-1998	208 (continuous)	USA	national	N/A	13,149	DX	DR	ICD-9	N (not subgroups), P	5
Pearson, 1996	1994-1995	52 (continuous)	England	Somerset	65,000	4,685	SY	DR	ICD-9	R	5
Probst, 2002	1996-1997	104 (continuous)	USA	national	N/A	19,409	DX	PT	ICD-10	P	5
Salvi, 2015	2011	1 day	India	national	N/A	204,912	DX	DR		P	2
Sayer, 1996	1990-1991	2 (per physician, over 12 months)	Australia	national	N/A	96,144	SY	PT, DR	ICPC	N	5
Soler, 2012	1995-2005 (Amsterdam), 2001-2005 (Malta), 2003 (Serbia)	132 (Amsterdam), 60 (Malta), 12 (Serbia) (all continuous)	Amsterdam, Malta, Serbia	national	15,318 (Netherlands), 9896 (Malta), 72,673 (Serbia)	838,896 (Netherlands), 70,177 (Malta), 207,323 (Serbia)	DX	PT	ICPC, ICPC-2	R	4
Wandell, 2013	2009-2011	104 (continuous)	Sweden	Stockholm County	1,987,827	3,810,843	DX	DR	ICD-10	N, P	4

Supplement 2-5. Quality assessment of included studies.



*Considered a representative sample of clinicians if there was evidence for at least 2/3 of the following: mixture of male/female clinicians, mixture of years in practice, mixture of practice sizes.

†Considered a representative sample of patients if there was evidence for at least 2/3 of the following: mixture of male/female patients, mixture of urban/rural, range in patient age.

Citation	Representative sample of clinicians	Representative sample of patients	Defined coding	Prolonged data collection	Retrospective or prospective	Total score
Binns, 2007	1	1	1	0	1	4
Britt, 1996	1	1	1	1	1	5
Britt, 2015	1	1	1	1	1	5
Brueton, 2010	0	1	1	0	1	3
Fleming, 2005	0	1	1	1	0	3
Harrison, 2011	1	1	1	1	1	5
Mash, 2012	0	1	1	1	1	4
Ministry of Health, 2004	1	1	1	1	1	5
Mohan, 2003	0	0	0	1	0	1
Murphy, 2015	0	1	0	1	1	3
National Center for Health Statistics, 2014	1	1	1	1	1	5
Pace, 2004	1	1	1	1	1	5
Pearson, 1996	1	1	1	1	1	5
Probst, 2002	1	1	1	1	1	5
Salvi, 2015	0	1	0	0	1	2
Sayer, 1996	1	1	1	1	1	5
Soler, 2012	0	1	1	1	1	4
Wandell, 2013	1	1	1	1	0	4

Supplement 2-6. Proportion of total visits accounted for by top reasons for visits, and proportion of total problems accounted for by top problems managed.

Reasons for visits	Top 3 (Britt, 2015)	Top 20 (Probst, 2002)	Top 30 (Britt, 2015)	Top 80 (Mash, 2012)	
Percent of visits	23%	46%	59%	83%	
Problems managed	Top 10 (Britt, 2015)	Top 10 (Brueton, 2010)	Top 23 (Pace, 2004)	Top 25 (Mash, 2012)	Top 35 (Britt, 2015)
Percent of problems	29%	52%	76%	53%	54%

Supplement 2-7. Subgroup data.

2-7a. Seasonality subgroups

	New Zealand – General (Ministry of Health, 2004)				United States of America – Specific (Pace, 2004)			
	Autumn	**Winter**	**Spring**	**Summer**	**Autumn**	**Winter**	**Spring**	**Summer**
1	Supplementary classification	Respiratory	Supplementary classification	Supplementary classification	Hypertension	Upper respiratory tract infection, unspecified	Upper respiratory tract infection, unspecified	Hypertension
2	Respiratory	Supplementary classification	Respiratory	Respiratory	Upper respiratory tract infection, unspecified	Hypertension	Hypertension	Routine Health Maintenance
3	Cardiovascular/ circulatory	Cardiovascular/ circulatory	Cardiovascular/ circulatory	Cardiovascular/ circulatory	Routine Health Maintenance	Routine Health Maintenance	Sinusitis	Diabetes
4	Nervous/ sense organs	Nervous/ sense organs	Nervous/ sense organs	Skin/ subcutaneous tissue	Sinusitis	Sinusitis	Routine Health Maintenance	Lipid
5	Injury/ poisoning	Injury/ poisoning	Injury/ poisoning	Nervous/ sense organs	Diabetes	Bronchitis/ bronchiolitis	Bronchitis/ bronchiolitis	Upper respiratory tract infection, unspecified
6	Skin/ subcutaneous tissue	Skin/ subcutaneous tissue	Musculoskeletal	Injury/ poisoning	Lipid	Asthma	Diabetes	Sinusitis
7	General/ unspecified	Psychological	Skin/ subcutaneous tissue	General/ unspecified	Bronchitis/ bronchiolitis	Acute otitis media	Lipid	Back pain/spinal pain
8	Musculoskeletal	Endocrine	General/ unspecified	Musculoskeletal	Arthritis (not back)	Diabetes	Back pain/spinal pain	Depression/ anxiety
9	Psychological	Musculoskeletal	Digestive	Psychological	Back pain/spinal pain	Depression/ anxiety	Depression/ anxiety	Arthritis (not back)
10	Digestive	Genitourinary	Genitourinary	Genitourinary	Depression/ anxiety	Arthritis (not back)	Arthritis (not back)	Asthma
11	Genitourinary	General/ unspecified	Infectious/ parasitic	Infectious/ parasitic	Asthma	Lipid	Asthma	Bronchitis/ bronchiolitis
12	Endocrine	Infectious/ parasitic	Psychological	Digestive	Acute otitis media	Back pain/spinal pain	Acute otitis media	Urinary tract infection
13	Infectious/ parasitic	Digestive	Endocrine	Endocrine	Pregnancy	Pregnancy	Urinary tract infection	Pregnancy
14	Cancer	Cancer	Cancer	Cancer	Headache	Headache	Dermatitis	Cardiovascular
15	Blood/ blood-forming organs	Blood/ blood-forming organs	Blood/ blood-forming organs	Blood/ blood-forming organs	Urinary tract infection	Urinary tract infection	Headache	Acute otitis media
16	Pregnancy/ perinatal	Pregnancy/ perinatal	Pregnancy/ perinatal	Pregnancy/ perinatal	Cardiovascular	Cardiovascular	COPD	COPD
17	Congenital	Congenital	Congenital	Congenital	COPD	COPD	Hypothyroid	Dermatitis
18					Dermatitis	Dermatitis	Pregnancy	Headache
19					Hypothyroid	Hypothyroid	Cardiovascular	Hypothyroid

2-7b. Clinician gender subgroups

	Male Clinician – General	**Female Clinician – General**
	Australia (Britt, 1996 and Harrison 2011)	Australia (Britt, 1996 and Harrison 2011)
1	Respiratory	Respiratory
2	Musculoskeletal	Genitourinary
3	Skin/subcutaneous tissue	Cardiovascular/circulatory
4	Cardiovascular/circulatory	General/unspecified
5	General/unspecified	Skin/subcutaneous tissue
6	Nervous system/sense organs	Musculoskeletal
7	Digestive	Nervous system/sense organs
8	Endocrine	Digestive
9	Psychological	Psychological
10	Genitourinary	Endocrine
11	Pregnancy/perinatal	Pregnancy/perinatal
12	Blood/blood-forming organs	Blood/blood-forming organs
13	Social problems	Social problems

2-7c. Patient gender subgroups

	Male Patient – General	Male Patient – Specific	Female Patient – General	Female Patient – Specific
	Ireland (Murphy, 2015), England (Pearson, 1996), Australia (Sayer, 1996)	England and Wales (Fleming, 2005)	Ireland (Murphy, 2015), England (Pearson, 1996), Australia (Sayer, 1996)	England and Wales (Fleming, 2005)
1	Respiratory	Symptoms unspecified	Respiratory	Symptoms unspecified
2	Skin/subcutaneous tissue	Upper respiratory tract infection, unspecified	Nervous system/sense organs	Upper respiratory tract infection, unspecified
3	Musculoskeletal	Arthritis (not back)	Skin/subcutaneous tissue	Arthritis (not back)
4	Digestive	Acute otitis media	Musculoskeletal	Gynecology
5	Nervous system/sense organs	Dermatitis	Cardiovascular/circulatory	Acute otitis media
6	General/unspecified	Hypertension	Genitourinary	Skin unspecified
7	Cardiovascular/circulatory	Back pain/spinal pain	Digestive	Hypertension
8	Genitourinary	Eye	General/unspecified	Back pain/spinal pain
9	Endocrine	Skin unspecified	Endocrine	Eye
10	Psychological	COPD	Psychological	Depression/anxiety
11	Supplementary classification	Depression/anxiety	Supplementary classification	Dermatitis
12	Injury/poisoning	Cellulitis	Blood/blood-forming organs	Urinary tract infection
13	Cancer	Acute MSK injury	Cancer	Abdominal unspecified
14	Infectious/parasitic	Infection unspecified	Injury/poisoning	COPD
15	Blood/blood-forming organs	Gynecology	Vaccines	Cellulitis
16	Vaccines	Dyspepsia	Breast	Infection unspecified
17	Social problems	Cardiovascular	Social problems	Acute MSK injury
18	Dental	Endocrine/ hypothyroidism	Dental	Dyspepsia
19	Renal	Abdominal unspecified	Hepatic	Cardiovascular
20	Hepatic	Metabolic immunity disorders other	Pregnancy/perinatal	Cancer

2-7d. Urban vs. rural subgroups

	United States of America – Specific (Probst, 2002)	
	Urban	Rural
1	Routine health maintenance	Routine health maintenance
2	Cough	Cough
3	Pharyngitis	Hypertension
4	Hypertension	Back pain/spinal pain
5	Fever	Progress visit
6	Progress visit	Pharyngitis
7	Acute otitis media	Dermatitis
8	Dermatitis	Acute otitis media
9	n/a*	Administrative medical
10	Abdominal unspecified	Medication
11	Upper respiratory tract infection, unspecified	Arthritis (not back)
12	Back pain/spinal pain	Upper respiratory tract infection, unspecified
13	Headache	Fever
14	Cardiovascular	Headache
15	Administrative medical	Abdominal unspecified
16	Medication	Cardiovascular
17	Diabetes	Diabetes
18	n/a*	
19	n/a*	
20	Arthritis (not back)	

*Not available - information in article was based on rural rankings and some urban conditions were not given.

Supplement 2-8. Ranking of general categories of conditions presenting to primary care.

Rank	Condition	Rank Score* (maximum score 17)	Number of Studies Included in (out of 6)	Highest Rank	Lowest Rank
1	Respiratory	16.8	6	1	2
2	Nervous system/sense organs	14.3	6	2	6
3	Cardiovascular/circulatory	12.8	6	3	10
4	Skin/subcutaneous	12.2	6	2	10
5	Musculoskeletal	11.7	6	3	8
6	General/unspecified	10.8	5	2	7
7	Digestive	10.3	6	5	11
8	Genitourinary	9.3	6	4	13
9	Endocrine	9.2	6	3	13
10	Supplementary classification	8	3	1	3
11	Psychological	7.2	5	7	12
12	Pregnancy/perinatal	3.8	3	7	16
13	Blood/blood-forming organs	3.7	4	11	13
14	Injury/poisoning	3.2	2	5	12
15	Social problems	2.8	3	12	13
16	Cancer	2.5	3	11	14
17	Infectious/parasitic	2.5	2	9	12

*Higher scores mean the condition was reported as a more common reason for visit in more studies.

[†]Studies included in this analysis were Binns et al. 2007, Brueton et al. 2010, Mash et al. 2012, Ministry of Health 2004, Murphy et al. 2015, Sayer & Britt 1996.

3 CHAPTER 3: MINIMAL CLINICALLY IMPORTANT DIFFERENCES ON COMMONLY USED DEPRESSION SCALES

3.1 INTRODUCTION

Depression is the third most common condition in primary care in developed countries,[1] and the third leading cause of lost disability-adjusted life years globally.[2] The assessment and quantification of depressive symptoms can be achieved using a wide variety of scales. While these scales may not be used consistently in clinical practice,[3] they are central to research. Scales measure the severity of depression, and when repeated, can identify and quantify a degree of recovery or decline. However, it can be difficult to assess what level of change on these scales is meaningful to patients.

The concept of the minimal clinically important difference (MCID) was proposed by Jaeschke et al.[4] as "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management". The MCID describes clinically significant change, which differs from statistical significance. Studies with large sample sizes can identify differences in scales which are statistically significant, but may not be clinically meaningful (i.e. attain an MCID). MCIDs have been identified for some depression scales, but these values are scattered throughout the literature and can be difficult to find.

To improve the utility and uptake of MCIDs in the management of depression and facilitate easier interpretation of clinical trials, it is essential that depression scales and their MCIDs be provided in one easy-to-access resource. The goals of our study were to systematically identify commonly reported depressions scales, their key characteristics (range of potential scores and

cut-offs for depression severity) and their MCIDs and method of MCID determination. We aimed to synthesize this information in an easily accessible and interpretable format for clinicians and researchers.

Methods of MCID Determination

The methods used to determine the MCID for a certain scale can be broadly categorized into three main types: anchor-based approaches, distribution-based approaches, and the Delphi method.

- *The anchor-based approach links changes on an outcome measure score (e.g. Hamilton Depression Rating Scale) to changes on a global rating of change score (e.g. Patient Global Impression of Change).[5] The anchor-based approach is the only method which directly incorporates patient assessment of change.*
- *The distribution-based approach uses statistical properties of the distribution of scores on a scale to determine the MCID, such as standard error of the mean, 0.5 standard deviation, effect size, and standardized response mean.[5]*
- *The Delphi method relies on consensus among experts in the specific subject area to determine an MCID value.[6]*

3.2 METHODS

We sought to identify all RCTs for the treatment of depression included in one or more Cochrane Systematic Reviews. To this end, the primary author searched the Cochrane Database of Systematic Reviews in September 2016 using the following strategy: " 'depression' in Record Title in Cochrane Reviews". The search was limited to reviews, as protocols did not provide the

necessary data (included studies). For each review, the number of studies analyzed and whether MCID was mentioned was recorded. From the "characteristics of included studies" section of each review, the names of the depression rating scales reported for each study were recorded, as well as descriptive information on each study (number of patients, intervention, duration, etc.). The number of studies using each scale was calculated.

For each scale reported at least once by Cochrane reviewers, the primary author carried out a search on PubMed using the following terminology: " 'name of the scale' AND (minimal clinically important difference OR MCID OR minimal important difference OR minimum clinically important difference OR "clinical importance")". A Google search (first 10 pages) for each scale was also performed using similar terminology. Any study that determined the MCID for a scale was included. The value of the MCID and the method of MCID determination were recorded, as well as the population from which the MCID was derived. All data analysis was descriptive in nature.

3.3 RESULTS

Eighty systematic reviews were retrieved, of which eight (10%) mentioned an MCID (data supplement 3-1). The reviews contained 1540 unique studies. Within these studies, 34 different scales for measuring depression were reported (Table 3-1). The most commonly reported scale was the Hamilton Depression Rating Scale (HAM-D), which was used in 55% of studies (842/1540). The Montgomery Asbergs Depression Rating Scale (MADRS) was reported in 18% of studies (n=278), and the Beck Depression Inventory II (BDI) was reported in 15% of studies (n=235). An additional 14 scales were reported in 1-5% of studies, and the remaining 17 scales

were mentioned in <1% of studies. Included studies reported a mean of 1.4 depression scales (range 0-5).

Established MCIDs were found for 10 scales: HAM-D, MADRS, BDI, Centre for Epidemiologic Studies Depression Scale (CES-D), Zung Depression Scale (ZDS), Hospital Anxiety and Depression Scale (HADS), Patient Health Questionnaire-9 (PHQ-9), Profile of Mood States (POMS), Edinburgh Postnatal Depression Scale (EPDS), and Quick Inventory of Depressive Symptoms (QIDS) (Table 3-2).

Six of the scales (60%) had more than one reported MCID, and the BDI had the most MCID estimates, at six. When more than one MCID existed for a scale, there was variability between MCID estimates. For example, on the MADRS, MCID estimates ranged from 1.6[7] to 9[8] on a 60-point scale. The BDI, ZDS, and HADS also had large ranges of MCID estimates (Table 3-2).

There was variability in how MCIDs were reported; some studies provided a numerical difference (i.e. a difference of 5 points on the PHQ-9[9]), whereas other studies provided a relative difference (i.e. a difference of 50% of baseline score on the PHQ-9[10]). Eighteen estimates (60%) were reported as numerical differences and eight (27%) as relative differences (Table 3-3). Four MCIDs (13%) were reported as both numerical and relative differences. Based on the midpoint of each scale, numerical scores were converted to percentages and vice versa (data supplement 3-2).

The majority of MCIDs were determined using anchor-based or distribution-based methods. Fifteen estimates (50%) were derived from an anchor scale, and twelve (40%) using distribution of scores (Table 3-3). Three MCIDs (10%) were determined using the Delphi approach.[10-12]

Of the anchor-based MCIDs, nine (60%) were patient reported, five (33%) were clinician reported, and one was not specified (Table 3-3). The most common scales used for anchoring were the Patient Global Impression (n=6) and the Clinical Global Impression (n=5). Two scales, HAM-D and BDI, had MCIDs estimated from both patient- and clinician-based anchors. There were no consistent differences between the MCID values based on the type of anchor used (data supplement 3-2).

Three studies used both anchor and distribution-based methods to estimate MCID values.[13-15] In two of these studies the distribution method provided a lower MCID estimate than did anchoring; in the other there was overlap between the two methods. There was no consistent pattern in the direction of differences between the two methods when looking across studies for the same scale (data supplement 3-2).

Six estimates were found for the MCID for deterioration of depression. In all cases the magnitude of the MCID for worsening depression was smaller than the magnitude of MCID for improvement, and in some cases a small decrease in the scale score (i.e. improvement) was indicative of the MCID for deterioration (data supplement 3-3).

3.4 DISCUSSION

This study compiles information on commonly used depression scales and their respective MCIDs, which is of use to both clinicians and researchers. Despite the movement toward using measures of clinical importance in reporting patient-oriented outcomes to provide meaningful context for results of interventions, we found that only 10% (8/80) of the systematic reviews we identified mentioned an MCID. Of 34 commonly reported depression scales, MCID estimates were identified for 10.

For the six scales which had more than one MCID estimate, there was variability in the estimates reported. This range of results could be due to differences in the methods used to determine MCID (i.e. anchor-based, distribution-based, or Delphi process), characteristics of the population each MCID was derived in, and/or differences in baseline scores of patients. We did not find any consistent patterns that would suggest using one method of derivation over another results in a higher or lower MCID estimate. This range in MCID values within scales presents problems for interpretation of clinical trial results. For example, consider the smallest value for MCID on the MADRS, 1.6 points, and the largest value, 9 points. Depending on which of these values is used, authors of trials or reviews may come to completely different conclusions if participants had a change in score between 2-9. If 1.6 is taken to be the MCID, a patient could experience several clinically important changes over the course of treatment before (if ever) reaching the much higher MCID of 9. We suggest that if several MCIDs of different values are available for a particular scale and are derived from a variety of methods, the one anchored to a patient's impression should be used. Anchoring to a patient scale is likely the most direct method of determining what level of change is important to a patient. However, the level of severity of a condition at baseline can also impact the MCID, so this may also be considered when choosing the most applicable value if several are available.

When scales are used in trials, authors commonly report the difference between the intervention and control groups in the mean change from baseline. It would be preferred for authors to also provide the baseline and mean change for each group. This would provide readers with a clear sense of the magnitude of change from baseline and the difference between groups. Additionally, this would enable comparing the mean changes in intervention group, placebo group, and difference in means to the MCID. In this way, readers can determine exactly where any clinically

important effects occur. In addition to analyzing continuous data of scales, it is strongly advised that authors report the number of patients in each group that attain the MCID. This dichotomous data can be analyzed for statistical differences and allows for calculation of the number needed to treat to attain an MCID.

Our main goal was to investigate MCIDs associated with improvement on depression scales, as the aim of depression therapies is to improve symptoms. However, some studies also reported MCIDs for worsening depression, which were consistently smaller in magnitude than for improvement. This means that patients require a much larger improvement before they feel that they have indeed improved, compared to a much smaller amount of deterioration before they feel that they have gotten worse. This reinforces the importance of using the MCID to interpret the effect of an intervention, as opposed to statistical significance, which would not make a distinction between these varied magnitudes of effect.

Depression is one of the most common conditions in primary care, and many trials aim to evaluate interventions for this burdensome disorder. Given the wide variety of depression scales available, we suggest that researchers include common scales to allow comparison of results between trials. These scales will also ideally have an MCID which can be used power calculations and in interpreting results. It is important that studies on depression target clinically important differences, not just statistical ones.

Table 3-1: Depression scales reported in *Characteristics of included studies* tables from Cochrane systematic reviews of depression.

Name of scale	Number of studies reported in
Hamilton Depression Rating Scale	842
Montgomery Asbergs Depression Rating Scale	278
Beck Depression Inventory II	235
Raskin Depression Scale	73
Center for Epidemiologic Studies Depression Scale	69
Zung Self-Rating Depression Scale	62
Research Diagnostic Criteria - Depression	39
Edinburgh Postnatal Depression Scale	38
Hopkins Symptom Checklist - Depression	37
Children's Depression Inventory	36
Structured Clinical Interview Diagnosis	35
Hospital Anxiety and Depression Scale	32
Patient Health Questionnaire-9	38
Geriatric Depression Scale	26
Feighner Criteria Depression	24
Mini International Neuropsychiatric Interview	23
Minnesota Multiphasic Personality Inventory - Depression Scale	15
Composite International Diagnostic Interview	15
Children's Depression Rating Scale	15
Diagnostic Interview Schedule	14
Quick Inventory of Depressive Symptomatology	10
Profile of Mood States	8
Primary Care Evaluation of Mental Disorders	8
Cornell Scale for Depression in Dementia	5
Depression Adjective Checklist	5
Schedule for Affective Disorders and Schizophrenia for School-Age Children	4
Bellevue Index of Depression	3
The Leeds Scale for the Self-Assessment of Anxiety and Depression - Depression Score	3
Schedule for Affective Disorders and Schizophrenia	2
Wakefield Self-Assessment Depression Inventory	2
Clinical Interview Schedule	1
Modified Stockton Geriatric Rating Scale	1
Yesavage and Brink scale	1

Table 3-2: Characteristics of depression scales with established minimal clinically important differences (MCID).

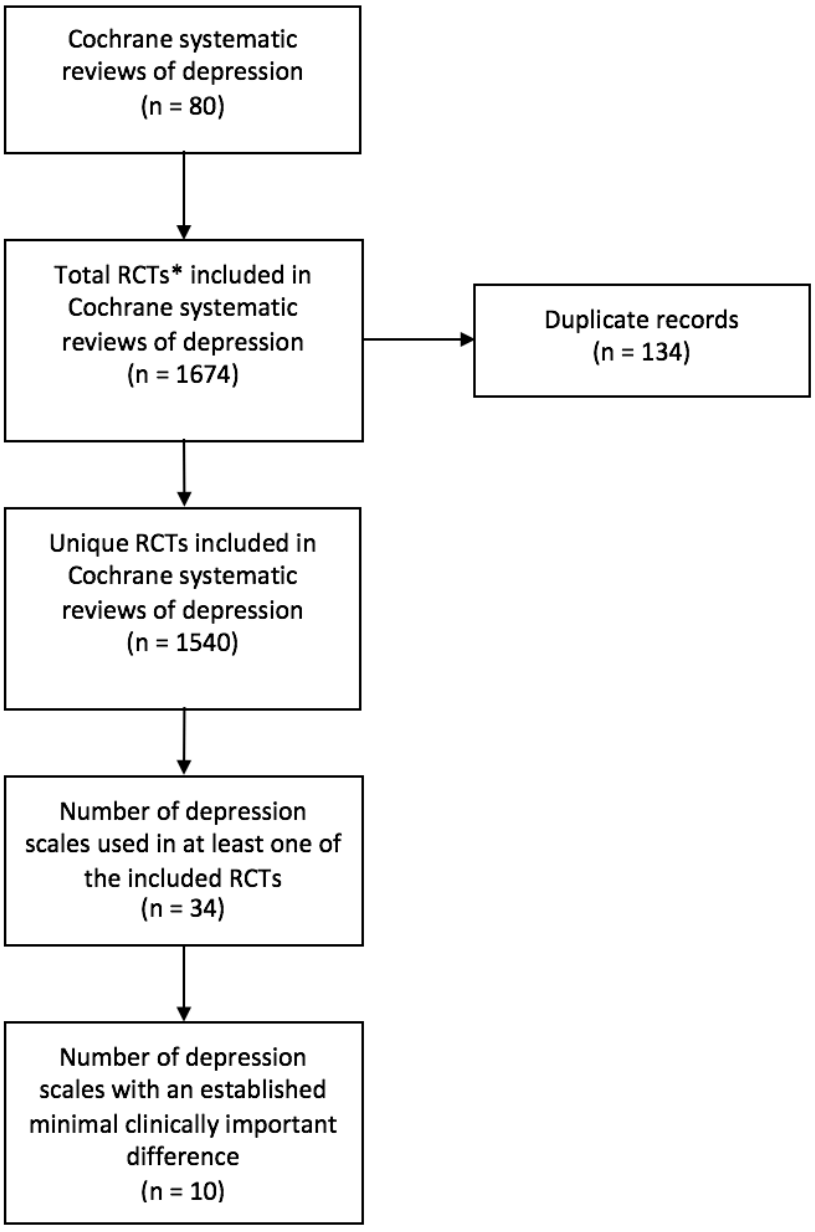
Scale Name	Range of Scores	Cut-offs for Depression Severity	Value of Minimal Clinically Important Difference	Method of Minimal Clinically Important Difference Derivation	Population Characteristics
Hamilton Depression Rating Scale	0-52 (17-item scale)	None: 0-7 Mild: 8-16 Moderate: 17-23 Severe: ≥24 (Zimmerman, 2013)	4-10 or 15-45% (Furukawa, 2007)	Anchor -Clinical Global Impression	Major depressive disorder
			27.1% (Rush 2003)	Anchor -Patient Global Impression	Major depressive disorder
	0-52 (21-item scale)	None: 0-7 Mild: 8-16 Moderate: 17-23 Severe: ≥24 (Zimmerman, 2013)	27% (Rush 2003)	Anchor -Patient Global Impression	Major depressive disorder
	0-75 (24-item scale)	None: 0-9 Mild: 10-19 Moderate: 20-29 Severe: ≥30 (UBC Hospital Mood Disorders Centre, 2009)	28% (Rush 2003)	Anchor -Patient Global Impression	Major depressive disorder
Montgomery Asbergs Depression Rating Scale	0-60 (10 items)	None: 0-6 Mild: 7-19 Moderate: 20-34 Severe: ≥35 (McDowell, 2006)	1.6-1.9 (Duru, 2008)	Distribution	Major depressive disorder
			13% (Bandelow, 2006)	Anchor - Clinical Global Impression	Major depressive disorder, panic disorder, anxiety disorders
			7-9 or 21-28% (Leucht, 2017)	Anchor - Clinical Global Impression	Major depressive disorder

Scale Name	Range of Scores	Cut-offs for Depression Severity	Value of Minimal Clinically Important Difference	Method of Minimal Clinically Important Difference Derivation	Population Characteristics
Beck Depression Inventory II	0-63 (21 items)	Minimal: 0-13 Mild: 14-19 Moderate: 20-28 Severe: ≥29 (McDowell, 2006)	2 or 17% (Button, 2015)	Anchor -Patient Global Impression	Major depressive disorder
			5 (Dworkin, 2008)	Distribution	Chronic pain
			5 (Hiroe, 2005)	Anchor - Clinical Global Impression	Major depressive disorder
			29.64% (Wilson, 2007)	Distribution	Chronic pain
			6.5 (Milgrom, 2005)	Delphi	Postnatal depression
			11 (Corsaletti, 2014)	Distribution	Smokers
Center for Epidemiologic Studies Depression Scale	0-60 (20 items)	Possible depression: ≥16 *May be higher in elderly, teenaged, or chronic pain populations	9 or 30% (Haase, 2016)	Anchor - Clinical Global Impression	Psychosomatic hospital inpatients
Zung Depression Scale	20-80 (20 items) *Converted to index score 25-100 by dividing by 0.8	Normal: 25-50 Minimal or mild: 50-59 Moderate: 60-69 Severe: ≥70 *Index scores (McDowell, 2006)	9 – anchor 8 – distribution (Hagg, 2003)	Distribution and anchor -Patient Global Impression	Chronic low back pain
			4.5 (Parker, 2013)	Anchor -Health Transition Index of SF-36, Satisfaction-based anchor	Suboccipital decompression
			4.9 (Parker, 2012)	Anchor -Health Transition Index of SF-36	Neural decompression and fusion

Scale Name	Range of Scores	Cut-offs for Depression Severity	Value of Minimal Clinically Important Difference	Method of Minimal Clinically Important Difference Derivation	Population Characteristics
Hospital Anxiety and Depression Scale	0-21 (depression subscale, 7 items)	None: 0-7 Possible depression: 8-10 Definite depression: ≥11 (McDowell, 2006)	1.4 (Puhan, 2008)	Distribution	COPD
			1.9-2.3 (Chan, 2016)	Distribution	Acute respiratory failure
			6 (Corsaletti, 2014)	Distribution	Smokers
			2.1 – anchor 1.6 – distribution (Curtis, 2014)	Distribution and anchor -Global Rating of Change (not specified whether patient or clinician)	COPD
			1.5-1.6 – anchor 1.6-1.8 – distribution (Smid, 2017)	Distribution and anchor -St. George's Respiratory Questionnaire	COPD
Patient Health Questionnaire-9	0-27 (9-item scale)	Minimal: 0-4 Mild: 5-9 Moderate: 10-14 Moderately severe: 15-19 Severe: ≥20 (Kroenke, 2001)	5 (Lowe, 2004)	Distribution	>60 years old
			50% (Kroenke, 2001)	Delphi	Primary care patients
Profile of Mood States	0-260 (65 items) *Depression subscale 0-60 (15 items)	N/A	2-12 subscale score (Dworkin, 2008)	Distribution	Chronic pain

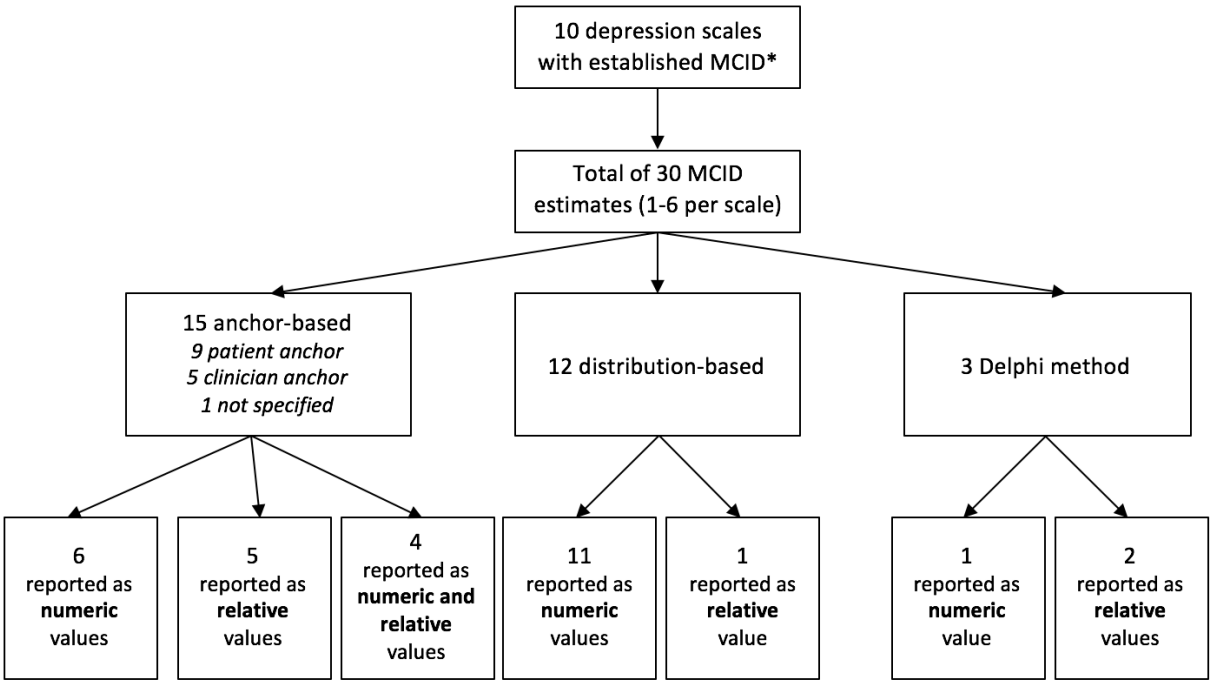
Scale Name	Range of Scores	Cut-offs for Depression Severity	Value of Minimal Clinically Important Difference	Method of Minimal Clinically Important Difference Derivation	Population Characteristics
Edinburgh Postnatal Depression Scale	0-30 (10 items)	Unlikely: 0-8 Possible: 9-11 Highly possible: 12-13 Probable: ≥14 (Perinatal Services BC, 2015)	15% (Morrell, 2009)	Delphi	Postnatal depression
Quick Inventory of Depressive Symptomatology	0-27 (16 items)	None: 0-5 Mild: 6-10 Moderate: 11-15 Severe: 16-20 Very severe: 21-27 (Rush, 2003)	28.5% (Rush 2003)	Anchor -Patient Global Impression	Major depressive disorder

Figure 3-1: Study flow diagram of Cochrane systematic reviews and depression scales.



*Randomized control trial

Figure 3-2: Flow diagram of methods of deriving (i.e. anchor- or distribution-based, Delphi method) and reporting (i.e. numeric or relative) minimal clinically important differences for depression scales.



*Minimal clinically important difference

3.5 REFERENCES

1) Finley CR, Chan DS, Garrison S, Korownyk C, Kolber MR, Campbell S, Eurich DT, Lindblad AJ, Vandermeer B, Allan GM. What are the most common conditions in primary care? A systematic review. Unpublished. 2017.
2) World Health Organization. The global burden of disease: 2004 update. Geneva (Switzerland): World Health Organization. 2008. Available at: http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf?ua=1
3) Zimmerman M, Roy-Byrne PP, Solomon D. Using scales to monitor symptoms and treat depression (measurement based care). *UpToDate*. 2016. Available at: http://www.uptodate.com/contents/using-scales-to-monitor-symptoms-and-treat-depression-measurement-based-care Accessed May 19, 2017.
4) Jaeschke R, Singer J, Guyatt GH. Measurement of health status: ascertaining the minimal clinically important difference. Control Clin Trials; 1989; 10:407-15.
5) Wright A, Hannon J, Hegedus EJ, Emerson Kavchak A. Clinimetrics corner: a closer look at the minimal clinically important difference. (MCID) J Man Manip Ther. 2012; 20(3):160-6.
6) McGlothin AE, Lewis RJ. Minimal clinically important difference: defining what really matters to patients. JAMA. 2014; 312(13):1342-3.
7) Duru G & Fantino B. The clinical relevance of changes in the Montgomery-Asberg depression rating scale using the minimum clinically important difference approach. Curr Med Res Opin. 2008; 24(5):1329-35.

8) Leucht S, Fennema H, Engel RR, Kaspers-Janssen M, Lepping P, Szegedi A. What does the MADRS mean? Equipercentile linking with the CGI using a company database of mirtazapine studies. J Affect Disord. 2017; 210:287-93.

9) Lowe B, Unutzer J, Callahan CM, Perkins AJ, Kroenke K. Monitoring depression treatment outcomes with the patient health questionnaire-9. Med Care. 2004; 42:1194-1201.

10) Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001; 16:606-13.

11) Milgrom J, Negri LM, Gemmill AW, McNeil M, Martin PR. A randomized controlled trial of psychological interventions for postnatal depression. Br J Clin Psychol. 2005; 44:529-42.

12) Morrell CJ, Warner R, Slade P, Dixon S, Walters S, Paley G, Brugha T. Psychological interventions for postnatal depression: cluster randomised trial and economic evaluation. The PoNDER trials. Health Technology Assessment. 2009; 13(30).

13) Hagg O, Fritzell P, Nordwall A. The clinical importance of changes in outcome scores after treatment for chronic low back pain. Eur Spine J. 2003; 12:12-20.

14) Curtis M, Kon S, Canavan J, Jones S, Nolan C, Clark A, Man W. The minimum important difference of the hospital anxiety and depression scale in COPD. Eur Respir J. 2014; 44:Suppl 58.

15) Smid DE, Franssen FME, Houben-Wilke S, Vanfleteren L, Janssen DJA, Wouters EFM, Spruit MA. Responsiveness and MCID estimates for CAT, CCQ, and HADS in patients with COPD undergoing pulmonary rehabilitation: a prospective analysis. JAMDA. 2017; 18:53-8.

16) Furukawa TA, Akechi T, Azuma H, Okuyama T, Higuchi T. Evidence-based guideliens for interpretation of the Hamilton rating scale for depression. J Clin Psychopharmacol. 2007; 27(5):531-4.

17) Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, … Keller MB. The 16-item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry. 2003; 54:573-83.

18) Bandelow B, Baldwin DS, Dolberg OT, Andersen HF, Stein DJ. What is the threshold for symptomatic response and remission for major depressive disorder, panic disorder, social anxiety disorder, and generalized anxiety disorder? J Clin Psychiatry. 2006; 67(9):1428-34.

19) Button KS, Kounali D, Wiles NJ, Peters TJ, Welton NJ, Ades AE, Lewis G. Minimal clinically important difference on the Beck Depression Inventoroy – II according to the patient's perspectice. Psyc Med. 2015; 45:3269-79.

20) Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, … Zavisic S. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. 2008; 9(2):105-21.

21) Hiroe T, Kojima M, Yamamoto I, Nojima S, Kinoshita Y, Hashimoto N, … Furukawa TA. Gradations of clinical severity and sensitivity to change assessed with the Beck Depression Inventory-II in Japanese patients with depression. Psychiatry Res. 2005; 135:229-35.

22) Wilson HD. Minimum clinical important differences of health outcomes in a chronic pain population: are they predictive of poor outcomes? Dissertation, The University of Texas at Arlington. 2007.

23) Corsaletti BF, Proenca MD, Bisca GK, Leite JC, Bellinetti LM, Pitta F. Minimal important difference for anxiety and depression surveys after intervention to increase daily physical activity in smokers. Fisioter Pesq. 2014; 21(4):359-64.

24) Haase I, Winkeler M, Imgart H. Anchor-based ascertaining of meaningful changes in depression symptoms using the example of the German short form of the CES-D. Neuropsychiatr. 2016; 30:82-91.

25) Parker SL, Godil SS, Zuckerman SL, Mendenhal SK, Wells JA, Shau DN, McGirt MJ. Comprehensive assessment of 1-year outcomes and determination of minimum clinically important difference in pain, disability, and quality of life after suboccipital decompression for Chiari malformation I in adults. Neurosurgery. 2013; 73:569-81.

26) Parker SL, Mendenhall SK, Shau DN, Adogwa O, Anderson WN, Devin CJ, McGirt MJ. Minimum clinically important difference in pain, disability, and quality of life after neural decompression and fusion for same-level recurrent lumbar stenosis: understanding clinical versus statistical significance. J Neurosurg Spine. 2012; 16:471-8.

27) Puhan MA, Frey M, Buchi S, Schunemann HJ. The minimal important difference of the hospital anxiety and depression scale in patients with chronic obstructive pulmonary disease. Health Qual Life Outcomes. 2008; 6(46).

28) Chan KS, Aronson Friedman L, Bienvenu OJ, Dinglas VD, Cuthbertson BH, Porter R, … Needham DM. Distribution-based estimates of minimal important difference for hospital

anxiety and depression scale and impact of event scale-revised in survivors of acute respiratory failure. Gen Hosp Psychiatry. 2016; 42:32-5.

29) Zimmerman M, Martinez JH, Young D, Chelminski I, Dalrymple K. Severity classification on the Hamilton depression rating scale. J Affect Disord. 2013; 150:384-8.

30) UBC Hospital Mood Disorders Centre. Summary sheet for the 24- and 29-item version of the Hamilton depression rating scale. 2009.

31) McDowell I. Measuring health: a guide to rating scales and questionnaires: Anxiety. Oxford Scholarship Online. 2006.

32) Perinatal Services BC. Edinburgh perinatal/postnatal depression scale scoring guide. 2015.

33) Vancouver Coastal Health. Cornell scale for depression in dementia. Geropsychiatric education program. 2017.

34) Leidy NK, Wyrwich KW. Bridging the gap: using triangulation methodology to estimate minimal clinically important differences (MCIDs). COPD 2005; 2(1):157-65.

35) Revicki DA, Cella D, Hays RD, Sloan JA, Lenderking WR, Aaronson NK. Responsiveness and minimal important differences for patient reported outcomes. Health Qual Life Outcomes 2006; 4(70).

Supplement 3-1. All Cochrane systematic reviews of depression retrieved.

	Cochrane Review
1	Selective serotonin reuptake inhibitors (SSRIs) versus other antidepressants for depression. Geddes J, Freemantle N, Mason J, Eccles M, Boynton J. Cochrane Database Sys Rev. 2006. 10.1002/14651858.CD001851.pub2
2	Caregiver support for postpartum depression. Ray K, Hodnett ED. 2001. 10.1002/14651858.CD000946.pub2
3	Antidepressants for depression in medical illness. Gill D, Hatcher S. 2000. 10.1002/14651858.CD001312.pub2
4	Psychological and pharmacological interventions for depression in patients with diabetes mellitus and depression. Baumeister H, Hutter N, Bengel J. 2012. 10.1002/14651858.CD008381.pub2
5	Pharmacologic treatment of depression in multiple sclerosis. Koch MW, Glazenborg A, Uyttenboogaart M, Mostert J, De Keyser J. 2011. 10.1002/14651858.CD007295.pub2.
6	Interventions for treating depression after stroke. Hackett ML, Anderson CS, House A, Xia J. 2008. DOI: 10.1002/14651858.CD003437.pub3.
7	Psychological interventions for depression in adolescent and adult heart disease. Lane DA, Millane TA, Lip GYH. 2013. DOI: 10.1002/14651858.CD004372.pub2
8	Aytpical antipsychotics for people with both schizophrenia and depression. Furtado VA, Srihari V, Kumar A. 2008. 10.1002/14651858.CD005377.pub2
9	Antidepressants plus benzodiazapines for major depression. Furukawa TA, Streiner D, Young LT, Kinoshita Y. 2001. 10.1002/14651858.CD001026
10	Antidepressants for people with both schizophrenia and depression. Whitehead C, Moss S, Cardno A, Lewis G, Furtado VA. 2002. 10.1002/14651858.CD002305
11	Psychological interventions for depression in heart failure. Lane DA, Yeong Chong A, Lip GYH. 2005. 10.1002/14651858.CD003329.pub2
12	Omega-3 fatty acids for depression in adults. Appleton KM, Sallis HM, Perry R, Ness AR, Churchill R. 2015. 10.1002/14651858.CD004692.pub4
13	Dance movement therapy for depression. Meekums B, Karkou V, Nelson EA. 2015. 10.1002/14651858.CD009895.pub2
14	Mirtazapine versus other antidepressive agents for depression. Watanabe N, Omori IM, Nakagawa A, Cipriani A, Barbui C, Churchill R, Furukawa TA. 2011. 10.1002/14651858.CD006528.pub2
15	Antidepressant treatment for postnatal depression. Molyneaux E, Howard LM, Mcgeown HR, Karia AM, Trevillion K. 2014. 10.1002/14651858.CD002018.pub2
16	Interventions (other than pharmacological, psychosocial or psychological) for treating antenatal depression. Dennis Cl, Dowswell T. 2013. 10.1002/14651858.CD006795.pub3
17	Escitalopram versus other antidepressive agents for depression. Cipriani A, Santilli C, Furukawa TA, Signoretti A, Nakagawa A, McGuire H, Churchill R, Barbui C. 2009. 10.1002/14651858.CD006532.pub2
18	Tryptophan and 5-hydroxytryptophan for depression. Shaw KA, Turner J, Del Mar C. 2002. 10.1002/14651858.CD003198
19	Alternating current cranial electrotherapy stimulation (CES) for depression. Kavirajan HC, Lueck K, Chuang K. 2014.

	10.1002/14651858.CD010521.pub2
20	Antidepressant prevention of postnatal depression. Howard L, Hoffbrand SE, Henshaw C, Boath L, Bradley E. 2005. 10.1002/14651858.CD004363.pub2
21	Third wave' cognitive and behavioural therapies versus treatment as usual for depression. Churchill R, Moore THM, Furukawa TA, Caldwell DM, Davies P, Jones H, Shinohara K, Imai H, Lewis G, Hunot V. 2013. 10.1002/14651858.CD008705.pub2
22	Alaprazolam for depression. Van Marwijk H, Allick G, Wegman F, Bax A, Riphagen II. 2012. 10.1002/14651858.CD007139.pub2
23	Antidepressants for depression in physically ill people. Rayner L, Price A, Evans A, Valsraj K, Higginson IJ, Hotopf. 2010. 10.1002/14651858.CD007503.pub2
24	Reiki for depression and anxiety. Joyce J, Herbison GP. 2015. 10.1002/14651858.CD006833.pub2
25	Antidepressants for the treatment of depression in people with cancer. Ostuzzi G, Mathcam F, Dauchy S, Barbui C, Hotopf M. 2015. 10.1002/14651858.CD011006.pub2
26	Continuation and maintenance treatments for depression in older people. Wilkinson P, Izmeth Z. 2016. 10.1002/14651858.CD006727.pub3
27	Exercise for depression. 2013. Cooney GM, Dwan K, Greig CA, Lawlor DA, Rimer J, Waugh FR, McMurdo M, Mead GE. 10.1002/14651858.CD004366.pub6
28	Music therapy for depression. Maratos A, Gold C, Wang X, Crawford M. 2008. 10.1002/14651858.CD004517.pub2
29	Antidepressants for treating depressioni in adults with end-stage kidney disease treated with dialysis. Palmer SC, Natale P, Ruospo M, Saglimbene VM, Rabindranath KS, Craig JC, Strippoli GFM. 2016. 10.1002/14651858.CD004541.pub3
30	Pharmacological treatment of depression in patients with a primary brain tumour. Rooney AG, Grant R. 2013. 10.1002/14651858.CD006932.pub3
31	Agomelatine versus other antidepressive agents for major depression. Guaiana G, Gupta S, Chiodo D, Davies SJC, Haederte K, Koesters M. 2013. 10.1002/14651858.CD008851.pub2
32	Cognitive behavioural therapy (CBT), third-wave CBT and interpersonal therapy (IPT) based interventions for preventing depression in children and adolescents. Hetrick SE, Cox GR, Witt KG, Bir JJ, Merry SN. 2016. 10.1002/14651858.CD003380.pub4
33	Screening and case finding instruments for depression. Gildbody S, House A, Sheldon T. 2005. 10.1002/14651858.CD002792.pub2
34	Paroxetine versus other anti-depressive agents for depression. Purgato M, Papola D, Gastaldon C, Trespidi C, Magni LR, Rizzo C, Furukawa TA, Watanabe N, Cipriani A, Barbui C. 2014. 10.1002/14651858.CD006531.pub2
35	Psychosocial and psychological interventions for treating antenatal depression. Dennis CL, Ross LE, Grigoriadis. 2007. 10.1002/14651858.CD006309.pub2
36	Psychological and pharmacological interventions for depression in patients with coronary artery disease. Baumeister H, hutter N, Bengal J. 2011. 10.1002/14651858.CD008012.pub3
37	Psychosocial interventions for depression in dialysis patients. Rabindranath KS, Daly C, Butler J, Roderick PJ, Wallace SA, MacLeod Am. 2005. 10.1002/14651858.CD004542.pub2
38	Fluoxetine versus other types of pharmacotherapy for depression. Magni LR, Purgato M, Gastaldon C, Papola D, Furukawa TA, Cipriani A, Barbui C. 2013. 10.1002/14651858.CD004185.pub3

39	Third wave' cognitive and behavioural therapies versus other psychological therapies for depression. Hunot V, Moore THM, Caldwell DM, Furukawa TA, Davies P, Jones H, Honyashiki M, Chen P, Lewis G, Churchill R. 2013. 10.1002/14651858.CD008704.pub2
40	Low dosage tricyclic antidepressants for depression. Furukawa TA, McGuire H, Barbui C. 2003. 10.1002/14651858.CD003197
41	Behavioural therapies versus other psychological therapies for depression. Shinohara K, Honyashiki M, Imai H, Hunot V, Caldwell DM, Davies P, Moore THM, Furukawa TA, Churchill R. 2013. 10.1002/14651858.CD008696.pub2
42	Amitriptyline for depression. Guaiana G, Barbui C, Hotopf M. 2007.
43	Psychosocial and psychological interventions for treating postpartum depression. Dennis CL, Hodnett ED. 2007. 10.1002/14651858.CD006116.pub2View
44	Relaxation for depression. Jorm AF, Morgan AJ, Hetrick SE. 2008. 10.1002/14651858.CD007142.pub2
45	Family therapy for depression. Jorm AF, Morgan AJ, Hetrick SE. 2008.
46	S-adenosyl methionine (SAMe) for depression in adults. Galizia I ,Oldani L, Macritchit K, Amari E, Dougall D, Jones TN, … Young AH. 2016. 10.1002/14651858.CD011286.pub2
47	Pharmacological treatment for depression during opioid agonist treatment for opioid dependence. Paolo Pani P, Vacca R, Trogu E, Amato L, Davoli M. 2010. 10.1002/14651858.CD008373.pub2
48	Oestrogens and progestins for preventing and treating postpartum depression. Dennis CL, Ross LE, Herxheimer A. 2008. 10.1002/14651858.CD001690.pub2
49	Acupuncture for depression. Smith CA, Hay PPJ, MacPherson H. 2010. 10.1002/14651858.CD004046.pub3
50	Antidepressants versus placebo for depression in primary care. Arroll B, Elley CR, Fishman T, Goodyear-Smith FA, Kenealy T, Blashki G, Kerse N, MacGillivray S. 2009. 10.1002/14651858.CD007954
51	Different regimens of intravenous sedatives or hypnotics for electroconvulsive therapy (ECT) in adult patients with depression. Lihua P, Su M, Ke W, Ziemann-Gimmel P. 2014. 10.1002/14651858.CD009763.pub2
52	Transcranial magnetic stimulation for treating depression. Rodriguez-Martin JL, Barbanoj JM, Schlaepfer TE, Clos SSC, Perez V, Kulisevsky J, Gironelli A. 2001. 10.1002/14651858.CD003493
53	Citalopram versus other anti-depressive agents for depression. Cipriani A, Purgato M, Furukawa TA, Trespidi C, Imperadore G, Signoretti A, Churchill R, Watanabe N, Barbui C. 2012. 10.1002/14651858.CD006534.pub2
54	Sertraline versus other antidepressive agents for depression. Cipriani A, la Ferla T, Furukawa TA, Signoretti A, Nakagawa A, Churchill R, McGuire H, Barbui C. 2010. 10.1002/14651858.CD006117.pub4
55	Ketamine and other glutamate receptor modulators for depression in adults. Caddy C, Amit BH, McCloud TL, Rendell JM, Furukawa TA, McShane R, Hawton K, Cipriani A. 2015. 10.1002/14651858.CD011612.pub2
56	Therapies for depression in Parkinson's disease. Ghazi-Noori S, Chung TH, Deane K, Rickards HE, Clarke CE. 2003. 10.1002/14651858.CD003465
57	Tricyclic drugs for depression in children and adolescents. Hazell P, Mirzaie M. 2013. 10.1002/14651858.CD002317.pub2
58	Active placebos versus antidepressants for depression. Moncrieff J, Wessely S, Hardy R. 2004. 10.1002/14651858.CD003012.pub2
59	Pharmacological treatment for psychotic depression. Wijkstra J, Lijmer J, Burger H, Cipriani A, Geddes J, Nolen WA. 2015.

	10.1002/14651858.CD004044.pub4
60	Psychostimulants for depression. Candy B, Jones L, Williams R, Tookman A, King M. 2008. 10.1002/14651858.CD006722.pub2.
61	Antidepressants for people with epilepsy and depression. Maguire MJ, Weston J, Singh J, Marson AG. 2014. 10.1002/14651858.CD010682.pub2
62	Psychotherapy for depression among incurable cancer patients. Akechi T, Okuyama T, Onishi J, Morita T, Furukawa TA. 2008. 10.1002/14651858.CD005537.pub2
63	Smoking cessation interventions for smokers with current or past depression. Van der Meer RM, Willemsen MC, Smit F, Cuijpers P. 2013. 10.1002/14651858.CD006102.pub2
64	Non-pharmacological interventions for depression in adults and children with traumatic brain injury. Gertler P, Tate Rl, Cameron ID. 2015. 10.1002/14651858.CD009871.pub2
65	Collaborative care for depression and anxiety problems. Archer J, Bower P, Gilbody S, Lovell K, Richards D, Gask L, Dickes C, Coventry P. 2012. 10.1002/14651858.CD006525.pub2
66	Antidepressants for treating depression in dementia. Bains J, Birks J, Dening T. 2002. 10.1002/14651858.CD003944
67	St John's wort for major depression. Linde K, Berner MM, Kriston L, 2008. 10.1002/14651858.CD000448.pub3
68	Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults. McCloud TL, Caddy C, Jochim J, Rendell JM, Diamond PR, Shuttleworth C, Brett D, Amit BH, McShane R, Hamadi L, Hawton K, Cipriani A. 2015. 10.1002/14651858.CD011611.pub2
69	Exercise in prevention and treatment of anxiety and depression among children and young people. Larun L, Nordheim LV, Ekeland E, Birger Hagen K, Heian F. 2006. 10.1002/14651858.CD004691.pub2
70	Milnacipran versus other antidepressive agents for depression. Nakagawa A, Watanabe N, Omori IM, Barbui C, Cipriani A, McGuire H, Churchill R, Furukawa TA. 2009. 10.1002/14651858.CD006529.pub2
71	Light therapy for non-seasonal depression. Tuunaienen A, Kripke DF, Takuro E. 2004. 10.1002/14651858.CD004050.pub2
72	Dietary supplements for preventing postnatal depression. Miller BJ, Murray L, Beckmann MM, Kent T, Macfarlane B. 2013. 10.1002/14651858.CD009104.pub2
73	Interventions for preventing depression after stroke. Hackett Ml, Anderson CS, House A, Halteh C. 2008. 10.1002/14651858.CD003689.pub3
74	Psycholoical treatments for depression and anxiety in dementia and mild cognitive impairment. Orgeta V, Qazi A, Spector AE, Orrell M. 2014. 10.1002/14651858.CD009125.pub2
75	Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. Cox GR, Callahan P, Churchill R, Hunot V, Merry SN, Parker AG, Hetrick SE. 2014. 10.1002/14651858.CD008324.pub3
76	Duloxetine versus other anti-depressive agents for depression. Cipriani A, Koesters M, Furukawa TA, Nose M, Purgato M, Omori IM, Trespidi C, Barbui C. 2012. 10.1002/14651858.CD006533.pub2
77	Fluvoxamine versus other anti-depressive agents for depression. Omori IM, Watanabe A, Cipriani A, Barbui C, McGuire H, Churchill R, Furukawa TA. 2010. 10.1002/14651858.CD006114.pub2
78	Psychosocial and psychological interventions for preventing postpartum depression. Dennis CL, Dowswell. 2013. 10.1002/14651858.CD001134.pub3

79	Hypnosis during pregnancy, childbirth, and the postnatal period for preventing postnatal depression. Sado M, Ota E, Stickley A, Mori R. 2012. 10.1002/14651858.CD009062.pub2
80	Marital therapy for depression. Barbato A, D'Avanzo BBD. 2006. 10.1002/14651858.CD009062.pub2

Supplement 3-2. Conversion of reported minimal clinically important difference (MCID) values from numerical to relative, or relative to numeric. Originally reported values in **bold**, converted values in *italics*.

Scale Name	Range of Scores	Cut-offs for Depression Severity	MCID Values – Numerical	MCID Values – Relative	Method of MCID Derivation
Hamilton Depression Rating Scale	0-52 (17-item scale) midpoint = 26	None: 0-7 Mild: 8-16 Moderate: 17-23 Severe: ≥24 (Zimmerman, 2013)	**4-10** *3.9-11.7* (Furukawa, 2007)	*15-38%* **15-45%**	Anchor -Clinical Global Impression
			7 (Rush 2003)	**27.1%**	Anchor -Patient Global Impression
	0-52 (21-item scale) midpoint = 26	None: 0-7 Mild: 8-16 Moderate: 17-23 Severe: ≥24 (Zimmerman, 2013)	*7* (Rush 2003)	**27%**	Anchor -Patient Global Impression
	0-75 (24-item scale) midpoint = 37.5	None: 0-9 Mild: 10-19 Moderate: 20-29 Severe: ≥30 (UBC Hospital Mood Disorders Centre, 2009)	*10.5* (Rush 2003)	**28%**	Anchor -Patient Global Impression
Montgomery Asbergs Depression Rating Scale	0-60 (10 items) midpoint = 30	None: 0-6 Mild: 7-19 Moderate: 20-34 Severe: ≥35 (McDowell, 2006)	**1.6-1.9** (Duru, 2008)	*5.3-6.3%*	Distribution
			3.9 (Bandelow, 2006)	**13%**	Anchor - Clinical Global Impression
			7-9 *6.3-8.4* (Leucht, 2017)	*23-30%* **21-28%**	Anchor - Clinical Global Impression

Scale Name	Range of Scores	Cut-offs for Depression Severity	MCID Values – Numerical	MCID Values – Relative	Method of MCID Derivation
Beck Depression Inventory II	0-63 (21 items) midpoint = 31.5	Minimal: 0-13 Mild: 14-19 Moderate: 20-28 Severe: ≥29 (McDowell, 2006)	**2** *5.4* (Button, 2015)	*6.3%* **17%**	Anchor -Patient Global Impression
			5 (Dworkin, 2008)	*15.9%*	Distribution
			5 (Hiroe, 2005)	*15.9%*	Anchor - Clinical Global Impression
			8.3 (Wilson, 2007)	**29.64%**	Distribution
			6.5 (Milgrom, 2005)	*20.6%*	Delphi
			11 (Corsaletti, 2014)	*34.9%*	Distribution
Center for Epidemiologic Studies Depression Scale	0-60 (20 items) midpoint = 30	Possible depression: ≥16 *May be higher in elderly, teenaged, or chronic pain populations	**9** *9* (Haase, 2016)	*30%* **30%**	Anchor - Clinical Global Impression
Zung Depression Scale	20-80 (20 items) *Converted to index score 25-100 by dividing by 0.8 midpoint = 62.5	Normal: 25-50 Minimal or mild: 50-59 Moderate: 60-69 Severe: ≥70 *Index scores (McDowell, 2006)	**9** – anchor **8** – distribution (Hagg, 2003)	*14.4%* *12.8%*	Distribution and anchor -Patient Global Impression
			4.5 (Parker, 2013)	*7.2%*	Anchor -Health Transition Index of SF-36, Satisfaction-based anchor
			4.9 (Parker, 2012)	*7.8%*	Anchor -Health Transition Index of SF-36

Scale Name	Range of Scores	Cut-offs for Depression Severity	MCID Values – Numerical	MCID Values – Relative	Method of MCID Derivation
Hospital Anxiety and Depression Scale	0-21 (depression subscale, 7 items) midpoint = 10.5	None: 0-7 Possible depression: 8-10 Definite depression: ≥11 (McDowell, 2006)	**1.4** (Puhan, 2008)	*13%*	Distribution
			1.9-2.3 (Chan, 2016)	*18.1-21.9%*	Distribution
			6 (Corsaletti, 2014)	*57.1%*	Distribution
			2.1 – anchor **1.6** – distribution (Curtis, 2014)	*20%* *15.2%*	Distribution and anchor -Global Rating of Change (not specified whether patient or clinician)
			1.5-1.6 – anchor **1.6-1.8** – distribution (Smid, 2017)	*14.3-15.2%* *15.2-17.1%*	Distribution and anchor -St. George's Respiratory Questionnaire
Patient Health Questionnaire-9	0-27 (9-item scale) midpoint = 13.5	Minimal: 0-4 Mild: 5-9 Moderate: 10-14 Moderately severe: 15-19 Severe: ≥20 (Kroenke, 2001)	**5** (Lowe, 2004)	*37%*	Distribution
			6.8 (Kroenke, 2001)	**50%**	Delphi
Profile of Mood States	0-260 (65 items) *Depression subscale 0-60 (15 items) midpoint = 30	N/A	**2-12** subscale score (Dworkin, 2008)	*6.7-40%*	Distribution

Scale Name	Range of Scores	Cut-offs for Depression Severity	MCID Values – Numerical	MCID Values – Relative	Method of MCID Derivation
Edinburgh Postnatal Depression Scale	0-30 (10 items) midpoint = 15	Unlikely: 0-8 Possible: 9-11 Highly possible: 12-13 Probable: ≥14 (Perinatal Services BC, 2015)	*2.3* (Morrell, 2009)	**15%**	Delphi
Quick Inventory of Depressive Symptomatology	0-27 (16 items) midpoint = 13.5	None: 0-5 Mild: 6-10 Moderate: 11-15 Severe: 16-20 Very severe: 21-27 (Rush, 2003)	*3.8* (Rush 2003)	**28.5%**	Anchor -Patient Global Impression

Supplement 3-3. Minimal clinically important differences (MCID) for improvement and deterioration of depression. Only studies which reported both improvement and deterioration MCIDs are included in this table.

Scale Name	Range of Scores	Cut-offs for Depression Severity	MCID Values - Improvement	MCID Values – Deterioration	Method of MCID Derivation
Hamilton Depression Rating Scale	0-52 (17-item scale)	None: 0-7 Mild: 8-16 Moderate: 17-23 Severe: ≥24 (Zimmerman, 2013)	Decrease of: 4-10 or 15-45% (Furukawa, 2007)	Increase of: 1 or 6%	Anchor -Clinical Global Impression
			Decrease of: 27.1% (Rush 2003)	Decrease of: 2%	Anchor -Patient Global Impression
	0-52 (21-item scale)	None: 0-7 Mild: 8-16 Moderate: 17-23 Severe: ≥24 (Zimmerman, 2013)	Decrease of: 27% (Rush 2003)	Decrease of: 0.3%	Anchor -Patient Global Impression
	0-75 (24-item scale)	None: 0-9 Mild: 10-19 Moderate: 20-29 Severe: ≥30 (UBC Hospital Mood Disorders Centre, 2009)	Decrease of: 28% (Rush 2003)	Decrease of: 2.8%	Anchor -Patient Global Impression
Montgomery Asbergs Depression Rating Scale	0-60 (10 items)	None: 0-6 Mild: 7-19 Moderate: 20-34 Severe: ≥35 (McDowell, 2006)	Decrease of: 7-9 or 21-28% (Leucht, 2017)	Increase of: 4	Anchor - Clinical Global Impression

Center for Epidemiologic Studies Depression Scale	0-60 (20 items)	Possible depression: ≥16 *May be higher in elderly, teenaged, or chronic pain populations	Decrease of: 9 or 30% (Haase, 2016)	Increase of: 4.5 or 19%	Anchor - Clinical Global Impression
Zung Depression Scale	20-80 (20 items) *Converted to index score 25-100 by dividing by 0.8	Normal: 25-50 Minimal or mild: 50-59 Moderate: 60-69 Severe: ≥70 *Index scores (McDowell, 2006)	Decrease of: 9 – anchor 8 – distribution (Hagg, 2003)	Increase of: 2 - anchor	Distribution and anchor -Patient Global Impression
Quick Inventory of Depressive Symptomatology	0-27 (16 items)	None: 0-5 Mild: 6-10 Moderate: 11-15 Severe: 16-20 Very severe: 21-27 (Rush, 2003)	28.5% (Rush 2003)	Increase of: 1.2%	Anchor -Patient Global Impression

4 CHAPTER 4: SUMMARY

4.1 OVERVIEW OF RESEARCH AND OBJECTIVES

Primary care is a crucial component of the healthcare system, as evidenced by the large numbers of patients and conditions seen in primary care.[1-3] Many countries, such as Australia and the United States, publish annual information on the visits patients make to primary care.[4,5] Having this information widely accessible is important not only for researchers, but also for policy makers and healthcare administrators. Some countries, such as Canada, do have information available on primary care, but it is not found in the indexed literature on scientific databases. For example, the Canadian Institutes for Health Information has reports available on their website describing various aspects of primary care, but these do not provide a comprehensive overview like the General Practice Activity reports in Australia or the National Ambulatory Medical Care Survey in the United States, and are not updated on a yearly basis.[4-6]

When I first became interested in common conditions in primary care, I was simply looking for literature that summarized the most common reasons patients visit their primary care professionals. However, to the best of my knowledge there has been no previously published systematic review on common conditions in primary care globally. Having this information available would provide direction and justification for undertaking research on specific topics within the broad range of health and disease states which present in primary care.

Thus, to overcome this gap in the literature I developed a research program with two main objectives. The first objective was to complete a systematic review of literature on the common reasons patients present to primary care. The main outcomes of this project were to rank reasons

for visits globally, and make comparisons between clinician-reported and patient-reported data, and between different economic groupings of countries.

I used my findings from this first project to inform the objectives for my second topic. Depression/anxiety was found to be the third most common RFV to primary care in developed countries, after hypertension (HTN) and upper respiratory tract infections (URTI), making it the most common condition in this list that is not derived from a surrogate marker and could be assessed using minimal clinically important differences (MCID).

Depression is a highly prevalent disorder, estimated to affect over 220 million people globally in 2004.[7] Depression is also a highly burdensome disorder, as measured by aspects of burden such as depression symptoms, decreased quality of life, suicide, disability, and family and economic burden.[8] In fact, it is the third leading cause of lost disability-adjusted life years globally.[7] Given the high prevalence and burden of depression, it is not surprising that there is a vast amount of literature published on all aspects of this disorder. Unfortunately, it can be challenging and time-consuming to search through this literature to find specific information, such as MCIDs for depression rating scales. I was interested in MCIDs because they provide an assessment of clinical importance for patient-reported outcomes, allowing investigators to interpret results without relying solely on statistical significance. Including measures of clinical importance is especially relevant in research where the effect of an intervention is primarily based on patient assessment of symptoms, such as depression.

Therefore, the second objective of my research was to investigate the MCID for scales pertaining to depression, one of the most common conditions in primary care. The main outcomes of this

project were to identify MCIDs for commonly used depression scales, and to summarize information on the scales and MCIDs in an easily accessible table.

4.2 SUMMARY OF FINDINGS

4.2.1 Common conditions in primary care

I found that the 10 most common clinician-reported RFV were URTI, HTN, routine health maintenance, arthritis, diabetes, depression/anxiety, pneumonia, otitis media, back pain and dermatitis. Within this short list, it is apparent that primary care provides management for a broad range of medical states, including acute symptomatic conditions like URTI and back pain, chronic medical conditions like hypertension and diabetes, and preventive care like routine health maintenance.

The 10 most common patient-reported RFV were cough, back pain, abdominal symptoms, pharyngitis, dermatitis, fever, headache, leg symptoms, unspecified respiratory, and fatigue. In contrast to the list resulting from clinician report, the patient-derived list does not include RFV for chronic asymptomatic medical conditions or preventive care, but is predominantly composed of symptomatic conditions.

Next I compared clinician-reported RFV between developed and developing countries. For both economic categories, URTI and HTN were the two most common RFV, confirming their high prevalence in primary care regardless of economic conditions or health system. There were other conditions that ranked similarly between developed and developing countries, such as arthritis, urinary tract infections, and diabetes. However, there were also some notable differences between the two groups of countries. For example, the third and fourth most common RFV in developed countries were depression/anxiety and back pain, but these conditions were not

present at all in the rankings for developing countries. Acute otitis media, dermatitis, abdominal unspecified, medication, cough, lipids, and routine health maintenance were ranked lower but also appeared only on the developed country list. In developing countries, pneumonia and tuberculosis were the third and fourth most common RFV, and neither of these appeared in the developed countries list.

4.2.2 Minimal clinically important differences on depression scales

I examined Cochrane systematic reviews on depression (n=80), which were comprised of 1540 unique studies. There were 34 different scales for measuring depression reported in these studies. I searched for information on the MCID for each of these scales, and identified MCID estimates for 10 of them: Hamilton Depression Rating Scale, Montgomery Asbergs Depression Rating Scale, Beck Depression Inventory, Centre for Epidemiologic Studies Depression Scale, Zung Depression Scale, Hospital Anxiety and Depression Scale, Patient Health Questionnaire-9, Profile of Mood States, Edinburgh Postnatal Depression Scale, and Quick Inventory of Depressive Symptoms.

For six of the scales more than one MCID estimate was found, and there was variability in both the values of estimates reported, and the methods of MCIDs derivation. Anchor-based and distribution-based methods were the most common ways to determine MCID estimates, with 15 (50%) being anchor-based and 12 (40%) distribution-based. Examining how the anchor-based MCIDs were derived, nine (60%) used patient reported scales, five (33%) used clinician reported, and one was not specified (7%). The Patient Global Impression (n=6; 40%) and the Clinical Global Impression (n=5; 33%) were the most commonly used anchor scales.

4.3 IMPLICATIONS FOR PRACTICE

Identifying the most common conditions in primary care provides evidence for how healthcare resources can be best allocated in primary care, as well as information to guide the continuing education of healthcare professionals. The majority of all office visits to physicians occur in primary care,[9] so examining which conditions present most commonly is important to improve allocation of limited resources. Policy makers and administrators may also find this information useful to address increasing demands for primary care services. For example, we found that routine health maintenance exams are the third most common clinician-reported RFV; however, the value of these appointments has been questioned and some groups advise against annual general medical exams.[10]

My results are also of benefit to those who develop training programs and competency-based exams for primary care trainees, to ensure that clinical abilities reflect the relative frequency of conditions that are seen in practice. For example, I found that depression/anxiety is the sixth most common clinician-rated RFV overall, and third most common RFV in developed countries, yet many primary care clinicians report feeling unprepared to manage mental health problems.[11] Training and evaluations should be focused on common conditions, so that clinicians feel better prepared to provide care to patients, and examinations accurately represent clinical performance.

Identifying the MCID for commonly used depression scales will be helpful for translating clinical research into information that is usable by clinicians. Using the MCID to evaluate the effect of an intervention will make it more straightforward for clinicians to interpret whether a treatment may have a meaningful effect on their patients. Additionally, using the MCID increases the ability of clinicians to monitor changes in depression symptoms over time to

determine whether their patients are responding to treatment, and provides a goal for improvement.

The results of this research will be highly applicable to primary care clinicians and researchers. Understanding which conditions present most often to primary care can be of assistance in the quest for more evidence-based and patient-oriented healthcare. Publishing the MCIDs for conditions commonly seen in primary care will improve how scientific knowledge is translated for use in healthcare, which may help professionals make recommendations for their patients and explain interventions to their patients.

4.4 IMPLICATIONS FOR FUTURE RESEARCH

Both of these projects will be useful for guiding future research in primary care and on conditions which can utilize the MCID. In my first study, I found that there was a lack of published literature meeting our inclusion criteria from certain geographic areas such as Canada, parts of Europe, and South America, as well as from developing countries in general. Therefore, more research is required on common conditions in primary care in many countries, and I suggest that primary care researchers look into this as a topic of interest. Another area that researchers may be interested in is how well primary care guidelines coincide with common conditions. For example, it would be informative to assess whether conditions that present more commonly have a larger number of associated guidelines and/or guideline recommendations, compared to conditions which present relatively less often.

This research also highlights the need for greater use of patient-centred measures of effect in the design, analysis and reporting of randomized trials, and encourages future studies to take a patient-oriented approach. Although there are many recommendations to use measures of clinical

significance in reporting outcomes,[12,13] 90% of the systematic reviews we retrieved on depression did not make use of MCID estimates. I encourage authors of future systematic reviews to analyze and interpret data using the MCID, to enhance understanding of how a treatment effect may be important to patients. When deciding which MCID estimate to use if more than one is available for a given scale, I support using the one derived from a patient anchor. If there are no applicable MCIDs determined by anchoring to a patient-based scale, research may be required to determine these MCID estimates.

Additionally, I have some recommendations regarding reporting of patient-oriented outcomes in clinical trials. First, authors should report baseline scores and mean change on scales for both the intervention and control groups, and not report just the difference in mean level of change between the groups. This would clarify the level of change attained in each group, and allow more straightforward comparisons between groups. As well, authors can compare the level of change in each group and the differences between groups to the MCID to interpret whether treatment effects are clinically significant in either group, or whether there are clinically significant differences between groups. Second, in addition to providing this continuous data on treatment effects, I advise that authors also report discrete data on the number of patients in each group that attain the MCID. This data allows further analysis of statistical differences between groups so that the number needed to treat to attain an MCID can be calculated.

4.5 LIMITATIONS

Despite the many strengths of my research, including the rigour of the systematic review protocol, the broad scope of literature searched, and the utility of reported results for guiding future research, this program of research was not without limitations. A challenge for both

projects was the reliance on published literature to provide accurate information of high quality. These topics were difficult to search for due to the breadth of terminology that could be used in reports describing the frequency of presentations to primary care, and the quantity of published literature on depression scales.

For the common conditions in primary care study, my ability to generalize the results to all developing countries was limited by the availability of data from only two countries, India and South Africa. Although there were two studies from each of these countries, it is possible that the inclusion of data from several more developing countries could change the results appreciably. Additionally, combining data from different types of coding systems (i.e. ICD, ICPD, Read) resulted in some loss of detail in the RFV, as I had to collapse some specific RFV into broader categories.

For the MCID in depression study, limits were mainly due to the vast amount of literature on depression. For example, it would have been interesting to determine the proportion of randomized controlled trials on depression that report MCIDs, but this would have required extracting data from 1540 different trials, which was not feasible.

4.6 CONCLUSIONS

I reviewed large-scale studies from 11 countries on five continents, finding that primary care clinicians manage an exceptionally broad range of clinical presentations globally. Although there was variation in the relative frequency of different RFV between countries, overall there was a high degree of consistency in the 10 most common RFV to primary care. Depending on whether RFV are reported by clinicians or patients however, does affect which conditions are reported. Thus, who is reporting the RFV should be considered when interpreting RFV data. I also found

that there were differences between developed and developing countries with regards to the most commonly reported RFV, although generalizations to all developing countries were limited. However, more large-scale primary care studies are required and this research serves as a call for primary care researchers around the globe to investigate common conditions in their regions.

One of the most common conditions in primary care, especially in developed countries, is depression, and a great deal of research has been done to evaluate interventions for this burdensome disorder. As there are a large number of different depression scales available for use by researchers and clinicians, I suggest that researchers include common scales, such as the HAM-D, MADRS, and BDI to increase consistency and allow comparison of results between trials. Ideally, the scales used by researchers will have a patient-anchored MCID available, which is then used in power calculations and interpretation of results. As depression is a symptomatic condition, it is critical that studies on depression aim to find clinically important differences, not just statistical ones.

4.7 REFERENCES

1) Green LA, Fryer GE, Yawn BP, Lanier D, Dovey SM. The ecology of medical care revisited. N Engl J Med. 2001;344:2021-5.
2) Stewart M, Ryan B. Ecology of health care in Canada. Can Fam Physician. 2015;61:449-53.
3) Starfield B, Lemke KW, Bernhardt T, Foldes SS, Forrest CB, Weiner JP. Comorbidity: implications for the importance of primary care in 'case' management. Ann Fam Med. 2003;1:8-14.
4) Britt H, Miller GC, Henderson J, Bayram C, Harrison C, Valenti L, et al. General practice activity in Australia 2014-15. General practice series no. 38. Sydney: Sydney University Press. 2015. Available at: <purl.library.usyd.edu.au/sup/9781743324523>
5) Centers for Disease Control and Prevention, National Center for Health Statistics. NAMCS 2014 most frequent reasons for visits to primary care practitioners [online]. Personal communication with Akintunde Akinseye (viu7@cdc.gov) 2017 Apr 25.
6) Canadian Institutes for Health Information. Primary health care. 2017. Available at: https://www.cihi.ca/en/primary-health-care#_Reports_and_Analyses
7) World Health Organization. The global burden of disease: 2004 update. Geneva (Switzerland): World Health Organization. 2008. Available at: http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf?ua=1
8) Lepine JP, Briley M. The increasing burden of depression. *Neuropsychiatr Dis Treat*. 2011; 7(Suppl 1)3-7.
9) National Center for Health Statistics (US). Health, United States, 2010: With Special

Feature on Death and Dying. Hyattsville (MD): National Center for Health Statistics (US); 2011 Feb.

10) Society of General Internal Medicine. Five things physicians and patients should question. Choosing Wisely. 2013 Sept 12. Available at: http://www.choosingwisely.org/wp-content/uploads/2015/02/SGIM-Choosing-Wisely-List.pdf

11) Osborn R, Moulds D, Schneider EC, Doty MM, Squires D, Sarnak DO. Primary care physicians in ten countries report challenges caring for patients with complex health needs. Health Aff. 2015;34(12):2104-12.

12) Lang T, Altman D. Basic statistical reporting for articles published in clinical medical journals: the SAMPL Guidelines. In: Smart P, Maisonneuve H, Polderman A, editors. Science Editors' Handbook, European Association of Science Editors, 2013.

13) Patrick DL, Guyatt GH, Acquadro C. Chapter 17: patient-reported outcomes. In: Higgins JPT, Green S, (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available at: www.cochrane-handbook.org

WORKS CITED

Allan GM, Finley C, McCormack J, Kumar V, Kwong S, Braschi E, … Garrison S. Are potentially clinically meaningful benefits misinterpreted in cardiovascular randomized trials? A systematic Examination of statistical significance, clinical significance and authors' conclusions. BMC Med. 2017; 15:58.

Bandelow B, Baldwin DS, Dolberg OT, Andersen HF, Stein DJ. What is the threshold for symptomatic response and remission for major depressive disorder, panic disorder, social anxiety disorder, and generalized anxiety disorder? J Clin Psychiatry. 2006; 67(9):1428-34.

Binns HJ, Lanier D, Pace WD, Galliher JM, Ganiats TG, Grey M, et al. Describing primary care encounters: the primary care network survey and the national ambulatory medical care survey. Ann Fam Med. 2007 Jan/Feb; 5(1):39-47.

Brignardello-Petersen R, Carrasco-Labra A, Shah P, Azarpazhooh A. A practitioner's guide to developing critical appraisal skills: what is the difference between clinical and statistical significance? JADA. 2013; 144(7):780-6.

Britt H, Bhasale A, Miles DA, Meza A, Sayer GP, Angelis M. The sex of the general practitioner: a comparison of characteristics, patients, and medical conditions managed. Med Care. 1996; 34(5):403-15.

Britt H, Miller GC, Henderson J, Bayram C, Harrison C, Valenti L, et al. General practice activity in Australia 2014-15. General practice series no. 38. Sydney: Sydney University Press. 2015. Available at: <purl.library.usyd.edu.au/sup/9781743324523>

Brueton V, Yogeswaran P, Chandia J, Mfenyana K, Modell B, Modell M, et al. Primary care morbidity in Eastern Cape province. S Afr Med J. 2010; 100:309-12.

Button KS, Kounali D, Wiles NJ, Peters TJ, Welton NJ, Ades AE, Lewis G. Minimal clinically important difference on the Beck Depression Inventoroy – II according to the patient's perspectice. Psyc Med. 2015; 45:3269-79.

Canadian Institutes for Health Information. Primary health care. 2017. Available at: https://www.cihi.ca/en/primary-health-care#_Reports_and_Analyses

Canadian Institutes of Health Research. Strategy for patient-oriented research. Government of Canada. 2016. Available at: http://www.cihr-irsc.gc.ca/e/41204.html

Centers for Disease Control and Prevention, National Center for Health Statistics. NAMCS 2014 most frequent reasons for visits to primary care practitioners [online]. Personal communication with Akintunde Akinseye (viu7@cdc.gov) 2017 Apr 25.

Chan KS, Aronson Friedman L, Bienvenu OJ, Dinglas VD, Cuthbertson BH, Porter R, … Needham DM. Distribution-based estimates of minimal important difference for hospital anxiety and depression scale and impact of event scale-revised in survivors of acute respiratory failure. Gen Hosp Psychiatry. 2016; 42:32-5.

Chang CH, Stukel TA, Flood AB, Goodman DC. Primary care physician workforce and medicare beneficiaries' health outcomes. JAMA. 2011; 305:2096-105.

Chuang-Stein C, Kirby S, Hirsch I, Atkinson G. The role of the minimum clinically important difference and its impact on designing a trial. Pharmaceut Statist. 2011; 10:250–6.

Copay AG, Subach BR, Glassman SD, Polly Jr DW, Schuler TC. Understanding the minimal clinically important difference: a review of concepts and methods. Spine J. 2007; 7(5):541-546.

Corsaletti BF, Proenca MD, Bisca GK, Leite JC, Bellinetti LM, Pitta F. Minimal important difference for anxiety and depression surveys after intervention to increase daily physical activity in smokers. Fisioter Pesq. 2014; 21(4):359-64.

Curtis M, Kon S, Canavan J, Jones S, Nolan C, Clark A, Man W. The minimum important difference of the hospital anxiety and depression scale in COPD. Eur Respir J. 2014; 44:Suppl 58.

Duru G & Fantino B. The clinical relevance of changes in the Montgomery-Asberg depression rating scale using the minimum clinically important difference approach. Curr Med Res Opin. 2008; 24(5):1329-35.

Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, … Zavisic S. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. 2008; 9(2):105-21.

Finley CR, Chan DS, Garrison S, Korownyk C, Kolber MR, Campbell S, Eurich DT, Lindblad AJ, Vandermeer B, Allan GM. What are the most common conditions in primary care? A systematic review. Unpublished. 2017.

Fleming DM, Cross KW, Barley MA. Recent changes in the prevalence of diseases presenting for health care. Brit J Gen Pract. 2005; 55(517):589-95.

Furukawa TA, Akechi T, Azuma H, Okuyama T, Higuchi T. Evidence-based guideliens for interpretation of the Hamilton rating scale for depression. J Clin Psychopharmacol. 2007; 27(5):531-4.

Green LA, Fryer GE, Yawn BP, Lanier D, Dovey SM. The ecology of medical care revisited. N Engl J Med. 2001; 344:2021-5.

Haase I, Winkeler M, Imgart H. Anchor-based ascertaining of meaningful changes in depression symptoms using the example of the German short form of the CES-D. Neuropsychiatr. 2016; 30:82-91.

Hagg O, Fritzell P, Nordwall A. The clinical importance of changes in outcome scores after treatment for chronic low back pain. Eur Spine J. 2003; 12:12-20.

Harrison CM, Britt HC, Charles J. Sex of the GP - 20 years on. Med J Aust. 2011; 195(4):192–6.

Hedayat AS, Wang J, Xu T. Minimal clinically important difference in medical studies. Biometrics. 2015; 71:33-41.

Hiroe T, Kojima M, Yamamoto I, Nojima S, Kinoshita Y, Hashimoto N, … Furukawa TA. Gradations of clinical severity and sensitivity to change assessed with the Beck Depression Inventory-II in Japanese patients with depression. Psychiatry Res. 2005; 135:229-35.

Hobbs FDR, Bankhead C, Mukhtar T, Stevens S, Perera-Salazar R, Holt T, et al. Clinical workload in UK primary care: a retrospective analysis of 100 million consultations in England, 2007-14. Lancet. 2016 Jun 4; 387(10035):2323-30.

Jaeschke R, Singer J, Guyatt GH. Measurement of health status: ascertaining the minimal clinically important difference. Control Clin Trials. 1989; 10:407-15.

Johnston BC, Alonso-Coello P, Friedrich JO, Mustafa RA, Tikkinen KAO, Neumann I, Vandvik PO, Akl EA, da Costa BR, Adhikari NK, Mas Dalmau G, Kosunen E, Mustonen J, Crawford MW, Thanbane L, Guyatt GH. Do clinicians understand the size of treatment effects? A randomized survey across 8 countries. CMAJ. 2015. Early release published at www.cmaj.ca on Oct 26, 2015.

Johnston BC, Thorlund K, da Costa BR, Furukawa TA, Guyatt GH. New methods can extend the use of minimal important difference units in meta-analyses of continuous outcomes measures. J Clin Epidemiol. 2012; 65:817-26.

Jones PW, Beeh KM, Chapman KR, Decramer M, Mahler DA, Wedzicha JA. Minimal clinically important differences in pharmacological trials. Am J Respir Crit Care Med. 2014; 189(3):250-5.

Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001; 16:606-13.

Lang T, Altman D. Basic statistical reporting for articles published in clinical medical journals: the SAMPL Guidelines. In: Smart P, Maisonneuve H, Polderman A, editors. Science Editors' Handbook, European Association of Science Editors, 2013.

Lee EC, Whitehead AL, Jacques RM, Julious SA. The statistical interpretation of pilot trials: should significance thresholds be reconsidered? BMC Med Res Methodol. 2014; 14(41).

Leidy NK, Wyrwich KW. Bridging the gap: using triangulation methodology to estimate minimal clinically important differences (MCIDs). COPD. 2005; 2(1):157-65.

Lepine JP, Briley M. The increasing burden of depression. Neuropsychiatr Dis Treat. 2011; 7(Suppl 1)3-7.

Leucht S, Fennema H, Engel RR, Kaspers-Janssen M, Lepping P, Szegedi A. What does the MADRS mean? Equipercentile linking with the CGI using a company database of mirtazapine studies. J Affect Disord. 2017; 210:287-93.

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009 Jul 21; 6(7):e1000100.

Lowe B, Unutzer J, Callahan CM, Perkins AJ, Kroenke K. Monitoring depression treatment outcomes with the patient health questionnaire-9. Med Care. 2004; 42:1194-1201.

Mash B, Fairall L, Adejayan O, Ikpefan O, Kumari J, Mathee S, et al. A morbidity survey of South African primary care. PLoS One. 2012; 7:e32358.

McDowell I. Measuring health: a guide to rating scales and questionnaires: Anxiety. Oxford Scholarship Online. 2006.

McGlothin AE, Lewis RJ. Minimal clinically important difference: defining what really matters to patients. JAMA. 2014; 312(13):1342-3.

Milgrom J, Negri LM, Gemmill AW, McNeil M, Martin PR. A randomized controlled trial of psychological interventions for postnatal depression. Br J Clin Psychol. 2005; 44:529-42.

Ministry of Health. Family doctors: methodology and description of the activity of private GPs: the national primary medical care survey (NatMedCa): 2001/02. Report 1. Wellington: Ministry of Health. 2004.

Mohan N, Nagavi BG. Development of standard therapeutic guidelines for selected common diseases for the primary health care centres of a south Indian district. Int J Pharm Pract. 2003; 11(3):169-74.

Morrell CJ, Warner R, Slade P, Dixon S, Walters S, Paley G, Brugha T. Psychological interventions for postnatal depression: cluster randomised trial and economic evaluation. The PoNDER trials. Health Technology Assessment. 2009; 13(30).

Murphy M, Brodie G, Byrne S, Bradley C. An observational study of public and private general practitioner consultations in the Republic of Ireland. Ir J Med Sci. 2015 Mar; 184(1):147-52.

National Center for Health Statistics (US). Health, United States, 2010: With Special Feature on Death and Dying. Hyattsville (MD): National Center for Health Statistics (US); 2011 Feb.

Office of the Surgeon General (US); Center for Mental Health Services (US); National Institute of Mental Health (US). Mental Health: Culture, Race, and Ethnicity: A Supplement to Mental Health: A Report of the Surgeon General. Rockville (MD): Substance Abuse and

Mental Health Services Administration (US); 2001 Aug. Available at: http://www.ncbi.nlm.nih.gov/books/NBK44249/

Osborn R, Moulds D, Schneider EC, Doty MM, Squires D, Sarnak DO. Primary care physicians in ten countries report challenges caring for patients with complex health needs. Health Aff. 2015; 34(12):2104-12.

Østbye T, Yarnall KS, Krause KM, Pollak KI, Gradison M, Michener JL. Is there time for management of patients with chronic diseases in primary care? Ann Fam Med. 2005; 3:209-14.

Pace WD, Dickinson LM, Staton EW. Seasonal variation in diagnoses and visits to family physicians. Ann Fam Med. 2004; 2(5):411-17.

Parker SL, Godil SS, Zuckerman SL, Mendenhal SK, Wells JA, Shau DN, McGirt MJ. Comprehensive assessment of 1-year outcomes and determination of minimum clinically important difference in pain, disability, and quality of life after suboccipital decompression for Chiari malformation I in adults. Neurosurgery. 2013; 73:569-81.

Parker SL, Mendenhall SK, Shau DN, Adogwa O, Anderson WN, Devin CJ, McGirt MJ. Minimum clinically important difference in pain, disability, and quality of life after neural decompression and fusion for same-level recurrent lumbar stenosis: understanding clinical versus statistical significance. J Neurosurg Spine. 2012; 16:471-8.

Patrick DL, Guyatt GH, Acquadro C. Chapter 17: patient-reported outcomes. In: Higgins JPT, Green S, (editors). Cochrane Handbook for Systematic Reviews of Interventions

Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available at: www.cochrane-handbook.org.

Pearson N, O'Brien J, Thomas H, Ewings P, Gallier L, Bussey A. Collecting morbidity data in general practice: the Somerset morbidity project. BMJ. 1996; 312:1517-20.

Perinatal Services BC. Edinburgh perinatal/postnatal depression scale scoring guide. 2015.

Probst JC, Moore CG, Baxley EG. Lammie JJ. Rural-urban differences in visits to primary care physicians. Fam Med. 2002; 34(8):609-15.

Puhan MA, Frey M, Buchi S, Schunemann HJ. The minimal important difference of the hospital anxiety and depression scale in patients with chronic obstructive pulmonary disease. Health Qual Life Outcomes. 2008; 6(46).

Revicki DA, Cella D, Hays RD, Sloan JA, Lenderking WR, Aaronson NK. Responsiveness and minimal important differences for patient reported outcomes. Health Qual Life Outcomes. 2006; 4(70).

Roland M, Guthrie B, Thomé DC. Primary medical care in the United Kingdom. J Am Board Fam Med. 2012; 25(S1):S6-11.

Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, … Keller MB. The 16-item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry. 2003; 54:573-83.

Salvi S, Apte K, Madas S, Barne M, Chhowala S, Sethi T, et al. Symptoms and medical conditions in 204 912 patients visiting primary health-care practitioners in India: a 1-day point prevalence study (the POSEIDON study). Lancet Glob Health. 2015; 3(12):e776-84.

Sayer GP, Britt H. Sex differences in morbidity: a case of discrimination in general practice. Soc Sci Med. 1996; 42(2):257-64.

Shi L, Macinko J, Starfield B, Wulu J, Regan J, Politzer R. The relationship between primary care, income inequality, and mortality in US States, 1980-1995. J Am Board Fam Pract. 2003; 16:412-22.

Smid DE, Franssen FME, Houben-Wilke S, Vanfleteren L, Janssen DJA, Wouters EFM, Spruit MA. Responsiveness and MCID estimates for CAT, CCQ, and HADS in patients with COPD undergoing pulmonary rehabilitation: a prospective analysis. JAMDA. 2017; 18:53-8.

Society of General Internal Medicine. Five things physicians and patients should question. Choosing Wisely. 2013 Sept 12. Available at: http://www.choosingwisely.org/wp-content/uploads/2015/02/SGIM-Choosing-Wisely-List.pdf

Soler JK, Okkes I, Oskam S, van Boven K, Zivotic P, Jevtic M, et al. An international comparative family medicine study of the Transition Project data from the Netherlands, Malta and Serbia. Is family medicine an international discipline? Comparing incidence and prevalence rates of reasons for encounter and diagnostic titles of episodes of care across populations. Fam Pract. 2012; 29:283-98.

Starfield B, Lemke KW, Bernhardt T, Foldes SS, Forrest CB, Weiner JP. Comorbidity: implications for the importance of primary care in 'case' management. Ann Fam Med. 2003; 1:8-14.

Starfield B, Shi L. Policy relevant determinants of health: an international perspective. Health Policy. 2002 Jun; 60(3):201-18.

Stewart M, Ryan B. Ecology of health care in Canada. Can Fam Physician. 2015; 61:449-53.

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al; Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA. 2000; 283:2008-12.

Terwee CB, Roorda LD, Dekker J, Bierma-Zeinstra SM, Peat G, Jordan KP, Croft P, de Vet HCW. Mind the MIC: large variation among populations and methods. J Clin Epidemiol. 2010; 63:524-34.

UBC Hospital Mood Disorders Centre. Summary sheet for the 24- and 29-item version of the Hamilton depression rating scale. 2009.

United Nations. Country classification. In: World economic situation and prospects 2012. New York: United Nations, 2012. p. 131-40.

Vancouver Coastal Health. Cornell scale for depression in dementia. Geropsychiatric education program. 2017.

Wandell P, Carlsson AC, Wettermark B, Lord G, Cars T, Ljunggren G. Most common diseases diagnosed in primary care in Stockholm, Sweden, in 2011. Fam Pract. 2013; 30(5):506-13.

Wang YC, Hart DL, Stratford PW, Mioduski JE. Baseline dependency of minimal clinically important improvement. Phys Ther. 2011; 91:675-88.

Willams JS, Ng N, Peltzer K, Yawson A, Biritwum R, Maximova T, et al. Risk factors and disability associated with low back pain in older adults in low- and middle-income countries: results from the WHO study on global AGEing and and adult health (SAGE). PLoS One. 2015; 10(6):e0127880.

Wilson HD. Minimum clinical important differences of health outcomes in a chronic pain population: are they predictive of poor outcomes? Dissertation, The University of Texas at Arlington. 2007.

World Health Organization. Millions with mental disorders deprived of treatment and care. [updated 2008 Oct 9; cited 2016 Aug 11]. Available at: http://www.who.int/mediacentre/news/releases/2008/pr37/en/

World Health Organization. The global burden of disease: 2004 update. Geneva (Switzerland): World Health Organization. 2008. Available at: http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf?ua=1

Wright A, Hannon J, Hegedus EJ, Emerson Kavchak A. Clinimetrics corner: a closer look at the minimal clinically important difference (MCID). J Man Manip Ther. 2012; 20(3):160-6.

Yarnall KS, Pollak KI, Østbye T, Krause KM, Michener JL. Primary care: is there enough time for prevention? Am J Public Health. 2003; 93:635-41.

Zimmerman M, Martinez JH, Young D, Chelminski I, Dalrymple K. Severity classification on the Hamilton depression rating scale. J Affect Disord. 2013; 150:384-8.

Zimmerman M, Roy-Byrne PP, Solomon D. Using scales to monitor symptoms and treat depression (measurement based care). UpToDate. 2016. Available at: http://www.uptodate.com/contents/using-scales-to-monitor-symptoms-and-treat-depression-measurement-based-care Accessed May 19, 2017.