CLINICAL TRIAL MANAGEMENT DURING COVID-19

20 May 2020

Inside

"There is no stopping people from discovering drugs and therapies. For as long as there is drug discovery, there is the conduct of clinical trials ."

Message from Philippine Clinical Research Professionals, Inc.

This newsletter contains recommendations representing the current thinking of the PCRP leadership and the best practices at this time.

As we all try to navigate the unprecedented change in our environment, it is important to reflect on how do we move forward as a research community, and define our so called "new normal" .

The overriding considerations remain the same in the role that we play as Monitors. These are :

1. Safety and well being of research participants, site staff and sponsor personnel;

2. Compliance to regulations, government directives, hospital policies, professional societies' codes, SOPs and standards;

3. Continuity of clinical research endeavors without compromising quality and safety;

The New Normal

Remote monitoring and the pivot to electronic platforms should be part of the game plan for the new normal. Now more than ever, Sponsors and CROs should seriously consider and maximize digital platforms and tools for monitoring activities. Partners and other stakeholders such as IRBs should consider shifting to electronic transactions for submission, payment and communication. Paperless or scan-destroy methods for forms handled by patients must be considered too. It is worthwhile for all stakeholders to shift to, or make available, electronic, contactless transactions and reduce or altogether eliminate the need for paper transactions.

It is our hope that you will find this newsletter useful as you manage the changes in our environment. You may also refer to the web links to local institutional requirements and references to national and international COVID-19 guidelines compiled and collated by PCRP.

To say that 2020 is proving to be the most challenging year is an understatement. It is beyond challenging. As we turn inward and re-assess our values as individuals and the values of our organization and of our work, we realize that it is the WORK THAT WE DO that serves as the silver lining behind these tough times. Clinical trials are indeed what is needed to find the cure and prevention for COVID-19.

With collaboration, teamwork and innovative thinking, we can soldier on and fulfil our mandate. It has always been a source of pride to be part of the clinical research industry, this is exponentially true at this time. So thank you for all that you do.

And .... let's all stay safe!

General Considerations

It is important for us to ensure that trial subjects, site staff and monitors are safe in managing clinical trials while COVID -19 is still a threat. Potential exposure to coronavirus infection should be minimized and altogether eliminated as we go on with daily activities in the clinical trials that we conduct in the Philippines.

COMMUNICATIONS : All changes to study processes i.e. in the monitoring plan must be discussed and agreed with the site staff, and even by the trial subjects themselves in some situations. There are specific recommendations such as direct IP delivery to patients or home visits in lieu of patient visit to the hospital that will need consent from trial subjects.

IRBs must be informed of changes to study processes. Major changes in the protocol must be in the form of an amendment and should wait for approval except those that have been put in place to eliminate risks to patients being exposed to coronavirus. These changes can be reported to IRBs at a later date. (continued on page 3)

Patient Visits

Whenever possible, it is best for on-site patient visits to be avoided during this time of COVID-19. There are several alternatives to on-site patient visits that may be considered to enable the study to continue monitoring the trial subjects' participation in the clinical study.

Remote Calls An alternative option for non-critical protocol visit is to conduct remote calls to the trial subjects. Remote contact of trial subject is valuable to assess the willingness to continue participation in the study, provide study updates or gather health status. Phone calls to check on trial subject's safety and compliance to the study protocol must be conducted in a regular basis. Trial subjects should be encouraged to call to the site for any question and/or changes in their health status.

Video Calls Another alternative is conduct video calls to enable site staff to see the patient via video. Video call may be suitable if the investigator needs to perform basic assessment with the trial subject.

Home Visits/Home Care Depending on the trial subject's location, home visits may be considered by the site for trial subject who cannot travel to the site and critical protocol assessment need to be performed such as physical assessment or collection of laboratory samples.

Tele-Health/Tele Medicine The investigator may consider utilizing the hospital's (investigator site) tele-health platform, if available.

Investigational Product (IP) Management

Changes to IP Management must be clearly communicated to the trial subject, Investigator and site staff. Any change in IP instruction and management must be documented.

<u>Direct to patient drug delivery</u> Alternative approach for studies that require take-home medications to trial subjects. This approach must have the agreement of the trial subject and such arrangement must ensure the protection of personal privacy information. Documentation of delivery and receipt of drugs delivered to the trial subject's home must be ensured. Remote monitoring of IP compliance of trial subject-must be followed up by site.

<u>IP dosing in alternate site</u> In some trials i.e. oncology studies where continuation of IP treatment is important, an alternative clinic treatment center may be identified. It is recommended that Investigator must be the one to administer the IP. If the investigator is not possible to personally administer the IP, the investigator should coordinate with the in-house physician from this location .

Qualification The alternate location for IP dosing and the physician's qualifications must be reviewed by the Sponsor. The approval of the IRB must be sought for this satellite site for IP administration. The alternate physician should be listed in the study delegation log as a sub-investigator.

Training Training on the proper handling and administration of IP must be provided to the new sub-investigator before any IP administration is allowed to be performed at this satellite site.

Safe Transport Trial subject's visit should follow safety precautions for travel to comply with the city regulation. Documentation of the subject visit and IP dosing at the satellite site must be comprehensive and the principal investigator should discuss the required documentation.

Drug Accountability Per patient drug dispensing and drug accountability at the satellite site will be the responsibility of the sub-investigator at the satellite site. The principal investigator should train the sub-investigator on the appropriate documentation in the Drug Accountability Form.

New!

Unified COVID-19 Algorithms available at the Philippine Society for Microbiology and Infectious Diseases (PSMID) Website

<https://www.psmid.org/>

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"Open Letter to Policy Makers on Clinical Trial Regulations in the Philippines during the COVID-19 Pandemic"

PCRP highlights the global explosion of drugs for COVID-19[1] that are under development.

With the opportunity to participate in COVID-19 global studies, PCRP pens recommendations to our stakeholders to ponder and act on.

This open letter is a call for collaboration among clinical trial policy makers and decision makers to answer the call of a united world against this dire and threatening emergency.

Philippines can make a difference too!

General Considerations (continued from Page 1)

Examples of amendments that would necessitate approval by IRBs before these can be implemented include change in recipient where IP will be delivered; change in personnel such as inclusion of temporary study site staff in alternate/satellite sites.

All COVID-19 related changes must be documented. For minor changes, notification to IRBs can de done in a compiled submission but it is recommended that notification about major changes be done immediately as possible. It is important to put all of these documents in one file for use in future audit or inspection.

Safety Considerations: If it is critical that trial subjects should go for onsite visits, it is recommended for sites to issue a medical appointment letter and subject ID card must be carried by the trial subjects as supporting documents when passing through border checkpoints to visit the clinical trial site. It is strongly recommended that a remote assessment should be made if subject is fit to travel and if there is a risk to COVID-19 exposure.

Trial subjects must comply with hospital requirements for personal safety protection during the visit and practice social distancing.

The same precautions must also be observed by site staff especially for patient-facing activities that need to be performed.

Monitors should conduct remote monitoring visits whenever possible and to reduce the time needed on-site. If an on-site visit cannot be avoided, it should be limited to those activities that are essential to be performed on site. In addition to mask, it is recommended that monitors wear gloves even if hospital does not require this for visitors.

It is also recommended that a request be made to ensure that the monitoring room be relocated to a room distant from the patient wards

Sponsors/CROs shall follow applicable government guidelines in re-opening offices for employees returning to work[2].

Work with your Principal Investigators to develop a Site Operational Plan that will embody protection of subjects, their companion, site staff and monitors.

Budget Discussions and Considerations

Any change and deviation from the normal study procedures will most likely entail a change in the study budget.

Site should comply with the institution recommended safety measures for trial subjects and assess the impact of such measures in the site study budget. For locations where public transport is suspended, increase of subject transport cost should likewise be assessed.

If home visits by site staff or by a 3rd-party vendor is considered as alternative to site visit and approved by IRB, impact on site budget should be assessed.

Use of tele-health or tele-medicine may provide convenience during the time of COVID-19 and cost associated with such system should be looked into.

The conduct of trial at the site is expected to adjust with the various restrictions the so called new norm will impose. This will require revision in existing site operating processes and adapt these to the current situation.

New Clinical Trials

Philippines can benefit to participate in COVID-19 clinical trials. This type of trial is currently given priority for expedited approval by Philippine FDA and by the IRBs. SJREB should be utilized for multi-center COVID-19 trials.

FDA and institutional IRBs continue to review both COVID-19 and non-COVID-19 protocols. The Institution's Clinical Trial Units can help speed up response to feasibilities. Most clinical investigators continue to express their interest to join global clinical studies.

Communication Channels

PCRP COVID-19 Community Google Drive
Access to official memos from government agencies - P-FDA, IRBs, and Institutions, industry guidance and partner vendors.
Link: https://drive.google.com/drive/u/1/folders/1iZd9y-o_gNcHlmRb5_1XJ9AIKQIsh_c0

Clinical Trial Questions During COVID-19 Emergency
Let us know your questions related to PFDA, BOQ, etc.
Link: https://forms.gle/L6AK5KkWg5DS63uU8

For other questions and comments, please email us at:
PCRPCOVID19@gmail.com

Monitoring

The final approach to monitoring has to align with specific guidelines from the sponsor and the Institution/REC. Specific set of guidance have been compiled by PCRP and can be found in our community google drive.

Remote Monitoring Remote monitoring activities to augment or as alternatives to on-site monitoring visits must be continued as much as possible with the monitor's safety as the primary consideration. Lack of public transportation is also a main concern.

Project Team, Sponsor and Principal Investigator must agree on a Remote Monitoring Visit Guidance, applicable for the site that will outline all specific tasks that are to be performed by the monitor, e.g. more frequent remote EDC reviews, centralized monitoring activities, remote SDV.

Critical data points for safety and efficacy end points should be defined and given the priority for source data verification.

Resuming Monitor Onsite Visits Only conduct onsite visits if remote visit cannot address the data review. It is suggested that onsite monitoring should be blended with remote monitoring activities.

Managers should assess if the monitor is fit to travel and assess the risk to COVID-19 exposure[2].

Plan for a contact-less onsite monitoring visit foregoing face-to-face meetings with site staff. Use face mask, gloves and goggles especially in handling paper source records.

Returning to Office *Employers shall develop a work arrangement that will reduce the number of people in the workspace and also reduce the need to travel, including work from home arrangements to those whose tasks can be done at home, and among employees at high risk[3].*

Investigator Engagement

Monitors to ensure there is open, positive communication lines with the investigator and site staff. These communication lines allow the monitor to determine current status of patients and the site, engage in constructive discussions of action plans for continuity of study activities during COVID-19 and other areas where the sponsor/CRO may provide support and guidance.

Urge investigators/site staff to continue heightened AE vigilance to patients including investigating reported symptoms suggesting possible COVID-19 infection. Any trial subject that will fall under DOH's categories of Positive, Probable and Suspected cases must be reported immediately to the Sponsor/CRO and to DOH COVID-19 Surveillance reporting process .

NEW!

DOH Department Memo 2020-0220 May 11, 2020 Interim guidelines on the return-to-work <http://www.doh.gov.ph/2019-nCov/interim-guidelines >

Official Statements from Clinical Trial Stakeholders

The Philippine FDA and the Single Joint Ethics Review Board (SJREB) are accepting clinical trial related applications during this time, although there are no official statement released at this time.

The FDA issued FDA Circular No. 2020-006-A on 02 April 2020 which allows companies to apply for clinical trial approvals by filing applications by email to the FDA. Prior to this, applications for clinical trials were filed manually at the FDA Action Center[4].

The Philippine Research Ethics Board issued the PHREB Resolution No. 20-001 last 13 April 2020 authorizing that RECs to conduct online meetings to review protocols[5].

Individual Institutions/RECs have issued specific guidance which can be accessed through their webpages.

PCRP continues to engage with Clinical Trial stakeholders, i.e. government and private agencies, institutions/hospitals, vendors and suppliers on areas that impact continuity of clinical trials in the Philippines.

References:

[1]Mullard, A (2020). Flooded by the torrent: the COVID-19 drug pipeline. Lancet World Report. 395 (10232) 1245-1246. DOI:https://doi.org/10.1016/S0140-6736(20)30894-1

[2] GOVPH (n.d.) ECQ and GCQ Guidelines. Available at: https://www.covid19.gov.ph/ecq-gcq-guidelines/

[3]DOH (n.d.) Department Memo 2020-0220, May 11, 2020, Interim guidelines on the return-to-work. Available at: http://www.doh.gov.ph/2019-nCov/interim-guidelines

[4]FDA(n.d.) FDA Circular 02 Apr. Available at: https://www.fda.gov.ph/fda-circular-no-2020-006-a-amendment-to-fda-circular-no-2020-006-entitled-guidance-for-applications-and-transactions-at-the-food-and-drug-administration-in-light-of-the-community-quarantine-dec/

[5]PCHRD (n.d.) PHREB Resolution No. 20-001. Available at: http://www.ethics.healthresearch.ph/index.php/phoca-downloads/category/18-phreb-resolutions

AN OPEN LETTER TO POLICY MAKERS ON CLINICAL TRIALS REGULATIONS IN THE PHILIPPINES DURING THE COVID-19 PANDEMIC

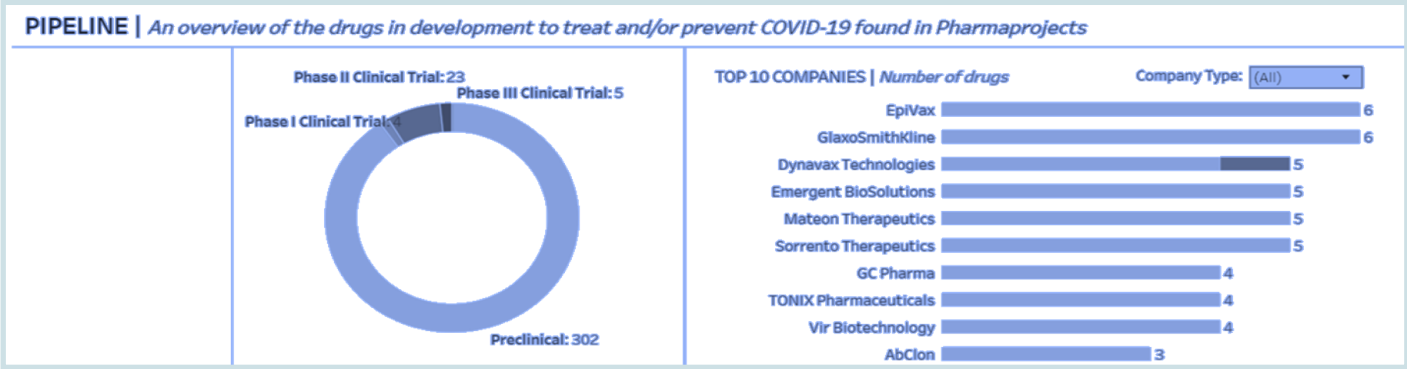
We write to you this letter to bring to your attention the potential role that our country may play in contributing to international efforts on research for COVID 19 treatments and COVID-19 vaccines.

Philippines has suffered much from this pandemic with 9,000 plus cases of COVID-19 as of May 3, 2020. Dire it may seem, but this number can greatly contribute to worldwide efforts in tackling COVID-19 and as a conscientious global partner in advancing science, we enjoin health regulators and other stakeholders to take heed in the urgency of this matter.

We, members of Philippine Clinical Research Professionals, Inc., take cognizance to the urgent call from Pres. Rodrigo Duterte's declaration during the Special ASEAN Summit on COVID-19 last 14 April 2020 to aggressively pursue vaccine research and development initiatives.

We now see an unprecedented effort from researchers globally, including the biopharmaceutical R&D (Research and Development) industry and academic sector, to develop therapeutics and vaccines for COVID-19 (Figure 1). We therefore suggest a shift in our local regulations to take advantage of international collaborative researches that are close to, or currently in clinical development stages (ie clinical trials), as they have the earliest chances of being approved and be available to society.

Figure 1. Shows that there are at least 334 drugs in development for the treatment and/or prevention of COVID-19 that will soon enter the Clinical Trials phase[1].



Please consider the following recommendations from PCRP for the country to effectively pursue vaccine and other COVID-19 treatment research and development activities. PCRP provides these critical recommendations to address capacity, readiness and attractiveness for Philippines to participate in international collaborative research:

Urgently setup, revise and update regulatory and institutional policies and mechanisms that will expedite the start-up of clinical trial activity in critical indications such as COVID -19 diagnostics, treatment, prevention, or cure.

The conduct of clinical trials is highly regulated ensuring that clinical trial participants are kept safe while benefiting from innovative treatments for a disease such as COVID-19 where there is no other proven therapeutic alternative. The Philippines' primary regulatory agencies are the Food and Drug Administration, Philippines (PFDA) and the Philippine Research Ethics Board (PHREB) that governs ethics review committees, including the Single Joint Ethics Review Committee (SJREB) of the Department of Health (DOH). The collaboration among these agencies have increased through the years. However, this emergency situation may require an even more transparent collaboration for a unified process to drive quality and speed in the review and approval of COVID-19 protocols.

Our usual regulatory and ethics review process takes between 60-90 days and therefore the current review processes for clinical trials does not support the needed swift conduct and turnaround of the COVID-19 trials.

In light of the COVID-19 emergency, regulators around the world have answered the need to fast track the review process. Regulatory agencies have released guidelines for evaluation of clinical trials related to the management of COVID-19. [2, 3, 4]. In Asia, our counterparts have started fast track reviews from 08 to 20 working days[5].

News articles have been written about Philippine's participation in the WHO-sponsored SOLIDARITY Trial[6, 7, 8]. SOLIDARITY Trial is an international collaboration of a big number of countries and it is very fitting for Philippines to take part in this important ground-breaking clinical trial comparing the current treatment recommendations for COVID-19.

As SOLIDARITY Trial is ongoing now in the Philippines, this trial can serve as the litmus-test for speed and quality in the start-up phase for future COVID-19 international protocols that we can participate.

Reduce, remove impediments or drastically simplify the flow and movement of research drugs, equipment, supplies and biological samples.

In addition to the clinical trial review and approval process by PFDA, SJREB and institutional RECs (Research Ethics Committees) for COVID-19 protocols, there are other regulatory requirements necessary to facilitate the everyday conduct of the trial. These include the transfer of human biological samples as regulated by the Bureau of Quarantine (BOQ) and importation of Investigational Products and ancillary materials as regulated by the PFDA, the Bureau of Customs (BOC) and the National Telecommunications Commission (NTC). Other service providers are also required, such as logistics companies/ couriers, central laborato-

The Philippine Clinical Research Professionals, Inc. (PCRP) is a professional organization of individuals engaged in the conduct of clinical trials in the Philippines. PCRP members belong to pharmaceutical companies and contract research organizations (CROs).

PCRP is committed to promote the high standards In clinical research conduct in the Philippines.

For more information about PCRP, go to www.pcrp.org.ph

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ries, etc. These additional requirements demand additional time to set-up and process.

Identify, set-up or capacitate existing study groups/research teams that can start-up and conduct research and development activities. For example, vaccine clinical trials can be conducted at separate facilities from hospitals or those used in routine healthcare delivery. Ethical review and oversight of these study groups/ research teams need to be taken into consideration.

Provide mechanism for easier access and faster monitoring and oversight of clinical trials to ensure trial participants protection while maintaining high data quality and integrity.

We humbly ask that our regulatory bodies consolidate efforts and commit to a streamlined, fast track process within a competitive timeline for:

- Regulatory and ethics review of the COVID-19 clinical trials
- Processing of necessary permits from regulatory agencies
- Agreed process for the flow of couriers transporting clinical trial investigational products and materials across borders and check points.

The usual end-to-end process to initiate a clinical trial in the Philippines takes between 4-6 months when all processes are put together, including the regulatory processes, personnel training, negotiating contracts, etc. This timeline needs to be shortened drastically so that Filipino patients suffering from COVID-19 may be able to benefit from these potential life-saving treatments because of our participation and for our country to contribute to international efforts in finding a vaccine to help future generations.

We as the Sponsors and Contract Research Organizations, who potentially may bring in global COVID -19 trials, also commit to fast track our own internal processes to facilitate this fast track process, easing the burden for trial participation by hospitals and investigators..

We are inspired by our President's call to prioritize, among others, the cooperation in science and research, especially in the development of vaccines and anti-viral treatments for COVID-19. Our ranks are ready to cooperate along with our researchers, institutions and government to make this happen.

PCRP is available for any consultation meetings and PCRP will always be a willing partner with much passion and service to future endeavors in clinical research for Philippines.

USEFUL LINKS

Official government issuances on COVID-19: <https://www.covid19.gov.ph/issuances/ >

Omnibus Guidelines on the Implementation of Community Quarantine in the Philippines : <https://www.covid19.gov.ph/wp-content/uploads/2020/05/Omnibus-Guidelines-v2-SOH_signed.pdf>

Daily Summary of news briefs, events and issuances in the Philippines : <https://www.covid19.gov.ph/covid-19-timeline/>

References:

[1] Informa Pharma Intelligence (2020). Coronavirus [online]. Available at: https://pharmaintelligence.informa.com/resources/key-topics/coronavirus

[2]Baker McKenzie (2020). COVID-19: A global review of healthcare and life sciences industry issues. [online] Available at: https://www.bakermckenzie.com/en/insight/publications/2020/04/covid19-global-glance-healthcare-life-sciences#asiapacific

[3]WHO (2020). African regulatory agencies, ethics committees to expedite COVID-19 clinical trial reviews. [online] Available at: https://www.afro.who.int/news/african-regulatory-agencies-ethics-committees-expedite-covid-19-clinical-trial-reviews

[4]ECRIN (2020). Fast track procedure for COVID 19 clinical trials. [online] Available at: https://www.ecrin.org/fast-track-procedure-covid-19-clinical-trials

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[7]CNN Philippine Staff (2020). PH to start clinical trial for potential COVID-19 treatments soon. CNN Philippines. [online] Available at: https://www.cnnphilippines.com/news/2020/4/23/who-solidarity-trial-in-philippines.html

[8]DOH (2020). PH SOLIDARITY trial for COVID-19 treatments receives green light from ethics review body press release/22 April 2020. [Online] Available at: https://www.doh.gov.ph/doh-press-release/PH-SOLIDARITY-TRIAL-FOR-COVID-19-TREATMENTS-RECEIVES-GREEN-LIGHT-FROM-ETHICS-REVIEW-BODY