Editorial

Improving the external validity of clinical trials: the case of multiple chronic conditions

Martin Fortin1,2, Susan M. Smith3

1Department of Family Medicine, Université de Sherbrooke, Sherbrooke, Quebec, Canada; 2Centre de santé et de services sociaux de Chicoutimi, Chicoutimi, Quebec, Canada; 3HRB Centre for Primary Care Research, Department of General Practice, Royal College of Surgeons, Dublin, Ireland

Abstract

The U.S. Department of Health and Human Services vision and strategic framework on multiple chronic conditions (MCCs) incorporates recommendations designed to facilitate research that will improve our knowledge about interventions and systems that will benefit individuals with MCCs (or multimorbidity). The evidence base supporting the management of patients with MCCs will be built through intervention trials specifically designed to address multimorbidity and identification of MCCs in participants across the clinical trial range. This article specifically focuses on issues relating to external validity with specific reference to trials involving patients with MCCs. The exclusion of such patients from clinical trials has been well documented. Randomized control trials (RCTs) are considered the “gold standard” of evidence, but may have drawbacks in relation to external validity, particularly in relation to multimorbidity. It may, therefore, be necessary to consider a broader range of research methods that can provide converging evidence on intervention effects to address MCCs. Approaches can also be taken to increase the usefulness of RCTs in general for providing evidence to inform multimorbidity management. Additional improvements to RCTs would include better reporting of inclusion and exclusion criteria and participant characteristics in relation to MCCs. New trials should be considered in terms of how they will add to the existing evidence base and should inform how interventions may work in different settings and patient groups. Research on treatments and interventions for patients with MCCs is badly needed. It is important that this research includes patient-centered measures and that generalizability issues be explicitly addressed.

Keywords: external validity, internal validity, clinical trials, comorbidity, multimorbidity, multiple chronic conditions

Introduction

Enhancing the external validity of clinical trials is one of the priority areas identified in the initiative launched by the U.S. Department of Health and Human Services (HHS) to strengthen efforts to address the challenge of the rising prevalence of multiple chronic conditions (MCCs), or multimorbidity, in the population [1]. This article specifically focuses on issues relating to external validity of evidence, with specific reference to trials involving patients with MCCs. We also consider some potential solutions to address the problem of low external validity of clinical trials for these patients. There are two distinct scenarios in relation to trials and multimorbidity. The first occurs where a trial has been specifically designed to test an intervention that addresses MCCs [2,3] and the second relates to the likelihood that participants in most clinical trials are likely to have multimorbidity to some extent and the question
is how generalizable the results of that trial are to all patients with MCCs. The challenge inherent to research in multimorbidity is that there is heterogeneity within the group. At its simplest level, MCCs includes patients with clear comorbid conditions, but this then expands out to more general multimorbidity, in which there is no prespecified index condition and there are multiple possible combinations and permutations of conditions and condition severity [4].

External validity, sometimes also referred to as generalizability, describes the applicability of interventions in settings beyond the original study. However, determining the external validity of a study is more difficult than determining its counterpart, internal validity. Internal validity describes the degree to which the design and conduct of a trial reduces the possibility of bias within that trial, and it can be judged using the list of items in guidelines on trial methodology and reporting, such as the CONSORT (Consolidated Standards of Reporting Trials) statement [5]. Determining whether the results of a trial are valid for patients other than those in the original study population requires detailed information on participant characteristics, clinical expertise, and an understanding of healthcare systems and settings, rather than statistical or methodological expertise [6]. External validity is considered a complex concept [6,7], and has been defined as “the overarching descriptor for all aspects of the design and performance that impact on the external usefulness of the result of a trial, independent of the ‘internal validity’ of the trial” [6].

General aspects that may impact on the external validity of trials can be divided into system and patient factors. Patient factors are reflected in the selection of patients and the potential differences between enrolled patients and the general patient population [6]. System factors include the setting of the trial, differences between trial protocol and routine practice, and potential impact of the intervention on service organization and costs for patients and providers, which, in turn, depend on financing within health systems. While there is a clear need for further studies of interventions in patients with multimorbidity [8], this paper specifically focuses on issues relating to external validity which are particularly relevant for those with MCCs.

### Challenges to external validity

One of the main challenges to external validity of trials is that most clinical trials targeting chronic conditions would find a high number of patients with MCCs during the recruitment process [9]. This situation applies particularly to trials involving patients in primary care settings because it is known that patients with MCCs constitute the majority of patients in this setting [10]. Nevertheless, the potential exclusion of such patients from clinical trials has been well documented [11,12]. Clinical trials should provide evidence to inform policy and practice regarding new treatments and interventions for all patients. This can be addressed either by specifically designing trials to test interventions that address multimorbidity or, in these trials, reporting of participant characteristics and intervention settings and components allowing for an interpretation of external validity. It is more difficult, in general, in clinical trials, where exclusion of patients with MCCs means that important information about the proper use of a treatment or intervention for those patients is not available. In other words, the exclusion of patients with MCCs limits the external validity of clinical trials for these patients [13–16]. However, many of these trials may have included patients with MCCs, but not identified them as such, and this is a problem frequently observed in reports of clinical trials where there is low reporting of data around participant characteristics that could have informed external validity [13,17]. For example, in a randomized trial of peer support for patients with type 2 diabetes, a secondary analysis of characteristics of all included patients indicated that 90% had MCCs, with 25% having four or more conditions. Within the cohort of 424 patients, there were 189 unique conditions [18]. This highlights the importance of fully reporting participant characteristics to facilitate a complete and correct interpretation of the generalizability of the trial’s results. Table 1 highlights other potential challenges to external validity, including whether patients with MCCs will agree to participate in clinical trials as they may already be overburdened by treatment and healthcare attendances [19]. Additionally, interventions may have a single-condition focus, making them of less interest and use to patients with MCCs, or there may be costs involved to intervention participation that act as a deterrent to those already experiencing high health service utilization and costs [20,21].

When seeking to find ways to improve the external validity of clinical trials for patients with MCCs, one soon encounters a barrier relating to the potential imbalance between internal and external validity in randomized controlled trials (RCTs) [22]. It can be argued that internal validity is a prerequisite for external validity as there is no point in trying to generalize evidence from a poor-quality trial [23]. RCTs are considered the “gold standard” of evidence because of their ability to reduce selection bias and other factors that could bias outcomes, so researchers usually aim to enhance internal validity by having replicable and clear
patient inclusion criteria that may lead to the exclusion of medically complex subjects. However, this will likely be at the cost of reducing external validity, which may initially seem to be of secondary importance. Results regarding the effectiveness of the intervention tested in an RCT with high internal validity will be more robust, but they will probably provide limited evidence to support care for patients with MCCs found in real life. A consequence of poor external validity of clinical trials is that clinical practice guidelines, which are often based primarily on expert review of the hierarchy of evidence from relevant clinical trials, can have limited utility for patients with MCCs or may lead to inappropriate use of interventions in these patients [24,25].

### Potential solutions

In the initiative launched by the HHS, one of the objectives identified within the goal of facilitating research to fill knowledge gaps was to enhance the external validity of clinical trials. To meet this goal, four objectives were outlined: (i) to develop methods to assess the inclusion of individuals with MCCs in clinical trials; (ii) to improve the external validity of trials by ensuring that individuals with MCCs are not unnecessarily excluded; (iii) to ensure that individuals with MCCs are not unnecessarily excluded from clinical trials for the approval of prospective drugs and devices; and (iv) to assess and strengthen postmarketing surveillance for potential intervention-related adverse effects and poor outcomes among individuals with MCCs. To increase the external validity of trials for individuals with MCCs is a challenging task and can be considered in individual areas.

### Consider alternative and complementary designs for trials in MCCs

Some possible solutions have been proposed to enhance the external validity of RCTs in general [22,26–28]. Within this ongoing discussion, Kaplan and colleagues [27] made an interesting point when they said, “evidence based medicine has made a leap from considering RCTs to be a high standard to being the only standard”. This suggests that we may need to reconsider our over-reliance on RCTs to measure intervention effects and make a greater use of alternative forms of evidence, particularly for patients with MCCs. Use of mixed research methods, i.e. combining experimental designs with parallel qualitative process evaluations, can provide converging evidence on intervention effects and may be a good way to address the problem of external validity. The accumulated evidence about an intervention would be gathered from a combination of RCTs and other methods that would provide more information to support the judgements related to external validity for patients with MCCs. Alternative designs

---

**Table 1** Issues related to the external validity of trials involving patients with multiple chronic conditions (MCCs).

| Issue                                      | Potential solution                                                                 |
|--------------------------------------------|-----------------------------------------------------------------------------------|
| Lack of clarity around participant inclusion and definitions | Need to have clear definitions of MCCs – whether derived from health record or patient report; condition counts vs. condition severity scores and whether restricted lists of included conditions applied |
| Participants with MCCs are less likely to consent to participate if disease burden is too high or if in poor health | Consider minimizing burden of participation in intervention |
| Participants with MCCs may see single-condition trial as being less relevant to them | Consider interventions that are not condition specific or that address specific concerns of MCCs, such as functional or physical performance |
| Prespecified ancillary analyses taking into account patients’ heterogeneity | Consider preplanning subgroup analyses based on condition counts, severity, and condition combinations |
| Age of participants with MCCs | Interventions for middle-aged adults with MCCs who are still working may need to be quite different from those for older participants |
| Chronic disease interventions designed around single conditions | Consider more generalized interventions, such as medicines management or support for self-management |
| Setting: primary vs. specialty care setting | Patient populations and clinicians will be quite different in both settings, but this may be less of an issue for patients with MCCs who commonly attend multiple healthcare providers |
| System financing issues | Avoid interventions that increase direct or indirect costs to patients or providers |
| Organizational setting | Intervention embedded in the system that reflects usual care for patients |
Further research on treatments for patients with MCCs is focused on organizational aspects of health care [32]. We have addressed the need to consider patients with MCCs, both in the evaluation of trials testing new health interventions generally and in trials testing interventions specifically designed to address multimorbidity. So far, the majority of research on interventions in MCCs has focused on organizational aspects of health care [32].

Consider alternative sources of evidence

Postmarketing surveillance of drugs as well as collection and analysis of administrative clinical data about interventions being applied to patients with MCCs would also provide valuable evidence. This is in agreement with the HHS strategy on strengthening post-marketing surveillance for potential intervention-related adverse effects and poor outcomes among individuals with MCCs. In some situations, expert opinions about the management of patients with MCCs passed down through consensus guidelines may be the only available source of “evidence”. Qualitative methods, treatment fidelity analysis, and epidemiological data, including prospective cohort studies, are other examples of additional sources of information, particularly around potential harm, as this generally requires larger sample sizes than generally found in RCTs. We believe that the acceptance of a new drug in the market as well as a new intervention in practice should rely on multiple sources of evidence incorporating data on patients with MCCs and not just be reliant on evidence from RCTs. This would help to ensure that individuals with MCCs are not unnecessarily excluded from evidence base for the approval of drugs and devices, as outlined in Strategy 3 of the HHS.

Consider secondary data analysis of existing trial evidence

Another approach to enhance the current evidence base to support management of MCCs would be to conduct secondary analyses of existing trial databases using available data relating to MCCs. This could be conducted by increasing trial datasets that are made available for public access, particularly for trials funded through government agencies [30]. This would provide further evidence of the potential effectiveness of the intervention in patients with MCCs. These analyses could be based on existing information on chronic conditions, but if this is not available, there may be other information in trial databases, such as counts of prescribed medicines, which can be a good proxy for MCCs [31].

The issues related to the external validity of clinical trials and possible solutions are summarized in Table 1. The key issue is that recruitment of patients with MCCs to trials will make RCTs more informative about the health impacts of a new intervention for the broader population.

Concluding remarks

We believe that the acceptance of a new drug in the market as well as a new intervention in practice should rely on multiple sources of evidence incorporating data on patients with MCCs and not just be reliant on evidence from RCTs. This would help to ensure that individuals with MCCs are not unnecessarily excluded from evidence base for the approval of drugs and devices, as outlined in Strategy 3 of the HHS.
Acknowledgments

We would like to acknowledge the contribution and support from José Almirall PhD, research professional at the Centre de santé et de services sociaux de Chicoutimi, in the preparation of this manuscript.

Conflicts of interest

The authors declare no competing interests.

References

1. U.S. Department of Health & Human Services. Multiple chronic conditions: a strategic framework. Optimum health and quality of life for individuals with multiple chronic conditions. Washington, DC: US Department of Health & Human Services; 2010.

2. Smith SM, Soubhi H, Fortin M, Hudon C, O’Dowd T. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. Cochrane Database Syst Rev 2012;4:CD006560.

3. Smith SM, Bayles EA, Mercer SW, Gunn J, Vestergaard M, Wyke S, et al. How to design and evaluate interventions to improve outcomes for patients with multimorbidity. J Comorbidity 2013;3:10–7.

4. Mercer SW, Smith SM, Wyke S, O’Dowd T, Watt GC. Multimorbidity in primary care: developing the research agenda. Fam Pract 2009;27:79–80.

5. Moher D, Schulz KE, Altman DG, CONSORTGroup. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001;357:1191–4.

6. Rothwell PM. External validity of randomised controlled trials: “to whom do the results of this trial apply?” Lancet 2005;365:82–93.

7. Dekkers OM, vom Elin E, Algra A, Romijn JA, Vandenbroucke JP. How to assess the external validity of therapeutic trials: a conceptual approach. Int J Epidemiol 2010;39:89–94.

8. Salisbury C. Multimorbidity: time for action rather than words. Br J Gen Pract 2013;63:64–5.

9. Fortin M, Dionne J, Pinho G, Gignac J, Almirall J, Lapointe L. Randomized controlled trial of preventive health care for older adults in primary care: effects on health and health services use. J Am Geriatr Soc 2005;53:1037–46.

10. Fortin M, Stewart M, Poitras ME, Almirall J, Maddocks H. A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology. Ann Fam Med 2006;4:104–8.

11. Boyd CM, Vollenweider D, Pulhan MA. Informing evidence-based decision-making for patients with comorbidity: availability of necessary information in clinical trials for chronic diseases. PLoS One 2012;7:e41601.

12. Jadad AR, To MJ, Emara M, Jones J. Consideration of multiple chronic diseases in randomized controlled trials. J Am Med Assoc 2011;306:2670–2.

13. Ahmad N, Boutron I, Moher D, Pitrou I, Roy C, Ravaud P. Neglected external validity in reports of randomized trials: the example of hip and knee osteoarthritis. Arthritis Rheum 2009;61:361–9.

14. Janson M, Edlund G, Kressner U, Lindholm E, Pahlman L, Skullman S, et al. Analysis of patient selection and external validity in the Swedish contribution to the COLOR trial. Surg Endosc 2009;23:1764–9.

15. Travers J, Marsh S, Caldwell B, Williams M, Aldington S, Weatherall M, et al. External validity of randomized controlled trials in COPD. Respir Med 2007;101:1313–20.

16. Stieg PG, Lopez-Sendon J, Lopez de Sa E, Goodman SG, Gore JM, Anderson FA, Jr., et al. External validity of clinical trials in acute myocardial infarction. Arch Intern Med 2007;167:68–73.

17. Ethgen M, Boutron L, Stieg PG, Roy C, Ravaud P. Quality of reporting internal and external validity data from randomized controlled trials evaluating stents for percutaneous coronary intervention. BMC Med Res Methodol 2009;9:24.

18. Teljeur C, Smith SM, Paul G, Kelly A, O’Dowd T. Multimorbidity in a cohort of patients with type 2 diabetes. Eur J Gen Pract 2013;19:17–22.

19. May C, MontoriVM, Mair FS. We need minimally disruptive medicine. BMJ 2009;339:b2803.

20. McRae I, Yen L, Jeon YH, Herath PM, Essue B. Multimorbidity is associated with higher out-of-pocket spending: a study of older Australians with multiple chronic conditions. Aust J Prim Health 2013;19:144–9.

21. Konig HH, Leicht H, Bickel H, Fuchs A, Gensichen J, Maier W, et al. Effects of multiple chronic conditions on health care costs: an analysis based on an advanced tree-based regression model. BMC Health Serv Res 2013;13:219.

22. Gaus W, Muche R. Is a controlled randomised trial the non-plus-ultra design? A contribution to discussion on comparative, controlled, non-randomised trials. Contemp Clin Trials 2013;35:127–32.

23. CONSORT Group. Generalisability (external validity, applicability) of the trial findings. Available from: http://www.consort-statement.org/consort-statement-20-22-discussion/item21_generalisability.[Last accessed Nov 2, 2013].

24. Fortin M, Contant E, Savard C, Hudon C, Poitras M-E, Almirall J. Canadian guidelines for clinical practice: an analysis of their quality and relevance to the care of adults with comorbidity. BMC Family Pract 2011;12:74.

25. Guthrie B, Payne K, Alderson P, McMordu ME, Mercer SW. Adapting clinical guidelines to take account of multimorbidity. BMJ 2012;345:e6341.

26. Lind KD. Excluding older, sicker patients from clinical trials: issues, concerns, and solutions. Available from: http://www.aarp.org/content/dam/aarp/research/public_policy_institute/health/2011/i57.pdf.[Last accessed May 17, 2013].

27. Kaplan BJ, Giesbrecht G, Shannon S, McLeod K. Evaluating treatments in health care: the instability of a one-legged stool. BMC Med Res Methodol 2011;11:65.

28. Bornhoft G, Maxion-Bergemann S, Wolf U, Kienle GS, Michelsen A, Vollmar HC, et al. Checklist for the qualitative evaluation of clinical...
studies with particular focus on external validity and model validity. BMC Med Res Methodol 2006;6:56.

29 Clarke M, Hopewell S, Chalmers I. Clinical trials should begin and end with systematic reviews of relevant evidence: 12 years and waiting. Lancet 2010;376:20–1.

30 Ross JS, Lehman R, Gross CP. The importance of clinical trial data sharing: toward more open science. Circ Cardiovasc Qual Outcomes 2012;5:238–40.

31 Huntley AL, Johnson R, Purdy S, Valderas JM, Salisbury C. Measures of multimorbidity and morbidity burden for use in primary care and community settings: a systematic review and guide. Ann Fam Med 2012;10:134–41.

32 Smith SM, Soubhi H, Fortin M, Hudon C, O’Dowd T. Managing patients with multimorbidity: systematic review of interventions in primary care and community settings. Br Med J 2012;345:e5205.