Safety monitoring of molnupiravir for treatment of mild to moderate COVID-19 infection in low and middle-income countries using cohort event monitoring: a WHO study

11 March 2022

Use of this protocol

This is a master protocol, which was approved by the WHO Ethics Review Committee (ERC) on 09.03.2022 (protocol ID; CERC.0155. It will be used by study sites who will submit a protocol to their national ERC. The only country-specific changes that should be made will be those to facilitate translation into the local language, address the specific concerns of the local ERC, and to add the names of the national principal investigators (PIs), members of the local study teams and the identity of the study sites. Amended site-specific protocols developed for implementation in countries based on this WHO master protocol must be approved by the WHO ERC prior to implementation.

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This protocol was adapted from the WHO protocol template: Protocol template to be used as template for observational study protocols for cohort event monitoring (CEM) for safety signal detection after vaccination with COVID-19 vaccines and WHO master protocol: Oxygen requirements and approaches to respiratory support in patients with COVID-19 in Low- and middle-income countries: a WHO study. The main differences between this protocol and that for the CEM protocol for safety signal detection after vaccination with COVID-19 vaccines are that this protocol provides the option of: pooling data to obtain the appropriate sample size; obtaining data on drug interactions, compliance, maternal and perinatal outcomes; and collecting information on lack of effect.

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Study Sponsor

WHO will sponsor at least six countries to implement this protocol. If Member States that are not sponsored by WHO wish to adapt and implement the master protocol, sources of funding need to be identified for the site-specific protocols.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
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<tr>
<td>CEM</td>
<td>Cohort event monitoring</td>
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<tr>
<td>COVID-19</td>
<td>Coronavirus disease 2019</td>
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<td>ERC</td>
<td>Ethics review committee</td>
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<tr>
<td>GEP</td>
<td>Good epidemiological practice</td>
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<tr>
<td>ICF</td>
<td>Informed consent form</td>
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<tr>
<td>LMIC</td>
<td>Low-to-middle income country</td>
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<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
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<tr>
<td>PT</td>
<td>Preferred term</td>
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<tr>
<td>PV</td>
<td>Pharmacovigilance</td>
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<tr>
<td>PVG</td>
<td>Pharmacovigilance team (WHO Headquarters)</td>
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<tr>
<td>SARS-CoV-2</td>
<td>Severe acute respiratory syndrome coronavirus 2</td>
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<tr>
<td>SAE</td>
<td>Serious adverse event</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Synopsis

Background and rationale: Molnupiravir, has been newly introduced onto the market as the first oral medicine for the treatment of non-severe COVID-19 disease. Pharmacovigilance has an important role to provide further evidence on the safety of this medicine in the general population. Pharmacovigilance will ensure potential safety issues are detected early and addressed without delay, and any impact on benefit risk ratio can be quickly identified and assessed. This protocol is designed to investigate the safety of molnupiravir using a cohort event monitoring methodology.

Objectives: The overall aim of this observational study is to monitor the safety of molnupiravir for the purpose of safety signal detection. The specific objectives include:

Primary objectives
1. to characterize and estimate the incidence of all adverse events (AEs, including serious adverse events (SAEs), medication errors, off-label use and misuse) occurring in enrolled patients.

Secondary objectives
1. to characterize and estimate the incidence of maternal and perinatal outcomes in women inadvertently exposed to molnupiravir during pregnancy and neonate/infant/child exposed during breastfeeding;
2. to detect signals of drug-drug interactions and interactions with traditional medicines;
3. to estimate the incidence of severe COVID-19 disease following treatment with molnupiravir, to detect possible lack of adherence to treatment or lack of effect.

Study design: A multicentre multi-country observational, prospective, single-arm, cohort study for the active safety surveillance of molnupiravir that will be conducted in health facilities that provide molnupiravir to patients.

Study period: Study enrolment will start when the first authorized dose of molnupiravir is prescribed in the participating study sites. Enrolled patients will be actively followed-up for three months after their last dose. Pregnant women inadvertently exposed to molnupiravir will be followed until the end of the pregnancy and their children will be followed up until the age of 12 months.

Population: Participants will be recruited among patients who are prescribed molnupiravir for treatment of non-severe COVID-19 disease at sites participating in this study. Study participation will be strictly voluntary. Inclusion criteria: written informed consent and molnupiravir as per national policy. Exclusion criteria: patients unable to comply with study procedures.

Variables: Exposure to molnupiravir for COVID-19 treatment. The start date of treatment and dose will be recorded. Outcomes include all AEs, SAEs, and maternal and perinatal outcomes events. Information on concomitant medications, traditional medicine and supplements, non-adherence to treatment and progression to severe COVID-19 disease will be collected. Data will be collected at the start of the study, daily for the five days of molnupiravir treatment, five days after treatment, then monthly for three months after the last dose. Pregnant women inadvertently exposed to molnupiravir will be further followed up every three months (day (D)184 and D274) until the end of the pregnancy and the neonate/infant will be followed up at birth and 6- and 12-months after birth.

Data sources: Data sources will include baseline information collected by study staff at recruitment, self-filled questionnaires (through mobile apps or Internet) or paper diaries, telephone survey or home visits by study staff. More than one type of data collection tool can be employed by study sites. A central hub will be set up to standardize the data collected, regardless of the tool used.

Sample size: The target study size is 30 000 patients treated with molnupiravir for COVID-19 disease. If no events are observed, this study size can rule out events occurring with a frequency of at least 1 per 10 000 with at least 95% confidence.

Data Analyses: Participation rates and demographic characteristics will be summarized using descriptive statistics. The mean and standard deviation, and median and range will be summarized overall and by age at enrollment, sex and country, when appropriate. Frequencies and percentages of outcomes will be provided by age group, sex and country when appropriate. Analyses of SAEs will include all patients. Frequencies and proportions of patients with identified SAEs will be calculated by time since start of therapy. A cumulative incidence will be calculated and plotted to visualize trends and identify inconsistent or unexpected patterns. For proportions, 95% confidence intervals will be calculated using an exact method.

Periodic reporting: Interim analyses will be performed monthly.

Ethics This non-interventional study will be conducted in accordance with the international ethical guidelines for epidemiology studies published by the Council for International Organizations of Medical Sciences (CIOMS), the Declaration of Helsinki and its amendments, good epidemiological practice (GEP) guidelines and any applicable national laws and guidelines. Written informed consent will be obtained from all participating individuals. Data protection and privacy regulations will be strictly observed when capturing, forwarding, processing, and storing patients’ data.
1. Background and rationale

In December 2019, the world witnessed an outbreak of respiratory disease caused by a novel coronavirus strain. The novel coronavirus was named ‘severe acute respiratory syndrome coronavirus 2’ (SARS-CoV-2), while the disease associated with it is referred to as coronavirus disease 2019 (COVID-19). The virus spread to an increasing number of countries worldwide and on 30 January 2020 the World Health Organization (WHO) announced that the outbreak was a public health emergency of international concern (PHIC).

Molnupiravir has been newly introduced onto the market as the first oral medicine available for the treatment of non-severe COVID-19. Molnupiravir is a prodrug of the ribonucleoside analog β-D-N4-hydroxycytidine (NHC), which is phosphorylated in cells to form the pharmacologically active ribonucleoside triphosphate (NHC-TP) which then induces an antiviral effect via viral mutagenesis. WHO has provided a conditional recommendation for molnupiravir for those at highest risk of hospitalization. It is indicated for treatment of mild-to-moderate COVID-19 in adults (>18 years) with a positive SARS-COV-2 diagnostic test who have an estimated 10% increase in the risk of hospitalization. It is to be taken at a dose of 800 mg (four 200 mg capsules) orally every 12 hours for five days with or without food. The conditional recommendation reflects the concern for widespread treatment with molnupiravir before more safety data become available, and mitigation strategies include undertaking active pharmacovigilance surveillance.1

Although clinical trials show that molnupiravir is generally well tolerated2 3 4 5 6 7 8 9, there are some concerns and unanswered questions about its safety. The main adverse events reported are dizziness, headache, diarrhoea, rash and urticaria. The main concerns are the potential mutagenic potential, teratogenicity in pregnancy and potential bone and cartilage toxicity. Authors of a study in animal cell cultures found mutations in cells treated with molnupiravir and recommend assessment of the mutagenic potential in host cell DNA with a focus on rapidly dividing cells.10 There are no human pregnancy data currently, however, animal studies demonstrate fetal developmental abnormalities with molnupiravir exposure and therefore molnupiravir is not recommended for use during pregnancy. To minimize risks, women of childbearing potential should use effective contraception during the five days of treatment and for four days after.

Additionally, molnupiravir is contraindicated in patients younger than 18 years due to potential bone and cartilage toxicity.11 There is also concern that molnupiravir’s mutagenic potential could induce mutations in the SARS-CoV2 virus further leading to increased resistance.12

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5 ClinicalTrials.gov. 2022. The safety of molnupiravir (EIDD-2801) and its effect on viral shedding of SARS-CoV-2 (END-COVID) - full text view - ClinicalTrials.gov (Last accessed on October 20, 2021).
Increased levels of alanine aminotransferase and decrease levels of haemoglobin have been reported in clinical trials but these were considered to be non-serious or not clinically meaningful.

Due to the urgent need to make therapeutic agents available for treatment of COVID-19, regulatory agencies are using fast track emergency procedures to expedite the approval process, based on limited clinical efficacy and safety data. Pharmacovigilance has an important role to provide further evidence on the safety of this medicine in the general population and to ensure potential safety issues are detected early and addressed without delay, and any impact on the benefit-risk ratio can be identified and assessed. To date, India, Europe, UK, and USA have granted emergency use listing for molnupiravir.

Cohort event monitoring (CEM) is an active surveillance method that can be used to follow-up early users of molnupiravir to ensure timely collection of post-market safety data. These data can then be taken into consideration by national regulatory authorities (NRAs) at the time of granting full-market authorization or making other regulatory decisions. This protocol is intended for the description of a study to investigate the safety of molnupiravir using a cohort event monitoring design.
2. Objectives

The aim of this observational study is to monitor the safety of molnupiravir in adults. It is currently indicated for patients with non-severe\(^1\) coronavirus disease with an estimated 10% increase in risk of hospitalisation. Molnupiravir should be administered as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset. It is proposed to conduct the study to detect and characterize any early safety signals in between 6 and 12 countries.

The specific primary objective is:

1. to characterize and estimate the incidence of all adverse events (AEs) (including serious adverse events -SAEs, medication errors, off label use and misuse) occurring in enrolled patients.

The secondary objectives are:

2. to characterize and estimate the prevalence maternal, and perinatal outcomes in women inadvertently exposed to molnupiravir during pregnancy and exposure in breastfed neonates, infants, and children;
3. to detect signals of drug-drug interactions and interactions with traditional medicines;
4. to estimate the incidence of severe COVID-19 disease following treatment with molnupiravir, to detect possible lack of adherence to treatment or lack of effect.

3. Methods

3.1 Study design

This is a master cohort event monitoring protocol for an observational prospective single-arm cohort study. Cohort Event Monitoring (CEM) is designed to be an observational study, to characterize adverse events and capture safety information beyond an RCT, in clinical practice and real-world settings, outside of a clinical trial construct. The CEM method has been used extensively in pharmacovigilance to detect safety signals of malaria, HIV and Tb medicines\(^{13-16}\). The study will be conducted in health facility sites where molnupiravir is provided by the national health authorities in between 6 to 12 countries across the six WHO regions. Study participants will be actively followed up from the start of molnupiravir therapy for up to three months after the last dose. In the case of inadvertent exposure in pregnancy, women will be followed up every three-months until the end of the pregnancy, whichever is longest, and their children will be followed up for 12 months after birth. Children who are exposed through breastfeeding will be followed up for three months after the last exposure date.

3.2 Study population

Participants will be recruited at participating sites that deliver prescribed molnupiravir to patients. Study participation will be strictly voluntary.

3.2.1 Inclusion criteria

- written informed consent, for patients who are illiterate, consent can be obtained from next of kin or a witness;
- patients who are prescribed molnupiravir as per national policy;
- a neonate/infant/ child of a women who was inadvertently exposed to molnupiravir in pregnancy or through breastfeeding will only be followed up if parental consent is given.
- parental consent, to follow up under 18-year-olds who have accidently been exposed to molnupiravir (off label use). For minors and adolescents, an assent form is also required (Annex 10).

3.2.2 Exclusion criteria

- individuals unable to comply with study procedures, depending on study set up in the country, e.g., unable to use mobile phone for data collection or paper diaries, live in areas where telephone and house visits are not possible.

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Information on age and gender for those who are excluded because they cannot comply or because they cannot consent will be collected anonymously. No personal identifiers will be collected from individuals who are excluded as no consent will be provided.

3.2.3 Withdrawal from the study

Participants will have the right to withdraw from the study for any reason, at any time. A participant will be considered lost-to-follow-up after three unsuccessful attempts to contact them by phone or home visit, followed by three unsuccessful attempts to contact their next of kin. The attempts to contact them will be documented. All efforts will be made to determine the underlying reason for withdrawal and, where possible, the primary underlying reason will be recorded. Withdrawn participants and those lost-to-follow-up will not be replaced after the enrollment period has ended. Should a participant decide to withdraw from the study, data collected up to the time of withdrawal will be used in the analyses.

3.3 Study sites

3.3.1 Country selection

The study will be implemented in low-to-middle income countries (LMICs), with at least one LMIC from each of the six WHO regions. LMICs will be defined as per the 2022 World Bank criteria and codes UMC, LMC and LIC:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>UMC</td>
<td>World Bank upper middle-income economies (GNI per capita of USD 4,096 - 12,695 in 2020)</td>
</tr>
<tr>
<td>LMC</td>
<td>World Bank lower middle-income economies (GNI per capita of USD 1,046 - 4,095 in 2020)</td>
</tr>
<tr>
<td>LIC</td>
<td>World Bank low-income economies (GNI per capita of USD 1,045 or less in 2020)</td>
</tr>
</tbody>
</table>

The following factors will be considered when selecting the countries:

- population size and projected use of molnupiravir;
- regulatory and supply status of molnupiravir;
- previous experience with conducting CEM studies with other medicinal products and maturity level of the national pharmacovigilance system as established using the WHO Global Benchmarking Tool;\(^\text{18}\)
- WHO region represented, with the aim of recruiting sites from each of the six WHO regions, to ensure a balanced representation;
- expression of interest in participation in the study;
- previous experience with or the capacity to monitor and follow-up patients (including through phone calls, if necessary).

A list of countries to prioritize will be developed. This will include mapping of molnupiravir roll-out plans in terms of when and how much they will receive.

3.3.2 Study sites

Study sites in the selected countries will be healthcare facilities where molnupiravir is delivered. Selection of study sites will consider the following factors: size, access to computer for data collection at the site-level, availability of sufficient human resources, expression of interest to participate, and previous experience with active surveillance. If there are multiple sites in selected countries, the selection of sites that represent different geographical areas will help mitigate selection bias.

A template for information to be added to the site-specific protocols is provided in Annex 1, for use after the countries and sites have been selected.

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3.4 Study period

3.4.1 Start of study and duration of follow-up

The time frame for enrollment will be the first day that molnupiravir is delivered or the first dose taken. Recruitment will be monitored during the study to assess whether recruitment goals are being reached. Individuals will be followed-up for all AEs for five days during the molnupiravir treatment and for five days after the last dose. Individuals will be followed up for SAEs for three months after the last dose. Molnupiravir has an effective elimination half-life of 3.3 hours, therefore it will be cleared from the system in the five days following the last dose. Women of childbearing potential will also be followed up monthly for three months to obtain information on any pregnancies occurring during or within 5 days of molnupiravir use. Pregnant women inadvertently exposed to molnupiravir will be followed until the end of their pregnancy and their infant will be followed up until the age of 12 months. Breastfed neonates/infants/children will be followed up as per standard follow up, i.e., for three months after last exposure to molnupiravir.

3.4.2 Study completion and study end

Participants will be considered to have completed the study:

- when they have completed the follow-up questionnaire three months after their last molnupiravir dose; or
- in pregnant women inadvertently exposed to molnupiravir, when the pregnancy ends and for those that end with a live birth, when the child is 12 months of age.

The study end is defined as the time at which the last enrolled subject has been followed for three months after last molnupiravir dose, or as above for pregnant women and their children.

3.5 Sample size

3.5.1 Sample size for overall cohort

Table 1 shows the sample sizes required to rule out an adverse event with a given frequency with 95% confidence. For example, if no events are observed with 30 000 participants, events with a frequency of 1 per 10 000 can be ruled out with 95% confidence. Adverse events with a frequency more than 1 per 10 000 could be detected with fewer participants (Table 1). The aim is to recruit patients from multiple sites in several countries to reach a cohort size of 30 000 as quickly as possible in order to confirm the safety of molnupiravir as early as possible. Since the pandemic situation and the number of COVID-19 cases can vary in different countries at different times, this may result in some countries recruiting more patients than others.

<table>
<thead>
<tr>
<th>Study sample size</th>
<th>Event frequency</th>
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<tbody>
<tr>
<td>10 000</td>
<td>1 per 3 333</td>
</tr>
<tr>
<td>20 000</td>
<td>1 per 6 666</td>
</tr>
<tr>
<td>30 000</td>
<td>1 per 10 000</td>
</tr>
<tr>
<td>40 000</td>
<td>1 per 12 500</td>
</tr>
<tr>
<td>50 000</td>
<td>1 per 16 666</td>
</tr>
<tr>
<td>60 000</td>
<td>1 per 20 000</td>
</tr>
<tr>
<td>80 000</td>
<td>1 per 25 000</td>
</tr>
<tr>
<td>100 000</td>
<td>1 per 33 333</td>
</tr>
<tr>
<td>150 000</td>
<td>1 per 50 000</td>
</tr>
<tr>
<td>500 000</td>
<td>1 per 166 666</td>
</tr>
</tbody>
</table>

3.6 Study variables

Study staff will collect data on covariates of interest when molnupiravir treatment is initiated.

3.6.1 Modes of data collection

All participants will complete questionnaires through a mobile app/website/ paper diary/visit to health facility/medical notes or through study staff following telephone calls or home visits. The data collection tool used will depend on the country and study site. More than one type of data collection tool can be used in a single site. A central hub will be set up to standardize the data collected, regardless of the tool used.

3.6.2 Data collection time points

The data collection time points are summarized below in Figure 1. Data will be collected at enrolment on the first day of treatment using the patient enrolment questionnaire (Annex 2). Data will then be collected daily for four days, on D1 to D4, during the molnupiravir treatment and on D9, five days after the last dose using the follow up questionnaire 1 (Annex 3). Data will then be collected monthly for three months after the last dose of molnupiravir (D34, D64, D94) using the follow up questionnaire 2 (Annex 4).

Pregnant women inadvertently exposed to molnupiravir will be followed up every three months until the end of the pregnancy and their children will be followed up at birth and 6- and 12-months after birth.

Figure 1  A. Data collection for all study participants and for children inadvertently exposed during breastfeeding. B. Data collection for pregnant women whose pregnancy was detected during followup and for their children. In this example, the assumption is that the pregnancy was detected at D64.

It is anticipated that the end of pregnancy date will vary in each pregnancy, hence there may be a lag time from the exact end of pregnancy date and date of follow-up questionnaire. Additionally, the pregnancy may be detected at different gestational ages, and end of pregnancy can occur before the first, second of third pregnancy questionnaire. If end of pregnancy is detected in earlier questionnaire, subsequent pregnancy follow-up questionnaires will not be sent. If further information on the pregnant women or fetus/neonate/infant is required for investigation (e.g. report of a malformation), study staff will contact treating clinicians/midwives and review medical notes.

3.6.3 Exposure of interest

The exposure of interest is at least one dose of molnupiravir (the current recommended dosage regimen is 800 mg twice daily for five days).
3.6.4 Study outcomes

**Pre-exposure events**

Information on specified AEs \(^{20}\) that occurred during the seven days prior to the start of molnupiravir treatment will be obtained retrospectively through the patient enrolment questionnaire (Annex 2), which will be completed by study staff at study site.

**All adverse events**

All AEs, defined as any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment, will be recorded. This will also include medication errors, off-label use and misuse. This information will be collected through a questionnaire that will be completed daily on D1 to D4 and then five days after the last dose on D9 (Annex 3). As the date on which the event occurred is important for the statistical analysis, the data collection tools and methods will capture the date or a close estimate of this date. If a participant does not remember the exact date, questions will be asked to capture the good estimate of the actual date.

**Serious adverse events**

SAEs are defined as an event that results in:

- death or is life-threatening;
- hospitalization or prolongation of hospitalization,
- persistent significant disability; or
- anogenital anomaly.

When possible, SAEs that result in in-patient hospitalization will be reported by the participant or their next of kin, and SAEs that result in death will be reported by their next of kin. Hospitalizations could occur because:

1) the COVID-19 disease in the patient has progressed, due to lack of effect or resistance;
2) a drug related SAE;
3) other unrelated reasons for hospitalizations.

Individual causality assessments should be done on all SAEs. This can be performed by a national Committee to review SAEs set up by the national pharmacovigilance system. Causality assessments give an indication of how likely the adverse event is due to molnupiravir. There are several causality assessments methods available, and the use of the WHO causality assessment is encouraged. Where possible patients or next of kin that have been hospitalized will be asked to provide a copy of the discharge letter and information on the hospital and treating physician. If a discharge letter is not available, the study staff will contact the hospital for further information on the medical diagnosis upon hospital admission. This is to obtain sufficient information to: standardize diagnosis, confirm the timing of the AE; obtain clinical information to define disease progression to severe or critical COVID-19 (as per WHO definition); rule out other possible causes of the AE (e.g. existing medical conditions, other medicines); and whether the reaction abated following discontinuation/end of treatment with molnupiravir. This information will help perform causality assessments and distinguish between hospitalizations due to COVID-19 or due to an adverse event related to molnupiravir use. All reported deaths will be followed up to assess the cause through the routine national pharmacovigilance system (Annex 4).

**Maternal and perinatal adverse outcomes**

Pregnant women who are inadvertently exposed to molnupiravir will be identified through the monthly follow-up questionnaires (Annex 4) during the three months following completion of molnupiravir treatment. Once their pregnancy is confirmed, the women will be followed up until the end of pregnancy and their child will be followed up at 6 and 12 months after birth (Annex 5). Additionally, neonates or infants indirectly exposed to molnupiravir through breastfeeding will also be followed up for three months following their last exposure (Figure 1).

**Concomitant medications, traditional medicine and supplements**

All concomitant medical conditions or health problems of the patient will be recorded, and any remedies used to treat or alleviate symptoms, including herbal and traditional medicines will be recorded, using the data collection forms at enrollment and follow up. Participants are likely to be familiar with local names of medicines, rather than international nomenclature, and

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\(^{20}\) WHO definition of adverse event: any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment.
should be encouraged to mention the name of any preparation, as used locally. Since study data are expected to be pooled across countries it is important that local study team translate local names of medicines to the internationally acceptable nomenclature, as this is not likely to be done reliably at the global site.

**Non-adherence to molnupiravir treatment**

Non-adherence to molnupiravir treatment and reasons will be recorded. These reasons for non-adherence may include, but are not limited to, the following: adverse events, patient feeling better/worse e.g. vomiting, patient wishing to keep a stock of the tablets.

**Severe COVID-19 disease**

Severe COVID-19 disease is defined as any of: oxygen saturation <90% while breathing ambient air; signs of pneumonia; signs of severe respiratory distress (in adults, accessory muscle use, inability to complete full sentences, respiratory rate >30 breaths per minute; and, in children, very severe chest wall in-drawing, grunting, central cyanosis, or presence of any other general danger signs including inability to breastfeed or drink, lethargy, convulsions or reduced level of consciousness). Severe COVID-19 disease usually results in hospitalization, requiring intensive care, or results in death. Hospitalization due to the progression to severe COVID-19 disease will be solicited throughout follow-up to collect information on: laboratory-confirmed diagnosis; hospitalization for COVID-19 disease; whether patient needed intensive care; and if COVID-19 resulted in death.

### 3.7 Study flow: data sources and data collection

Data will be collected at the time of enrollment, at the time of administration of the first dose of molnupiravir, and during follow-up. Data collection by the study site staff at the time of enrollment will take place at the site using an electronic tool. Data collection by the participants during follow-up will take place through at least one of the following methods: a mobile app, internet site, telephone calls, paper diary, home visits.

#### 3.7.1 Training

Training will be provided at each site for all staff involved in the study. Training will focus on: study objectives, methodology, roles and responsibilities, obtaining informed consent, definitions of adverse drug reactions (ADRs), AEs, SAEs, confidentiality and generating unique identifiers for participants, events to be reported, coding and the use of the Medical Dictionary for Regulatory Activities (MedDRA) and data collection tools.

#### 3.7.2 Enrollment

Potential participants will be informed about the study by study staff at participating health facilities that provide molnupiravir. Study staff will be available to answer any questions. Additionally, written material about the study will be given to participants. Enrollment will take place immediately after molnupiravir is dispensed/supplied to the patient, the study staff will administer and collect the signed informed consent form and complete the participants’ baseline information (demographic and medical) and pre-exposure event data. A unique identifier will be generated. To increase the quality of the self-reported data, participants will be asked to report any physician-made diagnoses and, if they are hospitalized, to provide data from their hospital discharge report, if available.

The number, age and gender of participants who choose not to consent or are not able to comply with follow-up will be recorded, at study sites at the point of enrollment. This information on age and sex of the patient can be obtained from the prescriptions provided, and no personal information or identifiers will be collected for these excluded individuals. Data will be recorded at the study site during the enrollment process, and stored as aggregate data.

#### 3.7.3 Follow-up

The participants will complete the study questionnaires at predefined time points during follow-up. Follow-up will be done either through telephone calls or home visits by study team members or through mobile apps, web links or paper diaries. For follow-up using mobile apps and web links, reminders will be sent to participants who do not complete the questionnaire through a push notification or an SMS. If the questionnaire is still not completed, study staff will phone the participant. After three unsuccessful attempts to contact the participant by phone, their next of kin will be contacted. After three unsuccessful attempts to contact their next of kin, the participant will be considered as lost to follow-up. There should be at least a one-week period between attempts to follow-up to allow time for response in patients who may not have responded due to hospitalization. E-data collection tools will have the facility to upload discharge/physician reports to provide more accurate information on any medical diagnosis made in relation to the reported adverse event. Efforts will be made to understand why there is a loss to follow up, e.g., is it due to a loss of interest from the patient, or due a more serious problem e.g., hospitalization and death. Following unsuccessful attempts to complete the questionnaire, patients will be asked if they would like to continue with this study, and if not, they will be asked why. Where possible and if available, this study should leverage other ongoing studies or link patients to electronic health data that can provide information on hospitalizations due to covid-19 to have a better understanding if lack of response is due to
hospitalization. Should any sites plan to link information to existing electronic health data, this process should be included in site specific protocols and the consent forms should clearly request permission to link and access this data.

3.7.4 Coding of AEs and SAEs

The adverse events reported by the participants during follow-up will be coded using Medical Dictionary for Regulatory Activities\textsuperscript{21} (MedDRA) preferred terms (PTs) by a member of the study team who has received MedDRA training.

3.7.5 Data collection at withdrawal or lost to follow up

If a participant withdraws from the study or is lost-to-follow-up, the follow-up for that participant will be terminated early and both the date and the reason will be recorded, if possible. If a safety signal is detected, a designated study team or the national pharmacovigilance centre may decide to contact the participant’s healthcare provider, for further investigation through the routine national surveillance programme.

3.8 Data analysis

The analysis plan will be fully described in a statistical analysis plan (SAP). All analyses will be documented in the final study report. Missing data will be accounted for in the analyses and interpretation of data.

3.8.1 Descriptive analysis of demographic and baseline characteristics

Participation rates over time will be described. Demographic characteristics will be summarized. The mean/median and standard deviation/range will be given for age at enrollment, overall and stratified by sex and by country, when appropriate. Frequencies and percentages will be provided by age group, sex, and country, data collection method, when appropriate. A record of the numbers of patients that are excluded because they have not consented or because they cannot comply with follow-up will be noted.

3.8.2 Statistical methods

Participants who complete the follow-up forms but do not report any event(s) will be considered as participants without event(s).

All analyses for AEs will be at the PT levels. For all AEs (serious and non-serious), the frequency and proportion (and 95% confidence interval) of participants with at least one AE will be calculated overall, by event type and by time since initiation of molnupiravir, in days. For each type of event, the duration (in days) will be calculated, and their mean/median and standard deviation/range will be reported as well as any sequelae. A cumulative incidence will be calculated and plotted to visualize trends and identify inconsistent or unexpected patterns.

Maternal and perinatal adverse outcomes

Observed maternal and perinatal outcomes will be compared with background event rates, if available from appropriate sources, to investigate whether the prevalence of the observed outcomes is higher than expected.

Self-controlled case series and self-controlled risk interval analysis

For acute SAEs with a known risk window, a self-controlled risk interval (SCRI) analysis will be considered, provided that the event satisfies the assumptions required for SCRI studies and that the risk window for the SAE of interest falls within 42 days of treatment, to allow sufficient time for the control period.

For acute non serious AEs data collected on events in the seven days prior to molnupiravir exposure will be compared with data about events reported during and after molnupiravir therapy, and a self-controlled analysis will be considered, provided that the event does not break the rule of assumptions required for this type of analysis.

The incidence of severe and critical COVID-19 disease will be estimated to capture lack of effect.

4 Data management

A data management plan (DMP) will be developed before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation.

Study staff or patients will enter data using an electronic tool at several time points. At the time of enrollment, study staff will enter data on informed consent, contact details and covariates, using an electronic tool and this will be transferred and stored in a password-protected database. Each participant will be linked to an anonymous study ID in the database. A locally designated data manager will be sent a password-protected copy of the online database (anonymized patient identifiers) for data analysis.

\textsuperscript{21} MedDRA: Medical Dictionary for Regulatory Activities: Coding dictionary for standardised medical terminologies. It was developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and is maintained by the ICH MedDRA Maintenance and Support Services Organization (MSSO). Medical terminologies are coded under a five-level hierarchical structure, the highest level terms are grouped into System Organ Class.
Safety monitoring of molnupiravir for treatment of mild to moderate COVID-19 infection in low and middle-income countries using cohort event monitoring

up data at each of the data collection time points will be entered either by study staff using an electronic tool (if collected through home visits or telephone) or by patients through a mobile app or web link. Data collected on paper will be entered by study staff using the electronic tool and then transferred and stored in a password-protected database or kept in a locked storage space, in accordance with national regulations. An identification log will be used, and this log will be stored in a secure, locked facility within the study country. The location of and responsibility for local database(s) will be determined on a case-by-case basis and will be in accordance with national regulations.

WHO will provide support for data management and access to electronic tools that will be stored in a secure WHO server housed in Geneva. The WHO team, within the capacity of system strengthening, will support the development of local data platforms. Study centres can decide to manage data locally or through the central WHO repository, depending on local circumstances.

Automatic quality checks will detect out-of-range or anomalous data, where applicable, for all data entered electronically. User testing of any data entry methods, whether electronic or on paper, will be performed prior to deployment.

4.1 Data security

The key-coded data obtained from this study will be stored in a secured database located at the WHO headquarters in Geneva. Data will be handled in accordance with all applicable data protection and privacy laws. No unauthorized persons will have access to the data. Data will be electronically archived and retained at WHO for three years, or for the duration required by the national laws and regulations at local research centres. After this delay the data will be destroyed. This is to enable completion of the study, to conduct and complete data curation processes, and to finalize the publication and archival process. These security measures will also apply to the informed consent forms (ICFs).

4.2 Data transfer

WHO will provide a data management tool to be used in the countries to store data collected nationally. Each country will have access to their own national data. The national data management tool will have a bridge to transfer relevant data to the national pharmacovigilance systems. The sharing of anonymized data will be done using standard WHO data sharing agreements with each study site (Annex 6). The data sharing agreement is a legal document that will cover permission for pooling data into the WHO repository, which will be located at WHO Headquarters (Geneva). A separate data sharing agreement will be needed to share data between WHO and other collaborators.

4.3 Source documents

The data sources for the exposure of interest will be study staff and participants. The data source for covariates will be the participants. The data sources for the study outcomes will be the questionnaires completed by study staff who do home visits or phone calls, the participants (or their next of kin, as appropriate), and medical notes.

5 Monitoring, analysis and reporting and quality assurance

5.1 Monitoring

A site initiation visit will be conducted to ensure the site is ready to start data collection. Study staff will be trained on the study procedures.

Remote and, when possible, on-site monitoring of the study conduct will be performed throughout the study period to assess the accuracy and completeness of the data.

5.2 Analysis and reporting

Interim analyses will be performed by an appointed member of the study team on a monthly basis. Should the analysis indicate any safety concerns, the study team will inform the relevant authorities. In addition, a safety signal review group will be set up, to investigate emerging signals. Reports of serious adverse events should be sent in real time to the national authorities who have the right to make decisions on how to communicate and act through their national regulatory systems.

The final analyses will be performed, and a full study report will be written within 20 weeks after the database lock. Market authorization holders will be informed of any safety concerns, local study teams will share results of the study with the national regulatory authorities for regulatory review, and with national infectious disease programme and national pregnancy surveillance programmes to inform policy decision. Additionally, the master protocol study team will share findings with the WHO Advisory Committee of Safety of Medicinal Products and the WHO guideline development group for the WHO therapeutics and COVID-19 living guidelines.

-11-
5.3 Quality assurance

Study sites may be subject to a quality assurance visit. If so, the site will be contacted in advance to arrange a monitoring visit. The investigator and site staff will guarantee direct access to all study documents for quality assurance monitoring.

6 Study management

This study will be performed by the investigator, with guidance, input, review and approval of the sponsor, including development of materials, recruitment, training and management of sites, electronic data capture and data management and analyses.

The investigator and all study staff will conduct the study in compliance with the version of this protocol approved by the national ethics committee. All personnel involved in the conduct of this study must be qualified by education, training, and experience to perform their tasks.

6.1 Dedicated scientific committee

A dedicated scientific committee (to be detailed in the site-specific protocol) will oversee the implementation and smooth running of the study. They will provide scientific, statistical and technical expertise, as needed.

6.2 Changes to the protocol

Study sites will submit this protocol to their national ethics review committee (ERC) with minor amendments to the protocol which will include the names of the national principal investigators (PIs), research teams and study sites. Following approval by the national ERC the site-specific protocols will be submitted to the WHO ERC prior to implementation.

6.3 Management and reporting of adverse events and adverse drug reactions

The study team will ensure that the healthcare workers in charge of providing molnupiravir at study sites are familiar with the national pharmacovigilance reporting and management processes as per national guidelines. The study team will liaise with the national regulatory authorities to ensure that provisions are in place (including reporting forms, procedures, and training) for efficient implementation.

Individual causality assessment will be done by the national pharmacovigilance centre as per national/routine PV system. An international dedicated signal detection group will be set up by WHO on a global level. This signal detection group will consist of individuals from the study teams and pharmacovigilance centres in each of the participating countries and the WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre). Upon signal review, the signal detection group will perform causality assessments on cases that have not been assessed via the national routine PV system. The signal detection group is also a platform in which data will be communicated and reviewed collectively by research groups from participating countries.

Contact information of the participants and their healthcare providers will be collected, and consent will be sought to use this contact information in case the national pharmacovigilance centre needs to investigate any potential safety signals that arise from the study.

The study team will be responsible for ensuring that all SAEs detected and reported in the context of this study will also be reported through the routine pharmacovigilance surveillance system to the responsible organization within the health ministry (national regulatory authorities or national pharmacovigilance centre), to ensure that all AEs are reported according to local regulation and that all SAEs are investigated appropriately. Causality assessments should be carried out on all SAEs.

Key performance indicators will include:

- Number of patients enrolled into the cohort monthly vs. number of patients that receive molnupiravir (this will vary according to number of COVID-19 cases).
- Number of patients completing questionnaires and numbers of home visits and telephone contacts monthly.
- Number of adverse events reported monthly.

7. Ethical considerations

7.1 Guiding principles

To ensure the quality and integrity of the research, this study will be conducted under the International Ethical Guidelines for Epidemiologic Studies published by the Council for International Organizations of Medical Sciences22, good epidemiological

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practice (GEP) guidelines, the ethical principles in the Declaration of Helsinki and any applicable national laws, regulations and guidelines. This is an observational study without medical intervention or change in clinical and diagnostic practices, therefore, there will be no direct benefit to the participants. Nevertheless, there will potentially be important societal benefits from this safety study. Close monitoring of the first cohorts being treated with molnupiravir are key to ensure safety and maintain public confidence for the roll-out of the medicine.

Additionally, data generated from this study will be reviewed by a dedicated subcommittee of the WHO Advisory Committee of Safety of Medicinal Products, to advise WHO on the safety of molnupiravir. This highlights the important social value and impact of this study. Understanding the safety of this novel product in resource-limited settings is a prerequisite to developing risk minimization measures to prevent harm.

7.2 Respecting participants’ autonomy
The study will use self-reported data and data collected as part of healthcare provision at designated outpatient sites. Participants will be informed about the study through the health facility in which molnupiravir is provided and will have the opportunity to ask questions to study staff. An ICF must be signed prior to the individual’s participation in the study (Annex 7 to be completed). When signing the ICF, individuals agree that the study team will be able to contact the designated health facilities at which they may have sought care during the study period. The purpose of this contact is to obtain medical confirmation of any SAEs that led to the hospital visit. The study-specific ICF will explain the purpose of the data collection, the foreseeable uses of the data, the intended goal of such use, who will have access to the data, the conditions and duration of data storage, and the ways in which the participant can contact the custodian and remain informed about future use. The ICF will explain that individual’s participation is completely voluntary and that they can decide to withdraw at any time during the study.

7.3 Participant confidentiality
No data whatsoever will be used, either alone or in conjunction with any other information, to establish the identity of any of the participants from whom data were obtained. All parties will ensure protection of participants’ personal data and will not include participants’ names on any study forms, reports, publications, or in any other disclosures, except where required by law. Local data protection and privacy will be observed in capturing, forwarding, processing, and storing patient data.

7.4 Independent ethics committee and institutional review board
Participating study sites will submit the site-specific protocols to national ethics committees or institutional review boards, in accordance with local regulations and will comply with any national ethics committees requirement. All site-specific protocols must be approved by WHO ERC prior to implementation.

8 Publication
Each site will be invited to share their anonymized data for pooled analysis and will also be able to publish their own data independently provided that patient identities are protected. To protect patient identity, any publications or presentations relating to the study will use only aggregate summary data. Further, after obtaining agreement from each study site, the use of the master protocol and harmonized collection of data will allow for pooled analyses, which in turn will contribute to rapid knowledge generation and strengthen the power of the data analysis to make recommendations. Reporting of site-specific results is up to individual investigators and should follow Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies and ideally be reported in such a way to allow for comparison of data across different study sites. If there are multiple sites within one country, one publication with data from all study sites is encouraged.

At the global level, dissemination will be done in the standard way to inform clinical management and WHO guideline development work. Findings from the global pooled analysis will be presented in reports and peer-reviewed publications.

Authorship will be determined using accepted international approaches, according to International Committee of Medical Journal Editors recommendations (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html), commensurate to contributions made.

9.0 Limitations
As follow up is only three months (or until the end of pregnancy and one year after the birth of an infant), long-term adverse events will not be detected using this study design. Long-term adverse events will be detected through routine pharmacovigilance.

There is a risk of selection bias as some participants will choose not to consent or will not be unable to comply with follow up. Anonymous information on how many participants are excluded for these reasons will be collected. Loss to follow up is a potential risk in this study, particularly if this is due to a patient being unable to respond because they are hospitalized. This risk of bias can be minimized by attempting to contact the patient three times, with at least one week between each attempt, and to follow up with next of kin in the same manner.
Annex 1: Site Specific template to be filled after country and site selection

[Paragraph describing the health facilities in which the study will be conducted]

Study sites will be health facilities in which molnupiravir is prescribed and used. Study sites within selected countries will be selected based on [SELECTION CRITERIA TO BE LISTED, e.g., size, access to computer for data collection at site-level, availability of sufficient human resources, interest in pharmacovigilance, and previous experience with CEM.]

Table 1: Study sites with principal investigators and contact details

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<tr>
<th>Site</th>
<th>Principal investigator</th>
<th>Email</th>
<th>Phone</th>
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Table 2: Study staff roles and responsibilities

<table>
<thead>
<tr>
<th>Study Staff</th>
<th>Roles and responsibilities</th>
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<tbody>
<tr>
<td></td>
<td>Obtaining consent forms</td>
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<td>Completing baseline questionnaire</td>
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<td>Follow-up</td>
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<td>Country specific analysis</td>
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<td>Focal point to National pharmacovigilance system</td>
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<td></td>
<td>Training</td>
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<td>Part of the WHO signal detection group</td>
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Table 3 Country specific inclusion and exclusion criteria

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<th>Inclusion criteria</th>
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<th>Exclusion criteria</th>
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Annex 2: Patient enrolment questionnaire

Health facility of the primary molnupiravir prescription: ......................................................
Name of investigator/study staff................................................................. Phone no.................................
Date........................................
Signature.................................

1. Patient details:
First name.............................................. Family name..................................................
Main language(s):........................................................................................................
Clinic number (if available) ..............................................
Unique ID no..................................................................
Consent obtained using annex 7: Yes/No.................................
Patient’s cell phone number to be contacted for follow-up:..................................................
Name of next of kin:..........................................................
Relationship of next of kin to patient:..................................................
Phone number of next to kin to be contacted for follow up:..........................................
Address: Door number
Locality 1
Locality 2
Province
Post code.......................................................................................................................
Date of birth: ....../....../....DD/MM/YY Age: ....years
Gender: Male☐ Female ☐ ☐ in case of Female, LMP

In case of female aged 15 to 45 years: Pregnant?: No☐ ☐ Uncertain☐ ☐ Yes ☐ If yes specify:
Best estimate of gestational age: _________________ weeks
Is the patient breast-feeding a child? Yes ☐ No ☐

2. Symptoms of patient at presentation:
History of fever Yes☐ No☐ Unknown☐
Cough Yes☐ No☐ Unknown☐
With sputum production Yes☐ No☐ Unknown☐
With haemoptysis Yes☐ No☐ Unknown☐
Sore throat Yes☐ No☐ Unknown☐
Runny nose Yes☐ No☐ Unknown☐
Wheezeing Yes☐ No☐ Unknown☐
Chest pain Yes☐ No☐ Unknown☐
Muscle aches Yes☐ No☐ Unknown☐
Joint pain  Yes☐  No☐  Unknown☐
Fatigue/malaise  Yes☐  No☐  Unknown☐
Loss of taste  Yes☐  No☐  Unknown☐
Loss of smell  Yes☐  No☐  Unknown☐
Shortness of breath  Yes☐  No☐  Unknown☐
Headache  Yes☐  No☐  Unknown☐
Vomiting/nausea  Yes☐  No☐  Unknown☐
Diarrhoea  Yes☐  No☐  Unknown☐
Other  Yes☐  No☐  Unknown☐

Please specify…………………………………………………………………………………..

3.  Date and result of SAR-CoV-2 PCR or antigen rapid test

………………………………………………………………………………………………………………………………………………

4.  History of previous COVID-19 disease?
COVID-19 disease prior to current diagnosis?  Yes☐  ☐ No ☐

Laboratory confirmed  Yes☐  ☐ No ☐

Probable but not laboratory confirmed  ☐  Yes ☐ No ☐

Date…………………………:

5.  Previous vaccination against COVID-19?

Yes ☐  No ☐

If yes:
Which COVID-19 vaccine did you receive? ______________________
How many doses did you receive? ____________________________
Date of last COVID-19 vaccine dose? ________________________

6.  All medical events with ONSET in the last 7 days (other than those related to COVID-19)

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<tr>
<th>Events</th>
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7. **Medical history and presence of other diseases**

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<thead>
<tr>
<th>Condition (tick if current or past)</th>
<th>Current</th>
<th>Past</th>
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8. **Concomitant medicines and supplements (including traditional medicines)**

<table>
<thead>
<tr>
<th>Medicine (brand name as stated on container)</th>
<th>Indication</th>
<th>Dose and frequency</th>
<th>Route of administration</th>
<th>Start/stop date</th>
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9. **Patient’s date of planned follow-up visit to health facility** ....../......DD/MM/YY
Annex 3: Follow up questionnaire 1 (for health facility and home visits)

- D1  - D2  - D3  - D4  - D9

Health facility of the primary molnupiravir prescription: .................................................................

Name of investigator/study staff: .......................................................... Contact no: .............................................

Date: ....../....../DD/MM/YY

Signature: ..........................................................

1. Patient details:

First name: ........................................... Family name: ..........................................................

Clinic number (if available): ..........................................................

Unique ID no: ..........................................................

Date of birth: ....../....../.... Age: .... years

If female:

Pregnant?: No □  Uncertain □  Yes □

If yes specify: please provide best estimate of gestational age: ______________ weeks

Is the patient breast feeding a child? Yes □  No □

2. Type of follow-up

Internet or mobile app/electronic tool for patient □  Date: ....../....../....

Telephone interview □  Date: ....../....../....

Attendance at health centre/clinic □  Date: ....../....../....

Visit at home □  Date: ....../....../....

Other (specify) .......................................................... □  Date: ....../....../....

Paper diary □  Date: ....../....../....

Lost to follow-up □  Date: ....../....../....

□ Attempt 1 Date: ....../....../....  □ Attempt 2 Date: ....../....../....  □ Attempt 3 Date: ....../....../....

Follow-up visit at home by: Name: ........................................... Signature: ...............................................

-20-
3. New medicines (including traditional medicines and supplements) taken at any time during treatment with molnupiravir

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Indication</th>
<th>Dose/Route &amp; frequency</th>
<th>Date started</th>
<th>Date stopped* *</th>
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**Please enter ‘C’ in this column if the medicine is continuing**

4. Describe new events or worsening problems during or after molnupiravir treatment

<table>
<thead>
<tr>
<th>Description of event</th>
<th>Date event started</th>
<th>Date event stopped*</th>
<th>Outcome** (A,B,C etc)</th>
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<tbody>
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<td>2.</td>
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<td>3.</td>
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<td>4.</td>
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**Please enter ‘C’ in this column if the event is ongoing**

**Outcome:**

A: resolved; B: resolving; C: resolved with sequelae; D: not resolved; E: death; F: unknown; G: severe.

Please notify the pharmacovigilance focal person or pharmacist if any rechallenge is performed, and provide the result when known.
4b Breastfed neonate/infant/child

Did the neonate/infant/child have any adverse events?
Yes ☐; No ☐

Age of infant:_____________________.

Describe any adverse events:__________________________________________

5. Abnormal laboratory tests results after starting molnupiravir treatment

<table>
<thead>
<tr>
<th>Test</th>
<th>Date</th>
<th>Result</th>
<th>Test</th>
<th>Date</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

6. Hospitalization

Any hospitalization since last date of contact ___________________________ Yes ☐ No ☐

If yes:
Date of hospital admission       ⏰/ ⏰/ ⏰
Date of discharge                 ⏰/ ⏰/ ⏰
Reason for hospitalization/ diagnosis: ________________________________

  COVID-19 disease ☐
  Other ☐

Please provide a copy of discharge letter (if available):__________________

Name and address of hospital: __________________________________________
Name and contact of treating physician: ________________________________
7. Was the molnupiravir treatment completed, i.e., 4x200mg every 12 hours for 5 days?

Start date: ..../..../......
End date: ..../..../......

<table>
<thead>
<tr>
<th>Date</th>
<th>Morning dose Taken</th>
<th>Evening dose taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>..../..../......</td>
<td>Yes ☐ No ☐</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>..../..../......</td>
<td>Yes ☐ No ☐</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>..../..../......</td>
<td>Yes ☐ No ☐</td>
<td>Yes ☐ No ☐</td>
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<tr>
<td>..../..../......</td>
<td>Yes ☐ No ☐</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>..../..../......</td>
<td>Yes ☐ No ☐</td>
<td>Yes ☐ No ☐</td>
</tr>
</tbody>
</table>

Reason for not completing treatment

........................................................................................................................................
........................................................................................................................................

Completion of this form is not an admission of causation by, or contribution to, the adverse event by the medicine(s) or by the reporting professional. This information will be analyzed and will contribute to the safe use of molnupiravir.
Annex 4: Follow up questionnaire 2 (for health facility and home visits)

☐ D34  ☐ D64  ☐ D94

Health facility: .................................................................
Name of investigator/study staff……………………………………… Phone no………………………………………
Date…………………………………………
Signature………………………………

1. Patient details:
First name……………………………… Family name………………………………………
Clinic number (if available) ………………………………………
Unique ID no………………………………………………...
Date of birth: ....../..../………. Age: .......years
If female:
Pregnant?:  No☐ Uncertain☐ Yes ☐
If yes specify: please provide best estimate of gestational age: ______________weeks
Is the patient breast feeding a child? Yes ☐ No ☐

2. Type of follow-up
Internet /mobile app/
electronic tool for patient ☐ Date ....../..../........
Telephone interview ☐ Date ....../..../........
Attendance at health centre/clinic ☐ Date ....../..../........
Visit at home ☐ Date ....../..../........
Other (specify) ……………………………… ................. ☐ Date ....../..../........
Paper diary ☐ Date ....../..../........
Lost to follow-up ☐ Date ....../..../........
☐ Attempt 1 Date ....../..../........ ☐ Attempt 2 Date ....../..../........ ☐ Attempt 3 Date ....../..../........

3. Hospitalization
Any hospitalization since last date of contact: Yes ☐ No ☐
Date of hospital admission: ....../..../........
Date of discharge: ....../..../........
Reason for hospitalization/ diagnosis…………………………………………………………
Name and place of hospital…………………………………………………………………...
4. Any other serious event (life threatening, caused disability)? Y/N

<table>
<thead>
<tr>
<th>Description of event</th>
<th>Date event started</th>
<th>Date event stopped***</th>
<th>Outcome** (A,B,C etc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>…./…./….</td>
<td>…./…./….</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>…./…./….</td>
<td>…./…./….</td>
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</tr>
<tr>
<td>3.</td>
<td>…./…./….</td>
<td>…./…./….</td>
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</tr>
<tr>
<td>4.</td>
<td>…./…./….</td>
<td>…./…./….</td>
<td></td>
</tr>
</tbody>
</table>

*Please enter ‘C’ in this column if the event is ongoing

**Outcome:
A: resolved; B: resolving; C: resolved with sequelae; D: not resolved; E: death; F: unknown; G: severe.

*Please notify the pharmacovigilance focal person or pharmacist if any rechallenge is performed, and provide the result when known

*If the exact date of the start of an event cannot be recalled; an approximation of the date should be solicited (e.g. one week*
Annex 5: Follow up questionnaire for pregnant women

☐ M3  ☐ M6  ☐ M9

Health facility: .................................................................

Name of investigator/study staff.................................................. Phoneno.................................................................

Date …./…./………………………………………………

Signature.................................................................

Information to obtain from the patient (through self-reporting tool or through study staff)

A. Patients’ details:

First name.............................................................. Family name..............................................................

Clinic number (if available) ..............................................................

Unique ID no.................................................................

Date of birth: …./…./……..…./…./…. Age: …..years

Obstetrician or pregnancy clinic: .................................................................

B. Stage of pregnancy at exposure

Date of last menstrual period (LMP) if known /best estimate of gestational age in weeks: .................................................................

Date of drug exposure ................................................................ (obtained from previous follow-up forms)

Gestational age at the time of exposure to molnupiravir............ (to be calculated by electronic tool)

C. Recreational alcohol and drugs

Alcohol consumption ☐ Yes ☐ No ☐ Unknown

Illicit/recreational drug use

D. Current pregnancy status

Pregnant ☐ See section F

Estimate date of delivery …./…./……..__________________

Abortion or miscarriage ☐ No ☐ Yes (see ☐ See section E)

Given birth ☐ No ☐ Yes (see sections ☐ See section G AND, H)

E. Abortion or miscarriage

Date of induced abortion or spontaneous abortion/ miscarriage …./…./……..__________________
F. Complications during pregnancy

Any pregnancy complications e.g., gestational diabetes, anaemia pre-eclampsia?

☐ Yes (provide details below)  ☐ No  ☐ Not known

<table>
<thead>
<tr>
<th>Date</th>
<th>Description of pregnancy complications</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
</tbody>
</table>

G. Delivery/ childbirth outcomes

Delivery date: ..../..... DD/MM/20__/____

Hospital birth: ☐ Yes ☐ Nodelivered ☐ Y ☐ N________________

If yes, name of hospital _______________________

Name of physician/midwife: _______________________

Mode of delivery: ☐ Vaginal delivery ☐ ☐ Caesarean section

Any complications during childbirth? (e.g., fetal distress, amniotic fluid abnormal)?

☐ Yes  ☐ No  ☐ Unknown

If yes, please describe below:


H. Neonatal outcomes

Date of birth: ..../..../_______

Time of birth: __________

Gestational age: _________

Birth weight: __________

Any complications with the baby at birth?

☐ Yes (give details below)  ☐ No

<table>
<thead>
<tr>
<th>Date complication observed</th>
<th>Description of any complication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</table>
Information to be obtain from medical notes or medical staff by study staff for further investigation, if possible

A. Source of information

Pregnant women □
Primary care physician □
Obstetrician □
Pediatrician □
Midwife □
Other □ please specify_______________

B. Obstetrical history

Number of previous pregnancies and outcomes: (live birth, miscarriage, elective termination, with information on length of gestation and context, late foetal death, ectopic pregnancy, molar pregnancy)

__________________________________________________________________________________________

Previous maternal pregnancy complications:
__________________________________________________________________________________________

Previous fetal/neonatal complications and type:
__________________________________________________________________________________________

History of subfertility: ______________________________________________________________
__________________________________________________________________________________________

C. Maternal medial history

Any risk factors for adverse pregnancy outcomes including environmental or occupational exposures e.g., hypertension, diabetes, seizure disorder, thyroid disorder, asthma, allergic disease, heart disease, depression or other psychiatric disorders, sexually transmitted disease, hepatitis, HIV (specify viral load, CD4 count), other: ........................................................................................................................................................................

........................................................................................................................................................................

........................................................................................................................................................................

........................................................................................................................................................................

D. Family history

History of congenital abnormality, or disabilities in the family (specify: paternal/maternal and relationship)

........................................................................................................................................................................

........................................................................................................................................................................
Consanguinity between parents (specify degree)

E. Neonatal information

Date of birth: ..../..../……..
Mother’s participantID
Birth weight

If neonate died, primary cause of death:

☐ Preterm/low birth weight
☐ Birth asphyxia
☐ Infection
☐ Birth trauma
☐ Congenital/birth defects
☐ Other
☐ Unknown

Any congenital anomalies

☐ Neural tube defects
☐ Microcephaly
☐ Congenital malformations of ear
☐ Congenital heart defects
☐ Orofacial clefts
☐ Congenital malformation of digestive system
☐ Congenital malformation of genital organs
☐ Abdominal wall defects
☐ Chromosomal abnormalities
☐ Reduction defects of upper and lower limbs
☐ Talipes equinovarus/clubfoot
☐ Other
Annex 6: Data sharing agreement

Schedule of particulars

This data-sharing agreement comprises of: (i) this Schedule of Particulars; (ii) Annex I – General Conditions; and (iii) Annex II – Project Description (together, the “Agreement”).

Pursuant to the terms of this Agreement, the Contributor hereby agrees to provide, and WHO hereby agrees to accept, the Data for the Purpose of Use and subject to the Restrictions on Use.

In this Agreement, the following expressions are defined as:

1. The "Contributor": [full legal name of your institution];
2. "WHO": the World Health Organization, 20 Avenue Appia, CH-1211 Geneva 27, Switzerland;
3. The "Data": any data, results and reports, unpublished or otherwise, collected during or resulting from the Project which are owned by the Contributor and provided by the Contributor to WHO during the term of this Agreement;
4. The “Parties”: the Contributor and WHO;
5. The "Project": as further described in Annex II;
6. The "Purpose of Use": the Data are provided to WHO for WHO to implement the Project which is summarized in Annex II and for use in related materials and activities, including but not limited to WHO’s internal research purposes;
7. The "Restrictions on Use": the Data shall not be used for any purpose other than the Purpose of Use;
8. The "Term of Agreement": [Unrestricted in time]; and
9. "Data Charges": the Data will be provided free of charge.

Acknowledged and agreed:

Signed for and on behalf of WHO

Signed for and on behalf of the Contributor

Title: Lead, Pharmacovigilance
Date:

Title:
Date:
Data Sharing Agreement
Annex I

GENERAL CONDITIONS

1. Use

1.1. The Data are supplied by the Contributor to WHO solely for the Purpose of Use and subject to the Restrictions on Use.

1.2. Other than for and within the Purpose of Use, the Data shall not be transferred, sold, offered for sale or otherwise used, without the prior written agreement of the Contributor.

1.3. WHO shall only allow parties who have a need to know for the Purpose of Use and who are bound by similar obligations of confidentiality and restrictions on use as contained in this Agreement to have access to the Data.

1.4. In implementing the Purpose of Use, WHO will: not attempt to identify or contact research participants included in the Data; Respect the confidentiality of the Data; and maintain the Data in a secure location on a password-protected, WHO-internal network protected by standard encoding and the WHO firewall for the duration of the Purpose of Use.

2. Confidentiality

2.1. The Data may incorporate confidential information of the Contributor. Accordingly, if and to the extent any such Data are clearly marked by the Contributor as “confidential”, WHO shall during the term of this Agreement and for a period of five years following its termination, treat such Data confidential and only disclose them under like obligations of confidentiality and restrictions on use as those contained herein. WHO shall be deemed to have fulfilled its obligations, if it exercises at least the same degree of care in maintaining confidentiality as it would in protecting its own confidential information.

2.2. However, the above mentioned obligations of confidentiality shall not apply to Data which: (i) can be shown to have been known to WHO at the time of its acquisition from the Contributor; (ii) are acquired from a third party, not in breach of any obligation of confidentiality to the Contributor; (iii) are independently devised or arrived at by, on behalf of, or for WHO without access to the Information; or (iv) enter the public domain otherwise than by breach of the undertakings set out in this Agreement.

3. Rights

3.1. Except for the rights explicitly granted to WHO hereunder, nothing contained in this Agreement shall be construed as conveying any rights under any patents or other intellectual property which either party may have or may hereafter obtain.

3.2. Nothing contained in this Agreement shall restrict the Contributor's right to sell, transfer, assign or distribute the Data to any other person for commercial or non-commercial purposes.

4. Publications

4.1. Subject to the Contributor’s proprietary rights, the results obtained through use of the Data within the Purpose of Use may be published by WHO and/or parties collaborating with WHO. In order to avoid prejudice to the Contributor’s proprietary rights, WHO shall transmit any material intended to be published or relevant portions thereof, to the Contributor under confidential cover for review at least ten days prior to its submission to any editor, publisher, referee or meeting organizer. In
absence of any objection by the Contributor within that ten day period concerning prejudice to its proprietary rights, the
publication may proceed, provided, however, that the Contributor shall be duly acknowledged in such publication.

4.2. WHO will prepare manuscript(s) of the results of the Purpose of Use for publication, pursuant to the terms of the
applicable protocol, and publish such manuscripts pursuant to WHO’s rules and regulations, including its policy on open access,
as contained at: http://www.who.int/about/policy/en/. WHO may further use the results of the Purpose of Use to update relevant
WHO recommendations and develop any guidelines, including publication thereof, and may further publish those results.

4.3. If a manuscript of the Research Activities is submitted for publication, WHO will in all events retain the Data until the
peer review process is completed, and then for one year after publication to ensure sufficient time to address any required
responses to the findings (e.g., letters to the editor).

4.4. WHO will ensure that all publications relating to the Data will appropriately acknowledge WHO, the Contributor, and all
other entities contributing data to the publication.

5. Undertakings of the Contributor

5.1. The Contributor represents and warrants that: It has obtained all rights and permissions necessary to transfer the Data to
WHO and for WHO to implement the Purpose of Use and all other activities relating to the Data as described herein; The Data
have been collected from clinical trials, observational studies, or surveillance systems that have been conducted in accordance
with all applicable laws; and The individual(s) to whom the Data relate have provided their ‘informed consent’ to participate in
the study wherein their data was collected if required by, and in accordance with, applicable laws.

5.2. Prior to transmitting the Data to WHO, the Contributor will: Verify whether approval from their local/relevant Ethics
Review Committee is required for the use of the Data for the Purpose of Use, and if that approval is required, obtain it; and
Anonymize all participant-level data in the Data, pursuant to agreed standards, to remove all information in the Data that could be
used to identify research participants.

5.3. The Contributor will transmit the Data to WHO securely, using secure file transfer protocol.

5.4. The Contributor will avoid providing to WHO any information relating to the Data or the Research Activities that relates
to a natural person, which, either directly or indirectly, in combination with other information available or likely to be available to
WHO, can identify such natural person.

5.5. The Contributor makes no warranty of the fitness of the Data for any particular purpose or any other warranty, either
express or implied. However, to the best of the Contributor’s knowledge, the use of the Data within the Purpose of Use shall not
infringe on the proprietary rights of any third party.

5.6. WHO agrees that (except as may explicitly be provided in this Agreement) the Contributor has no control over the use
that is made of the Data by WHO or parties collaborating with WHO in accordance with the terms of this Agreement.
Consequently, WHO agrees that the Contributor shall not be liable for such use.

6. Other Matters

6.1. Nothing in this Agreement shall be interpreted as establishing a partnership between the parties or establishing one party
as the agent of the other or conferring a right on one party to bind the other, except as may be specifically set out herein.
6.2. Without the prior written approval of the other Party, neither Party shall, in any statement or material of an advertising or promotional nature, refer to this Agreement or the relationship between the Parties, or use the name (or any abbreviation thereof) and/or emblem of the other Party.

6.3. Any dispute relating to the interpretation or application of this Agreement shall, unless amicably settled, be subject to conciliation. In the event of failure of the latter, the dispute shall be settled by arbitration. The arbitration shall be conducted in accordance with the modalities to be agreed upon by the parties or, in the absence of agreement, with the rules of arbitration of the International Chamber of Commerce. The Parties shall accept the arbitral award as final.

6.4. Nothing contained herein shall be construed as a waiver of any of the privileges and immunities enjoyed by WHO under national or international law and/or as submitting WHO to any national court or jurisdiction.

6.5. This Agreement sets forth the entire understanding between the parties and supersedes any prior agreements, written or verbal related to the Data. It shall only be capable of change by written amendment executed by duly authorized officers of the Parties.
Data Sharing Agreement
Annex II

PROJECT DESCRIPTION

Background

WHO has provided a conditional recommendation for molnupiravir, a novel oral medicine for treatment of non-severe COVID-19 in those at highest risk of hospitalization. The conditional recommendation reflects the concern for widespread treatment with molnupiravir before more safety data become available, and mitigation strategies include undertaking active pharmacovigilance surveillance. Cohort event monitoring (CEM) is an active surveillance method that can be used to follow-up early users of molnupiravir to ensure timely collection of post-market safety data.

This is a master cohort event monitoring protocol investigate the safety of molnupiravir. The study will be conducted in health facility sites where molnupiravir is provided by the national health authorities in between 6 to 12 countries across the six WHO regions. Study participants will be actively followed up from the start of molnupiravir therapy for up to three months after the last dose. Data from countries will be anonymized, pooled and stored in a repository at WHO Headquarters in Geneva. The data will be analysed to characterize and estimate the incidence of adverse events that occur during and after treatment with molnupiravir, so that potential safety issues are detected and addressed early so that any impact on benefit risk can be rapidly identified and assessed.
Participant information sheet

You are visiting this health facility to receive the first dose of molnupiravir as part of routine care. This health facility is participating in observational research, i.e., a study that observes patients without an intervention or changing their care, to understand more about side effects and safety of molnupiravir in patients with mild to moderate symptoms who have tested positive for COVID-19 and are at high risk of severe disease.

This study is taking place in several health facilities in at least six countries. Between 10,000 and 30,000 persons taking molnupiravir will be included in the study and will be followed up for three months after finishing the treatment with molnupiravir to understand more about its side effects. Molnupiravir is not recommended in pregnant women as there is no information on the safety of molnupiravir from clinical trials in pregnant women.

However, sometimes a woman may take molnupiravir without knowing that she is pregnant. If this occurs, the study will follow up the pregnant women until the end of pregnancy, and the child until the child is one year of age.

The study sponsor is [STUDY SPONSOR], and the principal investigators are [to be completed by country].

If you participate in the study, you will be interviewed at the start (during enrollment) and then you will receive regular questionnaires throughout the study period. In the initial interview, you will be asked about your medical and medication history, current COVID-19 symptoms and diagnosis, any medical events that you have experienced in the past seven days, your contact information and contact information of your next of kin. During the follow-up period you will be asked about any medical events that you experience during molnupiravir treatment and for five days after; and any serious events that may have occurred up to three months after taking molnupiravir. In the case of hospitalization, when possible, study staff may contact the hospital and treating physicians to confirm medical diagnosis.

By participating in the study you agree:

- to complete the study questionnaires [THROUGH MOBILE/INTERNET/TELEPHONE] (daily for each day of molnupiravir treatment course, five days after last dose, then monthly for three months;)
- to be contacted by phone and in case of non-response, your next of kin can be contacted;
- to provide information on the name of the hospital or treating physician, in the case of hospitalization, and to provide a summary of the discharge letter to study staff if available;
- that the [NATIONAL PHARMACOVIGILANCE CENTER, to be detailed in the protocol] may contact your healthcare provider to access medical records/notes, if further investigation is required;
- that, in the event you find that you are pregnant during the study, the [STUDY INVESTIGATORS and NATIONAL PHARMACOVIGILANCE CENTER, to be detailed in the protocol] may follow you until the end of your pregnancy, to monitor the safety of molnupiravir, when taken during pregnancy. Additionally, the child born following maternal exposure to molnupiravir will be followed up until the infant is one year old.

Agreeing to participate in this study will not affect or change the therapeutic treatment that you will receive for COVID-19 disease. Although there is no direct benefit to you from participating in the study, the community will benefit from your contribution as it will allow the public to have a better knowledge about the side effects of molnupiravir.

Your individual identity will be protected because the final information used for the research study will not bear your name, contact details or any other personal information about you that will allow you to be identified. The health facility will assign a responsible person to use and store the research data in a safe place.
Anonymized data obtained from this study will be shared with the national pharmacovigilance system in addition to WHO Headquarters, and will be stored in a secured database located at WHO Headquarters, Geneva. Your personal data will always be handled in accordance with all applicable data protection and privacy laws. All information about you as an individual is confidential and will be protected and only communicated to authorized persons. Any information collected from other doctors will be handled in the same confidential manner as those collected by the study doctor. Data will stored for three years, and will then be destroyed. Should you decide to stop participating in the study, all data collected up until the time of withdrawal will be used in the analyses.

A global team at WHO will investigate unusual and unexpected side effects.

If you are willing to participate in this study that will monitor the safety of molnupiravir, please sign and date this form. You are free to contact [XXX] to understand how your information will be used. If at any time you do not wish to share your information, you are free to contact [XXX] and withdraw from this study. Participation in this study is completely voluntary and you have the choice to say no and opt out of this research. Not participating, or withdrawing from this study, will not impact your access to healthcare.

I have read the above information, or it has been read to me. I have had the opportunity to ask questions about it and all questions have been answered to my satisfaction. I consent voluntarily to be a participant in this study.

Print name of participant ...............................................................................................................................................................

Signature of participant
Date ........../........../................... (Day/month/year)

Statement by the researcher/person taking consent: I have accurately read out the information sheet to the potential participant. I confirm that the participant was given every opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the consent has been given freely and voluntarily, and that the individual has not been coerced into giving consent. A copy of this informed consent form has been provided to the participant.

Print name of researcher/person taking the consent ............................................................

Signature of researcher/ person taking the consent
Date ........../........../................... (Day/month/year)
Annex 8: Informed consent form template for pregnant women

Participant information sheet

You are being provided with this information because you are participating in the [name of sponsor] study that is monitoring the safety of molnupiravir for treatment of COVID-19 disease and you were given molnupiravir during your pregnancy. Currently there is no information on how molnupiravir affects pregnancy or the baby from clinical trials. For this reason it is important that any pregnant women who has received molnupiravir during pregnancy is followed up through this study.

The study is taking place in several health facilities in at least six countries. If you participate in this part of the study, you will be followed up every three months until the end of your pregnancy. Information on what stage of pregnancy you received molnupiravir, medication and lifestyle history, complications during pregnancy including miscarriages or abortions, delivery and the baby will be collected. Study staff may need to obtain additional information by contacting your treating physicians/medical staff to obtain information on obstetrical, maternal and family history and information about your baby.

By agreeing to participate in this part of the study you agree:

- to complete the study questionnaires [THROUGH MOBILE/INTERNET/TELEPHONE] (every three months until the end of pregnancy);
- to be contacted by phone, and in case of non-response, your next of kin can be contacted;
- to provide information on the name of the centre where you delivered the baby, contact details of obstetrician / maternal facility that monitored your pregnancy;
- that the [NATIONAL PHARMACOVIGILANCE CENTER, to be detailed in the protocol] may contact your healthcare provider to access medical records/notes if further investigation is required.

Agreeing to be part of this study will not affect or change your obstetric medical care. The public will benefit from your contribution as it will allow the community to have a better understanding of the any effects molnupiravir might have on pregnancy or the child.

Your individual identity will be protected because the final information used for the research study will not bear your name, contact details or any other personal information about you that will allow you to be identified. The health facility will assign a responsible person to use and store the research data in a safe place.

Anonymized data obtained from this study will be shared with the national pharmacovigilance system and with WHO Headquarters, and the data will be stored in a secured database located at WHO Headquarters, Geneva. Your personal data will always be handled in accordance with all applicable data protection and privacy laws. All information about you as an individual is confidential and will be protected and only communicated to authorized persons. Any information collected from other doctors will be handled in the same confidential manner as those collected by the study doctor. Data will be stored for three years, and will then be destroyed. Should you decide to stop participating in the study, data collected up until the time of withdrawal will be used in the analyses.

If you are willing to participate in this study that will monitor the safety of molnupiravir during pregnancy, please sign and date this form. You are free to contact [XXX] to understand how your information will be used. If at any time you do not wish to share your information, you are free to contact [XXX] and withdraw from this study. Participation in this study is completely voluntary and you have the choice to say no and opt out of this research. Not participating, or withdrawing from this study, will not impact your access to healthcare.
I have read the above information, or it has been read to me. I have had the opportunity to ask questions about it and all questions have been answered to my satisfaction. I consent voluntarily to be a participant in this study.

Print name of participant ...............................................................................................................................................................

Signature of participant

Date ................../....................../................... (Day/month/year)

Statement by the researcher/person taking consent: I have accurately read out the information sheet to the potential participant. I confirm that the participant was given every opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the consent has been given freely and voluntarily, and that the individual has not been coerced into giving consent. A copy of this informed consent form has been provided to the participant.

Print name of researcher/person taking the consent .................................................................

Signature of researcher/ person taking the consent

Date ................../....................../................... (Day/month/year)
Annex 9: Parent consent form template

Information sheet

This informed consent form is for parents of neonates/infants being followed up after fetal exposure to molnupiravir, or parents of infants who received molnupiravir through breast milk.

You are receiving this consent form because you are enrolled in an observational study that is monitoring the safety of molnupiravir in patients with mild to moderate symptoms who have tested positive for COVID-19 and are at high risk of severe disease. You have informed the study team that you:

- [ ] Received molnupiravir during pregnancy
- [ ] Received molnupiravir whilst breastfeeding

The study sponsor is [STUDY SPONSOR], and the principal investigators are [to be completed per country]. We are doing research to understand the safety of molnupiravir in infants born to mothers who received molnupiravir during pregnancy or in children who are exposed to molnupiravir through breast milk. This study will help us understand the effects of molnupiravir in this population. Whenever researchers study children, we talk to parents and ask them for their permission. Please feel free to talk to the study team about this research and take the time to reflect on whether you would like your child to participate or not. If you consent to your child’s participation data will be collected through questionnaires:

- [select as appropriate]
  - from you by interview every 6 months until your child is one year of age (fetal exposure during pregnancy)
  - from you on days 0,1,2,3,4 during molnupiravir treatment, and days 9, 34, 64, and 94 after molnupiravir treatment (exposure through breastmilk).

By participating in the study you agree:

- to complete the study questionnaires at the time points listed above;
- the [NATIONAL PHARMACOVIGILANCE CENTRES, to be detailed in the protocol] may contact your child’s healthcare provider to access medical records/notes if further investigation is required.

This study will not lead to any changes in your child’s routine care. Your child will not be receiving any intervention as part of the study so, there will be no direct benefit to him/her from this research. Although there is no direct benefit to your child from participating in the study, the community will benefit from your contribution as it will allow the public to have a better understanding knowledge about the side effects of molnupiravir.

The individual identity of your child will be protected because the final information used for the research study will not bear their name, contact details or any other personal information that will allow your child to be identified. The study team will assign a responsible person to use and store the research data in a safe place.

The key-coded data obtained from this study will be shared with the national pharmacovigilance system and WHO Headquarters, and will be stored in a secured database located at WHO Headquarters, Geneva. Your child’s personal data will always be handled in accordance with all applicable data protection and privacy laws. All information about your child as an individual is confidential and will be protected and only communicated to authorized persons. Any information collected from other doctors will be handled in the same confidential manner as those collected by the study doctor. Data will be archived for three years, and will then be destroyed. Should you decide to withdraw your child from the study, data collected up until the time of withdrawal will be used in the analyses.
If the study observes an adverse event occurring more frequently than expected, this will be investigated by a global team convened by WHO.

If you are willing to consent to your child participating in this study that will monitor the safety of molnupiravir, please sign and date this form. You are free to contact [XXX] to understand how your information will be used. If at any time you do not wish to share your child’s information, you are free to contact [XXX] and withdraw from this study. Participation in this study is completely voluntary and you have the choice to say no and opt out of this research. Not participating, or withdrawing from this study, will not impact your child’s access to healthcare.

I have read the above information, or it has been read to me. I have had the opportunity to ask questions about it and all questions have been answered to my satisfaction. I consent voluntarily for my child to participate in this study.

Print name of child ...............................................................................................................................................................
Print name of parent 1 ...............................................................................................................................................................

Signature of parent 1
Date ............./....................../........................ (Day/month/year)

Print name of parent 2 ...............................................................................................................................................................

Signature of parent 2
Date ............./....................../........................ (Day/month/year)

Statement by the researcher/person taking consent: I have accurately read out the information sheet to the potential parent. I confirm that the parent was given every opportunity to ask questions about the study, and all the questions asked by the parent have been answered correctly and to the best of my ability. I confirm that the consent has been given freely and voluntarily, and that the individual has not been coerced into giving consent. A copy of this informed consent form has been provided to the parent.

Print name of researcher/person taking the consent ..........................................................
Signature of researcher/ person taking the consent
Date ............./....................../........................ (Day/month/year)
Annex 10: Assent consent form for minors and adolescents

Information sheet

This informed assent form is for children and adolescents <18 years who have been given molnupiravir for treatment of COVID-19 infection.

My name is [recruiting research staff/principle investigator] and my job is to research the safety of a medicine called molnupiravir. This medicine is used to treat people who have COVID-19. We would like to know about the side effects of this medicine.

I am going to give you information and invite you to be part of the research study. You can choose whether you want to participate. We have discussed this research with your parent(s) or guardian and they know that we are also asking you for your agreement. If you are going to participate in the research, your parent(s)/ guardian also have to agree. But if you do not wish to take part in the research, you do not have to, even if your parents have agreed.

You may discuss anything in this form with your parents or friends or anyone else you feel comfortable talking to. You can decide whether to participate or not after you have talked it over with them. You do not have to decide immediately.

There may be some words you do not understand or things that you want me to explain more about because you are interested or concerned. Please ask me to stop at any time and I will take time to explain.

By doing this research we can learn about the side/unwanted effects of the new medicine molnupiravir. If you decide that you want to do this the following things will happen:

1. Your parents will be asked questions about your health and any medical events that have happened before you took molnupiravir.
2. Your parents will be asked about any side effects and any medical events that you may have while taking molnupiravir and for three months after taking molnupiravir.
3. The research team will contact your doctors and review your hospital records.

I have checked with the child and they understand the study______________(initials)

Molnupiravir is not recommended for those that are under the age of 18 as it could affect bone development. Therefore, it is very important that anyone under the age of 18 who received the drug accidently is followed-up. Agreeing to be part of this study will not affect or change how doctors will treat your condition and there will be no direct benefits to you, however the study will help others by learning from your experience. We will not tell other people that you are in this research and we will not share information about you to anyone who does not work in the research study.

Information about you that will be collected from the research will be stored safely and no one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up in a secure place. It will not be shared with or given to anyone except [name who will have access to the information, such as research sponsors]

You do not have to participate in this research. No one will be mad or disappointed with you if you say no. It is your choice. You can think about it and tell us later if you want. You can say "yes" now and change your mind later and it will still be okay.

You can ask me questions now or later. You can ask the nurse questions. I have written a phone number and address where you can reach us or, if you are nearby, you can come and see us. If you want to talk to someone else that you know like your teacher or doctor or auntie, that's okay too.
I understand the research is about understanding the side or unwanted effects of molnupiravir used for COVID-19 infection. I understand that I will be asked questions about medical events that may have occurred while taking this medicine and for three months after.

I have read this information or have had the information read to me. I have had my questions answered and know that I can ask questions later if I have them.

I agree to take part in the research.

OR

I do not wish to take part in the research and I have not signed the assent below. __________(initialed by child/adolescent)

Print name of child ___________________
Signature of child: ___________________
Date: ____/_____/______ day/month/year

I have accurately read or witnessed the accurate reading of the assent form to the potential participant. I confirm that the child was given an opportunity to ask questions about the study, and all the questions asked by him/her have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

Print name of researcher ______________
Signature of researcher __________________
Date ___/_____/______ Day/month/year

Copy provided to the participant _______(initialed by researcher/assistant)

Parent/Guardian has signed an informed consent ___Yes ___No _____(initialed by researcher/assistant)
## Annex 11: Roles and responsibilities of stakeholders

<table>
<thead>
<tr>
<th>Team</th>
<th>Stakeholder</th>
<th>Roles and responsibilities</th>
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</thead>
</table>
| Master protocol team          | WHO HQ, regional and country offices                                        | • Develop the protocol  
• ERC of master protocol  
• ERC of site-specific protocol (after approval nationally)  
• Communicate findings to country specific teams  
• Coordinate different teams  
• Training                                                                                                                                                     |
| Country specific team         | Researchers or national pharmacovigilance programme or a mixture of both    | • Principle investigators  
• Recruit patients; provide informed consent forms  
• Fill out baseline questionnaire  
• Follow up patients (home visits, phone calls, send web follow up forms/push notifications)  
• Perform country specific analysis  
• Alert national authorities of any signals of concern  
• Training of study staff  
• Work with signal detection team on causality assessments                                                                                                                                                         |
| Data management team          | WHO HQ                                                                      | • Develop the data collection tools  
• Develop the data transfer and management tools, IT solutions  
• Assist countries to use the tools, training                                                                                                                                                                         |
| Data analysis team            | WHO HQ, WHO CC (UMC) Statistician                                          | • Write statistical analysis plan  
• Perform interim analysis (pooled events)  
• Perform final analysis  
• Communicate findings to country specific team                                                                                                                                                                   |
| WHO signal detection team     | WHO CC (UMC) Appointed persons from each participating country:             | • Review data for any signals  
• Signal validation, in depth review  
• Causality assessment  
• Compare background rates; determine if higher than expected                                                                                                                                                   |
<table>
<thead>
<tr>
<th>Team</th>
<th>Stakeholder</th>
<th>Roles and responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality assurance and monitoring</td>
<td>Implementing partners</td>
<td>• ERC of site-specific protocol (after approval nationally)</td>
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<tr>
<td></td>
<td></td>
<td>• Site initiation visit</td>
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<td></td>
<td></td>
<td>• Monitoring of the study conduct to assess the accuracy and completeness of the data</td>
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<tr>
<td></td>
<td></td>
<td>• Quality assurance visit</td>
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<tr>
<td></td>
<td></td>
<td>• Key performance indicators</td>
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