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COMMENTARY

Considerations regarding choice of primary outcome in clinical trials in deprescribing

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Deprescribing, the process of proactively reducing and discontinuing medications,[1] is increasingly recognized as an important part of patient care.[2–4] This is reflected by markedly expanded research activity within deprescribing, including numerous clinical trials.

When planning a clinical trial in deprescribing, there are multiple critical choices to make: Should the intervention be carried out in the hospital or in the primary care setting? Should the intervention target the behavior of the patient, the clinician, or both?[5] And should the intervention be based on a single specific tool or be a multifaceted intervention? All of this will ultimately depend on the scope of the study, including what specific barriers to deprescribing the intervention aims to address. In this commentary, we hope to address a final central question that, while currently less debated, strongly impacts the usefulness of the study findings: In which situations should what primary outcome be used?

In 2018, Rankin et al. proposed a set of 16 different core outcomes for trials aimed at improving the appropriateness of polypharmacy in older people.[6] This core outcome set raises important awareness to the critical choice of selecting which outcomes to measure. However, in many studies, it will be unfeasible to measure all of these diverse outcomes, not all of which will align with the focus of the intervention.[7] Further, the core outcome set provides no considerations on choice of primary outcome.[6] More recently, Aubert et al. reviewed the outcome measures used in 93 deprescribing intervention studies.[8] Across studies, 97% used at least one measure related to appropriate prescribing, most often complete drug cessation (85%). In comparison, only 34% used patient-reported measures (outcomes, preferences, and experiences), while 26% used measures of unintended consequences of deprescribing. This aligns with the conclusions reached by previous systematic reviews summarizing the effects of clinical deprescribing trials: Deprescribing is feasible and effective in reducing medication use, however, there is less evidence on the impact of deprescribing on clinical and patient-centered outcomes.[9–12]

We currently see three distinct lines of reasoning when choosing the primary outcome for clinical trials in deprescribing. All three have their merits, depending on the knowledge gap that a given study is intended to fill. Here, we describe these three lines of reasoning. Specifically, we address the focus of the lines, the potential impact of using the given outcomes as primary outcomes, and limitations and challenges related to these outcomes. We hope that this will inform a more explicit discussion on when to choose what primary outcome.

The first line of reasoning focuses on the process of deprescribing and the medications themselves. This results in primary outcomes such as 'number of medications reduced/discontinued' and 'change in number of medications'. As described above, this is currently the dominant outcome in clinical deprescribing trials. The main reasoning for choosing such outcomes is that they relate to the very essence of deprescribing, that is, whether a given intervention is able to reduce medication use. In this line of reasoning, such reduction is seen as inherently positive as it will translate into less treatment burden and lower medication expenses, while it will not be seen as a loss for the patient or cause any harm as the medications were considered unnecessary at the given time. Another advantage of such process-related outcomes is that they are both more feasible and cheaper to measure compared with many clinical and patient-centered outcomes. An example of when these outcomes are both reasonable and useful is in 'proof of concept' tests of new deprescribing interventions, where documenting that their implementation leads to reduced medication use can guide whether additional testing, using other outcomes, should be considered.[13] Another example is in testing simple deprescribing interventions focused on a specific drug or drug class, for

example, proton pump inhibitors,[14] where the consensus is that stopping can be expected to be safe. Process- and medication-related outcomes are, however, less valuable when testing complex deprescribing interventions targeting multiple medications. The main reason for this is that they rarely provide any evidence on whether a given intervention is able to target medications where reduction or discontinuation can be expected to lead to an improvement in health status for the individual patient, for example, via reduced side effects or other patient-centered outcomes. Health care professionals often report inertia towards deprescribing due to the challenge of weighing potential benefits and harms.[15,16] If considering the subsequent implementation of a deprescribing intervention, it seems unlikely that a 'median change of 1.5 medications per patient', with no specification of whether it is driven by discontinuation of, for example, vitamin and calcium supplements or cardiovascular prevention and antipsychotic therapy, will increase self-efficacy and thus deprescribing activities among clinicians. Similarly, and more importantly, a change in number of medications is in itself presumably of limited value to the patient compared with, for example, improved quality of life or reduced risk of falls.[17–19]

The second line of reasoning argues that reduction of intensity of therapy combined with documentation of no worsening in health status, that is, 'no change', can be viewed as positive. As such, it either leads to primary outcomes related to safety using a non-inferiority approach or include secondary outcomes related to safety, for example, scoring of symptoms or mortality. The main argument for this line of reasoning is that a documented absence of change in health status following deprescribing, for example, no worsening in the patient's symptoms, can be perceived as positive,[11,20] since it also translates into less treatment burden, fewer adverse drug events, and lower medication expenses. Of note, in this line of reasoning, the latter benefits are assumed, that is, need not be documented. An example of this line of reasoning is the OPTIMISE study, showing that reduction of antihypertensive treatment among patients aged ≥80 years treated with multiple antihypertensive medications was both possible and safe, as it was found to be non-inferior with regard to systolic blood pressure control at 12 weeks.[21] It is reasonable to assume that such trials will provide some certainty to clinicians considering deprescribing, as fear of unintended consequences is an established and central barrier to deprescribing.[15,16] However, in medicine, we rarely ask clinicians to actively do something with the purpose of not achieving any clinical benefit to the patient. While such studies are key to facilitating deprescribing when the physician's initiative is already there, they provide little incentive for the clinician to prioritize deprescribing in the first place.

The third line of reasoning focuses on documenting a direct benefit from deprescribing using clinical or patient-important outcomes. This includes primary outcomes such as mortality, functional level, and quality of life. The necessity of using such outcomes can be argued based on the fact that interventions are expensive in terms of both money and, more importantly, time from both health care personnel and patients. To support the potential later implementation of the interventions being tested, it is therefore considered necessary to document that a given intervention leads to an improvement of the patient's health status. Based on our understanding of health care professionals' barriers to deprescribing,[15,16] it is reasonable to assume that such evidence is in fact needed for busy clinicians to prioritize deprescribing activities as well as for payers to support it. Such outcomes should thereby be used whenever complex deprescribing interventions targeting multiple medications are tested, at least when the purpose is to establish a deprescribing intervention that should be implemented in clinical practice. There are, however, also important limitations and challenges related to the use of clinical endpoints. For trials to be sufficiently powered to detect a clinical meaningful difference in outcomes such as mortality or quality of life, it will usually require a large sample size and long follow-up. The conduct of large and expensive trials entails distinct challenges in many patient populations and settings relevant for deprescribing, for example, nursing home residents or patients with advanced dementia. However, frail populations also have a high rate of adverse outcomes as well as increased short-term mortality, meaning that large sample sizes and long follow-ups are not necessarily needed to evaluate the clinical effects of deprescribing in such populations. Nevertheless, challenges related to testing these interventions in frail populations can be substantial. As an example, assessment of quality of life in populations with a high degree of cognitive impairment (e.g., most nursing home populations) is very difficult. As such, insistence on strict clinical outcomes can result in interventions being tested on populations of lesser relevance to deprescribing and ultimately to key trials being dislodged from the clinical context they are intended to inform. There is therefore a clear need for identifying relevant outcome measures that are widely accepted as being clinically relevant while being more accessible than mortality and quality of life. Strong candidates for this are falls, admission rates, or activity of daily living assessment.

In this commentary, we have described three distinct lines of reasoning and discussed when they each can be considered most appropriate. We do this with the hope of catalyzing a discussion of the choice of primary outcomes in clinical trials in deprescribing. While we argue that there are important limitations to the currently preferred outcomes in clinical deprescribing trials, such as 'change in number of medications', there are, as also mentioned, numerous situations where such outcomes should be considered both reasonable and useful as primay outcomes. Nevertheless, for the field of deprescribing to mature and its findings to make their way into guidelines and clinical practice, it will be necessary to provide evidence of relevance to guideline writers, payers, clinicians, and patients alike. Settling how this is best achieved constitutes one of the core challenges for deprescribing researchers in the years to come.

CONFLICT OF INTEREST

Carina Lundby and Anton Pottegård have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Carina Lundby and Anton Pottegård contributed equally to this commentary.

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