Dr. Paul J. Simpson
International Audience Editor
Re: ID BMJ.2018.044306

03-Aug-2018

Dear Dr. Simpson,

Thank you very much for assessing our manuscript "Proposal to integrate information on treatment burden into clinical practice guidelines" and thank you for the invitation to resubmit a revised version of the manuscript. Thanks also to the reviewers who submitted their comments and recommendations.

We have provided a point-by-point response to the revision queries below. The major changes that we have made in response to the editor's and the reviewers' comments are as follows.

1) We have shifted the focus of the revised article from emphasising the importance of treatment burden towards outlining challenges and possible solutions to incorporating information on treatment burden into clinical practice guidelines. Specifically, we have elaborated on the collection of information on treatment burden and available measurement tools. We have outlined that these tools need to be evaluated for their suitability to provide information for guidelines.

2) We now clearly distinguish between the concepts of treatment workload and the impact of this workload on patients' functioning and well-being, both summarised under the umbrella term treatment burden.

3) We have emphasised that the weighing up of benefits of a treatment and the treatment workload and potential burden associated with it, is a process that should happen during shared decision making in the encounter between patient and clinician. Information on treatment burden in guidelines has the potential to provide high quality information on these aspects for developers of decision aids and could also facilitate shared decision making in the absence of decision aids for a specific clinical scenario.

4) We had to delete some content from the original manuscript draft to stay within the word limit.

Editors' Comments:

1. *Could the title be made more engaging?*

   Response: We have changed the title to "Integrating information on treatment burden into clinical practice guidelines: a call to action".

2. *The article spends a lot of time lot of time convincing readers that treatment burden is a problem but the editors felt it was a little light on how information on treatment burden could be collected, measured and included in guidelines in a practically useful way. The article says that trials should collect this information and box provides an example but would this be sufficient, systematic and rigorous enough? Could you expand on these, otherwise the article may feel too much like a review of treatment burden rather than a solution to tackle it.*

   Response:

We have shifted the focus of the revised article from emphasising the importance of treatment workload/burden towards outlining challenges and possible solutions to incorporating information on treatment workload/burden into clinical practice guidelines.

The information currently available on treatment burden for specific conditions and interventions is sparse and likely insufficient for most guidelines. The major challenges to achieve the integration of information on treatment burden in guidelines are therefore finding robust high quality methods for information collection and measurement of treatment burden, as well as finding meaningful ways of adding this information to clinical practice guidelines.

There are currently at least two validated measurement tools for self-reported burden of treatment for patients with chronic conditions.[1-3] The Treatment Burden Questionnaire (TBQ) consists of 7 items (2 of which have 4 sub-items), evaluating quantifiable workload as well as the impact of this workload on patients' lives, e.g. "Lab tests and other exams (frequency, time spent and inconvenience of these exams)".[1] The Patient Experience with Treatment and Self-management (PETS) is a 48-item measurement tool which focuses on the impact of treatment workload on patients' lives and well-being, e.g. "How much of a problem has it been for you to plan your daily activities around your medicine schedule?" (Responses: not at all, a little, somewhat, quite a bit, very much). The suitability of these tools to collect information for the use in clinical practice guidelines has yet to be evaluated, and the tools might have to be adjusted for this purpose.

We have added this information to the manuscript.

3. *Treatment burden is likely different for different groups of patients (for example, elderly or palliative care patients, there comes a point where the risks and burden of preventative treatment are deemed to outweigh the benefits) how should this information be included?*

Response: This comment makes the important point that treatment burden is not the same for all patients with the same condition, but depends on numerous factors such as a persons' context (age, disease burden, co-morbidities, social support network, patients' values and preferences).

To address this problem, we now clearly distinguish between the construct of treatment workload, which can be objectively measured, e.g. how many hours per week are spent on preparing/administering medications, and the subjective impact of this work on patients' quality of life. e.g. the need for regular exercise may be perceived as burdensome by one patient, whereas another patient may experience exercise as empowering action that improves their situation.[4] The best way of integrating information on treatment burden, especially the potential impact of treatment burden on patients' lives and well-being into guidelines has not been explored, and research is required to find ways of making this information useful to guideline users.

We have added this information to the manuscript.

4. *The article assumes that readers understand how guidelines are currently developed but not all readers will. Could you include some information to help readers. There's*

a related argument about patients being more involved in guideline development, which I think happens already at NICE.

Response: We have now included a paragraph on the process of guideline development.
"Clinical practice guidelines make recommendations for or against medical treatments based on the best possible available evidence. The first step in guideline development is to determine the purpose and the intended audience. Guideline authors including content and methodological experts as well as patients (and possibly carers) are than selected, and the questions that the guidelines will address are refined before the evidence is systematically synthesised and the quality of the available evidence is determined. The balance of desirable and undesirable consequences for a particular course of action is evaluated and recommendations (and their strength) are formulated.[5]"

5. *One of our clinical editors raised the following tension: "there are areas of multi-morbidity where guidelines don't exist, and where specialists give conflicting advice - what are GPs to do then? Might a practice lose out financially if they choose to prioritise a patient's agenda over figure-driven targets?" In other words how do we ensure that this is patient-led and meet's the patient's goals rather than clinicians'.*

   Response: Figure driven targets (e.g. proportion of patients with increased cardiovascular risk on statin treatment) are not always consistent with a patient-centred approach. A patient may for example decide that based on a number needed to treat (NNT) of 67 for somebody with an intermediate cardiovascular risk or 167 for somebody with a low risk to avoid a major adverse cardiovascular events, the potential benefits of statin therapy may not outweigh the treatment burden for them personally (are side effects/ harm part of treatment burden?).[6]

   We have now outlined that the process of weighing of pros and cons (including treatment burden) of different treatments happens during shared decision making, which should ensure that the final choice for or against a medical intervention aligns with the patient's values and preferences (rather than being driven by the clinician's agenda).

   Information on treatment workload/burden in guidelines has the potential to provide high quality information on these aspects for developers of decision aids and could further facilitate shared decision making in the absence of decision aids for specific clinical scenarios.

6. *Could you make it clearer that this is about what suits the patients rather than choosing treatments that require less time and input from the professionals side.*

   Response: We have now clarified this point in the manuscript and have emphasised the need for shared decision making.

   "The process of weighing of pros and cons (including treatment burden) of different treatments happens during shared decision making between patient and clinician. This should ensure that the final choice for or against a medical intervention aligns with the patient's values and preferences rather than being driven by the clinician's agenda. Information on treatment burden in guidelines has the potential to provide high quality information for developers of decision aids and could further facilitate

shared decision making in the absence of decision aids for specific clinical scenarios."

7. *Should guidelines also consider the burden for carers of conducting any of these activities as well?*

   Response: We agree that the burden for carers is an important aspect to consider when making treatment decisions. To systematically include information on treatment burden for carers in guidelines, however, is even more challenging, than including information on treatment burden experienced by patients, because patients' ability to self-manage their disease will vary significantly and the interpersonal dynamics between different types of carers (family, neighbour, professional carer) and the patient will have a significant impact on the experienced treatment burden.

   We have included the following statement in the manuscript:
   "We further suggest that the usefulness of integrating information on the potential burden for carers when enacting treatment recommendations should be explored."

8. *Paragraph on the bottom of page 4 is about shared decision making rather that being guided by a healthcare professional. If patients know the risks and understand, they should be able choose short term fixes if they feel it is right for them.*

   Response: We have changed the phrasing of this paragraph, emphasising shared decision making rather than guidance by a health professional. The following sentence was added.
   "It is therefore important to practice shared decision making, which enables patients, in collaboration with their clinician, to make conscious decisions for or against treatments, using evidence-based information."

9. *Further examples in Box 1 beyond the COPD guidance would be helpful.*

   Response: We have now added the examples of starting insulin treatment for type II diabetes mellitus and dietary interventions for chronic kidney disease.

Reviewer(s)' Comments to Author:

Reviewer: 1

Recommendation:

Comments:

1. *In this Analysis article, the authors raise an important point about treatment burden and make a strong recommendation that such burdens should be incorporated into guidelines. I've seen this in other fields (e.g. A move from "seizure free" to "seizure free, side effect free" in epilepsy). Their case is well argued and the examples given relevant to general practice, as well as providing future avenues of research.*

Response: We are encouraged by the reviewer's feedback that aiming for routinely incorporating treatment burden into guidelines will help to facilitate patient-centred research and clinical practice.

2. *Is there much good evidence for the burden of treatment beyond the anecdotal? In my experience the only time there is money invested in this area is if a pharma company has a product they think is "more convenient" they may do some post-launch research but this is likely to be biased.*

   We agree with the reviewer that pharmaceutical companies are unlikely to be invested in researching treatment burden associated with the products that they offer. Yet, there is a now an increasing body of evidence for the burden of treatment, and at least two validated measurement tools for treatment burden have been published to which we refer in the revised version of the manuscript.

3. *To fully implement this proposal, must we have to collect good evidence on treatment burden before we can formulate clinical guidance?*
   Response: We agree with the reviewer that first good evidence on treatment burden needs to be collected before information on treatment burden can routinely be included in clinical guidelines. We have now emphasised in the manuscript the current evidence gaps and challenges that need to be addressed in order to work towards integration of treatment burden information into guidelines. The following paragraphs were added to the manuscript.

   "The information currently available on treatment burden for specific conditions and interventions is sparse and likely insufficient for most guidelines. The major challenges to achieve the integration of information on treatment burden in guidelines are therefore finding robust high quality methods for information collection and measurement of treatment burden, as well as finding meaningful ways of adding this information to clinical practice guidelines.

   There are currently at least two validated measurement tools for self-reported burden of treatment for patients with chronic conditions.[1-3] The Treatment Burden Questionnaire (TBQ) consists of 7 items (2 of which have 4 sub-items), evaluating quantifiable workload as well as the impact of this workload on patients' lives, e.g. "Lab tests and other exams (frequency, time spent and inconvenience of these exams)".[1] The Patient Experience with Treatment and Self-management (PETS) is a 48-item measurement tool which focuses on the impact of treatment workload on patients' lives and well-being, e.g. "How much of a problem has it been for you to plan your daily activities around your medicine schedule?" (Responses: not at all, a little, somewhat, quite a bit, very much). The suitability of these tools to collect information for the use in clinical practice guidelines has yet to be evaluated, and the tools might have to be adjusted for this purpose."

4. *How is the best evidence gathered? A time and motion study? PROMS like the Treatment Burden Questionnaire? Ethnography?*

   Response: Patient-reported outcome measures based on the Treatment Burden Questionnaire (TBQ) or the Patient Experience with Treatment and Self-management (PETS) tool have the advantage that they can be used in large scale surveys. Their suitability to measure time spent on treatments is, however, limited and a time and motion study might be useful to collect this information. The study design has been used in healthcare mainly with the goal to understand workflow and time spent on different activities of health care professionals using observers. Further research

would be required to determine the feasibility of using this study design to document patients' treatment workload around the clock in different settings (home, grocery store, doctor's office etc.), as using observers in this context does not seem feasible.

We have added this information to the manuscript.

5. *I suppose we would also want to gather some evidence that it would change decisions, and these changes would be positive? There is a risk it might not help, of course (many good ideas don't!).*

   Response: We have emphasised the usefulness of information on treatment burden for shared decision making in the revised manuscript. While it is certainly desirable to demonstrate the effect of including information on treatment burden into guidelines, measuring "a positive change" has proven notoriously challenging in studies of shared decision making, as the goal of this process is a medical decision that is consistent with the patient's values and preferences. Outcome measures that reflect a "positive change" include therefore patient satisfaction with the decision making process and similar measures. Importantly, providing comprehensive information on treatment options (including treatment burden) is already justified on deontological grounds.

   We have included the following statement in the manuscript:
   "Information on treatment burden in guidelines has the potential to provide high quality information on these aspects for developers of decision aids and could further facilitate shared decision making in the absence of decision aids for specific clinical scenarios."

6. *While incorporating treatment burden into RCTs seems worthy, commercial sponsors won't do it unless regulators make them (or they think there is a compelling commercial reason), plus trials themselves are so burdensome (and biased in who sticks with them) that they probably distort the burden. So if I'm right, who should conduct this research and when / where / who pays?*

   Response: We agree that pharmaceutical companies' interest in measuring treatment burden in industry-sponsored randomised controlled trials (RCTs) is likely limited. Also, information collected in a real-life setting may differ from an RCT setting. Patient advocacy groups are likely to have a vested interest in the availability of information on treatment burden, and research partnerships between patient advocacy groups and investigators might be a promising avenue to progress the research agenda of treatment burden.
   We have added this information to the revised manuscript.

Reviewer: 2

Recommendation:

Comments:
Thank you for the opportunity to review your manuscript, "proposal to integrate information on treatment burden into clinical practice guidelines." This analysis piece is nicely written and clear. I think this goes into the right direction. Following are some personal critics and thoughts.

1. *In my opinion, using the words burden and workload interchangeably is not a good idea as I think that they relate to two very different constructs. The workload of care relates to "the work done by patients" (which may be objectively measured) while the*

burden of treatment would relate to "the impact of this work on patients' quality of life". In the article by Buffel du Vaure (cited by the authors), patient workload is clearly defined as: "all demands in their lives for health-related activities (HRAs) such as scheduling and attending appointments, preventive care, drug management, self-monitoring, visits to the doctor, laboratory tests, changes of lifestyle and paperwork". The definition of the burden of treatment initially coined in the article of Eton et al. may be more confusing: "We define "burden of treatment" as the workload of health care and its impact on patient functioning and well-being". In a later article, some authors chose to restrict the burden of treatment to "the impact of the work of being a patient on their functioning and well being" (Tran VT, BMC Med, 2015).It is important to differentiate these constructs as two patients with the exact same workload of care (same number of drugs, doctor visits, etc.) could live their treatment very differently. Studies have shown that physicians are very bad at estimating patients' burden of treatment because they believe that "high workload of care = high burden of treatment" while ignoring patients' integration of care activities in their lives.

Response: We have used the term treatment burden as an umbrella term for quantifiably treatment workload as well as the impact of this workload on patient functioning and well-being, as defined by Eton et al. We acknowledge that there are two different constructs under this term, quantifiable workload and impact of this workload on patient functioning and well-being. In the revised article we now clearly differentiate between these two constructs, but have chosen to continue to use the term treatment burden as umbrella term for both constructs, as in the original definition coined by Eton et al..

2. *I like the guidelines envisioned by the authors. Especially their propositions for sections such as: "treatment essentials (even on a bad day)". I fully agree that time spent by patients in health activities is only one aspect of the workload for patients. Maybe authors should emphasize the fact that "time is relative"; that the cost for patients of investing time for healthcare is not the same for all. The burden of treatment is complex, dynamic and dependant on the changes of patients' lives and of their familial, social or professional obligations. Similarly to (and maybe more than) treatment effect, reporting simple time estimates taken from studies conducted in distant and often different contexts, with patients who often have only one chronic condition, may mislead guideline users. Another thing to consider in integrating treatment burden into guidelines is that, by mixing "hard" information (time estimates with numbers) with "soft" information (e.g. emotional investment or discomfort for patients), some users will tend to ignore the latter and oversimplify burden of treatment to 'time spent' 'number of pills', sometimes resulting in more harm than good…*

   Response: We appreciate that there are variations in treatment burden including in quantifiable treatment workload and the impact of this workload on patients' life between different patients. We have outlined in our revised manuscript that one of the challenges in progressing the integration of treatment burden information into guidelines is the accurate representation of the variation in treatment burden experiences.

   "Treatment burden is not the same for all patients with the same condition, but depends on numerous factors such as a persons' context (age, disease burden, co-morbidities, social support network, patients' values and preferences). The need for regular exercise, for example, may be perceived as burdensome by one patient, whereas another patient may experience exercise as empowering action that improves their situation.[4] The best way of integrating information on treatment burden

into guidelines, reflecting the variations in treatment burden experiences, has not yet been explored. Research is required to find ways of making this information useful to guideline users. We further suggest that the usefulness of integrating information on the potential burden for carers when enacting treatment recommendations should be explored."

We acknowledge that a certain risk of misinterpretation and misuse of information on treatment burden in guidelines is possible, as any evidence-based information (even when presented in balanced decision aids) can be twisted by people driven by a certain agenda. Nevertheless, we are convinced that shining a light on the aspect of treatment burden in guidelines (including quantifiable workload and the potential impact of this workload on patients' lives) will raise awareness of the issue and will generally contribute to a constructive dialogue.

Reviewer: 3

Recommendation:

Comments:
Summary:
The authors address the often-unrecognized treatment burden of patients with chronic diseases and multimorbidity and its consequences. The analysis paper recommends that future guidelines should embrace these construct and the associated concept of minimally disruptive medicine (MDM).

Relevance
The topic is of major importance and the article is interesting for guideline developers and physicians and may further contribute to the ongoing debate about 'making better guidelines'

Strengths
The manuscript is clear and well written, the line of arguments is balanced, well structured and examples of treatment burden illustrate the manifold of its aspects and consequences.

Minor Comment:

1. *The authors mention the relevance of the topic for patients with multimorbidity but the line of argument could be strengthened: it is well accepted that the use of multiple disease-oriented guidelines in patients with multimorbidity may have harmful consequences due to potential interactions and a cumulating (and sometimes) unbearable treatment burden. However, it has been increasingly recognized that "we have little with which to replace them". Furthermore, key principles on how to handle multimorbidity such as the "Ariadne principles" put an emphasis on the careful and critical use of guidelines in multimorbidity. The applicability of guidelines in patients with multimorbidity would be supported enormously when treatment burden would be made explicit. In particular in patients with multimorbidity, clinical decision making has to take into account trade-offs between competing outcomes and prioritization is needed.*
   References
   (1) Guthrie B, Payne K, Alderson P, McMurdo ME, Mercer SW. Adapting clinical guidelines to take account of multimorbidity. BMJ 2012; 345:e6341.
   (2) Roland M, Paddison C. Better management of patients with multimorbidity. BMJ 2013; 346:f2510.
   (3) Muth C, van den Akker M, Blom JW, Mallen CD, Rochon J, Schellevis FG et al. The Ariadne principles: how to handle multimorbidity in primary care consultations. BMC Med 2014; 12:223.

Response: The reviewer raises the important issue of multi-morbidity and the challenges of having to apply multiple disease-specific guidelines to one patient. We have now emphasised in the manuscript that making treatment burden explicit would support the applicability of guidelines in patients with multimorbidity as clinical decision making particularly in this patient group has to consider trade-offs between competing outcomes and prioritization.

We have cited the paper on the Ariadne principles, which is very pertinent to the topic of our paper, suggesting sharing of realistic treatment goals, prioritisation of health problems that takes into account the patient's preferences, and individualised treatment.

We have added the following paragraph to the manuscript:
"Clinical decision making particularly in patients with multimorbidity has to consider trade-offs between competing outcomes and prioritisation. The "Ariadne principles" on how to handle multimorbidity in primary care consultations emphasise the careful and critical use of guidelines in multimorbidity, promote sharing of realistic treatment goals by physicians and patients, and prioritising health problems in accordance with the patient's preferences.[7] Making treatment burden explicit in guidelines would support the applicability of guidelines in patients with multimorbidity in line with these principles."

Reviewer: 4

Recommendation:

Comments:
Dobler and colleagues propose that information on treatment burden should be included in guideline recommendations - e.g. estimated time and effort required of patients to follow a recommendation, patients' emotional investment, and patients' discomfort - in order to support patients in making informed decisions aligned with their values and preferences. They propose that this information should be added as an explicit statement in the evidence to decision framework, and that future clinical trials should collect information on the time patients spend on treatments, as well as on cost and emotional investment.

The authors provide a compelling argument that incorporating treatment burden in guidelines could be useful to facilitate elicitation of values and preferences and engagement in shared decision-making. The authors astutely note that patients faced with overwhelming treatment burden "may resort to self-guided treatment prioritization," which would (ideally) be better optimized if discussed with their healthcare provider. However, I have some concerns.

1. *First, it would be important to ascertain the feasibility for guideline developers to write these statements (ideally in a standardized way), and second, the applicability for clinicians and patients to interpret and use them. The authors present an intriguing area of innovation for more patient-centred guidelines, and provide an illustrative theoretical example, but it would be useful to see this strategy implemented before considering incorporating it into the evidence to decision framework. For example, there could be user testing by clinicians/guideline developers and patients/caregivers about whether this would be useful, and if so, how it should be presented. It would be important to see whether adding burden of treatment ultimately influences shared decision-making.*

Response: We agree with the reviewer that there are a number of challenges that need to be addressed before information on treatment burden can routinely be incorporated into the evidence to decision framework. In the revised manuscript we now describe these challenges and possible solutions in more detail and outline how information on burden of treatment can be used for tools that facilitate shared decision making.

2. *In addition, I feel that there is some overlap with the proposed burden information and the information one may find in decision aids. While clearly distinct, it would be helpful if the authors could mention this, since decision aids are integral to guidelines and shared decision-making.*

   Response: We agree with the reviewer that decision aids in many cases already attempt to address the topic of treatment burden. We have now included a paragraph in the revised manuscript in which we mention in this and where we outline how information on treatment burden in guidelines could be used when developing decision aids.

   The following paragraph was added to the manuscript.
   "The process of weighing of pros and cons (including treatment burden) of different treatments happens during shared decision making between patient and clinician. This should ensure that the final choice for or against a medical intervention aligns with the patient's values and preferences rather than being driven by the clinician's agenda. Information on treatment burden in guidelines has the potential to provide high quality information for developers of decision aids and could further facilitate shared decision making in the absence of decision aids for specific clinical scenarios."

Specific minor comments

1. *Page 3 lines 14-22: "This can result in substantial treatment burden to patients with chronic conditions. While treatment burden in particular affects patients with multi-morbidity, a single chronic condition, such as cystic fibrosis or insulin-dependent diabetes mellitus, can also result in a significant treatment workload for patients." I feel that making an argument that single conditions can also be burdensome within the first paragraph of the introduction detracts from the main message. I would suggest to rephrase this as a more inclusive overall statement and focus on reporting burden.*

   Response: We have deleted the sentence that differentiates between treatment burden in patients with a single disease and those with multiple chronic conditions.

2. *Page 5 lines 27-31: "The need for strategies in situations where patients' capacity to implement all recommended treatments is overstretched, has been recognised, but there are currently no widely accepted solutions to address the problem." There is an extra comma between "overstretched" and "has".*

   Response: This sentence has been deleted to stay within the word limit.

Yours sincerely,

Claudia C. Dobler

References

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5. Jaeschke R, Jankowski M, Brozek J, et al. How to develop guidelines for clinical practice. *Minerva anestesiologica* 2009;75(9):504-8. [published Online First: 2008/11/13]
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