MJ - Decision on
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Body: 04-Jul-2018

Dear Dr. Dobler

Thank you for sending us this paper and giving us the chance to consider your work.

We sent it out for external peer review and discussed it at the Analysis manuscript committee meeting (present: Paul Simpson, Navjoyt Ladher, Robert Redelmeier, Emma Rourke, Cat Chatfield and Anya de Iongh).

Unfortunately we do not consider it suitable for publication in its present form. However if you are able to amend it in the light of our and the reviewers' comments, we would be happy to consider it again.

The reviewers' and editors' comments are at the end of this letter.

We hope that you will be willing to revise your manuscript and submit it within 4-6 weeks.When submitting your revised manuscript please provide a point by point response to our comments and those of any reviewers. We also ask that you keep the revised manuscript within the word count of 1800-2000 words.

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If accepted, your article will be published online at bmj.com, the canonical form of the journal. Please note that only a proportion of accepted analysis articles will also be published in print.

I hope you will find the comments useful. Please don't hesitate to contact me if you wish to discuss this further.

Yours sincerely

Paul J. Simpson, PhD
International Audience Editor
psimpson@bmj.com

**IMPORTANT INFORMATION TO INCLUDE IN A RESUBMISSION

Key messages
This is a box at the end of the article containing 2-4 single sentence bullet points summing up the main conclusions.

Instead of returning a signed licence or competing interest form, we require all authors to insert the following statements into the text version of their manuscript:

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Editors' Comments:

:: Could the title be made more engaging?

:: 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. 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.

:: 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?

:: 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.

:: 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’.

:: 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.

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

:: 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.

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

Reviewer(s)' Comments to Author:

Reviewer: 1

Recommendation:

Comments:
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.

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.

To fully implement this proposal, must we have to collect good evidence on treatment burden before we can formulate clinical guidance?

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

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!)

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?

Additional Questions:
Please enter your name: Paul Wicks

Job Title: VP of Innovation

Institution: PatientsLikeMe

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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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.
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.
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…

Additional Questions:
Please enter your name: TRAN Viet Thi

Job Title: Researcher

Institution: INSERM

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 3

Recommendation:

Comments:
Reviewer: Christiane Muth, Goethe University, Frankfurt / Main, Germany
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'¹.
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:
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".² 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.³ 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.

Additional Questions:
Please enter your name: Christiane Muth

Job Title: Senior Researcher

Institution: Institute of General Practice, Goethe University, Frankfurt / Main

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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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. 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. 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.

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.
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".

Additional Questions:
Please enter your name: Lyubov Lytvyn

Job Title: PhD student

Institution: McMaster University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

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Funds for a member of staff?: No

Fees for consulting?: No

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