PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Management of Chlamydia Cases in Australia (MoCCA): protocol for a non-randomised implementation and feasibility trial
AUTHORS	Goller, Jane; Coombe, Jacqueline; Temple-Smith, Meredith; Bittleston, Helen; Sanci, Lena; Guy, Rebecca; Fairley, Christopher; Regan, David; Carvalho, Natalie; Simpson, Julie; Donovan, Basil; Tomnay, Jane; Chen, Marcus; Estcourt, Claudia; Roeske, Lara; Hawkes, David; Saville, Marion; Hocking, Jane

VERSION 1 – REVIEW

REVIEWER	Smith., M. Kumi School of Public Health, University of Minnesota Twin Cities, Div of Epidemiology & Community Health
REVIEW RETURNED	07-Oct-2022

GENERAL COMMENTS	A thorough and well written protocol paper for an exciting study. A few suggested comments for improvement below. Introduction The third and fourth paragraph seem to miss a key opportunity to discuss the public health significance of improving CT care in GP settings. As is currently written, a reader might mistakenly conclude that CT management should be exclusively delivered in STI specialty clinics. A more compelling framing might instead focus on the need for broad scalability of any clinical interventions to achieve population level impact. And that doing so will require improving capacity in GPs since they are presumably more prevalent (and possibly less likely than STI clinics to trigger anticipated stigma in patients?). A related point but lines 33-34 are a little hard to follow. Do the authors mean to say that STI related care must compete with other health needs in general practices? Clarifying this would improve readability. Methods Between the Proctors taxonomy, the Consolidated Framework for Implementation Research, and the Normalization Process Theory, this reviewer is a little confused about how all these framework and models weave together into a coherent approach. Perhaps a summative sentence distinguishing the roles of each? The sample description of “up to 20” is slightly confusing after reviewing the sample size calculations provided. If the authors feel confident that adequate power could be achieved with fewer than 20 clinics, perhaps they could provide an acceptable range? Data Analysis How does the analysis plan for impact outcomes account for the highly customized and variable nature of the intervention (e.g. working with each practice individually for 3-6 months to identify

	appropriate intervention components; choice of adopted intervention components will depend on each practice's interest, priorities and geographical location)? As is written, it appears the intervention will be coded as a binary indicator (pre vs. post-intervention). Will the analysis not makes use of the rich information about the specific components implemented by each practice?

REVIEWER	Martin, Kevin London School of Hygiene & Tropical Medicine, Clinical Research Department
REVIEW RETURNED	11-Nov-2022

GENERAL COMMENTS	The study protocol described by Goller et al. is thoughtful, well-written, and clearly presented. It also has a solid theoretical underpinning, and the intervention has been developed with input from providers and patients. The proposed study aims to optimise delivery of interventions proven to be effective for chlamydia management, in order to close the implementation gap. I suggest a small number of minor comments, mostly related to providing additional information or justification related to study methodology. Introduction Page 5, lines 39-42: "Other Australian data show low PID diagnosis rates in general practice suggesting PID is underdiagnosed in this setting.9" I'm interested in how this comparison was made, and on what data the "expected" PID rates were based i.e. was it based on diagnoses from other services, such as specialist sexual health clinics or hospitals, or modelled based on chlamydia rates in Australia? Consider expanding on this sentence slightly to explain this. Methods Page 11, line 32: "Google analytics – will be collected monthly to ascertain website usage and pages used." Please consider stating a priori how website usage will be defined i.e. by number of website/page visits in total, visits by person, time spent on the website etc Page 12, line 42-44: "We will conduct interviews with up to 40 staff from the 20 general practices to assess our qualitative implementation outcomes." If possible, please provide justification for your choice of conducting up to 40 staff interviews. Page 12, table 3: "Adoption#" It is unclear as to what the "#" is referring to, as there is no corresponding # above or below the table. Page 13, lines 42-43: "Other outcomes will include chlamydia reinfection rates (proportion of those who re-test chlamydia positive) and PID rates (proportion of women aged 15-44 years diagnosed with PID)."

	For PID rates, how will you account for a potentially changing denominator as individuals join or leave the general practice list? Page 13, lines 52 – 54: "Additional costs to implement and maintain the intervention (compared to the usual care pathway) will be estimated using trial protocols and budgets." Although extraction of costs from trial protocols and budgets alone will likely take account of all the financial costs in delivering the intervention, I wonder whether there may be additional economic costs that may not be captured (for example, clinic staff time, additional clinic space that may be required for sorting postal tests, any other subsidised goods), that may need to be collected or supported by data from secondary sources? If focussing on financial costs only, consider stating this.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 Comments to the Author:

A thorough and well written protocol paper for an exciting study. A few suggested comments for improvement below.

Reviewer 1 comment	**Authors response**
Introduction The third and fourth paragraph seem to miss a key opportunity to discuss the public health significance of improving CT care in GP settings. As is currently written, a reader might mistakenly conclude that CT management should be exclusively delivered in STI specialty clinics. A more compelling framing might instead focus on the need for broad scalability of any clinical interventions to achieve population level impact. And that doing so will require improving capacity in GPs since they are presumably more prevalent (and possibly less likely than STI clinics to trigger anticipated stigma in patients?). A related point but lines 33-34 are a little hard to follow. Do the authors mean to say that STI related care must compete with other health needs in	Thank you for these helpful comments. We agree that our introduction would benefit from a stronger focus on the public health significance of strengthening chlamydia care in general practice. On rereading, we also agree that the sentence about competing health needs is a little unclear. The sentence was intended to convey that general practice provides care for a broad range of health issues, rather than solely sexual health care. We have altered paragraphs 3 and 4 to emphasise the public health implications of scale up in general practice and deleted the sentence about competing health needs. The paragraphs are now as follows. "In Australia specialist STI care is provided in sexual health and family planning services. However, these specialist services are at capacity and not widely available outside of

general practices? Clarifying this would improve readability.	metropolitan areas. General practice is Australia's mainstream primary care setting, it is readily accessible and where most chlamydia infections are diagnosed and managed;[13, 14] making it a key setting for optimising chlamydia management. General practice data show that most diagnosed chlamydia infections are followed up for antibiotic treatment.[15] However, high reinfection rates of up to 22%[16] suggest missed opportunities for notifying and treating sexual partners. Australian STI management guidelines recommend retesting for reinfection at around 3 months after treatment.[17] Retesting rates in Australian general practice are low; 24.6% within 4 months of treatment in one study.[18] Where measured PID diagnosis rates in Australian general practice were 42 per 10,000 consultations for women aged 16-33 years compared with 210 per 10,000 consultations for women aged 16-49 years attending a sexual health clinic.[9, 19] Whilst acknowledging the risk for PID is likely to be higher for women attending sexual health clinics, other Australian data show general practitioners (GPs) have expressed hesitancy in conducting pelvic examinations to support a PID diagnosis, potentially reducing their capacity to diagnose PID.[20] Interventions for strengthening chlamydia management (e.g. mailed

	specimen kits, links to partner notification websites in chlamydia test results) have improved retesting and uptake of partner notification discussions in specialist sexual health and family planning clinics.[21, 22] Patient-delivered partner therapy (PDPT), a method of expediting partner treatment, has been shown to be effective at reducing reinfection and acceptable to patients and partners.[23, 24] However, to date, these interventions have not been implemented in Australian general practice. The Management of Chlamydia Cases in Australia (MoCCA) study seeks to address gaps in chlamydia management through implementing interventions that have been found to be effective at improving chlamydia management in specialist sexual health services. In particular, MoCCA focuses on interventions found to improve testing for repeat infection within recommended timeframes, improve partner management, including use of PDPT where appropriate (eg. PDPT is not recommended for patients at high risk of HIV infection such as men who have sex with men), and increasing clinician confidence in diagnosing PID. In this trial, we aim to determine how best to implement the MoCCA interventions to improve chlamydia case management in general practice. We hypothesise that implementation of the MoCCA interventions will be feasible and acceptable. We will also test the exploratory hypotheses that MoCCA will increase chlamydia re-testing among those diagnosed with chlamydia and increase PID detection. Our results will be used to inform subsequent mathematical and economic modelling of the impact of the MoCCA interventions on chlamydia outcomes at a population level and to understand the potential impacts of scale up of the interventions across general practice where many thousands of Australians are diagnosed with chlamydia each year.”

Methods [redacted] Between the Proctors taxonomy, the Consolidated Framework for Implementation Research, and the Normalization Process Theory, this reviewer is a little confused about how all these framework and models weave together into a coherent approach. Perhaps a summative sentence distinguishing the roles of each?	Thank you for seeking clarification. We have provided further explanation in the methods to outline that i) Proctors taxonomy was used to define the implementation outcomes (eg. acceptability, adoption, feasibility), ii) the Consolidated Framework for Implementation Research will be used to assess the contextual elements that influence implementation of our interventions, and iii) Normalisation Process Theory will be used to understand changes in how people think about and use the interventions. The introductory paragraph of the methods now reads: "We will conduct a non-randomised mixed methods implementation and feasibility trial where our primary aim is to implement MoCCA interventions in general practice and measure their uptake by assessing acceptability, adoption, appropriateness, feasibility, fidelity, costs, penetration and sustainability as outlined in Proctors taxonomy of implementation outcomes.[25] As secondary aims, we will explore the impact of the interventions on chlamydia re-testing, re-infection and PID diagnosis in general practice. Our approach is guided by the Consolidated Framework for Implementation Research (CFIR), that provides a framework with five domains; namely i) intervention characteristics, ii) inner setting (eg. culture, communication) iii) outer setting (eg. patient needs, resources), iv) characteristics of individuals (eg. knowledge and beliefs about the intervention), and v) process (eg. planning) to allow us to assess the contextual elements that influence

	implementation. To complement the CFIR, the Normalisation Process Theory (NPT), will help us understand the cognitive and social processes used by staff to establish and embed interventions into routine practice. [26, 26, 27] Together the CFIR and NPT add explanatory strength for understanding interactions between implementation processes and contextual determinants.[26] "
The sample description of "up to 20" is slightly confusing after reviewing the sample size calculations provided. If the authors feel confident that adequate power could be achieved with fewer than 20 clinics, perhaps they could provide an acceptable range?	Thank you for pointing this out. The aim of the study is to recruit 20 general practices and we have altered our wording to reflect this.
Data Analysis How does the analysis plan for impact outcomes account for the highly customized and variable nature of the intervention (e.g. working with each practice individually for 3-6 months to identify appropriate intervention components; choice of adopted intervention components will depend on each practice's interest, priorities and geographical location)? As is written, it appears the intervention will be coded as a binary indicator (pre vs. post-intervention). Will the analysis not makes use of the rich information about the specific components implemented by each practice?	Thank you for this point. As the reviewer has highlighted, there is likely to be heterogeneity between practices and clinicians in the specific intervention components implemented, thereby potentially influencing our impact outcomes. Our primary impact analysis to inform the design of a future large-scale trial will assess the impact of the "overall" MoCCA intervention as implemented which allows general practices to customise the intervention. To investigate the specific components of the MoCCA interventions on impact outcomes, we will perform exploratory analyses of the components of the intervention implemented and their adoption. Our impact analysis now reads as follows: "We will assess our impact outcomes to inform the design of a future large scale trial through quantitative analyses of

	patient attendance, clinical and laboratory data. Retesting rates will be measured as the proportion of those diagnosed with chlamydia who are retested within 2-4 months (3 months + 1 month). Other outcomes will include chlamydia reinfection rates (proportion of those who re-test chlamydia positive) and PID rates (proportion of consultations for women aged 15-44 years with a PID diagnosis). We will assess our impact outcomes by comparing outcomes between the 12 month intervention (operation phase) and 12 month pre-intervention periods. Poisson regression models, with a binary indicator for pre- and post-implementation and adjustment for a priori defined potential confounders, and robust standard errors to account for clustering by clinic, will estimate the impact of the overall MoCCA intervention immediately post implementation (presented as a Rate Ratio (95% Confidence Interval)."

Reviewer: 2 - Comments to the Author:

The study protocol described by Goller et al. is thoughtful, well-written, and clearly presented. It also has a solid theoretical underpinning, and the intervention has been developed with input from providers and patients. The proposed study aims to optimise delivery of interventions proven to be effective for chlamydia management, in order to close the implementation gap. I suggest a small number of minor comments, mostly related to providing additional information or justification related to study methodology.

Reviewer 2 comment	**Authors response**
Introduction Page 5, lines 39-42: "Other Australian data show low PID diagnosis rates in general practice suggesting PID is underdiagnosed in this setting." I'm interested in how this comparison was made, and on what data the "expected" PID rates were based i.e.	Thank you for seeking clarification. There are limited data for PID rates in Australian general practice. However, where measured PID rates in general practice are substantially lower than in sexual health clinics. Whilst acknowledging the different level of risk for PID in these settings we have altered this sentence

was it based on diagnoses from other services, such as specialist sexual health clinics or hospitals, or modelled based on chlamydia rates in Australia? Consider expanding on this sentence slightly to explain this.	to compare PID rates in general practice to PID rates in sexual health clinics to as follows: "Where measured PID diagnosis rates in Australian general practice were 42 per 10,000 consultations for women aged 16-33 years compared with 210 per 10,000 consultations for women aged 16-49 years attending a sexual health clinic. Whilst acknowledging the risk for PID is likely to be higher for women attending sexual health clinics, other Australian data show general practitioners (GPs) have expressed hesitancy in conducting pelvic examinations to support a PID diagnosis, potentially reducing their capacity to diagnose PID."
Methods Page 11, line 32: "Google analytics – will be collected monthly to ascertain website usage and pages used." Please consider stating a priori how website usage will be defined i.e. by number of website/page visits in total, visits by person, time spent on the website etc	Thank you for this suggestion. We have added a sentence defining the website usage data to be included so that our google analytics section reads as follows: *"Google analytics* – will be collected monthly to ascertain website usage. These data will include new and total users per month, pages visited, and time spent on the website."
Page 12, line 42-44: "We will conduct interviews with up to 40 staff from the 20 general practices to assess our qualitative implementation outcomes." If possible, please provide justification for your choice of conducting up to 40 staff interviews.	Thank you for seeking clarification. Our aim is to conduct around 40 interviews, with the aim of interviewing at least one person from each clinic at two time points. This is similar to our earlier research focusing on implementation of complex interventions,

	in which we conducted 24 interviews at one point in the study and reached saturation of themes. However, the number of interviews conducted will take into consideration the current context at the time, such as
	how busy our clinics are, and if they are available for interview, as well as the richness and complexity of the data that we collect. We have altered the manuscript to allow for group interviews in consideration that it may suit some clinics to have multiple staff participate collectively and to reflect that the number of interviews conducted will consider the richness and complexity of data collected, to read as follows: *"Interviews with a think aloud component* – in which general practice staff are asked about their views about the MoCCA interventions, their usefulness, how they are integrated into the workflow and why they are or are not being adopted into practice. We will conduct approximately 40 individual or group interviews across the 20 clinics, seeking to interview at least one person from each clinic at two interview time points (3 and 12 months) during the intervention period. The number of interviews will take into consideration the current context at the time (eg. how busy the clinics are and staff availability for interview), as well as the richness and complexity of the data collected. Concurrent analyses will inform the need for further interviews."
Page 12, table 3: "Adoption#" It is unclear as to what the "#" is referring to, as there is no corresponding # above or below the table.	Apologies, this is a typographical error and we have deleted it.
Page 13, lines 42-43: "Other outcomes will include	Thank you for seeking clarification.

chlamydia reinfection rates (proportion of those who re-test chlamydia positive) and PID rates (proportion of women aged 15-44 years diagnosed with PID)." For PID rates, how will you account for a potentially changing denominator as individuals join or leave the general practice list?	The denominator for PID rates will be all those aged 15 to 44 years who have attended the practice during the trial period for a consultation.
Page 13, lines 52 – 54: "Additional costs to implement and maintain the intervention (compared to the usual care pathway) will be estimated using trial protocols and budgets." Although extraction of costs from trial protocols and budgets alone will likely take account of all the financial costs in delivering the intervention, I wonder whether there may be additional economic costs that may not be captured (for example, clinic staff time, additional clinic space that may be required for sorting postal tests, any other subsidised goods), that may need to be collected or supported by data from secondary sources? If focussing on financial costs only, consider stating this.	Thank you for pointing this out. We do intend to capture economic costs associated with delivering the intervention, and have revised this section as follows: "Additional economic costs to implement and maintain the intervention (compared to the usual care pathway) will be estimated using trial protocols and budgets along with interviews of general practice staff to estimate clinic staff time and other resources required to set up and deliver the intervention. We will adopt a 'health care system' perspective to estimate total costs associated with implementation of the MoCCA interventions and calculate costs for MoCCA's three components (partner notification, re-testing, PID detection) and further break this down into specific interventions (eg. mailed specimen kits). Costs will be grouped by expenditure category such as staffing or

	consumables and then into ‘fixed’ vs ‘variable’ costs, to tease out issues associated with throughput and capacity utilisation. Results will be presented in terms of intervention activities and used to inform subsequent mathematical and economic modelling (protocol to come) of the impact of MoCCA interventions on the population chlamydia burden to guide plans for scale up across Australian general practice.”

VERSION 2 – REVIEW

REVIEWER	Smith., M. Kumi School of Public Health, University of Minnesota Twin Cities, Div of Epidemiology & Community Health
REVIEW RETURNED	30-Nov-2022

GENERAL COMMENTS	Great improvements to the paper. One final suggestion would be the inclusion of some citations on the newly added statement that "STI specialist services are at capacity."

REVIEWER	Martin, Kevin London School of Hygiene & Tropical Medicine, Clinical Research Department
REVIEW RETURNED	23-Nov-2022

GENERAL COMMENTS	I am happy with the authors' responses to my comments.

VERSION 2 – AUTHOR RESPONSE

Thank you to the reviewers for their positive feedback on our revised manuscript for publication in BMJ Open.

In response to our revised manuscript, one reviewer suggested we include some citations relevant to the statement that "STI specialist services are at capacity."

IN paragraph 3 of the introduction we have added two references to the sentences “In Australia specialist STI care is provided in sexual health and family planning services. However, these specialist services are at capacity and not widely available outside of metropolitan areas.[8, 13]”

These references are to the current Australian STI strategy and a review of STI services in the Australian state of Victoria by the Victorian Department of Health.