Dear Colleagues:

We attach a revised version of our paper " Healing an Ailing Pharmaceutical System: A Prescription for Reform" for your further consideration for publication in the BMJ.

The paper has been revised in keeping with the suggestions of the editors and reviewers. Specifically:

The editors:

1. **Requested that we shorten the manuscript from 4200 to about 3300 words and reduce the number of figures and tables.** The current version is 3215 words long. We have retained tables 1 and 2, the Panel, and figure 2. If you wish, we could move the Panel to the supplementary material, or eliminate it. We have moved the other figure and tables to the supplementary file, and could eliminate some or all of these if you deem it wise.

2. **Asked that we address the difficulty of achieving the proposed reforms in the current political context.** We have added a paragraph on this issue (page 21, line 1-9)

3. **Felt that the economic analysis might best be pursued as a separate article.** We feel that some, even rough, cost estimation, is important to address concerns about the fiscal, and hence political feasibility of the reforms we propose. We have moved the table presenting the estimate to the supplementary material, and emphasize in the text the uncertainty of our estimate. Additionally, the table has been updated based on the latest estimates from the National Health Expenditures, number of uninsured, and Mr. Nussbaum's concerns (See response to Mr. Nussbaum, comment 2 below).

Professor Maynard:

Main comments

1. **Recommended that we clarify the term "medical need".** We now briefly address this issue in the section of the manuscript where we describe covered medications (page 8, line 4-5).

2. **Urged us to specify a role for cost-effectiveness analysis in determining what drugs are covered.** The reforms we propose incorporate mechanisms - some quite novel - to lower drug prices and facilitate universal coverage of all uniquely effective medications. However, we recognize that cost-effectiveness analyses may be useful and necessary in some circumstance and have amended our manuscript to reflect this (page 8 line 6-7; page 9 line 7).

3. **Noted that finite health budgets require prioritization, and hence cost-effectiveness bodies like NICE in the UK**. See response to point #2 above.

4. **Observed that patents allow drug firms to maximize price and profits, but also stimulate innovation, and commended Finkelstein and Temin's proposal to delink pharmaceutical R&D from marketing and sales efforts.** We propose a different approach to "delinkage" of R&D and production (i.e. direct public funding of pre-clinical and clinical R&D). We have included a citation to Finkelstein and Temin's proposal (page 6, line 13, reference #13), but space constraints preclude addressing this alternative in detail.

5. **Remarked that our promise to provide "complete objective information" about drugs is not obtainable.** The phrase has been revised to read "comprehensive and unbiased information…" (page 7, line 4).

Additional comments

1. **Noted progress in making trial data available from new trials, but persistent problems in the availability of older trials.** We now emphasize the need for greater transparency in both future and past trials (page 14, line 1).

2. **Observed that the lack of user charges for drugs in Wales, Scotland, and Northern Ireland is not the cause of low drug prices in these countries.** We have clarified that these countries use other mechanisms to control drug spending. (page 7, line 20-21).

3. **Urged us to cite Archie Cochrane in connection with our goal of making all needed medication free.** We have done so (page 8, line 2-3).

4. **Wondered how "blue sky thinking" R&D would be funded when prices are more tightly controlled, and again commended Finkelstein and Temin's approach**. As noted above, space constraints preclude detailed discussion of that, or other alternative proposals for pharmaceutical reform. We have added a citation to recent work indicating a disconnect between drug prices and R&D spending (page 8, line 20-22, reference #35), and emphasize the alternative stimuli for innovation - e.g. public funding for drug development - included in our proposal (page 12, line 1-18).

5. **Made a point about the persistence of price discrimination.** We are not clear what the reviewer meant here, but would be happy to address it after further clarification.

6. **Noted that public drug production does not have a track record of success, and that profits are an effective (although perhaps not cost-effective) way to promote pharmaceutical innovation.** As outlined in our manuscript, we envision public drug production as a seldom-used backstop - e.g. if the national health program couldn't negotiate a reasonable price for a generic drug, or in case of a public health emergency. Hence, it would be unlikely to impede drug innovation. Additionally, as noted in the response to #4 above, the manuscript includes a number of provisions aimed at maintaining, and hopefully increasing therapeutic innovation as prices are controlled. We have not added material on this but could do so if you wish.

7. **Cited promising experience with "counter promotion" (or academic detailing).** We have added a brief note (and relevant references) proposing the use of this form of provider education (page 19, line 12-14).

8. **Noted that user fees are a form of a tax on the ill and transform public into private spending.** We fully agree, but have not lengthened our discussion of user fees because of space constraints.

9. **Remarked on the troublesome nature of the pharmaceutical marketplace.** We do not believe that a response from us was called for.

Overview

Commented on the threats to universalism internationally, asked how such a proposal might be implemented in the current political context, and again emphasized cost-effectiveness analysis. As noted in our response to the editors, we have added a brief concluding paragraph on political feasibility. We address the role of cost effectiveness analysis in point 2 of the main comments above.

Professor Warburton:

1. Suggested a ban on industry "detailing", and notes that doing so would produce large savings that could help fund our proposal, and academic detailing in particular. While we would like to see such a ban, U.S. courts would almost certainly rule it unconstitutional. Hence, we've elected not to include it in our proposal. We have, however, noted the deleterious effects of industry detailing (page 18, line 2), and the potential benefits of academic detailing (page 19, line 8-14).

Mr. Nussbaum:

1. **Recommended that we give more emphasis to the strengths of the current pharmaceutical policy model.** We have added material on some positive achievements of the current model (page 6, line 7 and page 10, line 18). However, the purpose of our proposal is to describe how the current pharmaceutical systems of the US and Canada should be fundamentally reformed, so inevitably we focus more on its current weaknesses than its strengths.

2**. Worried that our estimate of U.S. drug spending did not include all drugs (e.g. biological agents covered under Medicare part B), and noted that we propose very modest savings.** He is correct that CMS's National Health Expenditures' (NHE) estimates on pharmaceutical spending include only retail drug expenditures. As noted in our response to the Editors, we have revised the figures in E-Table 5 to reflect non-retail drug expenditures, and detail our approach to their estimation in the notes that follow that table. This change modestly increased our estimate of net savings. While, as the reviewer noted,

these net savings are overall modest in proportion to total drug spending, this is because we envision devoting the vast majority of the savings to assuring universal, comprehensive drug coverage, increased public sector R&D spending, and augmented funding for the FDA.

3. **Argued that our emphasis on patients' problems in affording medications ignored programs (e.g. out-of-pocket maximums in insurance programs and drug rebates) that protect patients.** Unfortunately, clear data indicates the inadequacy of these programs. For instance, as we note in the manuscript, in 2014, 35 million non-elderly adults in the U.S. reported being unable to fill a prescription because of costs (Collins SR, Rasmussen PW, Doty MM, et al. The rise in health care coverage and affordability since health reform took effect: findings from the Commonwealth Fund Biennial Health Insurance Survey, 2014. *Issue Brief (Commonw Fund)* 2015;2:1-16). We have chosen not to add material documenting the failure of the approaches cited by the reviewer, but could certainly do so.

4. **Lauded the FDA Safety Sentinel System as a useful big data approach to drug-safety monitoring.** We now cite this initiative, noting its promise, and also its limitations (page 16, line 22-23).

5. **Noted that market forces can produce drug price reductions, as in the case of drugs to treat hepatitis C.** Unfortunately, extensive experience confirms that reliance on market forces is unlikely to achieve sufficient price reductions, necessitating other cost control mechanisms, such as those we outline. For instance, in the case of hepatitis C regimens, despite the introduction of competitor drugs and a fall in prices, sofosbuvir-based regimens remain extremely expensive (sofosbuvir/velpatasvir: $74,760; ledipasvir/sofosbuvir: $94,500, and sofosbuvir/velpatasvir/voxilaprevir: $74,760). (*The Medical Letter on Drugs and Therapeutics*. October 9, 2017). Because of space constraints we have not amplified our argument on this point.

6. **Felt that our critique of the pharmaceutical industry's track record on R&D failed to adequately acknowledge recent innovative therapies.** As noted, we have added material noting the advances achieved by industry (page 6, line 7 and page 10, line 18), although we maintain that these advances are not commensurate with R&D expenditures (e.g. the resources devoted to the development of “me-too” drugs).

7. **Advocated more use of "real world evidence" in evaluating the efficacy of new drugs.** While we agree that observational studies play an important role in pharmaceutical research, especially in regards to drug safety (page 16, line 19-20), we do not believe that observational studies can replace randomized clinical trials in the assessment of drug efficacy (see: Davis C, Lexchin J, Jefferson T, et al. “Adaptive pathways” to drug authorisation: adapting to industry? *BMJ* 2016;354 doi: 10.1136/bmj.i4437).

8. **Noted that reduced adherence to drug regimens is due to multiple factors, not merely high out-of-pocket costs for drugs.** We now specifically make this point (page 7; line 16-17).

9. **Advised adjustment of the drug spending figures for rebates, as well as the "US contribution to global pharmaceutical company profitability."** The official NHE drug expenditure figures we used do, in fact, account for rebates ("The prescription drug estimates are adjusted to account for manufacturers' rebates that reduce insurers' net payments for drugs"; https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/downloads/dsm-15.pdf). And although we agree with the reviewer that the US contributes to global pharmaceutical profitability, we believe that those profits are excessive, and come at too high a cost, as we describe in the manuscript.

10. **Suggested that we explore the effect of regulating drug prices on medical investment and innovation.** We acknowledge that the reforms we propose could prove a disincentive to private sector R&D (page 12, line 1-2). To offset this, we propose a sharp increase in direct public R&D investment outside of the patent system. Because of space limitations we have not added to our discussion of this issue.

11. **Felt that our critique neglected the "strengths and challenges and the opportunities to reform our current model".** Our manuscript summarizes the host of current problems in the U.S. and Canadian pharmaceutical systems to indicate what led us to propose a quite radical overhaul of those systems. We have added some material on innovations under the current system (as discussed in point 6 above), and reference other, less comprehensive approaches to pharmaceutical policy reform (page 6, line 13). However, given space constraints and the widespread agreement on the need for reform, we have elected not to dwell on the strengths of current policies.

Thanks to you and the reviewers for your thoughtful comments on this paper. We remain open to further revisions at your discretion.

Sincerely,

Adam Gaffney and Joel Lexchin, on behalf of the US/Canadian Pharmaceutical Reform Working Group