

# Deprescribing and medicines optimisation, two sides of the same coin? Considerations for design of interventional studies

Frank Moriarty<sup>1</sup> and Carmel Hughes<sup>2</sup>

<sup>1</sup>RCSI University of Medicine and Health Sciences

<sup>2</sup>Queen's University Belfast

February 14, 2023

## Abstract

Interventions to promote deprescribing are an important focus of research. Key decisions for such interventions are whether to target one or multiple medicines, and whether the intervention scope is deprescribing, or also extends to other aspects of medicines optimisation. This article reflects on how these decisions impact on developing interventions and measuring outcomes. Many behavioural strategies are common to deprescribing and medicines optimisation, however operationalisation may differ. Aspects to consider include the burden of multiple simple interventions versus one complex intervention, the extent to which the approach to deprescribing can be specified as part of the intervention, and variability in how the intervention is delivered across patients and providers. Outcomes should be selected based on the intervention target and scope and the audience for whom evidence is being produced. These may include medication changes, and process outcomes to assess intervention delivery. Targeting single medications may allow for a focus on specific clinical or symptom-related outcomes, rather than more general outcomes such as adverse drug reactions. Cost-related outcomes are also important to inform implementation decisions, and modelling approaches may be more feasible for interventions targeting single medications.

## Introduction

Worldwide, our populations are living longer, but with a greater burden of health conditions. The presence of multiple conditions (i.e. multimorbidity) drives prescribing of medications, and many people, in particular older adults, are on multiple medications (or polypharmacy).(1) Medications are often continued when they are no longer needed or pose a greater risk of harm than benefit. Such potentially inappropriate prescribing can impact quality of life, cause adverse drug reactions, consume healthcare resources, and increase mortality.(1)

Deprescribing, the process of stopping or reducing such medications, is one important way to address this.(2) Deprescribing interventions focus on actions to reduce the number of medications, congruent with the historical view that polypharmacy is inappropriate and increases risk of harm. However, there is increasing recognition that the number of medicines itself is not harmful, as having multiple long-term conditions may need multiple medicines. Therefore, improving the appropriateness of polypharmacy through medicines optimisation may involve starting or increasing medicines as well as stopping in many circumstances.(3) Deprescribing can be considered as one important component of medicines optimisation. Given the many barriers to deprescribing and limited implementation in routine practice, it is understandable that significant attention is given to assessment of deprescribing interventions as a high priority.(2)

There is substantial heterogeneity among trials which evaluate deprescribing, as many interventions also combine deprescribing with other actions to promote appropriate polypharmacy.(3) There can be variation in the study designs used (e.g. randomised trials, controlled before and after studies), as well as important

differences in the intervention target (focused on one medication or many) and the scope of the intervention (solely deprescribing, or also including other aspects of medicines optimisation in addition to deprescribing).

In developing and evaluating deprescribing interventions, the decisions regarding the intervention target and scope are critical. Here, we reflect on how these decisions (one versus many medications, and deprescribing versus medicines optimisation) can affect other study design considerations, specifically developing interventions and measuring outcomes.

### *How to do it?*

Guidance from the United Kingdom Medical Research Council on developing and evaluating complex interventions provides a suitable framework for deprescribing intervention development, from selecting intervention components and translating these into an intervention package, through to feasibility testing and evaluation.<sup>(4)</sup> Many of the behavioural strategies, sometimes described as behaviour change techniques (active components of the intervention) used in deprescribing are relevant for broader medicines optimisation approaches, and so components of interventions may be interchangeable. However when it comes to operationalisation of either process in practice, there may be differences.<sup>(5)</sup>

Considering how the intended target and scope reflect the reality of clinical practice is important for intervention development. Often patients may have more than one medication issue that requires intervention, and an accumulation of single interventions targeting various medication issues may increase workload for providers. This may also add to the substantial treatment burden among people with multimorbidity (i.e. the work required to manage their conditions), associated with delivery of care centred around many single conditions and disease guidelines. A suite of components as part of a complex intervention targeting multiple medicines may provide a more cohesive, and sustainable, approach than multiple single-medicine focused interventions. The acceptability of these approaches should also be considered; clinicians and patients may find efforts to optimise all medicines at the outset challenging, whereas starting with a single medicine may provide early success encouraging an incremental approach to optimise multiple medicines.

Targeting multiple medicines presents additional complexity to an intervention, such as in assessing what should be deprescribed (or optimised), and how to do it. An intervention may have to involve multiple criteria to identify medications to deprescribe or optimise, and a set of medication-specific deprescribing guidance. Alternatively, a more general approach relying on implicit judgement of the healthcare professional could be used, which will increase heterogeneity in intervention delivery. In contrast, a single medication target may allow a greater degree of specification of the approach to deprescribing or medicines optimisation, likely yielding greater intervention fidelity.

Where changes to multiple medications are required, the need to decide the priority, timing, and order of these changes will also increase the potential for variation in intervention delivery.<sup>(6)</sup> This may have implications for deciding when to measure outcomes in a study. The time to implement multiple medication changes may be highly variable between patients. For example, medications may require varying lengths of time to taper while deprescribing, and some medications may be deprescribed sequentially rather than all at once. Therefore, the study length of follow-up will need to be sufficient to allow all changes to be implemented, and for any effect on outcomes to occur.

### *How to measure success?*

Outcome selection for an interventional study will inevitably stem from the intervention scope and target; in considering what would be a success, it is important to reflect on the goals of the intervention, and the audience for whom evidence is being produced. Particularly for deprescribing trials, no change in clinical or patient-reported outcomes may be considered a success, assuming success is judged as a reduction in the number of medications. This should be decided a priori, with the study design and analysis planned appropriately to evaluate non-inferiority in clinical outcomes. In contrast for medicines optimisation trials, a reduction in medicines may not always occur (or be appropriate), and therefore some benefit in other outcomes may be the goal and basis for designing and powering the study. Process outcomes are important

regardless of intervention focus, to assess whether the behavioural strategies have been delivered. For deprescribing, process outcomes could also include the number of participants who had a medicine (or medicines) deprescribed or, similar to above, the mean reduction in the number of medicines. However, using similar measures in a medicines optimisation trial may not fully capture the degree to which actions have been taken, and a small or negligible reduction in the mean number of medicines could be underpinned by a large, balanced number of medicines stopped and started.(7)

Outcomes should be selected with regard to what is meaningful for stakeholders, including patients, health-care professionals, and decision-makers who may wish to implement the intervention being assessed.(8) Core outcome sets can be drawn on as a means of enhancing consistency and cumulative evidence across trials.(9) Arguably these should be tied to trials with the same intervention scope and targets (i.e. core outcomes for medicines optimisation interventional studies may not all be relevant or useful for a deprescribing interventional study of a single medication class).

Focusing on single medications may facilitate selection of outcomes that are highly specific to that context (and potentially more meaningful to patients), both for clinical and patient-reported outcomes e.g. sleep quality as an outcome if deprescribing hypnotic agents, cognition for anticholinergic agents. It may be difficult to assess success using measures that reflect general medicines optimisation, particularly where such generic or global health measures may not be sensitive to changes in medications.(8) In such cases, outcomes often include measures of prescribing appropriateness, adverse drug reactions, and medicines-related hospitalisations, where the attributable risk due to inappropriate prescribing, and preventability via medications optimisation, may be low.

Costs and cost-effectiveness are important for decision-makers. For interventions targeting many medications, estimating the indirect costs saved through averting adverse outcomes is challenging when these events are likely rare, diverse, and potentially difficult to measure. Although costs relating to occurrence of a generic adverse drug reaction or medicines-related hospitalisation could be estimated, these may have limited acceptability among decision-makers, and add significant uncertainty to the cost-effectiveness estimate. In contrast, for single medication interventions, evidence on the known risks of continued prescribing can be integrated with the effectiveness of the intervention in reducing such prescribing to estimate the incremental costs and benefits of implementing the intervention, and can be extrapolated over a timeframe beyond the trial duration.(10)

### *Conclusions*

Decisions on the target and scope of deprescribing interventions have many implications. Some scenarios may add further complexity, such as interventions targeting fall-risk increasing drugs. Although these medications share a common adverse event, they are likely to represent a diverse group of medication classes, including benzodiazepines, antihypertensives, and antimuscarinics, which may each require a different, tailored approach to deprescribe. However, this does also differ from studies which aim to optimise all medications a person may be taking, in that sub-optimal prescribing of medications unrelated to falls may not be addressed, if considered out of the scope of the intervention. Similarly there may be grey areas with regard to intervention scope (particularly if not clearly described in the study report), and even when broader medicines optimisation is explicitly specified as the scope, deprescribing actions may predominate.

For studies evaluating interventions that aim to promote deprescribing, decisions on targeting one medicine or many, and extending the scope from deprescribing to medicines optimisation are critical. Focusing on these choices will clarify approaches to study design, and help to advance the field of deprescribing.

**Acknowledgements:** FM was a member of the Junior Investigator Intensive Program of the US Deprescribing Research Network, which is funded by the National Institute on Aging (R24AG064025).

**Conflict of Interest Statement:** None.

## References

1. Hill-Taylor B, Walsh KA, Stewart S, Hayden J, Byrne S, Sketris IS. Effectiveness of the STOPP/START (Screening Tool of Older Persons' potentially inappropriate Prescriptions/Screening Tool to Alert doctors to the Right Treatment) criteria: systematic review and meta-analysis of randomized controlled studies. *J Clin Pharm Ther* [Internet]. 2016;41(2):158–69. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26990017>
2. Thompson W, Reeve E, Moriarty F, Maclure M, Turner J, Steinman MA, et al. Deprescribing: Future directions for research. *Res Soc Adm Pharm*. 2019;15(6).
3. Rankin A, Cadogan CA, Patterson SM, Kerse N, Cardwell CR, Bradley MC, et al. Interventions to improve the appropriate use of polypharmacy for older people. *Cochrane Database Syst Rev* [Internet]. 2018 Sep 3 [cited 2018 Sep 27];(9). Available from: <http://doi.wiley.com/10.1002/14651858.CD008165.pub4>
4. Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. *BMJ* [Internet]. 2021 Sep 30 [cited 2023 Jan 29];374. Available from: <https://www.bmj.com/content/374/bmj.n2061>
5. Isenor JE, Bai I, Cormier R, Helwig M, Reeve E, Whelan AM, et al. Deprescribing interventions in primary health care mapped to the Behaviour Change Wheel: A scoping review. *Res Soc Adm Pharm*. 2021 Jul 1;17(7):1229–41.
6. Scott IA, Hilmer SN, Reeve E, Potter K, Le Couteur D, Rigby D, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med* [Internet]. 2015;175(5):827–34. Available from: <http://archinte.jamanetwork.com/article.aspx?doi=10.1001/jamainternmed.2015.0324>
7. McCarthy C, Flood M, Clyne B, Smith SM, Wallace E, Boland F, et al. Medication changes and potentially inappropriate prescribing in older patients with significant polypharmacy. *Int J Clin Pharm* 2022 [Internet]. 2022 Nov 16 [cited 2023 Jan 29];1:1–10. Available from: <https://link.springer.com/article/10.1007/s11096-022-01497-2>
8. Bayliss EA, Albers K, Gleason K, Pieper LE, Boyd CM, Campbell NL, et al. Recommendations for outcome measurement for deprescribing intervention studies. *J Am Geriatr Soc* [Internet]. 2022 Sep 1 [cited 2023 Jan 29];70(9):2487–97. Available from: <https://pubmed.ncbi.nlm.nih.gov/35648465/>
9. Rankin A, Cadogan CA, Ryan C, Clyne B, Smith SM, Hughes CM. Core Outcome Set for Trials Aimed at Improving the Appropriateness of Polypharmacy in Older People in Primary Care. *J Am Geriatr Soc*. 2018;66(6):1206–12.
10. Moriarty F, Cahir C, Bennett K, Fahey T. Economic impact of potentially inappropriate prescribing and related adverse events in older people: A cost-utility analysis using Markov models. *BMJ Open*. 2019;9(1).