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ORIGINAL ARTICLE

Describing deprescribing trials better: an elaboration of the CONSORT statement

Jeanet W. Blom[a,*], Christiane Muth[b], Paul Glasziou[c], James P. McCormack[d], Rafael Perera[e], Rosalinde.K.E. Poortvliet[a], Mattijs E. Numans[a], Petra Thürmann[f], Ulrich Thiem[g,h], Sioe Lie Thio[a], Mieke Van Driel[i], Martin Beyer[b], Marjan Van den Akker[b,j], J. Andre Knottnerus[j]

[a]*Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands*
[b]*Institute of General Practice, Goethe University Frankfurt/Main, Frankfurt am Main, Germany*
[c]*Institute for Evidence-Based Healthcare, Faculty of Health Sciences & Medicine, Bond University, Gold Coast, Australia*
[d]*Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, Canada*
[e]*Nuffield Department of Primary Care Health Sciences, Medical Statistics, University of Oxford, Oxford, UK*
[f]*Department of Clinical Pharmacology, University of Witten/Herdecke, Helios University Hospital Wuppertal, Witten, Germany*
[g]*Centre of Geriatrics and Gerontology, Albertinen-Haus, Hamburg, Germany*
[h]*Geriatrics and Gerontology, University Medical Centre Eppendorf, Hamburg, Germany*
[i]*Faculty of Medicine, Primary Care Clinical Unit, The University of Queensland, Brisbane, Australia*
[j]*Department of General Practice, Care and Public Health Research Institute, Maastricht University, Maastricht, The Netherlands*

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Abstract

Objective: The objective of this study was to identify key features to be addressed in the reporting of deprescribing trials and to elaborate and explain CONSORT items in this regard.

Study Design and Setting: As a first step in a multistage process and based on a systematic review of deprescribing trials, we elaborated variation in design, intervention, and reporting of the included trials of the review. We identified items that were missed or insufficiently described, using the CONSORT and TIDieR checklists. The resulting list of items, which we considered relevant to be reported in deprescribing trials, were discussed in a single-round Delphi exercise and subsequently in a full-day face-to-face meeting with an international panel of 14 experts. We agreed on CONSORT items for further elaboration with regard to design and reporting of deprescribing trials.

Results: We identified seven CONSORT items on trial design, participants, intervention, outcomes, flowchart, and harms, where the investigators of deprescribing trials should take into consideration specific aspects, such as whether or not to use placebo or how to inform participants.

Conclusion: This article presents an elaboration to the CONSORT statement for the reporting of deprescribing trials. It may also support investigators in motivated design choices.

Keywords: Deprescribing; Reporting guidelines; CONSORT statement; Study design; Primary care; Randomized controlled trial

1. Introduction

Deprescribing medication is increasingly acknowledged as an important way to reduce inappropriate medication and medication overload [1]. In older patients, the prevalence of polypharmacy, mostly defined as five or more medications [2], is approximately 30–40% across Europe [3]. This poses an extra challenge to clinical care, as older people with polypharmacy are more often prone to adverse drug reactions [4] and poor adherence [5]. Potential risks may outweigh the benefits [6–8]. However, deprescribing is also a key issue in tackling problems of overuse and misuse in younger patients, such as is the case for opioids [9] and benzodiazepines [10].

We define deprescribing as ''the process of withdrawal of medication, supervised by a health care professional'' which is partly based on the definition proposed by Reeve

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* Corresponding author. Public Health and Primary Care, Leiden University Medical Center PO Box 9600, 2300 RC Leiden, The Netherlands, Tel: +31 71 5268444.

E-mail address: j.w.blom@lumc.nl (J.W. Blom).

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What is new?

Key findings

- All CONSORT-items are applicable to deprescribing trials but certain items need more elaboration: trial design, participants, intervention, outcomes and harms, and the flowchart.

What this adds to what was known?

- The article presents an elaboration/explanation of the CONSORT statement with regard to specific considerations in deprescribing trials, addressing both single and multiple medication deprescribing.
- The proposed framework supports the reporting of a deprescribing trial, but also the planning of its design and measurements of fidelity and outcomes to capture the entire deprescribing process.

What is the implication and what should change now?

- Deprescribing trials require specific design and outcome measurement issues to be carefully considered and described.
- As appropriate medication advice increasingly involves deprescribing, registration authorities and public supervision should stipulate well designed and reported deprescribing studies as a criterion for medication registration.

et al. previously. [11] Not only can deprescribing aim to improve outcomes but it also includes discontinuation of medication that is unnecessary or was initially prescribed for good reasons, but can later become inappropriate—for example, when there is no longer an indication for it, or when harms outweigh the benefits [11,12]. Moreover, this definition takes into consideration that deprescribing is a process rather than just the act of stopping a drug, which may include decision making in prioritization when simplifying regimens, avoiding harms when tapering dosages, and taking into account patient preferences. Furthermore, the process of deprescribing is closely intertwined with attitudes and behaviors of clinicians and patients [13,14].

To address these challenges, an increasing number of deprescribing trials has been conducted, often evaluating multifacetted (i.e., complex) interventions to reduce medication overload [15–18]. Deprescribing trials need to report all relevant information to support the clinician in replicating the process in their practice and to allow estimating the internal and external validity of the results. Among the many reporting guidelines [19], the CONSORT statement for the reporting of randomized controlled trials and the TIDieR statement for the adequate reporting of (complex) interventions are most applicable for deprescribing trials [20,21]. A recent systematic review of deprescribing trials concluded that the quality of reporting needs to be improved, as deprescribing trials failed to adequately report important characteristics, such as patient selection and recruitment, choice of control condition, and length of follow-up [22,23].

We aimed first to contribute to improving the specific reporting of deprescribing trials, addressing both single and multiple medication deprescribing, and second to supporting the design of a trial and its measurements of fidelity and outcomes capturing the entire deprescribing process. We elaborated and explained deprescribing trial-relevant items of the CONSORT statement to an international group of experts also taking into account the TIDieR statement.

2. Methods

Using the results of a systematic review of deprescribing trials, which included studies evaluating the discontinuation or tapering of single or multiple medications [22], we set up a multistage process to develop a reporting guide on deprescribing trials. First, we (J.W.B., S.L.T.) assessed the RCTs included in the aforementioned review to explore the variation in design, intervention, and reporting, using the CONSORT and TIDieR checklists [20,21]. From this process, we identified items that were missed or insufficiently described. Subsequently, we (J.W.B., S.L.T.) made a list of items considered relevant to be reported in deprescribing trials. Second, in a single-round Delphi exercise, this list was sent to an international panel of 14 experts on pharmacology (J.Mc.C., P.T.), geriatric medicine (U.T.), general practice and clinical epidemiology (J.W.B., P.G., S.L.T., C.M., M.V.D.A., M.V.D., M.B., M.E.N., J.A.K., R.K.E.P.), statistics (R.P.), and reporting quality guidelines (P.G.) to be complemented with suggestions based on their expertise.

Third, the results from the Delphi process were presented and discussed in a full-day face-to-face meeting with the expert panel to agree upon on CONSORT items to be elaborated and explained with regard to specific considerations in deprescribing trials. The TIDieR statement on the appropriate reporting of interventions was also taken into consideration to avoid redundancies to existing universal reporting guidelines. Subsequent to the meeting, we elaborated and explained the CONSORT items with regard to design and reporting of deprescribing trials considering selected examples to illustrate the items under consideration. The multistage process was prepared by the first and last author and led by the first author.

3. Results

In the included trials of the systematic review [22], we identified the following omissions in outcome reporting—either as missed information or as incomplete reporting: relapse of symptoms, restart of medication and the

incidence of adverse events. In the Delphi process, the following issues were raised for elaboration: recruitment and selection of study participants, relevant details of the deprescribing intervention, adequate selection of the control condition, and specific considerations on sample size and harms. During the meeting, we determined the reporting of deprescribing trials following the CONSORT statement and the TIDieR statement would suffice. We identified no new issues that had not been covered by both statements in general. However, we identified the need for further explanation of the following CONSORT items with regard to deprescribing (see also supplemental table):

3: Trial design (3a).
4: Participants (4a).
5: Intervention
6: Outcomes (6a).
13: Flowchart (13b).
14: Follow up (14a).
19: Harms.

3.1. CONSORT item 3a—trial design

3.1.1. 3a: Description of trial design (such as parallel, factorial) including allocation ratio

We considered the following subjects important with regard to study design of a deprescribing trial: Placebo medication or no medication in the intervention group, noninferiority design, and the unit of randomization.

3.1.1.1. Placebo medication or no medication in intervention group. It is common and sometimes required to use placebo or sham interventions as a comparator in randomized controlled trials to control for the placebo and nocebo effect to detect beneficial effects as well as the adverse effects of the actual treatment [24,25]. In deprescribing trials, the use of placebo medication is less straightforward because deprescribing usually includes discontinuation of the visible act of being prescribed medication (example 1) [23]. From a methodological perspective, we should consider that placebo-controlled deprescribing, where the active intervention to be tested is in fact deprescribing, would require ''placebo deprescribing'' as a control condition [23]. This would then control for the visible act of deprescribing while in fact the pharmacological intervention is continued, and would need a highly sophisticated design in which the administration of medication is masked, for example, via other, not deprescribed medication, or food. To our knowledge, such a design has never been used, perhaps because of its obvious complexity.

When the aim of the trial is to study the specific pharmacological effect of deprescribing, then placebo-controlled deprescribing in accordance with one of two design options would be advisable: first, the aforementioned comparison with placebo deprescribing, and second, by comparing a deprescribing group receiving placebo with a control group continuing to use the medication (example 2). In the latter option, however, the practically important element of ending the visible act of taking pills is not part of the evaluation.

In deprescribing trials, it should be explicitly reported whether or not a placebo has been used, including a justification and explanation what placebo entails in which of the compared groups.

Example 1

In a trial to determine the effect of withdrawing diuretic medications on edema in patients who were prescribed diuretics for ankle edema, participants continuing their diuretics were compared with those who stopped using them. The outcome was the presence of edema at several time intervals. In this trial, no placebo was used because the researchers were interested in the overall effect of withdrawing diuretics compared with continuation of the treatment, as this is the intervention that would actually take place in practice. Moreover, in this scenario it would be tricky to use a placebo because of the many different types and combinations of diuretics in practice [8].

Example 2

The DART-AD trial aimed to assess whether continued treatment with antipsychotics in people with Alzheimer's disease is associated with an increased risk of mortality. The intervention group received a placebo [26].

3.1.1.2. When noninferiority trials may be applicable. Deprescribing trials may assess effectiveness addressing two kinds of outcomes:

1. A noninferiority or equivalence outcome implies that the patient is not worse off after stopping the medication. For instance, their quality of life or functioning or the manifestation of symptoms is not worse than when they were taking the medication. Therefore, from a clinical perspective, it is often not necessary to demonstrate that discontinuing is better, as not taking the medication reduces their risk of medication related harm and reduces cost. Accordingly, a deprescribing trial design can work with one-sided testing [27]. See also the CONSORT extension on reporting of noninferiority and equivalence trials (example 3) [28].
2. A superiority outcome implies that deprescribing would lead to an improvement of the patient's well-

Example 3

The benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness is tested in a clinical trial set in palliative care. It is known that prescribing statins for primary or secondary prevention for people with a life expectancy of many years is beneficial, but the participants of this study had a limited life expectancy. The trial aimed to study if discontinuing was not clinically inferior to continuing medication and therefore used a noninferiority design [29].

being, for instance, owing to a lower risk of adverse drug reactions. Superiority of deprescribing a single medication compared with continuation can also be shown in a noninferiority trial if the positive effect of deprescribing is obvious, or if the study shows noninferiority on the primary outcome but superiority on other outcomes [30].

3.1.1.3. Unit of randomization. Prescriber barriers/enablers to deprescribing have been described and are related to problem awareness; inertia, that is, the failure to act; self-efficacy; and feasibility of altering prescribing given external constraints [25]. Clinicians need to change their attitude toward deprescribing to overcome these barriers. When it is likely that the clinicians' attitude can influence the outcomes, that is, there is a high risk of the clinician giving the control group similar treatment (contamination), a cluster-randomized design may be preferred with the clinician or practice as the unit of randomization (example 4) [20,24].

Example 4

The ECSTATIC trial (Evaluating Cessation Statins and Antihypertensive Treatment in primary Care) is a cluster-randomized controlled trial designed to determine whether deprescribing preventive cardiovascular medication in patients without a strict indication for such medication in accordance with current guidelines is safe and cost-effective in comparison with usual care in general practice. A cluster-randomized design was used in which randomization at general practice level was performed. As participants were receiving the intervention from their general practitioner, the uptake of the intervention can be influenced by the general practitioner's way of working. In this case, a cluster-randomized design is useful [30].

3.2. CONSORT item 4—participants

3.2.1. 4a: Eligibility criteria for participants

3.2.1.1. Selecting and inviting participants. Deprescribing trials can address clinical questions such as the cessation of inappropriate medication, or societal questions like a reduction of cost-ineffective treatments, or questions with a focus on the patient's perspective, such as the reduction of treatment burden or adverse effects. The trial's objective has consequences for the methods used for case finding and patient recruitment. For example, when a reduction of adverse effects is the focus, patients will be invited to participate in the trial when the adverse effect is detected. In trials targeting specific drugs a systematic case finding method based on electronic medical records notes may be applicable [30].

However, apart from the trial's objectives, other reasons may impact the selection of participants. The patient's (un) willingness to attempt deprescribing has been reported to be prone to similar enablers and barriers as in prescribers [13], as well as the prescriber's perception of the patient's willingness to accept and maintain deprescribing [14]. In addition, the way patients are involved in the decision process about deprescribing plays a large role in a patient' decision to participate (example 5) [31,32].

Important for clinicians reading the study report is information about how patients were selected and included in the trial, to gain an unbiased idea about the intervention effect and its applicability to an individual patient.

Example 5

The statin deprescribing trial for palliative care patients was based on the hypothesis that the adverse effects of continuing statin use would outweigh the beneficial effects. Incorporating patient preferences in the decision to discontinue was seen as a key element as there was no clear superior option with clinical benefit. However, the fact that patients who were not willing to discontinue medication were not included in the trial, could be seen as selection bias [29].

3.2.1.2. Information supplied to the participants. Deprescribing implies that patients have to stop taking a treatment they are used to or for which they may even have developed pharmacological dependency [31]. The idea of deprescribing thus may cause resistance in prescribers as well as patients. For patients, the deprescribing authority (medical specialist, clinical pharmacist) might strongly influence the willingness to stop medication [33]. Furthermore, patients (dis)agreement with ''appropriateness'' of cessation, absence/presence of a ''process'' for cessation (such as time to discuss with the physician), and negative/positive

"influences" to cease medication (such as opinions of family or previous experiences with cessation), and "fear" of cessation and "dislike" of medication play an important role [14,31]. It is therefore important to report how and by whom various arguments are presented and discussed and what safety netting is offered.

3.3. CONSORT item 5—intervention

3.3.1. 5: The interventions for each group with sufficient details to allow replication, including how and when they were actually administered

In deprescribing trials, interventions can be either simple or complex. They are usually developed based on a theory or previously established evidence and may be inspired by clinicians wanting to deprescribe a drug due to a lack of added value, by pharmacists [34] or by health insurance providers. As deprescribing is associated with attitudes and behavior and deprescribing interventions often imply behavior changes, describing the incentives and barriers within a trial is important to inform future implementation. This can be done by following the TIDieR checklist. This description will include the approach/framework used to establish behavioral change of the patient, the prescriber or other health professionals involved. Of particular importance is the setting: during a routine office visit, during hospital stay, and which caregivers and/or relatives are involved. Sometimes patients seek advice from other care providers about their medication. Therefore, collaboration with other care providers is important to keep track of the medication the patient is using or not using. Deprescribing could lead to withdrawal-related effects, which also requires a constructive collaboration between hospital physicians and primary care to monitor patients after deprescribing [35].

The schedule of the discontinuation process, that is, time frame of tapering and the dosage-scheme, the time frame of monitoring and the items to monitor, should be included. Because this process is far more complex than simply starting a new medication, a clear description of the process should be provided. The protocol should describe criteria for when and how to restart the medication (example 6).

Example 6

The ECSTATIC trial added an appendix to the article including the schedule of the discontinuation process of antihypertensive and lipid-lowering medication, the time frame for monitoring and the items to monitor, that is, which symptoms to ask for. In addition, the health professionals involved were mentioned. In a workshop at the start of the study, all health professionals were informed about the study [30].

Apart from the intervention, clear information about the usual care option should be provided. In a cluster-randomized trial, primary care physicians in the control group may receive some sort of intervention, too, for example, a lecture about multimorbidity and polypharmacy, but without special training for deprescribing, the materials and further support. Deprescribing may also be part of usual care. It is therefore necessary to document medication changes in the control group as well.

3.4. CONSORT items 6, 19 and 14a—outcomes, harms and follow up time

3.4.1. Outcomes

3.4.1.1. 6a: Completely define prespecified primary and secondary outcome measures, including how and when they were assessed (and what length of follow-up was chosen); with reasons. The improvement/equivalence of outcomes is related to the reduction/equivalence of harmful effects of medications and may cover a full range of potential outcomes, such as the reduction/equivalence of hospitalization and mortality, the improvement/equivalence of quality of life, physical and cognitive functioning, and the prevention of falls. Deprescribing may also contribute to a patient's satisfaction about the medication regimen and treatment burden. However, the attribution of deprescribing effects on clinical and patient-relevant outcomes may sometimes be difficult, in particular in older patients with multiple conditions and medications. Therefore, process measures are often chosen such as the withdrawal or dose reduction of particular medications (example 7) [36], the reduction in high-risk prescribing indicators [35], or the reduction of the total number of medications [36]. Moreover, the assessment and detailed description of fidelity may be necessary to address the nature of deprescribing as a multilevel process. Figure 1 provides an overview on different levels of fidelity and outcome issues in deprescribing. Although not all levels will apply to every deprescribing trial, a systematic approach should guide the planning process on what to measure as well as the reporting.

Example 7

Outcomes in a randomized trial in family practice on withdrawal from long-term benzodiazepine use were reported as "success, no use or no more than once every 15 days; reduced, at least a 50% reduction in initial dose; failure, no change or a decrease smaller than 50%" [36].

3.4.2. Harms

3.4.2.1. 19: All-important harms or unintended effects in each group. Adverse drug reactions (ADRs) are defined as an "appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal

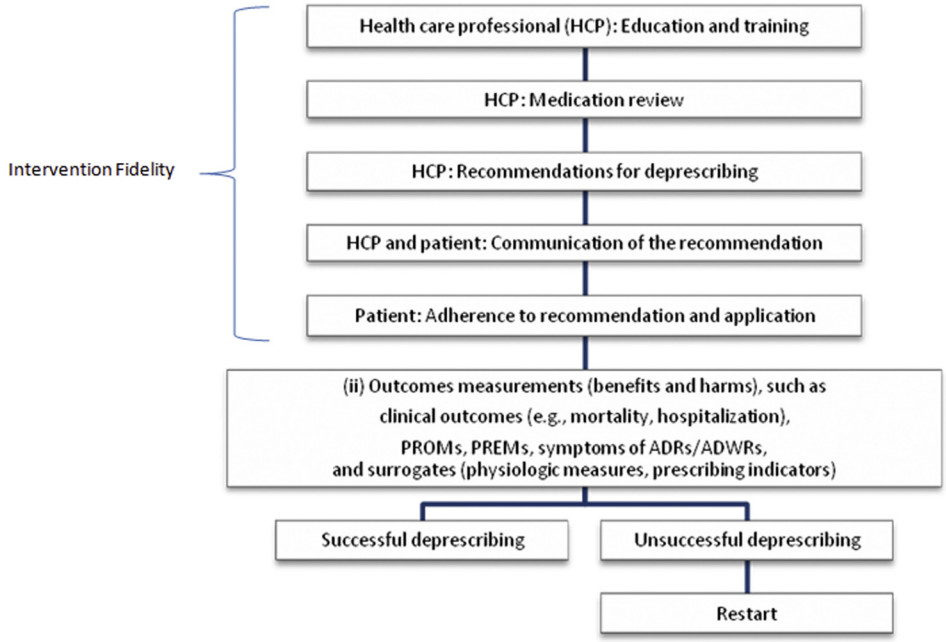

Fig. 1. Multilevel measurement issues of fidelity and outcomes in deprescribing. PROMs, patient-reported outcome measures; PREMs, patient-reported experience measures.

product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product'' [37]. ADRs may mediate the outcome in a medication trial as well as in deprescribing trials where adverse drug withdrawal reactions (ADWRs) may arise (Fig. 2). ADWRs are usually subsumed to ADRs [38] and may occur in different forms: (i) true physiological withdrawal reactions, such as gastric complaints as a rebound phenomenon after stopping a proton pump inhibitor [39], or (ii) onset of new symptoms after the discontinuation of benzodiazepines and opioids [36] (example 8), and (iii) symptom relapse, such as worsening edema after withdrawing diuretic therapy for heart failure [8]. These forms have different consequences in clinical management. Although ADWRs of i and ii gradually fade over time and are often preventable by means of appropriate strategies such as slowly tapering dosages or temporarily prescribing comedication, a (iii) symptom relapse with a subsequent restart of the medication indicates the failure of deprescribing. The reporting of all-important harms or unintended effects in each of the intervention and control group should therefore also include the form of ADWR when possible. Sometimes, this may be difficult,for example, as in the reporting of ADWRs in the discontinuation of serotonin-noradrenalin reuptake inhibitors, where a clear classification is hampered by the

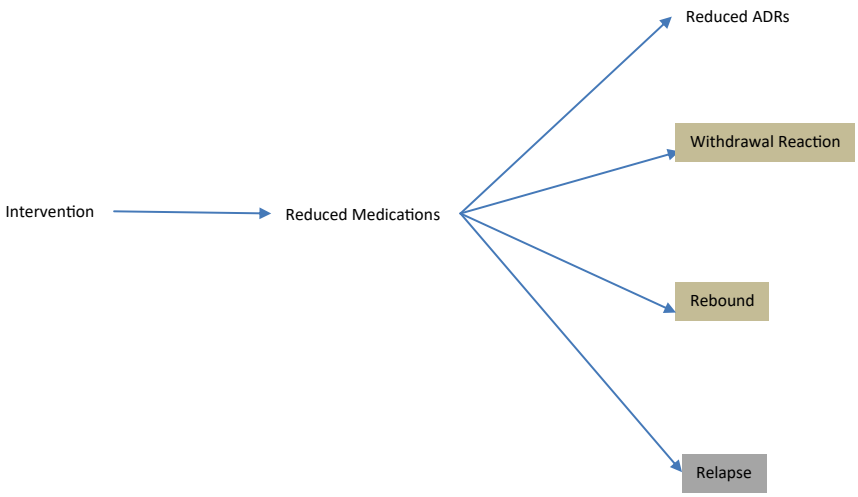

Fig. 2. Outcomes in deprescribing trials.

Example 8

"An adverse event will be defined as any unfavorable or unintended sign, symptom, or disease that could reasonably be associated with discontinuation of BZD [benzodiazepines]. These include tremor, anxiety, insomnia, convulsions, irritability, and dizziness. Physicians will report any withdrawal symptom related to BZD discontinuation to the trial coordinating center, and the data will be analyzed by a safety committee" [36].

multiplicity of symptoms, which may be easily misidentified as signs of relapse [40].

3.4.3. Follow-up time

3.4.3.1. 4a: Dates defining the periods of recruitment and follow up.

In a medication trial, the length of follow-up is decided by the expected time to effect. However, in a deprescribing trial one has to have an expectation about when not to expect an effect of withdrawal any more. Therefore, the follow-up time to measure outcomes and harms should be of sufficient length to cover critical periods of potential relapses and withdrawal symptoms. For instance, in single medication discontinuations, the minimal length of the follow-up time may be guided with regard to the duration of action of the medication to be stopped [41]. However, usually time frames for benefits and harms are much longer and can take weeks, months or years. For example, in deprescribing trials of antihypertensive medication, one may measure a relevant increase in blood pressure after a few weeks; however, more of concern is the hospitalizations due to hypertensive crisis, myocardial infarction, and stroke. In polypharmacy trials, the observed time frames of restarts after discontinuation may be taken into account [42,43]. Whatever rationale motivates the determination of follow-up length, it should be reported to support physicians in clinical management of their patients (example 9) [8].

Example 9

In the trial to stop the use of diuretics in patients who use it for ankle edema, the follow-up time was explained as follows: "The length of the follow-up period was chosen on the basis of literature in which a rebound effect of diuretic withdrawal of 3 weeks was mentioned. To work with a safe margin, we choose a follow-up period of 6 weeks. Because the first objective of our study was to investigate the effects of withdrawal, and not whether withdrawal could be achieved for a substantial period of time, a limited period was appropriate" [8].

3.5. CONSORT item 13b—flowchart

3.5.1. 13b: For each group, losses and exclusions after randomization, together with reasons

The flow chart of the trial gives information on participation and refusal to participate or patient drop out. This information is highly relevant for the external validity. Ideally, reasons for nonparticipation are known. In a deprescribing trial, reasons for dropping out of the trial are of particular importance, as they might have to do with withdrawal reactions or reoccurrence of symptoms [40].

4. Discussion

We propose an elaboration of the CONSORT statement for randomized controlled trials to enable more transparency in the reporting of deprescribing trials. Including points relevant to prescribing/deprescribing trials in a revised CONSORT statement would be a good way to facilitate this. As in all trials, in deprescribing trials all phases of the protocol need to be thoroughly addressed both in design development and reporting. Although design features for deprescribing trials are often equally relevant for trials of new drugs, owing to the nature of deprescribing trials, more detail is required for a number of CONSORT items: trial design, participants, intervention, outcomes and harms, and the flowchart. Deprescribing trials are not new, but the deprescribing perspective of rational and safe use of medication has received more attention over the past few years. Initiatives, such as "deprescribing.org" [44] and the "Australian Deprescribing Network (AdeN)" [45], provide support for clinicians and researchers. These elaborations are relevant both for readers of deprescribing trials and researchers planning a deprescribing trial.

The CONSORT statement provides a checklist to guide reporting of randomized trials to allow greater standardization and transparency of the trial process for users of research [46]. Most medical journals now require authors of trials to submit the CONSORT checklist with their article and these are often published with the trial. Similar consensus statements for the reporting of other designs have emerged, such as STROBE [47] for observational studies and STARD [48] for diagnostic studies. Extensions to CONSORT have been developed to cater for trials with a specific design feature, such as cluster-randomized trials or noninferiority and equivalence trials. Our group of experts on deprescribing trials agreed that when deprescribing trials use a conventional parallel group randomized trial design all CONSORT items are applicable, but more detail is needed only for specific items.

Specific design issues are directly related to the clinical aim of deprescribing. In planning a deprescribing trial, the

implications for the hypothesis to be tested, the sample size, and the type of analysis must be thoroughly thought through. For example, because continuing a medication would be more intrusive and more expensive than discontinuation, it should be sufficient to demonstrate that discontinuation is not clinically worse than continuation (i.e., that continuation is not better). This means that a noninferiority design with one-sided testing (and thereby a smaller sample size) would suffice [27]. In addition, in contrast to usual (''prescription'') drug trials, when the intervention is focused on discontinuation of medication and the control condition is in fact continuation of this medication [23], one could consider the role of blinding. There is an essential difference between blinded (purely pharmacological) discontinuation and open discontinuation of the clinical act of prescribing medication, and it is important to select the most appropriate option for the clinical research question at stake.

A recent observational study of reporting in deprescribing trials points to the variability of reporting and, more specifically, the lack of detail about the intervention [49]. Sufficient information about the interventions, including the ''usual care'' option, is important for clinical interpretation of the results and replicability of the intervention in clinical practice. Likewise, it is important that the results are reported in more detail; for instance, who stopped completely or partly (e.g., dose reduction), who restarted medication (and for what reason), and who assessed the outcomes. Harms reporting should allow the estimation of incidence and severity of any ADWRs and include whether or not ADWRs were expected and what was done to mitigate the impact of ADWRs throughout the trial. As with any other intervention trial, a prespecified protocol needs to be available and any planned outcome measures have to be reported as well as the number of and reasons for missing values.

This CONSORT elaboration for deprescribing trials is based on a consensus building process. Experts in the field of deprescribing from a wide range of countries and continents have contributed to this elaboration document. However, as with all consensus processes, not all experts were involved and some perspectives may have been missed. However, this document is presented as a ''work in progress'' and as the suggested elaborations are being used and assessed reporting guidance can be refined and improved.

Finally, taking the process of medication cessation and deprescribing scientifically seriously should be accompanied by better funding and regulation policies. Public and private resources for funding deprescribing studies should be substantially extended. Deprescribing studies are currently scarce, which is in huge contrast with the growing acknowledgment of polypharmacy and medication overload and its impact on patients and society [50]. The research agenda is clearly biased as sponsors of trials studying the effects of new medication are generally not interested in studying the effects of deprescribing that same medication. In this context, it would help if public supervision and registration authorities require, as with all clinical trials, well-designed and -reported deprescribing studies as a criterion for medication registration. Such requirements would considerably increase the quality and safety of care.

CRediT authorship contribution statement

Jeanet W. Blom: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Supervision, Project administration. **Christiane Muth:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Supervision. **Paul Glasziou:** Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **James P. McCormack:** Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **Rafael Perera:** Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **Rosalinde.K.E. Poortvliet:** Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **Mattijs E. Numans:** Investigation, Formal analysis, Writing - review & editing. **Petra Thürmann:** Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **Ulrich Thiem:** Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **Sioe Lie Thio:** Investigation, Formal analysis. **Mieke Van Driel:** Investigation, Formal analysis, Writing - review & editing. **Martin Beyer:** Investigation, Formal analysis. **Marjan Van den Akker:** Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **J. Andre Knottnerus:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Supervision.

Supplementary data

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