Appendix B: Additional Information

1. Protocol

BACKGROUND

There are roughly 75 million people in the United States with multiple chronic conditions (MCC), and 65% of total health care spending in the nation is used for this quarter of the population.[1] In 2010 only 32% of Medicare fee-for-service beneficiaries had zero or one chronic condition, while 32% had two or three, 25% had four or five, and 14% had six or more chronic conditions.[2]

However, randomized controlled trials (RCTs) frequently exclude patients with MCC.[1,3-7] In a systematic sampling of high impact general medical journals, 81% of RCTs reviewed excluded patients with MCC.[7] A similar review sampling both general and specialized high impact medical journals found patients with MCC were excluded from 63% of all RCTs and 90% of RCTs that explicitly or implicitly mentioned MCC. Only 2% of RCTs explicitly included patients with MCC.[5] Furthermore, when these patients are not excluded, reporting of co-occurring chronic conditions is limited.[3,4,8] An in-depth survey of clinical trials revealed only a 44% reporting rate of participant comorbidities.[3] This inconsistency between the characteristics of eligible patients in RCTs and the characteristics of the actual patient population with the disease reduces confidence in applying trial results to the patient population.[3,6] Consequently, the knowledge base for multiple chronic conditions is largely limited by the reliance on clinical trials that strive to maximize internal validity by excluding patients with comorbidities.[1]

It is well established that behavioral and psychological factors play a large role in outcomes for numerous chronic conditions, such as cancer, cardiovascular disease, and diabetes.[9] In an in depth analysis of actual causes of US deaths in the year 2000, the three leading causes were behavioral based and largely modifiable: tobacco use (18.1%), poor diet and physical inactivity (15.2%), and alcohol consumption (3.5%).[10] These figures illuminate the importance of testing behavioral/psychosocial interventions within RCTs. Yet, the inclusion of MCC patients specifically in such trials has not been studied. As these patients account for roughly 25% of the US population, this is an area that warrants further examination.

Description of the condition

The challenge of treating patients who have MCC is further exacerbated by the large variance in how chronic condition is defined, which is problematic when comparing results across studies and attaining accurate prevalence rates. Among peer reviewed literature and public information sources, there is much inconsistency in several dimensions of the definition, such as the duration, effect on function and well-being, and need for medical attention.[11] To address this issue, an MCC working group at the Office of the Assistant Secretary of Health (OASH) within the US Department of Health and Human Services (HHS) compiled a list chronic conditions that met the definition for chronicity, are prevalent and have potential to be modifiable by public health and/or clinical interventions. The definition OASH used defined chronic illnesses as conditions that last a year or more and require ongoing medical attention and/or limit activities of daily living. This resulted in a compilation of 20 conditions (Table 1).[11]

Table 1: OASH List of Chronic Conditions
Arthritis
Asthma
Autism spectrum disorder
Cancer
Cardiac arrhythmias

Chronic kidney disease
Chronic obstructive pulmonary disease
Congestive heart failure
Coronary artery disease
Dementia (including Alzheimer's and other senile dementias)
Depression
Diabetes
Hepatitis
Human immunodeficiency virus (HIV)
Hyperlipidemia
Hypertension
Osteoporosis
Schizophrenia
Stroke
Substance abuse disorders (drug and alcohol)

Why it is important to do this review

The evaluation of representation of individuals with MCC in RCTs over the past 15 years is necessary in order to determine if behavioral and psychosocial intervention research that considers individuals with multiple chronic conditions should emerge as a research priority. We aim to perform the review, evaluation and summarization of data regarding the representation of individuals with multiple chronic conditions in RCTs of behavioral and psychosocial interventions published in general medical, behavioral medicine, behavioral science, health psychology, social science, and public health journals.

OBJECTIVES

With this review we seek to test the hypothesis that individuals with multiple chronic conditions are underrepresented in RCTs of behavioral and psychosocial interventions published in general medical, behavioral medicine, behavioral science, health psychology, social science, and public health journals. The overall goals of the project are as follows:

Goal 1: Conduct a systematic review to assess the frequency with which research participants with MCC are represented in all or a representative subset of RCTs of behavioral and psychosocial interventions published in general medical and specialized journals, published within the last decade or decade and a half, that focus on behavioral medicine and behavioral science, health psychology, social science, and public health.

Goal 2: Determine whether there are significant differences by type of journal or over time in the frequency with which research participants with MCC are represented in RCTs of behavioral and psychosocial interventions.

These goals will be accomplished with the following objectives:

Objective 1: Perform a systematic review of a representative sample of the peer-reviewed literature over the past 15 years (2000-2014) to describe, quantify, and critically appraise the inclusion of individuals with MCC in RCTs designed to develop and/or test the efficacy or effectiveness of behavioral and psychosocial interventions to modify health behaviors, improve health-related quality of life, psychosocial functioning, and/or health outcomes.

Objective 2: Describe and analyze how inclusion/exclusion of individuals with MCC in RCTs differs across time and by journal type. As appropriate, consider other factors such as components of intervention.

METHODS

Criteria for selecting studies for this review

Types of studies
All randomized controlled trials testing the efficacy or effectiveness of behavioral or psychosocial interventions to modify health behaviors, improve health-related quality of life, psychosocial functioning, and/or health outcomes.

Types of participants
All human adults (18+) with at least one chronic condition.

Types of conditions
For purposes of selecting studies, we will consider the following 20 chronic conditions as potential targets of the interventions: arthritis, asthma, autism spectrum disorder, cancer, cardiac arrhythmias, chronic kidney disease, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, dementia (including Alzheimer's and other senile dementias), depression, diabetes, hepatitis, human immunodeficiency virus, hyperlipidemia, hypertension, osteoporosis, schizophrenia, stroke, substance abuse disorders (drug and alcohol).

Types of interventions
For the purpose of this review, we define "behavioral or psychosocial intervention" to mean any intervention that is non-pharmacological and non-surgical. Additionally, there must be some aspect of direct communication with an individual (or small group) whether this is in person, by phone, by internet, etc. This ensures that participants are enrolled at the individual level, meaning that we will not include interventions that are only performed at a community, campus, etc level.

Comparison groups can be usual care, pharmacological interventions, surgical interventions, or a lesser dose of the treatment. Interventions may include a behavioral or psychosocial intervention in addition to a drug or surgery, as long as the comparison group is not receiving the same behavioral or psychosocial intervention.

Types of outcome measures

Primary outcomes

- Exclusion of individuals with multiple chronic conditions
    - Whether exclusion used names of specific conditions or used general terms such as comorbidities or coexisting disease explicitly
    - Proportion of participants excluded due to MCC
- Inclusion of individuals with multiple chronic conditions
    - Proportion of participants included with multiple chronic conditions
    - Which specific conditions were included

Secondary outcomes

- Additional details of each trial that could potentially be used in the meta-analyses, including year, type of journal (general or specialized), components of intervention, and quality of trial.

Search methods for identification of studies
The search strategy will be developed by an MLIS clinical librarian with expertise in searching for systematic reviews. We anticipate searching multiple databases (MEDLINE, EMBASE, etc) for English-language trials published from 2000 to 2014. Hand-searching will not be performed.

We will then apply our sampling strategy (see *Sampling plan* below) in order to create a representative sample of the peer-reviewed literature on RCTs designed to develop and/or test efficacy or effectiveness of behavioral and psychosocial interventions over the past 15 years.

Data collection and analysis

Sampling plan
We expect our search strategy to produce an extremely large number of results that would not be possible to manage in a reasonable amount of time. In order to reduce the number of trials to be screened we have a developed a sampling plan. This will result in a project that is manageable in the allotted time frame and provides meaningful results without imposing unnecessary restrictions on study selection and inclusion criteria that would reduce the representativeness of our sample.

Three separate literature searches (using identical keywords and in the same databases) will be done within defined time periods (2000-2004, 2005-2009, 2010-2014). Within each time-period group, search results will be randomly ordered. The study selection process (application of inclusion/exclusion onto each article) will be performed on the randomly ordered results until the desired number of studies for extraction meeting inclusion/exclusion criteria have been identified (200 per time period for a total of 600 articles).

Selection of studies
Two independent reviewers will screen the titles and the abstracts based on the following exclusion criteria:
1. Not an RCT with original data
2. Not a primary report (will not include protocols, posttrial follow-up studies, secondary subgroup analyses, etc)
3. Not published in English
4. Not targeting at least one of chronic conditions of interest (see *Types of conditions*)
5. Not testing a behavioral or psychosocial intervention or not including an accepted comparison group (see *Types of interventions*)
6. Not including patients with at least one chronic condition
7. Not enrolling participants at the individual level
8. Not human adult subjects (18+)

Excluded articles and a reason for exclusion will be carefully documented. Any disagreement between the two authors will be resolved by a third party. If the title and the abstract is not clear to determine to reject, or disagreement is not resolved by discussion, the full-text of the article will be retrieved. Reviewers assessing study eligibility will not be blinded to the names of the authors, journals, and other publication details.

Data extraction and management

Characteristics of included studies and data will be extracted independently by two reviewers using a standard abstraction form. The abstraction form will be created and used in REDCap. REDCap is uniquely suited to meet the needs of an effective and efficient data extraction process. It allows form creators to require specific entry formats for individual questions (ensuring reviewers input data in a consistent format), allows for multiple types of response formats (dropdown menus, select all, select only one, open-ended text entry, etc), and performs data validation to improve accuracy of extraction. In addition REDCap has a built in "Double Data Entry" feature, which allows multiple users to input data from a single source and automatically compares the entries and identifies differences. Disagreements that are identified by the "Double Data Entry" feature will be resolved by a third party (project manager).

Data extracted will include the following:

- Basic study characteristics (journal, journal type, journal impact factor, publication year, funding source, article title, author, country/region, trial registration, and study protocol access)
- Intervention details (enrollment/intervention duration timeframes, condition(s) targeted, number of study arms, description of comparison group including number/age/sex etc, description of intervention group including number/age/sex etc, studywide characteristics/sample size, and type/description of intervention components)
- Eligibility details (reporting of eligibility, general/specific/vague exclusion criteria, proportion of excluded patients with MCC, and justifications for exclusions)
- Patient selection details (CONSORT participant flow, MCC inclusion implicitly or explicitly, proportion of included participants with MCC, specific MCC mentioned, and how information regarding targeted and other MCC was obtained)
- Quality assessment (selection bias, performance bias, detection bias, attrition bias, and reporting bias)
- Outcomes (presence of primary outcome, type of primary outcome, how primary outcome is measured, result of primary outcome, author conclusions, subgroup analyses, and effect modification)

Assessment of methodological quality in included studies

Two reviewers will independently assess methodological quality of the trials independently. Disagreements will be resolved by a third party. The quality of the RCTs will be assessed using a modified version of the Cochrane Collaboration's Risk of Bias tool, which evaluates seven domains including selection bias, performance bias, detection bias, attrition bias, reporting bias, and 'other bias.'[12] For each domain, the trial is given a rating of low risk of bias, high risk of bias, or unclear risk of bias. We will use this information in analysis in several ways, by using individual items, domains, or overall quality. For this review we will remove the "other bias" domain as it is unnecessary for the scope of this generalized report and is better suited for more specialized studies.

Dealing with missing data and duplicate studies

As a key part of this review is to assess the reporting of information regarding MCC, no attempts will be made to contact authors for additional information. For each extraction item there will be an option to list as "not reported." Duplicate studies will not be included, and only one article will be used for each trial.

Data synthesis

Analyses will be determined by specifics of data extracted (both type and volume) from selected studies; however, we anticipate that the large scope of this review will provide enough data to perform the following analyses.

We will summarize and describe the studies, populations, interventions, and outcomes included to verify that we have a representative sample. Assessment of inclusion of patients with MCC will greatly depend on how the information is presented in included studies, but we intend to perform such analyses as (1) calculating the proportion of studies explicitly excluding patients with MCC, (2) synthesizing a list of and frequency of each chronic condition present in patients in trials, (3) performing a proportions meta-analysis to estimate average proportion of patients within a trial that have MCC when they are included.

Key outcomes regarding inclusion of patients with MCC can be stratified by time category, journal type (general vs specialized), quality of study (as measured by our original quality tool and the GRADE process) and by other key variables identified throughout the process. Additionally time can be used as continuous variables in a meta-regression.[13,14] Study quality overall score can be used in a meta-regression or individual quality categories can be used to explore relationship with inclusion of patients with MCC and address issues of bias. Study quality data will also be used to descriptively assess the body of evidence.

We will also descriptively synthesize and report any challenges of recruiting as described by the primary authors of the RCTs included in this SRMA.

Additionally, publication bias will be explored.[15]

We anticipate all meta-analyses performed will be done so with a random effects model.
Data analysis will be performed using STATA 12.0 (College Station, TX), which provides a comprehensive set of meta-analysis routines, with additional analysis in R (3.1.0) as needed.

Assessment of heterogeneity
If any meta-analyses are performed, statistical heterogeneity will be assessed with the Cochran's Q and Higgins I^2 statistic.[16] We anticipate that the amount of heterogeneity will suggest that the random effects model is appropriate.

Subgroup analysis and investigation of heterogeneity
Key outcomes regarding inclusion of patients with MCC can be stratified by time category, journal type (general vs specialized), quality of study and by other key variables identified throughout the process. If meta-analyses are performed, time can be used as a continuous variable in a meta-regression.[13,14] Study quality overall score can be used in a meta-regression or individual quality categories can be used to explore relationship with inclusion of patients with MCC and address issues of bias.

References

1. Parekh AK, Barton MB. The challenge of multiple comorbidity for the US health care system. *JAMA : the journal of the American Medical Association.* Apr 7 2010;303(13):1303-1304.
2. Agency for Healthcare Research and Quality. National Healthcare Disparities Report, 2013. Rockville, MD May 2014.

3. Boyd CM, Vollenweider D, Puhan MA. Informing evidence-based decision-making for patients with comorbidity: availability of necessary information in clinical trials for chronic diseases. *PLoS One.* 2012;7(8):e41601. PMC3411714:
4. Fortin M, Dionne J, Pinho G, Gignac J, Almirall J, Lapointe L. Randomized controlled trials: do they have external validity for patients with multiple comorbidities? *Annals of family medicine.* Mar-Apr 2006;4(2):104-108. PMC1467012:
5. Jadad AR, To MJ, Emara M, Jones J. Consideration of multiple chronic diseases in randomized controlled trials. *JAMA: the journal of the American Medical Association.* 2011;306(24):2670-2672.
6. Ritchie CS, Zulman DM. Research priorities in geriatric palliative care: multimorbidity. *Journal of palliative medicine.* Aug 2013;16(8):843-847. PMC3717194:
7. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. *JAMA : the journal of the American Medical Association.* Mar 21 2007;297(11):1233-1240.
8. Kenning C, Coventry PA, Bower P. Self-management interventions in patients with long-term conditions: a structured review of approaches to reporting inclusion, assessment, and outcomes in multimorbidity. *2014.* 2014-08-28 2014;4(1):9.
9. Trask PC, Schwartz SM, Deaner SL, et al. Behavioral medicine: the challenge of integrating psychological and behavioral approaches into primary care. *Effective clinical practice : ECP.* Mar-Apr 2002;5(2):75-83.
10. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. *JAMA : the journal of the American Medical Association.* Mar 10 2004;291(10):1238-1245.
11. Goodman RA, Posner SF, Huang ES, Parekh AK, Koh HK. Defining and Measuring Chronic Conditions: Imperatives for Research, Policy, Program, and Practice. *Preventing Chronic Disease.* 2013;10:E66.
12. Higgins J. Green S. Cochrane handbook for systematic reviews of interventions version 5.1. 0. 2008.
13. Colditz GA, Berkey CS, Mosteller F, et al. The efficacy of bacillus Calmette-Guerin vaccination of newborns and infants in the prevention of tuberculosis: meta-analyses of the published literature. *Pediatrics.* Jul 1995;96(1 Pt 1):29-35.
14. Colditz GA, Brewer TF, Berkey CS, et al. Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. *JAMA : the journal of the American Medical Association.* Mar 2 1994;271(9):698-702.
15. Sterne JA, Egger M, Smith GD. Investigating and dealing with publication and other biases in meta-analysis. *BMJ (Clinical research ed.).* 2001;323(7304):101-105.
16. Higgins J, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in medicine.* 2002;21(11):1539-1558.

2. Differences between protocol and report

This section summarizes the main changes in methods for our review. We found that some aspects included in our original protocol were impractical based on the scope of our report, the time restraint for completing the project, and/or another unexpected factor. For example, in our original objectives we planned to analyze how inclusion of individuals with MCC in RCTs differed across journal impact factor and if this was associated with the efficacy or effectiveness of interventions. We also planned to describe the challenges of recruiting individuals with MCC to participate in trials and identify improvements for future studies regarding reporting and inclusion of individuals with MCC. After beginning extraction we determined that we would have only a very small number of articles from high impact journals and a very large number from low/average impact journals given that we did not use impact factor in our inclusion criteria. Although previous reviews purposefully chose high impact journals, we wanted a more representative sample of RCTs. Additionally, we addressed the possibility of looking into journal impact factor, efficacy/effectiveness of interventions, challenges of recruiting individuals with MCC, and improvements for future studies regarding reporting and inclusion of individuals with MCC in our implications for future research section as these topics were better suited for a more in depth and extended review. Furthermore, we also anticipated conducting an exploratory analysis regarding the primary outcome of the trial as one of our secondary outcomes. Again, we found that this aspect would be better suited for comprehensive report, and we identified this in our future directions section.

Another change that was made was extending and specifying our data extraction parameters. Through more extensive research and input from key informants, we narrowed our criterion for data extraction to be more specific to our primary and secondary outcomes. Additionally, we originally anticipated assessing the quality of the RCTs using a modified version of the Cochrane Collaboration's Risk of Bias tool, which evaluates seven domains including selection bias, performance bias, detection bias, attrition bias, reporting bias, and 'other bias.' However, before beginning extraction we removed the "other bias" domain as this element was an unnecessary consideration under the scope of this review and is better suited for more specialized studies. This determination was also addressed in the "Assessment of risk of bias in included studies" section of our report.

We planned to stratify our key outcomes by journal impact factor and intervention components (outcomes targeted, index disease targeted, type of intervention). As stated previously, we found that these factors were not pertinent to the scope and aim of this generalized report and would be better suited in a more expansive research paper focusing on these aspects of reporting in RCTs. The possibility of including these components was addressed in our future directions section.

A Mann-Whitney meta-analysis to explore the relationship between efficacy/effectiveness of interventions and inclusion of MCC was not feasible given the small amount of trials that reported outcome information in the necessary format for this analysis.

Ultimately we determined that the changes made from our original protocol did not impact the strength of our report, and, in addition, these differences are addressed in our future directions section as aspects that should be considered in a more comprehensive report.