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|---|---|
| Protocol title | A virtual cohort to measure monkeypox vaccine uptake and efficacy in Australia |
| Short title | TraX: Tracking our communities' responses to the monkeypox (MPX) outbreak. |
| HREC Reference number | HC220592 |
| ClinicalTrials.gov Identifier | N/A |
| Protocol version | 1.2 |
| Protocol date | 19th November 2022 |
| Amendment date | N/A |
| Amendment version | N/A |
| Coordinating institute | Kirby Institute, Faculty of Medicine, UNSW Sydney |
| Funding | New South Wales Ministry of Health<br>Department of Health Victoria |
| Protocol Co-Chairs (Co-PC) | Professor Andrew Grulich<br>Dr Mohamed A. Hammoud |
| Coordinating investigator | Dr Mohamed A. Hammoud |

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# PROTOCOL SYNOPSIS

| | |
|---|---|
| **Title** | A virtual cohort to measure monkeypox vaccine uptake and efficacy in Australia |
| **Short title** | TraX: Tracking our communities' responses to the monkeypox (MPX) outbreak. |
| **Rationale and aim** | In the context of the monkeypox virus (MPX) health emergency, New South Wales Health and the Department of Health Victoria have commenced vaccinating high-risk gay, bisexual, and other and other males or non-binary people who have sex with cis or trans men (GBMSM+) with an unlicensed third generation smallpox vaccination under the Therapeutic Goods Administration (TGA) emergency use authorisation.<br><br>The recommended approach is two doses administered subcutaneously, a minimum of 28 days apart. This approach has equivalent immunogenicity to an older smallpox vaccine, but as it has not previously been used to prevent clinical monkeypox, the degree of clinical efficacy is uncertain. In the context of a global vaccine shortage, and consistent with advice from the Australian Technical Advisory Group on Immunisation (ATAGI), the New South Wales (NSW) and Victorian governments will use a dose sparing approach in some recipients. This will involve administration of a 1/5$^{th}$ reduced dose intra-dermal (ID) administration of MPX vaccines rather than the standard dose administered subcutaneously.<br><br>While one high quality clinical study has demonstrated non-inferior immunogenicity of the ID regimen, the degree to which the dose-reduced regimen will prevent clinical disease is uncertain. This project will investigate MPX vaccine uptake and real-world effectiveness in Australia. |
| **Primary objectives** | 1. Determine the baseline prevalence of past MPX infection and the prospective incidence of MPX over 12 to 18 months of follow-up.<br>2. Determine vaccine effectiveness, adjusted for risk behaviour, measured separately for subcutaneous and intra-dermal routes, and separately for pre-exposure and post-exposure vaccination, and by time since vaccination.<br>3. Measure vaccine uptake and determine predictors of vaccine uptake. |

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| Secondary objectives | 1. Measure predictors and severity of breakthrough infections after vaccination.<br>2. Identify under-vaccinated sub-populations to enable public health response. |
| Inclusion criteria | • Age 18 years or older.<br>• All people (whether cis or trans men, cis or trans women, or non-binary) who<br>• Report sex with cis and trans gay, bisexual, and other males or non-binary people who have sex with cis or trans men (GBMSM+) in the preceding 12 months.<br>• Currently living in Australia. |
| Recruitment | Community-recruited sample through online platforms, community organisations, and sector partners including Health Departments, including at clinics at which vaccination occurs. |
| Number of planned participants | • Sample size for the estimation of monthly incidence of vaccine coverage: 2,000.<br>• Sample size for the estimation of vaccine efficacy over 12 months of follow-up: 14,949 (3,000 initially unvaccinated and 12,000 initially vaccinated). |
| Study design | Entirely online, self-directed, self-report prospective observational study.<br><br>Our study is an entirely online self-report observational study of a vaccine uptake and effectiveness. The study team is not involved in the vaccination intervention which is being implemented by state and territory health departments as part of the response to the MPX public health emergency. |
| Study procedures | This study is an online cohort study and eligibility assessment, consent, and survey completion is entirely self-directed and automated through our data collection system.<br><br>Following consent and enrolment, we will collect data relevant to the research objectives (monkeypox diagnosis and severity, vaccination, risk behaviour) each week for a minimum of 52-weeks and up to 78 weeks depending on date of recruitment. In addition to very brief (< 3 minute) weekly questionnaires, there will be slightly more detailed questionnaires at baseline, 6 and 12 months, and exit survey. Follow-up continues until the last enrolled participant has been followed for 52-weeks. |
| Study duration | Eighteen months, comprising 6 months of open recruitment and a minimum of 52-weeks of follow-up per participant. |

# Schedule of assessment

| Items | Baseline | Weekly | Six-monthly | Optional one-off modules |
|---|---|---|---|---|
| Informed consents | X | | | |
| Optional consent | X | | | |
| Demographics | X | | | |
| MPX vaccination | X | X | X | |
| MPX vaccination tolerability and side effects | | | | X |
| MPX testing | X | X | X | |
| MPX positive diagnosis module | | | | X |
| Experience of MPX diagnosis | | | | X |
| Sexual behaviours | X | X | X | |
| COVID-19 infection history | X | | | |
| HIV and STI testing | X | | X | |
| ARV use | X | | X | |

# Study timeline

| | 2022 | | | | 2023 | | | | | | | | | | | | 2024 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | September | October | November | December | January | February | March | April | May | June | July | August | September | October | November | December | January | February | March | April | May |
| Steering committee | • | • | • | • | | • | | | • | | | • | | | • | | | • | | | • |
| Funding | • | • | | | | | | | | | | | | | | | | | | | |
| Ethics approval | • | | | | | | | | | | | | | | | | | | | | |
| Enrolment | • | • | • | • | • | • | • | | | | | | | | | | | | | | |
| Data collection | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • | | |
| NSW Health reporting | | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • | | |
| Analysis & reporting | | | | | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • | |
| Publications & conference | | | | | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |

# PROTOCOL TEAM

## COORDINATING INSTITUTE


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# PROTOCOL STEERING COMMITTEE

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- Dr Mohamed A. Hammoud

## PROTOCOL STEERING COMMITTEE MEMBERS

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- Professor Raina MacIntyre
- Professor Rebecca Guy
- Professor Gail Matthews
- Dr Nicholas Medland
- Dr Fengyi (Jeff) Jin
- Dr Benjamin Bavinton
- Professor Martin Holt
- Dr Vincent Cornelisse
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- Heath Paynter
- Dr John Rule
- Jane Costello
- Simon Ruth
- Nicolas Parkhill AM
- Richard Keane
- Matthew Vaughan
- James MacGibbon

# ABBREVIATIONS

| | |
|---|---|
| ATAGI | Australian Technical Advisory Group on Immunisation |
| Co-PC | Protocol Co-chairs |
| FDA | Food and Drug Administration |
| GBM | Gay and bisexual men |
| GBMSM | Cis or trans gay, bisexual, and other males or non-binary people who have sex with cis or trans men |
| GMT | Geometric mean titres |
| ID | Intra-dermal |
| LGBTQ+ | Lesbian, gay, bisexual, trans, queer, and other sexuality, gender, and bodily diverse people |
| MVA-BN | Modified vaccinia Ankara manufactured by Bavarian Nordic |
| MPX | Monkeypox |
| NSW | New South Wales |
| PISCF | Participant Information Statement and Consent Form |
| PrEP | Pre-exposure prophylaxis |
| PRSP | Prevention Research Support Program |
| STI | Sexually transmissible infections |
| TGA | Therapeutic Goods Administration |
| TraX | Tracking the community response to monkeypox |
| US | United States |
| WHO | World Health Organization |

# 1 BACKGROUND AND RATIONALE

## 1.1 BACKGROUND

Since early May 2022, more than 40,000 cases of monkeypox virus (MPX) have been identified globally in non-endemic countries.[1,2] On July 23 2022, the World Health Organization Director declared the monkeypox outbreak a Public Health Emergency of International Concern.[3] Cis gay, bisexual, and other men who have sex with men (GBM) account for more than 95% of cases.[4,5] Cases have also been described in trans men and women, mostly due to sexual contact with GBM, and it is anticipated that cases will also emerge in cisgender women who have sex with GBM. Transmission is through close skin-to-skin contact with someone who is MPX-positive. Some evidence suggests MPX can also be spread through large respiratory droplets or contaminated surfaces,[1,2] and the presence of live virus suggests it may also be transmitted in semen.[6] The current outbreak initially occurred in highly sexually active men who attended large Pride events and sex parties in North America and Europe, and observational data overwhelmingly suggest sexual transmission with no airborne transmission and very limited household transmission.[1,7]

Globally, the public health response to MPX has primarily focused on the rapid and targeted rollout of the third-generation smallpox vaccine based on modified vaccinia Ankara manufactured by Bavarian Nordic (MVA-BN, Australian trade name JYNNEOS®) to those most at risk of MPX infection. MVA-BN was licensed for smallpox prevention in the United States and Europe based on the fact that in vaccine-naïve individuals it produces geometric mean titres (GMT) of vaccinia-specific antibody which are non-inferior to those produced by the second-generation smallpox live-virus vaccine ACAM2000. MVA-BN is based on a highly attenuated strain of vaccinia which is replication incompetent in humans, meaning it is safe to be used in immune deficient populations. The vaccine is recommended to be administered as two 0.5 ml doses, administered subcutaneously, separated by at least 28 days. The United States Food and Drug Administration (FDA) also granted a monkeypox prevention indication. This was based on the fact that variola, vaccinia and monkeypox viruses are orthopoxviruses belonging to the poxviridae family and vaccinia-based vaccines induce cross protection for orthopoxviruses, and evidence from non-human primates that MVA-BN protects against lethal monkeypox challenge. Thus, the evidence for protection against clinical monkeypox in human remains somewhat uncertain because clinical studies have not been performed in humans prior to the current epidemic. A study in 1988 estimated 85% protection of first generation smallpox vaccines against monkeypox, but was done at a time when residual immunity from exposure to natural smallpox and from vaccination was high.[8] Forty years after smallpox eradication, we estimate virtually no residual immunity to vaccinia in New South Wales (NSW) and only 10% of the population being ever-vaccinated.[9,10] MVA -BN is not yet registered by the Therapeutic Goods Administration (TGA), but it is being used in Australia under an exemption provided by section 18A of the Therapeutic Goods Act 1989, which ensures that vaccines are available urgently to address public health threats.[11]

With limited doses of MVA-BN available, current estimates suggest that vaccine demand in Australia and elsewhere will far exceed supply, and it is uncertain what proportion of those at risk will be covered by existing supplies. Given the lack of vaccine supply, GBM most at risk of MPX infection have been prioritised.[11]

In the global context of demand exceeding supply, vaccine dose-sparing approaches which may allow more people to be vaccinated have been discussed including two main approaches. The first is giving one dose only, or by substantially delaying the second dose. However, one dose has inferior immunogenicity to two doses, and there are thus concerns it may be less clinically effective. The second approach is administering a one-fifth dose (0.1ml rather than 0.5ml) intradermally rather than subcutaneously, with the standard minimum 28 days spacing. The intra-dermal route has historically been used as a means to enhance the immunogenicity of rabies, inactivated polio and influenza vaccines.[12-15] The only study of the immune response to this regimen for MVA-BN demonstrated that the reduced dose administered intra-dermally resulted in non-inferior immunogenicity to MVA-BN administered subcutaneously. Based on this result, on 9 August 2022, the US FDA issued an emergency use authorisation allowing two doses of the reduced intra-dermal dose.[16] US authorities have commenced use of the reduced-dose intra-dermal regimen, thus allowing five times as many men to be vaccinated with a regimen that has equivalent immunogenicity to the subcutaneous administration of the standard dose. On 26 August 2022, Australia's technical advisory group on immunisation released advice which also allowed intra-dermal administration.[17]

With limited vaccine availability in a public health emergency, and an urgent need to administer doses to as many GBM as possible, current advice on the best dosing strategies is rapidly evolving. In the context of the MPX health emergency, New South Wales Health and the Department of Health Victoria have started using reduced dose intra-dermal administration of MVA-BN to GBM at risk of MPX. While one high quality clinical study has demonstrated non-inferior immunogenicity, the degree to which the two-dose intra-dermal regimen will prevent clinical disease is unknown. The World Health Organization's guidance on monkeypox vaccination recommends that vaccination should occur in a research framework, and that observational approaches to assess vaccine efficacy should be carefully designed to minimise bias.[18]

## 1.2 RATIONALE

Data are required to address two key public health issues:

### 1.2.1 VACCINE COVERAGE

In the setting of insufficient vaccine supply, and a population for which there is no accurate denominator estimate, regular timely measures of the proportion of those at risk who have been vaccinated are required to inform public health action to guide vaccine roll-out.

### 1.2.2 VACCINE EFFICACY

As outlined above, there is no direct clinical evidence that MVA-BN prevents clinical monkeypox in humans. By following a cohort of participants who receive vaccination as part of the public health response over a period of some months, we will be able to examine vaccine efficacy, defined as the incidence of disease among the vaccinated divided by the incidence of the disease in the unvaccinated. By collecting information on the date of vaccination, number of doses received, timing of receipt of vaccine if administered post high-risk exposure, and route of receipt (subcutaneous or intradermal), we will be able to calculate vaccine efficacy by number of doses, time since vaccination, and by route of vaccination. It is likely vaccine uptake will be associated with high-risk behaviour, so it will be critical that we collect regular information on risk behaviour to allow vaccine efficacy estimates that are corrected for risk behaviour. We will also collect data on disease severity in those with MPX to see if cases in the vaccinated are less severe than in the unvaccinated. In this international public health emergency, it is critical that we commence data collection as soon as possible, to allow estimates of disease in the unvaccinated, and to describe the rate of vaccine uptake in those at risk.

# 2 STUDY AIM AND OBJECTIVES

## 2.1 STUDY AIM

This project will investigate MPX vaccine uptake and real-world effectiveness in Australia.

## 2.2 PRIMARY OBJECTIVES

1. Determine the baseline prevalence of past MPX infection and the prospective incidence of MPX over 12 to 18 months of follow-up.
2. Determine vaccine effectiveness, adjusted for risk behaviour, measured separately for subcutaneous and intra-dermal routes, and separately for pre-exposure and post-exposure vaccination, and by time since vaccination.
3. Measure vaccine uptake and determine predictors of vaccine uptake.

## 2.3 SECONDARY OBJECTIVES

4. Measure predictors and severity of breakthrough infections after vaccination.
5. Identify under-vaccinated sub-populations to enable public health response.

# 3 STUDY DESIGN

## 3.1 SUMMARY OF STUDY DESIGN

To address the study objectives, this project will rapidly initiate an entirely online prospective observational study that will systematically survey participants each week for a minimum of 52 and up to 78 weeks to measure the short-term impacts of MPX and to detect trends throughout the MPX epidemic. Enrolment will occur for the first 6 months of the study period. If the epidemic is ongoing after 18 months, further follow-up may be considered. Participants will not be reimbursed for their participation, nor will their participation incur any expenses.

We will systematically follow individual participants each week for up to 18 months (12 months for those participants recruited at the end of month six). The weekly surveys will include questions on MPX testing, vaccination, and diagnosis, while also asking about sexual behaviours, including use of condoms and sexual positioning to determine any associations with the site of MPX infection. Each week, participants who indicate they have had a vaccination or positive diagnosis will answer additional questions, including severity of symptoms and location of infection.

Through the community-recruited sample, we will be able to identify uptake of MPX vaccines by age, sexual risk behaviours, and geographical coordinates (postcode). These data will allow us to identify subpopulations of under-vaccinated communities to inform targeted public health campaigns.

In consenting participants, data linkage will validate self-reported MPX infection and any significant adverse events to MPX infection and vaccination. Consent to data linkage is an optional component to the study.

## 3.2 AUTOMATED COHORT METHODOLOGY

Online, automated methodology enables person-specific study pathways to be executed based on each participant's unique history and real-time responses without researcher involvement.[19] Development of this automated methodology was part-funded by the New South Wales Ministry of Health via the Prevention Research Support Program (PRSP). Leveraging existing infrastructure, this project is uniquely placed to monitor and detect trends in MPX infection and vaccine uptake and facilitates rapid monthly reporting. This proven methodology has been used to describe the rapid uptake of PrEP use following the widespread availability in Australia among a national sample of GBM between 2014 and 2019,[20,21] and more recently has enabled the documentation of the impact the COVID-19 pandemic had on the use of HIV pre-exposure prophylaxis (PrEP).[19,22] Ongoing automated weekly data collection since early 2020 has provided unique data in the short- and long-term impacts of the COVID-19 pandemic on HIV prevention and mental health,[23,24] allowing for rapid monthly reporting to NSW Health of key trends.[25,26]

### 3.2.1 STUDY DESIGN RATIONALE

As part of an ongoing cohort study of the impact of the COVID-19 pandemic among GBM, Co-PC Hammoud developed a world-first cohort-management system to automatically monitor, detect, and report data trends, and compare pre- and post-intervention scores in real-time, allowing for individually customised questionnaires.[24,27]

Our cohort infrastructure enables person-specific study pathways to be executed based on each participant's unique history and real-time responses without researcher involvement, such as automatically disabling redundant questions for participants who previously indicated an infection or vaccination.

## 3.3 NUMBER OF PARTICIPANTS

To address the objectives relating to vaccine coverage, we require a minimum of 2,000 participants. The minimum number of participants needed to address the vaccine efficacy objective is 15,000 (at least 3,000 of whom should initially be unvaccinated) . See section 9 for calculations.

The target population for this study is populations considered at high risk of MPX exposure as defined by the World Health Organization's (WHO) interim guidance on vaccines and immunisation for monkeypox.[18] For the purpose of this study, this includes:

- All people (whether cis or trans men, cis or trans women, or non-binary) who
- Report sex with cis and trans gay, bisexual, and other males or non-binary people who have sex with cis or trans men (GBMSM+) in the preceding 12 months.

# 4 ENROLMENT OF PARTICIPANTS

## 4.1 ELIGIBILITY CRITERIA

Eligibility for this study has been adapted from the WHO interim guidance on vaccines and immunisation for monkeypox.[18]

### 4.1.1 INCLUSION CRITERIA

All inclusion criteria must be met to participate in the study.

- Age 18 years or older.
- All people (whether cis or trans men, cis or trans women, or non-binary) who
- Report sex with cis and trans gay, bisexual, and other males or non-binary people who have sex with cis or trans men (GBMSM+) in the preceding 12 months.
- Currently living in Australia.

## 4.2 STUDY PROMOTION

This study will enrol a community-recruited sample. We will use a wide range of digital platforms to reach a diverse sample of participants across Australia, including gay and bisexual geolocation dating apps such as Grindr™ and Scruff™, and social media sites such as Facebook™, Instagram™, and Twitter™. Social media advertisements will target participants living in Australia and whose profile activity reflects aspects of GBMSM+ identity.

Our community partner organisations will also promote the study through their dedicated social media networks and email newsletters. Advertisements and news stories may also be published on other websites with relevance to the target populations (e.g., websites of community partners and other GBMSM+, HIV, and trans and gender diverse organisations).

Participants of previous studies conducted in Australia and expressed interest to participate may also be invited to take part in this study.

Study information will also be distributed in NSW and Victorian sexual health clinics and MPX vaccination centres. Participants who attend clinics for NSW Health funded MPX vaccination will be offered participation at the site of vaccination. Each clinic will be provided with advertising material containing a unique QR code to allow us to determine where each participant was recruited. Local Health Districts will not be actively engaged in recruitment nor the consent process, and therefore we do not anticipate the need for site-specific approval. Regardless, we will submit an application for site-specific approval should it be required for the distribution to clinics of promotional material.

All recruitment advertisements will direct respondents to the study web page, which provides:

- The participant information sheet (available to read from the study website or download a PDF copy).
- A detailed description of the study aims.
- Requirements for participation.
- The time required for survey completion.
- Information about ethical approval.
- Study contact information.

Once the participant clicks on the "Enrol Now" button on the study website, they will be redirected to the online consent form where they will be screened for eligibility prior to providing consent. In a previous online cohort study, we successfully recruited 3,500 GBM through this method (HC14075 and HC200286).

Recruitment will commence until UNSW HREC and ACON provide approval.

## 4.3 ENROLMENT PROCESS

Enrolment, eligibility assessment, and consent is self-directed. Participants will be required to confirm their understanding of all study requirements, their willingness to participate in weekly surveys, and to provide an email address to receive weekly reminders to complete their survey. The database will automatically generate a deidentified participant ID and individualised link will remove the need for direct researcher contact. Participants can withdraw their consent from the study at any time via an automated link that will be included in all email communications.

## 4.4 PREVENTING DUPLICATED REGISTRATION

Participants' email addresses and mobile phone numbers collected at consent will act as a secondary ID code to prevent duplication of enrolment. The secondary ID is not available for access by any research staff. Rather, it automatically checks for duplications in the database, disabling people from registering with the same details. People, however, can register more than once using different email addresses and mobile numbers. As we have reduced the number of identifying information collected and will not be collecting system identifiers such as IP address, geolocation, or geographic coordinate, there is little control in preventing duplicated registrations using different details beyond what we have proposed. Since there is no monetary gain from participating in the study other than from automatically entering a weekly raffle, we anticipate no concern for duplicated registration. We base this assumption on our experience executing multiple studies using the same method across different populations,[28] research questions,[29-31] and internationally.[32]

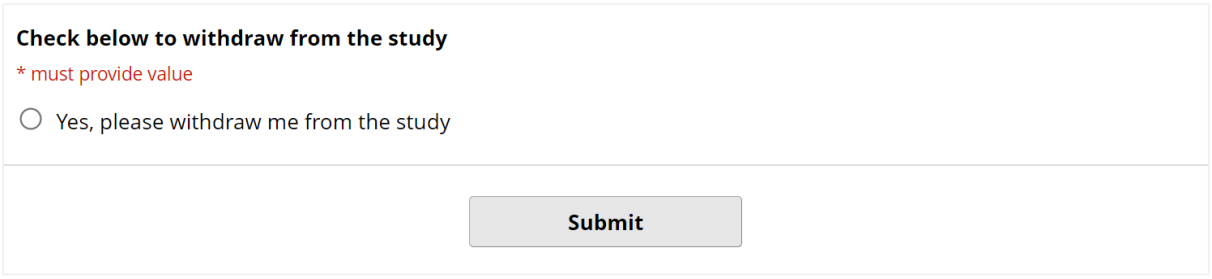
## 4.5 PARTICIPANT WITHDRAWAL

Participants will have the option to withdraw their consent at any point throughout the study. Details on how to withdraw from the study will be provided at the time of consent,

outlining a simple procedure and multiple means of withdrawal. Participants have two options to withdraw their consent:

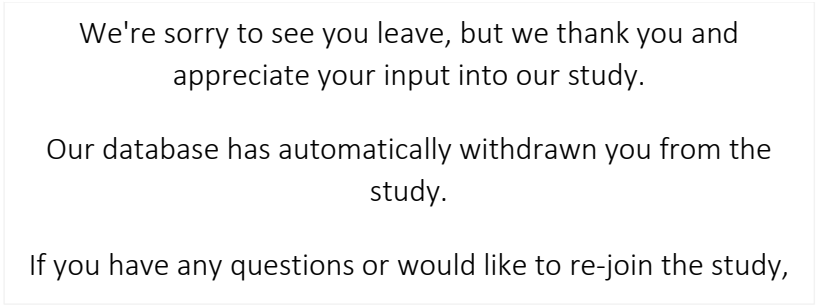
1. Participants can contact the study team on the email provided in the consent form, or by replying to any email notification received requesting their consent be removed from the study.
2. All email notifications sent to the participant will include a link to withdraw their consent. Each link contains the participant's unique, deidentified study identification number. By clicking this link, participants will be automatically redirected to a 'Withdraw consent from study' page and the database will automatically bring up the withdrawal page associated with their record (Figure 1).

*FIGURE 1. AUTOMATED WITHDRAW CONSENT*




Participants simply click on their link and click Submit. A confirmation of withdrawal will be displayed to the participants.

*FIGURE 1. AUTOMATED CONFIRMATION OF WITHDRAWAL*




Once submitted, all scheduled notifications are deleted, and all future communications are disabled. Error proofing programming prevents the withdrawn participants from receiving any future study notifications, including future extension, newsletters, and overrides their consent to be contacted for future research.

## 4.6 INCENTIVES TO PARTICIPATE

Participants will not be reimbursed for their participation, nor will their participation incur any expenses. To facilitate retention, participants can opt-in at the consent stage to be

eligible for weekly raffle prizes commencing at their second week of participation. Participants who complete their weekly questionnaire within 48 hours of initial invitation will enter a raffle to win one of four weekly prizes in the form of $50.00 electronic gift cards. Winners will be randomly selected each week by STATA. Winners will be notified each Thursday by automatically sending a link for their gift cards to their nominated email or mobile number.

## 4.7 COMMUNICATION PLAN

### 4.7.1 ADVERTISING

Online advertisements will consist of short messages that briefly describe the purpose of the study. Participation will be voluntary. To minimise potential biases and analyses, promotional material will contain a unique QR code to allow us to identify participants who heard about the study while receiving a vaccination at a NSW and Victorian sexual health clinic or other vaccination centre.

All recruitment advertisements will direct respondents to the study web page, which provides:

- The participant information sheet (available to read from the study website or download a PDF copy).
- A detailed description of the study aims.
- Requirements for participation.
- The time required for survey completion.
- Information about ethical approval.
- Study contact information.

Once the participant clicks on the "Enrol Now" button on the study website, they will be redirected to the online consent form where they will be screened for eligibility prior to providing consent.

# 5 STUDY ENDPOINTS

## 5.1 PRIMARY ENDPOINTS

1. Incidence of MPX among study participants, adjudged for risk behaviour.
2. Vaccine effectiveness, adjusted for risk behaviour, measured separately for subcutaneous and intra-dermal routes, and separately for pre-exposure and post-exposure vaccination.
3. Vaccine uptake and factors predictors of vaccine uptake.

## 5.2 SECONDARY ENDPOINTS

4. Incidence and predictors and severity of breakthrough infections after vaccination.
5. Identify factors of under-vaccinated sub-populations to enable public health response.

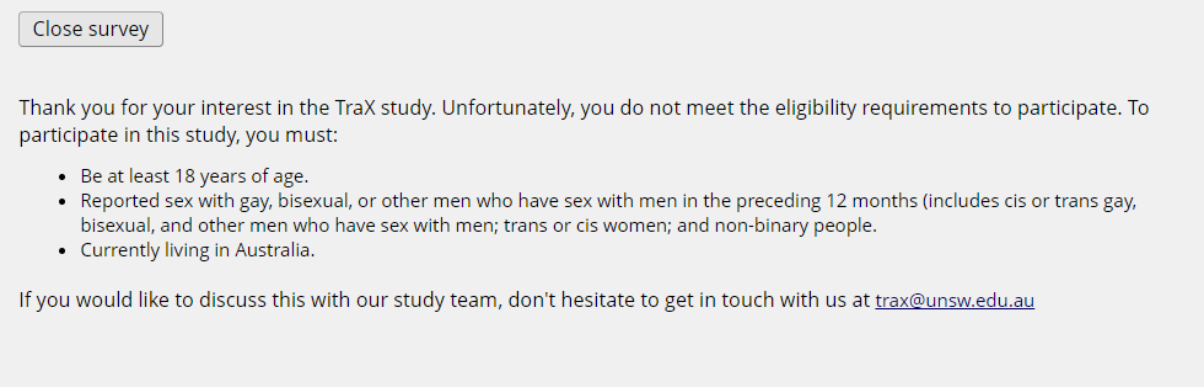
# 6 STUDY ASSESSMENTS AND FOLLOW-UP PROCEDURES

## 6.1 AUTOMATICALLY ASSESSING ELIGIBILITY

After reading the participant information sheet and when the participants click on the "Enrol Now" button, they will be redirected to the online consent form hosted on UNSW Sydney's REDCap database. Prior to assessing eligibility, participants will be asked to confirm they have read and understood the participant information sheet, understood the requirements of the study, and provide consent to proceed to assessing their eligibility.

Eligibility will be verified automatically through REDCap without the involvement of the research team to further protect participant confidentiality.[33] If participants are not eligible, they will not be able to register into the study nor provide any identifying information. Those considered ineligible will be automatically provided an explanation as to why they do not meet the study criteria and provided contact details for the study should they wish to discuss further. Reason(s) for ineligibility will automatically be displayed on the criteria the participant does not meet. See Figure 2 for an example of a participant not meeting the criteria.

*FIGURE 2. NOTIFICATION OF INELIGIBILITY TO PARTICIPATE IN STUDY.*




Participants who meet the eligibility requirements will proceed to providing consent.

## 6.2 INFORMED CONSENT PROCESS

Consent will be sought from all participants. Participants who meet the eligibility requirements will be progressed to an e-Consent form embedded within REDCap. Participants will consent on enrolment to complete weekly surveys. They will not be required to reconsent at every data-collection round. Identifying information, such as given name and date of birth is not a requirement to participate in the study. This online consent process is appropriate for our data collection method and participant group as this is an entirely online cohort study. Participants are required to provide an email address and have the option to provide a mobile number to allow text message notifications. On completion, participants will receive a locked PDF copy of their consent form via their nominated email account.

All recruitment advertisements will be directed to the study website which provides a detailed description of the study aims, inclusion criteria, requirements for participation, information about ethical approval, and study contact information. Participants will be provided with the Participant Information Statement and Consent Form (PISCF) through the study webpage and have the option to download a PDF. Participants will be asked to read the PISCF before consenting and to contact the researcher(s) if they have any questions.

### 6.2.1 VERIFYING ENROLMENT

We will implement a verification process following participants decision to consent in the research to check and authenticate email addresses and mobile numbers. A verification process ensures the details entered are from an authentic participant and that we have connected to the email address and mobile number owners.

Upon completing their consent, participants will receive an email or text message asking them to click a link to verify their registration. By clicking the link, their registration is verified, and the automatic study process for this participant is activated. If the link is not clicked, they will receive one reminder. Failure to verify their registration following the reminder will automatically terminate their record, and all data will be permanently deleted.

## 6.3 OPTIONAL CONSENTS

Participants will be invited to provide optional consents for additional aspects of the study.

### 6.3.1 DATA LINKAGE

We will seek consent to link data with commonwealth and state agency health and disease-related registries and databases and obtain state-based Population and Health Services Research Ethics Committee approval to conduct data linkage. Such registries include the Australian Immunisation Register, MPX, HIV, and sexually transmissible infections (STI) registries. This information will allow calculating the rates of MPX, HIV and STI diagnoses in the study. Further approval via a modification request will be sought prior to commencing data linkage. We will collect additional identifying information needed for data linkage from participants who provide consent. These identifiers include full name, date of birth, postcode of residence, and Medicare number (if available).

### 6.3.2 CONSENT TO BE CONTACTED TO PARTICIPATE IN FUTURE STUDIES

Participants can also provide consent to be contacted to participate in embedded studies. These studies may include providing biological samples and clinical data at or around the time of vaccination and MPX diagnosis, will each be the subject of separate ethics approvals. , and will run in parallel to this project. This approach will enable us to target, assess eligibility automatically, and invite participants into new clinical studies being administered by the Kirby Institute.

## 6.4 BASELINE

Newly enrolled participants will complete a brief baseline questionnaire after completing their first weekly response (approx. 10-15 minutes to complete). The baseline survey will collect demographic characteristics, HIV status, MPX awareness and vaccine history. Baseline items will also include a brief measure of attitudes towards vaccines, as this will be an important indicator determining the likelihood of refusing a vaccination.

## 6.5 WEEKLY QUESTIONNAIRE

The weekly questionnaire will take approximately 1 minute to complete depending on individual responses to items on sexual behaviour. Weekly questionnaire items include MPX testing, vaccination, diagnosis, and sexual behaviours.[2,6,34-36]

### 6.5.1 WEEKLY DIARY INVITATIONS

Participants will be sent an email or text message notification containing an individual, deidentified URL link to their weekly questionnaire every Monday at 5:00 am and are asked to complete their entry within 48 hours. All participants who did not complete their entry within 24 hours will be automatically sent one reminder on the following Tuesday at 5:00 am. Participants who provide their mobile number will receive one final text message reminder on Tuesdays at 11 am.

## 6.6 BIANNUAL ITEMS

Items relevant to MPX but not needing to be captured as frequently will be asked at baseline, then every six months. These items include questions on STI testing and diagnoses, HIV testing among non-HIV positive GBM, use of antiretrovirals as HIV treatment or prevention, and viral load among HIV positive GBM.

## 6.7 MPX- DIAGNOSIS

If a participant indicates a new positive MPX diagnosis in a weekly questionnaire, a disease severity and experience module will be enabled. Items included in this module were developed using data from the United States Centre for Disease Control and Prevention and the World Health Organization Global Clinical Data Platform Monkeypox Case Report Form.[37,38] These items include information on symptoms, severity of infection, and type of vaccination. This will be enabled in the week of diagnosis, and then weekly for 4 more weeks to cover the disease period.

# 7 RISK TO PARTICIPANTS

It is possible that some participants may experience some anxiety by providing answers about sensitive, personal information, including HIV status and history of other sexually transmitted infections (STI), sexual partners and behaviours, and health-seeking behaviours. Given the association between the current MPX outbreak and GBM, some participants may also be acutely aware of the potential for stigma associated with MPX.

To mitigate against these potential risks, participants will be informed that they have the option of stopping or withdrawing from the study at any point, including partway through completing a survey. In the event that the survey raises any issues for participants, we will provide support contact through the study website and at the end of the survey, including directing participants to lesbian, gay, bisexual, trans, queer and other sexuality, gender, and bodily diverse people (LGBTQ+) specific counselling and support services. Any social harms from participating in this study will be avoided through maintaining confidentiality and distance from both the researchers and our partner organisations.

Based on the research teams extensive experience (sometimes decades) of research in GBMSM+ sexual health, including HIV, we believe participation in this study may also include benefits to participants. Through our longstanding partnerships with LGBTQ+ health organisations, the study team is aware that MPX is a significant health concern among GBMSM+. GBMSM+ in Australia are generally familiar with sexual health research and often willingly volunteer and appreciate contributing to research that might directly benefit their health. Moreover, participants will be able to access information and health resources about MPX provided through our study webpage and at the end of the survey.

# 8 PRIVACY AND CONFIDENTIALITY

## 8.1 CONFIDENTIALITY OF PARTICIPANT RECORDS

All information provided by study participants will be maintained in confidence and divulged only as necessary to the ethics committee and institution employees directly involved in the study. Both ethics committee members and employees must also understand the confidentiality requirements for any information divulged to them. The data generated by this study will be considered confidential.

Confidentiality of all data is strictly maintained at all times and in accordance with UNSW Sydney policy. Study data are collected and managed using REDCap, a UNSW Sydney approved data capture platform hosted at the University of New South Wales. At enrolment, participants are required to provide consent to be contacted via an email and optional text message invitation to participate in the online surveys developed using REDCap software. The email address will be entered directly into the e-Consent capture via a secure online enrolment form in REDCap. The secure e-Consent form will store the preferred email address so that the questionnaire system can send participant invitations to complete the questionnaires and send automatic reminders if the participant does not complete a questionnaire within the scheduled timeframe. All identifying information is stored separately from participants' completed questionnaires. Access to any data or identifying information will be protected by secure barriers at each level of access.

Participants are given a unique study identifier which is used to link all data sources. The questionnaires will be electronically coded and stored in a secure REDCap database. Questionnaires will not contain individuals' identifying details. Access to any data or identifying information will be protected by secure barriers at each level of access. The data will only be accessible to the research team directly involved with managing the questionnaires or analysing the data. A password and individualised access name is required to access the database, and an administrator from that site must also have set specific permissions to enable this access. All computers involved with the research are password protected, and access to those computers is restricted to those with a key to locked offices and an electronic security pass that allows access to the building.

Any identifying information that is collected to enable participants to be contacted for follow up is stored on a separate database from the survey, under equally secure conditions (including computer security, password restrictions, physical and site security measures, and access limited only to the research staff). Record matching can only occur through the numerically coded, unique study identifier available only to the investigating researchers. Further steps to safeguard the confidentiality of individual participants are taken at the publication stage by using group data where possible and by changing identifying details where necessary.

## 8.2 DATA SECURITY

REDCap is a secure, web-based software platform designed to support data capture for research studies, providing:

1. An intuitive interface for validated data capture
2. Audit trails for tracking data manipulation and export procedures
3. Automated export procedures for seamless data downloads to common statistical packages.
4. Procedures for data integration and interoperability with external sources.

REDCap has detailed policies on data privacy, backup/redundancy, and disaster recovery. It is compliant and certified under both the EU-U.S. Privacy Shield and Swiss-US Privacy Shield. At regular intervals, these data will be downloaded from REDCap to a secure computer at the Kirby Institute, UNSW Sydney. All electronic databases will be protected by password and UNSW Sydney firewalls. Only designated researchers will have access to databases downloaded from REDCap.

## 8.3 RECORD RETENTION

The study team will retain all study documents, including essential documents and participant files, for at least 7 years after the completion of the study.

# 9 ANALYSIS AND STATISTICAL CONSIDERATIONS

## 9.1 SAMPLE SIZE

### 9.1.1 VACCINE COVERAGE

Based on a total sample size of unvaccinated men and an expected monthly incidence of vaccination of 5%, following 2000 initially unvaccinated men will give us 80% statistical power to detect a vaccination incidence between 4.1% and 6.0% per month.

Sample size for the estimation of monthly incidence of vaccine coverage, assuming 2,000 or 4,000 initially unvaccinated men are recruited (80% statistical power, 2-sided alpha of 0.05).

| Sample size | True monthly incidence of vaccination in the community | Sample size |
|---|---|---|
| Assuming 2,000 initially unvaccinated men recruited | | |
| 2,000 | 1% | 0.6 – 1.5 |
| 2,000 | 5% | 4.1 – 6.0 |
| 2,000 | 10% | 8.7 – 11.4 |
| Assuming 4,000 initially unvaccinated men recruited | | |
| 4,000 | 1% | 0.7 – 1.4 |
| 4,000 | 5% | 4.3 – 5.7 |
| 4,000 | 10% | 9.1 – 11.0 |

### 9.1.2 VACCINE EFFICACY

Power calculations for vaccine efficacy require an unvaccinated comparison arm. These calculations are made more complex by the fact that most men who are unvaccinated at baseline will become vaccinated as roll-out continues. The pace of this is uncertain, however in the calculations below, we assume that 80% of initially unvaccinated men will become vaccinated over the 12 months.

Sample size calculation for the estimation of vaccine efficacy over 12 months of follow-up. These calculations are for 80% statistical power, 2-sided alpha of 0.05, and assume that 80% of men who are initially unvaccinated become vaccinated by the end of the 12-month follow-up.

| Vaccine efficacy | MPX incidence | Percentage initially unvaccinated | Total number | Total Sample required | Sample size initially unvaccinated | Sample size |
|---|---|---|---|---|---|---|

| | in the unvaccinated | | of events required | | | initially vaccinated |
|---|---|---|---|---|---|---|
| 60% | 1% | 20% | 117 | 25304 | 5161 | 20244 |
| | | 30% | 101 | 20527 | 6159 | 14369 |
| | | 40% | 100 | 19053 | 7622 | 11432 |
| | 3% | 20% | 117 | 8404 | 1681 | 6724 |
| | | 30% | 101 | 6816 | 2045 | 4772 |
| | | 40% | 100 | 6324 | 2530 | 3795 |
| 70% | 1% | 20% | 56 | 14949 | 2990 | 11960 |
| | | 30% | 51 | 12459 | 3738 | 8722 |
| | | 40% | 53 | 11838 | 4736 | 7103 |
| | 3% | 20% | 56 | 4965 | 993 | 3972 |
| | | 30% | 51 | 4137 | 1242 | 2896 |
| | | 40% | 53 | 3929 | 1576 | 2364 |
| 80% | 1% | 20% | 25 | 8656 | 1732 | 6925 |
| | | 30% | 25 | 7531 | 2260 | 5272 |
| | | 40% | 27 | 7409 | 2964 | 4446 |
| | 3% | 20% | 25 | 2874 | 575 | 2300 |
| | | 30% | 25 | 2500 | 750 | 1750 |
| | | 40% | 27 | 2458 | 984 | 1475 |

Based on the above table, if we assume an MPX incidence in the unvaccinated of 1 per 100 person-years, 20% of participants in the initially unvaccinated arm and 80% of those initially unvaccinated becoming vaccinated by the end of 12-months of follow-up, a total of 14,949 GBM+ followed up for 12- month is required to give us 80% statistical power to detect a vaccine efficacy of 70% in reducing MPX incidence in the vaccinated arm.

As outlined above, this central estimate is that we will require a minimum of about 15,000 participants, about 3000 of whom will be initially unvaccinated and 12000 initially vaccinated.

### 9.1.3 VACCINE EFFICACY

## 9.2 OUTCOME MEASURES

The main outcome measures will be:

### 9.2.1 PRIMARY OUTCOME MEASURES

1. MPX Incidence per 100 person years of MPX
2. Vaccine effectiveness, adjusted for risk behaviour, measured separately for subcutaneous and intra-dermal routes, and separately for pre-exposure and post-exposure vaccination.
3. Vaccination Incidence per 100 person years, and predictors of vaccine uptake.

### 9.2.2 SECONDARY OUTCOME MEASURES

4. Incidence per 100 person years in breakthrough infections after vaccination. Severity of disease in breakthrough cases.
5. Identify under-vaccinated sub-populations to enable public health response.

## 9.3 STATISTICAL ANALYSES

The analyses will be described in detail in a full Statistical Analysis Plan. Analyses will be conducted using appropriate longitudinal regression models with time-varying exposures. Data analysis will be conducted by a research officer at the Kirby Institute, under the leadership of the Principal and Investigator and Co-Investigators, using STATA (StataCorp, College Station, TX, USA). The research team has extensive expertise in the analyses of longitudinal data.

### 9.3.1 VACCINE UPTAKE

- Incidence will be stratified by key demographic and risk-related predictors of vaccination.

### 9.3.2 VACCINE EFFICACY

- Disease incidence: Number of events observed (new MPXV infections) divided by total person years followed, presented as cases per 100 person-years.
- Vaccine efficacy: (incidence in unvaccinated – incidence in vaccinated, divided by incidence unvaccinated)
- Multivariate: controlled for behaviour using Cox regression.

# 10 DISSEMINATION

Similar to the monthly reports provided to NSW Health for the COVID-19 pandemic,[25,26] we will provide monthly reports summarising key trends in MPX infection and vaccination. This will include MPX vaccination rates stratified by key demographic and behavioural predictors, and MPX incidence rates. Additionally, results will also be disseminated through published reports, journal articles, conference presentations, local workshops, community newspaper/magazine articles, and consultations to professional organisations. The data will also be presented in other media formats if these become available.

Results will be disseminated through published reports, journal articles, conference presentations, local workshops, community newspaper/magazine articles, and consultations to professional organisations. The data will also be presented in other media formats if these become available. In whatever format these data are presented, confidentiality will always be protected as outlined.

Findings will be made available to participants in the same manner as outlined above. Participants are provided this information and how they can access reports of findings on the information sheet. Reports of findings will also be publicised on the Kirby Institute website.

Working in collaboration with national peak body organisations, our results will be disseminated through community public heath campaigns to reach a wider audience. Subject to funding support from government health agencies, this study will produce monthly reports summarising key trends in MPX infection and vaccination. This will include MPX vaccination rates stratified by key demographic and behavioural predictors to inform government health agencies' response to the pandemic.

# 11 PUBLICATION POLICY

Authorship of publications arising from this study must conform to the standards of the meeting or journal where the research findings will be reported.

All investigators named on the study protocol will be invited to be an author on each paper, as will any other investigators/individuals that make a substantial contribution. The invited investigators/individuals are free to make their own decisions whether to become authors on any paper arising from the study. However, as recommended in the authorship considerations proposed by the International Committee of Medical Journal Editors, those who make a written statement that they meet each of the following conditions will be included as a co-author:

1. Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; and
2. Drafting the article or revising it critically for important intellectual content; and
3. Final approval of the version to be published.

All prospective authors of all publications will be notified of publication plans in sufficient time to participate fully in authorship or otherwise to have input into the content and review of the manuscript.

Authorship order will depend on the relative contribution of the individual authors. Procedures for deciding order of authorship should be developed by consensus of the authors at the earliest appropriate time in the development of the manuscript or presentation. In general, the first named author will be the individual who writes the manuscript/presentation. In general, the senior (last) author will be a senior investigator who has expertise in the subject matter of the manuscript/presentation, and who has closely supervised the writing of the manuscript/presentation.

Acquisition of funding, collection of data or general supervision of the research group alone does not constitute authorship.

If the number of people meeting the journals or meeting's criteria for authorship is greater than the journal or meeting standards allow, a collective authorship designation may be used if allowed by the journal or meeting. The specific designation will be decided by consensus of the authors and study investigators. If a collective authorship is used, the persons responsible for the publication or presentation (i.e. those who otherwise would have been individually named as authors) will be specified in a manner agreed to by the journal or meeting.

At an appropriate place in the publication or presentation, as consistent with the standards of the journal or meeting, one or more statements should specify:

1. Acknowledgment of contributions that do not justify authorship, including technical help and financial or material support; and
2. Financial relationships that may constitute a perceived conflict of interest.

Each person acknowledged by name should give permission in writing or by email to be acknowledged. Exceptions may be made if the person is deceased or cannot be contacted.

This policy applies regardless of the organisation or institution of the investigator responsible for drafting the publication or presentation.

This policy also encompasses the publication and presentation of data from sub-studies.

# 12 ETHICS COMMITTEE

The Principal Investigators are responsible for obtaining ethical approval for the protocol and participant information and informed consent forms in compliance with local regulatory requirements prior to entering any participant into the study. The approval letter/document must clearly identify the protocol and all documents approved by the ethics committee including version number and date of the protocol and participant information and consent form.

We will seek approval from the UNSW Human Research Ethics Committee. This study will be conducted in accordance with the ethical principles laid out in the UNSW Human Research Ethics Committee guidelines and the National Statement on Ethical Conduct in Research Involving Humans.

The research proposal will also be reviewed concurrently with the ACON Research Ethics and Review Committee and Throne Harbour Health Community Research Endorsement Panel to reviews the appropriateness of language, indicators and survey questions, the potential benefits and risks to participants.

Prior to data linkage, we will also seek approval from the NSW Population and Health Services Research Ethics Committee for the ethical review of our proposed NSW-based data linkage. For national data linkage (eg with the Australian immunization register) and for data linkage in other jurisdictions, other health ethics permissions will be obtained.

# 13 LEGAL ISSUES

The study investigators will consult throughout the study with the UNSW Sydney legal teams when necessary to address any arising legal issues related to the study implementation and will deal with such issues in an appropriate and timely manner, in accordance with the local and regulatory requirements.

# 14 STUDY OVERSIGHT AND MANAGEMENT COMMITTEES

## 14.1 STUDY MANAGEMENT TEAM

The study management team is responsible for ongoing study management, coordination and implementation. It includes the study investigators and personnel based at the Kirby Institute, Faculty of Medicine, UNSW Sydney, and will meet frequently (at least monthly).

## 14.2 PROTOCOL STEERING COMMITTEE

The Protocol Steering Committee is responsible for prioritising research topics, developing protocols, facilitating and monitoring the conduct of the research, and reporting study results in a timely manner. The Protocol Steering Committee will conduct its business through periodic meetings (at least annually). The Protocol Steering Committee includes all named investigators, plus associate investigators, including representatives of key community organisations. Governance

This research protocol is funded by the Kirby Institute, UNSW Sydney and the NSW Health department. The study is coordinated through the Kirby Institute, UNSW Sydney. The Kirby Institute has established governance and implementation structures which use resources efficiently to deliver program objectives on schedule.

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