Peer Review File

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Reviewer A

The authors describe a protocol for developing a number of different models for evaluating lung cancer interventions in Australia. While the overall idea for a comprehensive approach to lung cancer control is interesting, it is unclear what this study adds to the literature.

Comment 1: As noted, it is unclear what this study adds to the literature. The current protocol seems more suited for a grant application or a report noting the results of a specific project for a funding agency. In contrast, lessons learned from initiating the LEAPp framework would be useful for both modellers and public health experts in other countries. A broader description of the SAG group and how the inputs from the different stakeholders were integrated into the framework would be highly interesting and provide insights into whether the current setup would be feasible in countries other than Australia and how such an approach should be established.

Reply 1:

We thank the reviewer for providing this perspective. As noted, we present a protocol for a comprehensive program of modelled evaluations of lung cancer interventions in Australia. The purpose of our study protocol is aligned with many of the objectives of study protocols more generally, including a reduction in publication bias, distinguishing between hypothesis generating and hypothesis testing lines of enquiry, informing research communities about what research activities are being carried out to prevent unnecessary duplication of work and to encourage collaboration. A more specific aim was to present our unique approach to optimising lung cancer control: no prior body of work has assessed the relative benefits of a variety of interventions across lung cancer development and progression to guide policy decisions.

However, we agree that the protocol included many details of work completed to date and take the point that this may not be suited to a protocol paper. As such, we have revised the manuscript to include a more concise description of prior work and have added more detail on planned evaluations (addressed in Comment 2 and Reply 2). As suggested, we have also added a discussion around 'lessons learned' that other researchers may find useful (p18-19, line 569-588). We have also added more details on how we have engaged with the SAG (p8-9, line 245 - 264):

Changes in the text 1a:

(p8-9, line 245 - 264):

A SAG with representatives from all states and territories of Australia was convened to guide the initial research strategy of LEAPp. Its members were appointed from a wide spectrum of medical and scientific fields across the lung

cancer control continuum, including research academics, clinical specialists, general practitioners, and policy experts, through an invitation to a prioritisation workshop. The group also included public representatives, such as lung cancer survivors and their spokespersons. The objective of the workshop was to prioritise lung cancer interventions and research questions for evaluation. The workshop was structured into sessions covering intervention touch points from primary prevention through to palliative care. Prior to the meeting, issues that were considered in and out of scope were articulated, and extensive scoping reviews were conducted to identify existing and emerging lung cancer interventions including: national and international smoking prevalence policy benchmarks, smoking cessation, screening, early diagnosis, treatments for both NSCLC and SCLC, interventions for side effects and complications of treatment, and psychosocial interventions. SAG members identified lines of enquiry likely to have the greatest impact on lung cancer outcomes in Australia and agreed to ongoing engagement in self-identified areas of interest and expertise. As LEAPp has evolved and intersected with these areas, SAG members have provided expert guidance on research design and outcomes. SAG members have also been invaluable as mentors to post-graduate students and early career researchers, and as partners on funding applications.

The involvement of clinicians, patient representatives, and policy experts ensures relevance of outcomes to the real-world setting. The next step is to capture clinical, policy, and community input to guide parameterisation of the health economic models and to establish prior distributions for Bayesian analyses where existing data are scarce. The SAG will also be key to disseminating findings through their professional networks.

Changes in the text 1b:

(p18-19, line 569-588).

To date, successes of LEAPp have come from the integration of modelling with stakeholder engagement and access to high quality datasets. We had access to a large suite of quality historical and longitudinal data, and comprehensive in-house research expertise (in systematic reviews, epidemiology, statistics, statistical/mathematical modelling, research implementation and policy). The expertise available from other more advanced in-house cancer simulation models has also been highly beneficial. We have also learned that collaboration with national and international experts can provide opportunities for comparative analysis and access to additional data that could be used, for example, for validation of our models. Overall, the process of combining all the components of our program has been organisation-intensive and required a careful strategy balancing the slow process of model building with the more immediate need for research outputs. Modelling and large-scale health data are most powerful when harnessed within a broader framework of lived experience, including patient and clinician perspectives and the constraints and needs of public policy. The SAG and ongoing involvement with advocacy organisations in the not-for-profit sector, such

as Cancer Council and the Lung Foundation Australia, has been integral to identifying community-relevant issues, evidence gaps, and stakeholders. The direct involvement of the SAG in research design, and meaningful engagement with NGOs and community networks leads to more equitable and applicable research; we expect that this will result in research outputs that maximise improvements in lung cancer control in Australia.

<u>Comment 2:</u> The authors refer to various ongoing and planned analyses, but generally little detail is provided. An example of this is the authors' description of the development of a model for lung cancer screening (Policy1-Lung), which is suggested to follow the structure of another model. It is unclear why this model was chosen as a basis, nor how the Policy1-Lung model will be exactly specified. The authors mention that "Policy1-Lung will be calibrated using outputs from our Australian smoking history simulator, national cancer statistics and CanDLe outputs, screening trial data, epidemiologic data on smoking generated by LEAPp, evidence reviews, and other parameters based on SAG input and stakeholder consultation.", but this is quite broad and relatively uninformative. Having some more details on the planned analyses and how the data sources will be exactly used to inform the model(s) would be useful to the reader.

Reply 2:
We thank the reviewer for the suggestion of adding more information about the ongoing and planned analyses and the lung cancer natural history microsimulation model (*Policy1-Lung*). As such, we have revised the manuscript to include a more concise description of prior work (e.g., we removed text related to published work on statistical projections of smoking-related deaths, (p12-13, line 372-381) and have added more detail on planned evaluations (p16, line 482-507). We have also added a more detailed description of the *Policy1- Lung* simulation model (p13-14, line 401-426).

Changes in the text 2:
(p11, line 323-326)
LEAPp initially used a statistical projection approach to estimate the impact of historical smoking trends on future rates of lung and other smoking-related cancers (7, 56-58). Using age-period-cohort modelling that accounted for smoking trends within each period, this work estimated…

(p11, line 334 – 347)
These analyses generated predictions of future tobacco-related cancer rates at an aggregate level and are useful for providing policymakers with rapid insights to enable priority setting. The next step is to develop a dynamic microsimulation model of life-course smoking behaviours for the Australian population (59). This type of model can account for differences in smoking behaviours at an individual level, such as duration and intensity, and can output detailed smoking histories by

age, sex and birth cohort. Similar to the U.S. Smoking History Generator developed by the Cancer Intervention and Surveillance Modeling Network (CISNET) (60,61), our Australian Smoking History Simulator will be used to underpin projections of lung cancer and other smoking-related diseases given changes in smoking initiation, cessation, and/or intensity.

(p13, line 395-426)
It [Policy1-Lung] will simulate individuals' events relating to the 'natural history' of lung cancer including preclinical and clinical lung cancer, and deaths due to lung cancer or other causes (Figure 2). The structure of the pre-clinical 'states' for an individual in *Policy1-Lung* resembles that of MISCAN-Lung (63), which has been utilised by the CISNET Lung working group to investigate the benefits and harms of hundreds of different lung cancer screening strategies (9). The 2-stage clonal expansion carcinogenesis and pre-clinical stage-progression model was chosen because it was most similar to our other in-house models of bowel (10) and cervical cancer (11). The parameterisation of the event rates and the estimation of the parameter-values will be performed by a Bayesian calibration (or evidence synthesis) procedure. This includes SAG and expert input to determine a suite of possible models with distinct parameterisations and prior beliefs about the parameter values; then parameter-values that are most compatible with the data listed above (smoking behaviour, cancer incidence and survival, screening test characteristics and stage outcomes, and all-cause mortality by smoking status) are found using Markov Chain Monte Carlo methods, and finally a model selection process is applied guided by goodness-of-fit statistics. Once calibrated, the model will be validated using independent data sources, such as the PLCO trial data. The model will be used to evaluate the impact of population lung cancer control measures, including the number of lives saved and health system costs, and will initially be used to evaluate lung cancer screening, comparing the effects of participation and screening adherence rates on effectiveness and cost-effectiveness. Ultimately, the model can be tailored to address the interplay between tobacco control, screening, and therapeutic innovation, by assessing the relative benefits of a combination of interventions across lung cancer development and progression.

(p16, line 481-507)
2. Priority analyses and evaluations
A list of priority modelled analyses and evaluations are listed in Table 1. Broadly, these cover epidemiological forecasts for lung cancer patient populations and evaluations of interventions to reduce lung cancer incidence and mortality, as well as other chronic diseases caused by smoking. Epidemiological forecasts of patient or screening-eligible populations will be used to estimate future demand for health resources, particularly systemic therapies and lung cancer screening, and will inform budget impact analyses in health technology assessments. The long-term health and economic benefits of renewed investment in mass media anti-

smoking campaigns will be forecast using the macrosimulation platform, with a potential extension to analyses of restrictions on tobacco retail outlets. Modelling assumptions would be underpinned by data from prior campaigns (e.g., (66–68)) and experiences from other jurisdictions (e.g., (69,70)).

Priority evaluations of the National Lung Cancer Screening Program as recommended by Cancer Australia (34) will include analysis of the impact of participation and screening adherence, and will combine estimates of the eligible population, using the Australian Smoking History Simulator, estimates of the numbers of lung cancers detected from the Policy1-Lung natural history model, and estimates of lung cancer costs and survival from txSim. Resource utilisation data, nodule detection rates, and follow-up procedures, will be obtained from the International Lung Screen Trial (71,72). Other planned program-related evaluations include analyses of potential alterations to the program, such as changes to eligibility, screening intervals, and the incorporation of smoking cessation interventions; driven by data including from the international experience in implementation, expert input, and Policy1-Lung's scenario-modelling capability. The impact of these interventions will be assessed in terms of one or more of; health outcomes, resource use, costs, and cost-effectiveness. Lastly, potential analyses could consider investment strategies for combinations of tobacco control and lung cancer screening interventions, or improvements in the adherence or updates to lung cancer care guidelines (37).

Comment 3: This reviewer has some questions about the integration of some of the different models in the toolkit. For example, the txSim is developed separately from the Policy1-model and the authors note that "Model outputs from txSim can then be applied to lung cancer incidence rates generated from Policy1-Lung to estimate contemporary costs of treatment". Why did the authors choose such an approach, rather than directly integrating the txSim model into the Policy1-model? In particular, the direct integration of treatment into a natural-history model (with or without screening) has shown to powerful, for example in breast cancer screening (Plevritis, JAMA, 2018). It is uncertain whether a simple application to the incidence rates (without fully accounting for the natural-history of the disease) would be similarly effective.

Reply 3: The reviewer questions the approach of separating *Policy1-Lung* and TxSim models and provides an example of model that incorporates treatment into the microsimulation model (Plevritis et al. 2018). While it is within our means to implement the suggested approach, we believe that it would suffice to simply apply cost and survival estimates specific to patient/tumour characteristics known at diagnosis, given that such characteristics will be tied to the pre-clinical natural history of lung cancer (e.g., costs and survival estimates specific to histological, molecular subtype, or smoking history).

Further, there are practical advantages to developing the two models separately.

First, it allows us to easily deploy each to address research questions for which only one model is necessary (e.g., the impact of a new treatment on lung cancer survival). Second, using pre-calculated costs and survival estimates as parameter inputs reduces the computational burden placed on Policy1-Lung.

Reviewer B

This protocol described a promising simulation modeling framework to investigate potential policies, interventions, and their combinations to reduce lung cancer burdens in Australia. I only have minor comments and edit suggestions.

Comment 1: Line 159-160: I am not sure how population prevalence and intensity estimates could serve as input to a microsimulation model, which takes individual smoking histories as input.

Reply 1: Thank you reviewer for the comment - we have added an additional explanation of the Policy1-Lung model into the manuscript that provides information on the role of prevalence and intensity estimates in the model.

Changes in the text 1:

For changes in the text, please see Reviewer A, Changes in the text 2.

Comment 2: Line 382: Please revised "Lung group" to "Lung Working Group."

Reply 2: As suggested by the reviewer, we inserted “working” in the sentence.

Changes in the text 2:

(p13, line 397-401)

The structure of the pre-clinical ‘states’ for an individual in *Policy1-Lung* resembles that of MISCAN-Lung (63), which has been utilised by the CISNET Lung working group to investigate the benefits and harms of hundreds of different lung cancer screening strategies (9).