STANDARD OPERATING PROCEDURE (SOP)

TITLE: COVID MEASURES FOR CLINICAL RESEARCH ASSOCIATES (CRA)

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Applicable Clinique Research Site(s):	All

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Signature:	
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1. PURPOSE:

The purpose of this SOP is to describe the Covid measures for Clinical Research Associate undertaken at Clinique Research and to ensure:

- All relevant parties (sponsors and sites) are consulted and can support the project.
- The proposed trials are a strategic fit and aligns with Clinique Research's core values.
- Research projects have the best possible outcome in terms of recruitment, patient safety, budget, and time frames.

2. SCOPE:

All clinical trials to be monitored and managed at Clinique Research.

3. APPLICABILITY:

This applies to all Clinique Research employees, contract staff and to all relevant external persons or parties proposing to engage in the clinical trial services at Clinique Research.

4. GLOSSARY OF TERMS:

Please refer to Clinique Research SOP Glossary of Terms (see Related Documents).

5. PROCEDURE:

It is very difficult to predict the impact on clinical trial activity during a full pandemic situation as it will be complicated by trial staff being re-deployed to assist with core healthcare activities, as well as potential illness amongst the trial teams subjects and restrictive measures in place in sites. When trial activity continues, Sponsors are expected to continue to meet their obligations with respect to clinical trials legislation, guided where necessary by Clinique Research, Site Country's Centre for Disease Control (CDC).

5.1 Changes to Ongoing Trials

- Sponsors should consider in their risk assessment whether the following measures could be the most appropriate during COVID-19. Measures should generally be agreed with investigators and could be:
    - Conversion of physical visits into phone or video visits, postponement or complete cancellation of visits to ensure that only strictly necessary visits are performed at sites.
    - A temporary halt of the trial at some or all trial sites.

- Interruption or slowing down of recruitment of new trial participants – the feasibility of including new trial participants in an ongoing trial needs to be critically assessed.
- Extension of the duration of the trial.
- Postponement of trials or of activation of sites that have not yet been initiated.
- Closing of sites. In case it is not feasible for a site to continue participation at all, the sponsor should consider if the trial site should be closed and how this can be done without compromising the rights, safety and well-being of trial participants and data validity.
- If unavoidable (it should be justified that this is a truly exceptional situation based on the personal benefit-risk ratio for the individual trial participant), transfer of trial participants to investigational sites away from risk zones, or closer to their home, to sites already participating in the trial, or new ones, could occur. Initiation of new trial sites is generally not expected in the current situation unless no other solution exists for the trial participant. If there is an urgent need to open a new trial site for critical trial visits, for example outside the hospital, this may be implemented as an urgent safety measure first, followed by a substantial amendment application for the approval and initiation of this additional site. In such cases, it is important that trial participants as well as investigators (both receiving and sending) are in agreement about the transfer, that the receiving site has the possibility to access previously collected information/collected data (including necessary medical records) for the trial participant and that any eCRF can be adjusted accordingly to allow the receiving site to enter new data. The impact on trial participants should be considered and arrangements made such as providing adequate transportation.
- There may be a need for critical laboratory tests, imaging or other diagnostic tests to be performed, (e.g. blood cell count, liver function test, X-ray, CT, MRI, ultrasonography, ECG etc.), e.g. for trial participant safety or the integrity of the trial. In case the trial participant cannot reach the site to have these performed, it is acceptable that laboratory, imaging or other diagnostic tests are done at a local laboratory or relevant clinical facility authorized/certified (as legally required nationally) to perform such tests routinely, if this can be done within local restrictions on social distancing. The sites should inform the sponsor about such cases. Local analysis can be used for safety decisions. If this is a trial endpoint and biological samples cannot be shipped to the central laboratory, analysis should be performed locally and then explained with detailed justification, assessed and reported in the clinical study report following ICH E3. In these cases, it is

important that the sponsor is given access to the normal ranges and certification information of any additional laboratory used in order to support the use and evaluation of results.

- **Risk Assessment**
- The safety of the trial participants is of primary importance, and risks of involvement in the trial, with added challenges due to COVID-19, should be weighed against anticipated benefit for the trial participants and society.
- All decisions to adjust clinical trial conduct should be based on a risk assessment by the sponsor. It is expected that the sponsor performs a risk assessment of each individual ongoing trial and the investigator of each individual trial participant and implement measures, which prioritize trial participant safety and data validity. In case there's conflict, trial participant safety always prevails.
- These risk assessments should be based on relevant parties' input and should be documented on an ongoing basis. It is important that sponsors in their risk assessment consider prioritization of critical tasks in the clinical trial and how these are best maintained.
- The sponsor should reassess risks as the situation develops. This reassessment should also be documented as part of the sponsor's trial master file.
- It is possible that, with the escalation of the pandemic, local circumstances lead to a local change in risk assessment, therefore the need to implement additional measures may arise, and an investigator-driven risk assessment might be necessary. This assessment should be documented in the investigator's site master file and communicated to the sponsor.
- The potential impact of COVID-19 on trial participants who may be determined as being part of a-risk group for COVID-19 or who are in trials involving treatments, which may increase such risks, should be carefully considered when deciding to start or continue such clinical trials.

5.2 Changes to Clinical Research Associate Monitoring

- Certain Clinique Research's responsibilities, such as monitoring and quality assurance activities need to be re-assessed and temporarily, alternative proportionate mechanisms of oversight may be required.
- The priority when considering any change is to protect the rights, safety and wellbeing of trial participants. As part of the risk assessment, a risk-based approach to monitoring should be taken, focusing on certain sites, certain data points and certain processes that are critical to ensure the rights, safety and well-being of trial participants and the integrity of the trial

(and trial data). The sponsor should consider the extent and nature of monitoring that would be eligible in each specific trial under this exceptional situation, and weigh this against the extra burden that introduction of any alternative measures would put on site staff and facilities. The monitoring plan should then be revised in accordance with these considerations, in order to strike an acceptable balance between appropriate oversight and the capacity of the trial site.

- Results of adjusted monitoring/review measures and their impact should be reported to the sponsor in monitoring reports and in the clinical study report, where applicable.
- It is essential that robust follow-up measures are planned and ready to be implemented when the situation is normalized. This should include increased on-site monitoring for a period that is sufficient to ensure that the impact of the reduced monitoring can be rectified, and problems resolved or properly documented. Data subject to remote source data verification are likely to require re-monitoring, if it was based on pseudonymized documents, which cannot be considered as source documents, and considering that remote monitoring is expected to only have focused on the most critical information.
- Adjusting monitoring activities may include a combination of the following:
    - ❖ On-site monitoring
        - Cancelling or postponing of on-site monitoring visits and extending of the period between monitoring visits are likely to be necessary.
        - To the extent on-site monitoring remains feasible, it should take into account national, local and/or organizational social distancing restrictions, the urgency (e.g. source data verification can often be postponed) and the availability of site staff and should only be performed as agreed with trial sites.
        - Additional measures regarding on-site monitoring may include limited, targeted on-site monitoring identifying higher risk clinical sites, if not already applicable for the trials of concern.
        - The on-site monitoring plan will need to be adapted and alternative measures (like those outlined below put in place or relied on to a greater extent if already present.

    - ❖ Centralized monitoring and central review of data collected
        - Centralized monitoring of data acquired by electronic data capture systems (e.g. eCRFs, central laboratory or ECG / imaging data, ePROs etc.) that are in place or could be put in place provides additional monitoring capabilities that can supplement and temporarily replace on-site monitoring through a remote evaluation of ongoing and/or cumulative data collected from trial sites, in a timely manner.

- ❖ Off-site monitoring
  - Additional off-site monitoring activities could include phone calls, video visits, e-mails or other online tools in order to discuss the trial with the investigator and site staff, to get information on the clinical trial progress, to exchange information on the resolution of problems, review of procedures, trial participant status as well as to facilitate remote site selection and investigator training for critical trials.

- ❖ Remote Source Data Verification (SDV)
  - Remote SDV may be considered for trials:
- ✓ Involving COVID-19 treatment or prevention
- ✓ Investigating serious or life-threatening conditions
- ✓ Where the absence of SDV for critical data may likely pose unacceptable risks to participants' safety or the reliability/integrity of trial results
- ✓ Involving particularly vulnerable participants such as children or those temporarily (e.g. trials in emergency situations) or permanently (e.g. trials in patients with advanced dementia) incapable of giving their informed consent or
- ✓ In pivotal trials

- The sponsor should determine the extent and nature of remote SDV that they consider needed for each trial under this exceptional situation and should carefully weigh it against the extra burden that introduction of any alternative measures would put on site staff and facilities.
- In the case of these trials, principal investigators would make their own determination as to whether the situation at their clinical site allows any of the following options for remote SDV:
  - ✓ Sharing pseudonymized copies of trial related source documents with the monitor; this may be done electronically where manageable by the site staff
  - ✓ Direct, suitably controlled remote access to trial participants' electronic medical records
  - ✓ Video review of medical records with clinical site team support, without sending any copy to the monitor and without the monitor recording images during the review

- For COVID-19 trials starting now, when remote SDV is foreseen, it should be described in the initial protocol application (and informed consent form). In case of ongoing trials, introduction of remote source data verification should be submitted, in line with national law or temporary national emergency measures, via a substantial amendment. These

provisions should be in line with the principles of necessity and proportionality and in a way that protects trial participants' rights and should not place any disproportionate burden on site staff as determined by the investigator and trial site staff.

- Remote SDV can be carried out only in agreement with the Principal Investigators.
- Remote SDV should not be carried out if adequate data protection, including data security and protection of personal data even if pseudonymized, is not ensured.

6. VERSION CONTROL:

Document History	
Version	**Summary of Changes**
1.0	N/A – First Issue

7. APPENDIX:

A Pictorial Representation of Mask and Mask-Wearing
A Pictorial Representation of Hand Washing
A Pictorial Representation of Sanitizer