INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

November 2021

Implementing Arrangement Extended

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

September 14, 2021

Dr. Dante Saksono Harbuwono, Sp.PD-KEMD, Ph.D.
Vice Minister
Ministry of Health
Republic of Indonesia

Dear Dr. Dante S. Harbuwono,

The National Institutes of Health (NIH) refers to the Implementing Arrangement between the National Institutes of Health of the Department of Health and Human Services of the United States of America and the National Institute of Health Research and Development of the Ministry of Health of the Republic of Indonesia on Infectious Disease Research, signed at Bethesda and Jakarta on December 14 and 23, 2016, respectively ("the Arrangement").

Article 9 of the Arrangement provides that the Arrangement "may be extended by mutual written consent of the Parties." Through an exchange of letters in January and April 2019, the Arrangement was extended for two years until December 23, 2021. NIH proposes that the Arrangement be further extended for a three-year period with effect from December 23, 2021.

If the National Institute of Health Research and Development of the Ministry of Health of the Republic of Indonesia agrees with the proposal set forth above, NIH further proposes that this letter and the affirmative letter in reply from the National Institute of Health Research and Development of the Ministry of Health of the Republic of Indonesia shall constitute an extension agreement between the two agencies, which shall enter into force on the date of the letter in reply.

Sincerely,

Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health
U.S. Department of Health and Human Services

VICE MINISTER OF HEALTH
REPUBLIC OF INDONESIA

Ref No : KS.01.02/Wamenkes/085/2021 September 15, 2021
Subject : Implementing Arrangement NIH and MOH

Dr. Antony Fauci
Director, National Institute of Allergy and Infectious Diseases (NIAID)
U.S. Department of Health and Human Services

Dear Dr. Fauci,

First of all, allow me to thank your warm welcome and hospitality during our visit to NIH on September 14th 2021. I also would like to acknowledge the receipt of your letter dated September 14, 2021, regarding Implementing Arrangement between the National Institutes of Health (NIH) of the Department of Health and Human Services of the United States of America and the National Institute of Health Research and Development of the Ministry of Health (MOH) of the Republic of Indonesia on Infectious Diseases Research.

The Ministry of Health of the Republic of Indonesia welcomes the proposal of National Institutes of Health to extend the Arrangement for the period of 3 (three) years, starts from 23 December 2021 until 23 December 2024.

Currently, the Ministry of Health of the Republic of Indonesia is working on any strategic actions, initiating a health transformation in several pillars, including a reform in human capital and referral healthcare reform by improving access to quality healthcare through health human resources development.

In this regard, I would like to stressed out the importance of the human capital reform, especially to have exchange of knowledge and expertise between health resources towards our health system strengthening. Other areas of research collaboration that could be explored would be Antimicrobial Resistance (AMR), Malaria, Tuberculosis (TB), real-time laboratory surveillance and Covid-19. I look forward to a further close collaboration between the NIH and MOH.

Thank you for your support and cooperation.

Yours sincerely,

Dante S. Harbuwono, MD, PhD, Endocrinologist

Breaking News!

Our cooperation with the US-NIH that has existed since 2011 can continue with the signing of the extension of the Implementing Arrangement (IA) for a period of three years starting from December 2021 to December 2024. With this extension, our network will be able to continue our activities and achieve our network's goals to contribute more for the research community and clinicians.

Let's join hand and continue to work towards the greater good!
M. Karyana / Head of INA-RESPOND Steering Committee

MASTHEAD

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THANK YOU

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FEATURES

INA-RESPOND Newsletter

TRIPOD, PROACTIVE, & ORCHID Study Updates

By: Eka Windari R., I Wayan Adi Pranata, Lois E. Bang, Melinda Setiyaningrum, Nur Latifa Hanum, Retna Mustika Indah, Riza Danu Dewantara

STUDY UPDATES

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The INA-RESPOND secretariat has announced an official letter and a final report on site closure to the hospital director and the local ethics commission. All study documents have been sent to be archived at Indo Arsip. Final report for NIHRD will be submitted in the end of November.

Other ongoing activities regarding TRIPOD are summarized below:

1. Fifty-Two isolates sent to BSL 3 Facility, Central Lab Padjajaran University, Bandung for sub-cultured has grown, 3 isolates did not grow. The 49 isolates were extracted (DNA) and 32 isolates was done (DST). The next 30 isolate for subculture is on process.
2. Collaboration within the RePORT network on Epidemiology of TB Progression and Outcomes Study, using the TRIPOD data
3. Manuscripts writing: TRIPOD 1st manuscript will be finalized after getting feedback from US author, 2nd manuscript that discuss Performance comparison of afb microscopy and Xpert compared to afb culture is being prepared by Manuscript writing team.
4. Working on TRIPOD sub-study, using specimen from baseline to diagnose histoplasmosis.
5. Inviting the network to submit the Ideas on TRIPOD specimens used. Per protocol, there are 8 types of specimens collected on TRIPOD study for future used.

Status for Repository specimens is provided in figure 1.

Site	Specimen Type	Whole blood (EDTA) - DNA	Whole blood (Heparin) - PBMCs	Whole blood (Heparin) – Plas-ma	Whole blood (PAXgene) - RNA	Urine	Saliva	Sputum	MTB Isolate
520 (n=32)	BL (32)	90	22	91	27	125	62	19	36
	M1 (24)	NA	18	64	21	99	NA	16	12
	M2 (24)	NA	22	68	24	93	NA	11	0
	EOT (15)	NA	28	45	15	60	30	2	0
560 (n=108)	BL (108)	382	204	328	102	440	216	131	272
	M1 (95)	NA	188	285	94	381	NA	107	60
	M2 (87)	NA	172	261	86	348	NA	91	20
	EOT (73)	NA	142	219	73	292	146	75	20
570 (n=128)	BL (128)	438	177	380	121	519	254	119	196
	M1 (104)	NA	162	311	103	416	NA	43	92
	M2 (97)	NA	162	294	98	392	NA	22	38
	EOT (80)	NA	162	243	81	320	160	4	12
580 (n=83)	BL (83)	235	130	210	67	308	147	26	42
	M1 (44)	NA	70	102	38	156	NA	18	6
	M2 (38)	NA	54	81	36	148	NA	16	0
	EOT (29)	NA	50	71	27	124	61	8	0
590 (n=89)	BL (89)	340	170	255	84	344	147	78	55
	M1 (59)	NA	98	147	49	196	NA	17	8
	M2 (56)	NA	80	120	41	164	NA	8	0
	EOT (40)	NA	46	72	24	96	46	9	0
600 (n=25)	BL (25)	100	50	75	25	100	50	50	30
	M1 (13)	NA	26	39	13	52	NA	26	4
	M2 (11)	NA	22	33	11	44	NA	22	4
	EOT (9)	NA	20	30	10	40	20	20	0
550 (n=25)	BL (25)	95	48	72	24	100	51	10	27
	M1 (20)	NA	36	54	19	68	NA	7	7
	M2 (20)	NA	36	54	17	72	NA	6	4
	EOT (15)	NA	26	39	13	52	25	0	2

Figure 1. Site Close Out Visit Schedule and updates Jun 2021

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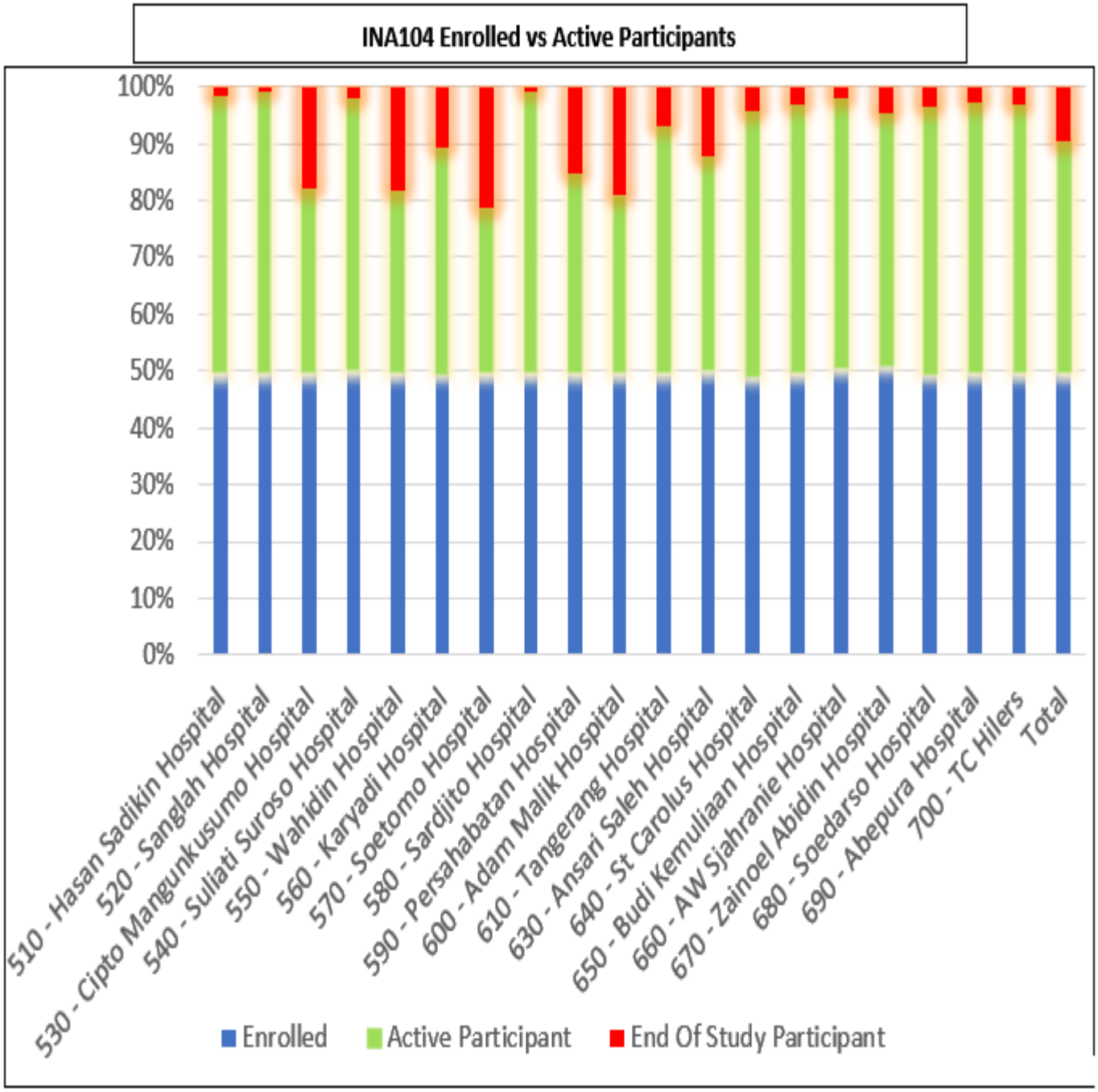
According to the data on 29 October 2021, from 4,336 subjects enrolled, 817 subjects had ended their study due to some reasons: 435 subjects completed the study, 180 subjects died, 40 subjects moved away to a city where no PROACTIVE site is available, 30 subjects withdrew, 25 subjects were lost to follow up and 5 subjects had negative HIV test result. As of October 24, 2021, there are 3,480 active subjects in this study. Below is the Chart of Enrolled and Active Participants by Sites:

Meanwhile, Onsite SMV (Site Monitoring Visit) was conducted at Site 540 (Suliati Saroso Hospital) on October 26 - 28, 2021



INA107 PARTICIPANT STATUS

Based on uploaded CRFs as of 8 November 2021, a total of 136 participants were enrolled in ORCHID study, which consisted of 104 participants from site 610 (RSU Kabupaten Tangerang, Tangerang) and 44 participants from site 521 (RS Universitas Udayana, Denpasar). 137 participants (95%) already completed this study, 2 participants passed away during the study, and 5 participants decided to not continue the study and categorized as other (figure 1).

Up to 8 November 2021, a total of 130 participants (90%) were identified as positive SARS-CoV-2, and only 14 participants (10%) were identified as negative SARS-CoV-2. In site 610, the number of participants identified as positive SARS-CoV-2 was 95 participants (91%), and 9 participants were identified as negative SARS-CoV-2. While in site 521, 35 participants (88%) were identified as positive SARS-CoV-2 and 5 participants (12%) were identified as negative SARS-CoV-2 (figure 2).

Based on pathogen identification data, in site 521, pathogens from 17 participants (43%) are identified as COVID-19 with others, and pathogens from 18 participants (45%) are identified as COVID-19 only. While in site 610, 91 participants' (88%) pathogen are identified as COVID-19 only, following 4 participants (4%) who are identified as COVID-19 with others. 11 participants are not confirmed for any pathogen, 2 participants in Site 521 and 9 participants in site 610. In site 521, two participants are identified to have typhoid infection, and one participant is identified a single infection of Dengue (figure 3).

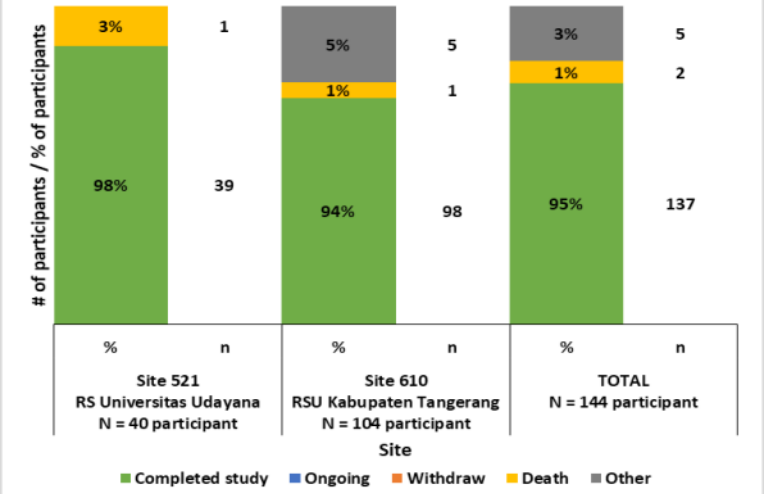


Figure 1. Participant status per site based on uploaded CRF as of 8 November

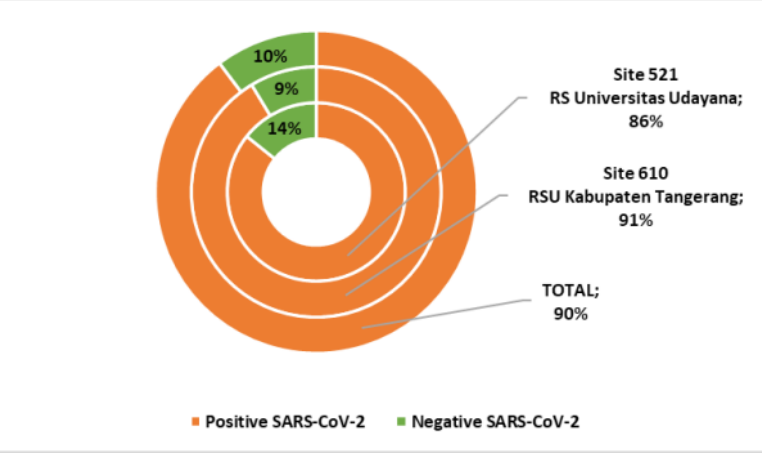


Figure 2. SARS-CoV-2 identification at enrolment based on uploaded CRF per 8 November 2021.

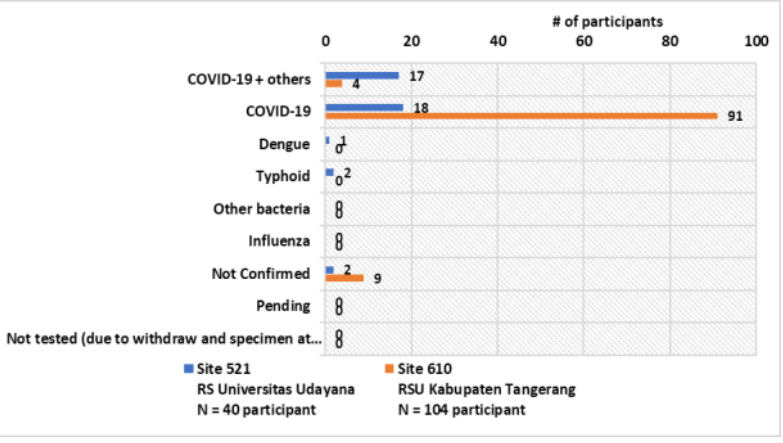


Figure 3. Pathogen identification based on uploaded CRF per 8 November 2021

INA-RESPOND Newsletter

ORAL ANTIVIRUS FOR COVID-19 (PART 1)

By: Yan Mardian

The coronavirus disease 2019 (COVID-19) pandemic continues to grow. Protective vaccines have been developed within unprecedented timelines, but current supplies are too low to cover worldwide demand in the coming months. Moreover, a significant number of people are either unable, due to pre-existing medical conditions, or unwilling to be vaccinated, and global access challenges remain. Unlike vaccines that can prevent infection, antivirals act as a second line of defense. Furthermore, SARS-CoV-2 is likely to become endemic, leading to the emergence of vaccine-resistant variants and reinforcing the need to develop antiviral therapeutic agents. Researchers worldwide are urgently looking for interventions to prevent new infections, prevent disease progression, and lessen disease severity for those already infected. SARS-CoV-2 specific therapeutics are urgently needed to prevent more severe disease, hospitalization, and death. Treatment may also reduce the period of infectivity.

Development of Antiviral for Covid-19

Developing the new antivirals is an expensive and difficult endeavor, especially for acute respiratory diseases, for which the window for treatment is short. Historically antiviral drug development has focused on a "one bug, one drug" approach, targeting proteins common to specific groups of viruses. Researchers started screening molecular collections, such as the California Institute for Biomedical Research's ReFRAME, to test if any FDA-approved drugs and investigational compounds were effective against SARS-CoV-2. Laura Riva, a computational biologist formerly at the Sanford Burnham Prebys Medical Discovery Institute in California, conducted one such screen along with her colleagues and identified more than a dozen compounds, including remdesivir, that blocked SARS-CoV-2 replication in animal and human cells (1). While such antivirals can be extremely effective, viruses produce very few proteins of their own, giving drug makers limited options. There's also the risk of the drugs damaging cells. Some viral proteins can be unique in that they don't overlap with the ones produced by the host, making them ideal targets for antiviral drugs. But if the target proteins do overlap or perform the same functions as the human host cells, there is potential for collateral damage, resulting in side effects. Once drugmakers have identified a target, the compound has to go through a lengthy testing phase. The first step involves demonstrating that the compound works on infected cells in Petri dishes, then assessing if it is safe and effective in laboratory animals, and finally in human clinical trials. Therefore, normally making antiviral therapies for new viruses can take at least a decade (2). However, the urgency presented by COVID-19 meant finding new ways to use old drugs.

While research on new therapeutic agents for COVID-19 is key, there is also great interest in evaluating the potential of already existing medicines against COVID-19. The urgency amid the pandemic has caused interest in repurposing other drugs targeted for other diseases. The known safety profiles, shortened development timelines, and well-established markets for most of the already existing compounds proposed for COVID-19 are particularly advantageous compared to new drug discovery in a pandemic situation. However, repurposing approved drugs in the search for small molecule antiviral agents that target SARS-CoV-2 has thus far been minimally effective (3). So far, Gilead's remdesivir, originally developed for Ebola infections, is the only such repurposed antiviral drug that has received approval from the U.S. Food and Drug Administration to treat hospitalized patients with COVID-19 (4). When used in a hospital setting, its effect is modest. In a phase 3 trial, researchers found that it shortened recovery time by a median of 5 days (5). However, its wider use is limited by intravenous delivery due to the limited

oral bioavailability. The therapeutic benefits of remdesivir are also under ongoing debate as WHO has issued a conditional recommendation against the use of remdesivir in hospitalized patients, regardless of disease severity, as there is currently no evidence that remdesivir improves survival and other outcomes in these patients based on the results of multinational SOLIDARITY trial (6).

Other than Remdesivir, three anti-SARS-CoV-2 monoclonal antibodies (mAbs) that target the spike protein has been shown to have a clinical benefit SARS-CoV-2 infection. During the infection of host cells by SARS-CoV-2, the spike (S) glycoprotein of SARS-CoV-2 plays the most crucial role in viral entry and cell fusion. The spike protein is further divided into S1 and S2, which mediate host cell attachment and invasion. Through its receptor-binding domain (RBD), S1 attaches to angiotensin-converting enzyme 2 (ACE2) on the host cell; this initiates a conformational change in S2 that results in virus-host cell membrane fusion and viral entry. The mAbs can specifically bind to SARS-CoV-2 RBD, block the interaction between SARS-CoV-2 RBD and the human ACE2 receptor, and thus block viral attachment and entry into human cells, leading to efficient neutralization of the virus (7). Studies have shown that MAbs are effective in preventing SARS-CoV-2 infection in household contacts of infected patients and during SARS-CoV-2 outbreaks in skilled nursing and assisted living facilities, which can cut the risk of hospitalization and death by up to 85 percent (8). The three Mab products (Bamlanivimab plus etesevimab, Casirivimab plus imdevimab, and Sotrovimab) have received Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA) for the treatment of mild to moderate COVID-19 in non-hospitalized patients with laboratory-confirmed SARS-CoV-2 infection who are at high risk for progressing to severe disease and/or hospitalization (9). Despite the benefits, mAbs are costly, must be administered through an IV in a medical setting, and, in poor nations, scarce or absent. Yet without widespread vaccination, those populations remain vulnerable to COVID-19 and need affordable medicines.

As an acute viral infection triggers COVID-19, the antiviral therapeutics will be most effective if given within the early stages of the infection when viral load is at its maximum, during rapid replication of SARS-CoV-2 in nasopharyngeal and respiratory epithelium (10). Thus, an orally available direct-acting antiviral would be essential for such treatment in an outpatient setting. A new generation of orally available broad-spectrum antivirals is emerging that should allow initiation of treatment early after infection and prevent further systemic dissemination of the virus and development of systemic inflammation. A pill could make treating patients earlier in their infection much easier — and more effective than intravenous treatment, which requires certain medical resources for infusion and patient monitoring at the hospital. With the medical system under intense pressure, oral antiviral drugs that can reduce the viral burden from the initial stages of infection and are easy to use are required. This therapeutic agent is expected to contribute to patients' early treatment and help keep hospitals from overflowing and thus relieve the pressure on the medical system (11).

How the antiviral works

The development of effective intervention strategies relies on the knowledge of molecular and cellular mechanisms of coronavirus infections, which highlights the significance of studying virus-host interactions at the molecular level to identify targets for antiviral intervention and to elucidate critical viral and host determinants that are decisive for the development of severe disease. During the intracellular life cycle (Fig. 1), coronaviruses express and replicate their genomic RNA to produce full-length copies that are incorporated into newly produced viral particles. Upon the entry, the uncoating by nucleocapsid degradation allows the release into the cytoplasm of the viral RNA, ready for translation. The 5′- and 3′-UTRs flank the coding region with the two-thirds of the genome from the 5′-end comprising two overlapping open reading frames (ORFs), ORF1a and ORF1b, that encode for polyproteins pp1a (4382 amino acids) and pp1ab (7073 amino acids), respectively. The autoproteolytically processing by 3CL or Main (Mpro) and PLpro affords 16 nonstructural proteins (nsp1–16), which form the replicase/transcriptase complex (RTC). The RTC includes different enzymes and cofactors involved in post-translational polyprotein processing, RNA synthesis, maturation, and virions assembly and egress, which therefore can constitute ideal viral targets for drug discovery, being essential for the virus life cycle and devoid of a close host homologue. Genomic ss-(+)-RNA transcription proceeds through (−)-strand intermediates that serve as templates for the production of both

genomic and subgenomic RNAs, which are capped and polyadenylated as the full genomic RNA. The subgenomic RNAs are then translated into the four structural and some accessory proteins (12). On the basis of the prominent roles in intracellular steps of viral life cycle, the amount of biochemical/structural data and the knowledge acquired on inhibitors of homologues proteins in other CoVs and other RNA viruses, the 3CLpro and the nsp12 RdRp are at moment the most relevant viral targets to identify specific anti-CoVs agents (13).

Previous research efforts to develop antiviral agents against the members of the coronavirus family suggested the ACE2 entry receptor, the RNA-dependent RNA polymerase (RdRp), and the main protease (Mpro) as suitable drug targets (Fig. 2). As there is a high chance that coronaviruses will undergo mutations to become a new infectious virus, identification of promising targets for antiviral therapies against SARS-CoV-2 should exploit the structural similarities among different coronaviruses and focus on those proteins that are highly conserved across multiple

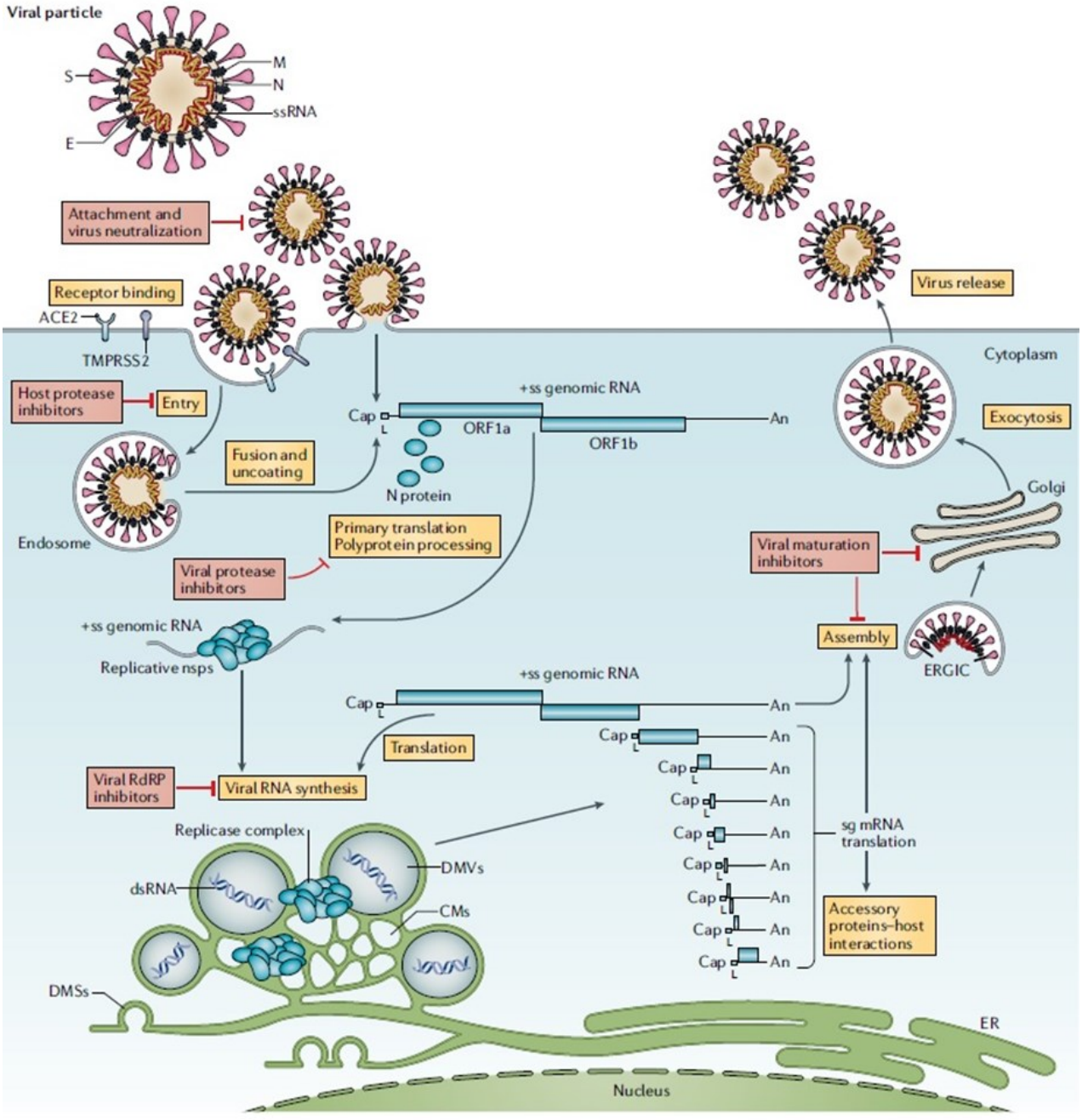
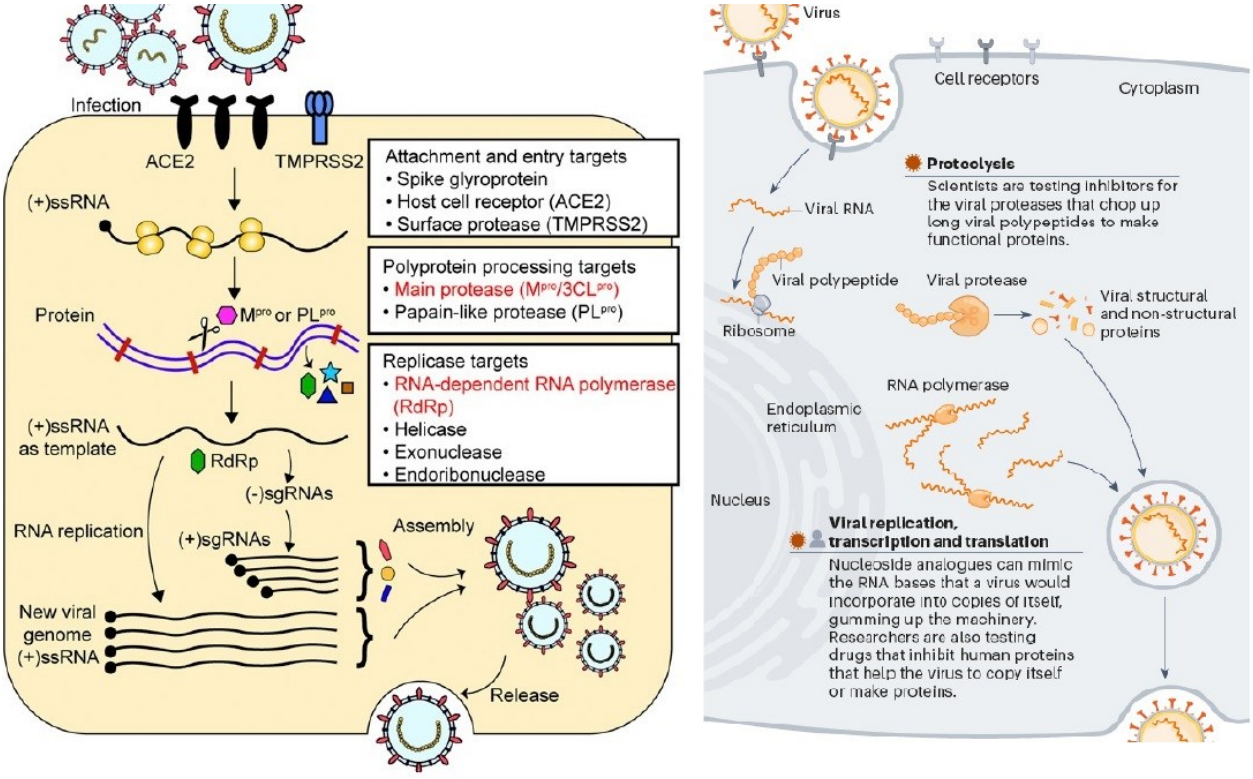


Figure 1. SARS-CoV-2 virion and life cycle

Figure 2. Drug targets against SARS-CoV-2



coronaviruses. Among the several potential targets of coronaviruses, replication-related enzymes, such as RdRp and protease, are highly conserved. Drugs that inhibit conserved proteases, such as Mpro and papain-like protease (PLpro), can prevent replication and proliferation of the virus by interfering with the posttranslational processing of essential viral polypeptides and can also reduce the risk of mutation-mediated drug resistance. Replication of SARS-CoV-2 depends on RNA-dependent RNA polymerase (RdRp), and thus RdRp is also a promising drug target for the treatment of coronaviruses (14). Remdesivir has shown antiviral activity against SARS-CoV-2 in vivo in rhesus monkeys through the targeting of RdRp (15). Computational drug repurposing is an effective approach to find new indications for the drugs already approved for other functions. This virtual drug screening strategy, comprising the pre-docking filtering, docking simulation, and post-docking filtering processes, was applied to identify drug candidates targeting two key enzymes of SARS-CoV-2, Mpro and RdRp, using their crystal or cryoelectron microscopy (cryo-EM) structures (14).

Investigational oral antiviral candidates for COVID-19:

Molnupiravir

Molnupiravir (MK-4482/EIDD-2801) is an investigational, originally designed to fight the flu, orally administered form of a potent ribonucleoside analog that inhibits the replication of SARS-CoV-2. Molnupiravir has been shown to be effective in several preclinical models of SARS-CoV-2, including for prophylaxis, treatment, and prevention of transmission. Like remdesivir, molnupiravir targets the RdRp, which mediates replication and transcription of the coronavirus genome, leading to increased frequency of G-to-A and C-to-U transition mutations (Fig. 3). This will disrupt the fidelity of SARS-CoV-2 genome replication and prevents viral propagation by fostering error accumulation in a process referred to as 'error catastrophe', which forces the SARS-CoV-2coronavirus to mutate itself to death (lethal mutagenesis). Molnupiravir was also shown to inhibit propagation of the SARS-CoV, MERS-CoV, and SARS-CoV-2 viruses, re-enforcing its pan-coronaviral inhibitory profile. Treatment with molnupiravir failed to induce viral-resistance mutations, which suggests a high genetic barrier to immune evasion (16).

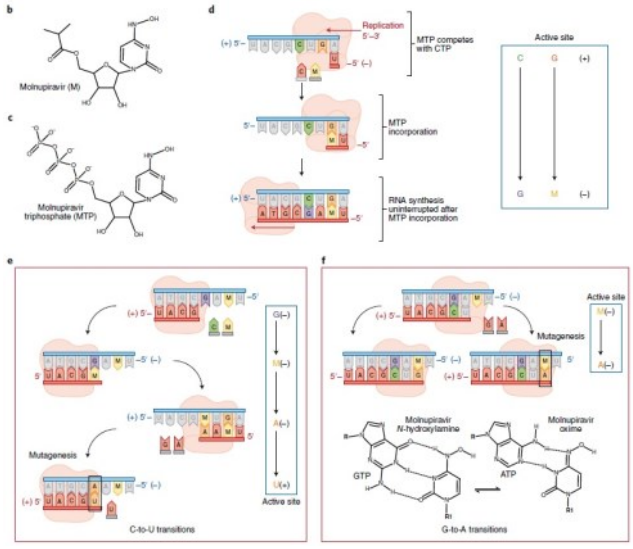


Figure 3. Schematization of mutagenic pathway by Molnupiravir

The accumulation of mutations pushes viral replication over the 'error threshold' that demarcates the replication fidelity required for viability. This mechanism distinguishes Molnupiravir from remdesivir, which impedes the progression of viral RdRp, and provides insights into alternative mechanisms of RdRp inhibition. Finally, Molnupiravir possesses excellent pharmacokinetic properties, which include oral administration. An orally bioavailable antiviral will have far-reaching benefits in tackling the spread of COVID-19 in hard-to-reach communities worldwide. As with all therapeutic agents, off-target effects are a concern. In its triphosphate form, Molnupirivar is a substrate for the mitochondrial RNA polymerase, which can also incorporate MTP as a U or C analog. Reassuringly, the study noted that mitochondrial function over 14 days was not significantly inhibited, and another study did not observe mutagenesis of host mRNA. However, it has been suggested that exposure to Molnupiravir can be mutagenic to host DNA during host DNA replication. Therefore, the potential off-target effects will require further investigation (11,16).

In their press release last October, Merck announced that Molnupiravir significantly reduced the risk of hospitalization or death among people with COVID-19 based on an interim analysis of Phase 3 MOVe-OUT trial in at risk, enrolling non-hospitalized adult patients with mild-to-moderate COVID-19. At the interim analysis, molnupiravir reduced the risk of hospitalization or death by approximately 50%; 7.3% of patients who received molnupiravir were either hospitalized or died through Day 29 following randomization (28/385), compared with 14.1% of placebo -treated patients (53/377); p=0.0012. In addition, through Day 29, no deaths were reported in patients who received molnupiravir compared to 8 deaths in patients who received placebo. At the recommendation of an independent Data Monitoring Committee and consultation with the U.S. FDA, recruitment into the study is being stopped early due to these positive results (17). Although interim findings aren't yet peer-reviewed, the companies jointly applied for an emergency use FDA authorization of the pill on October 11; while the U.K. has authorized Molnupirvair's use on November 4. The drug needs to be given needs to be given within the first five days of symptoms onset, at about $700 per tx course (twice daily for five days).

[To be continued to part 2 (Dec 2021)]

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We received a courtesy visit from The National Brain Center Hospital (NBCH) in preparation to develop a collaboration between NBCH and NINDS (National Institute of Neurological Disorder and Stroke).

From left to right: Prof. Amal Sjaaf, dr. M. Karyana, dr. Nizar Yamanie, dr. Dewi Lokida, dr. Yuli Felistia,
Dr. Anwar Santoso, dr. Herman Kosasih.

INA-RESPOND Newsletter

FROM OUR PARTNER

CENTRALIZED REMOTE CLINICAL TRIALS MONITORING DURING THE COVID-19 PANDEMIC

By: Regulatory Compliance and Human Subjects Protection Program (RCHSPP) Clinical Trials Monitoring (CTM) Group

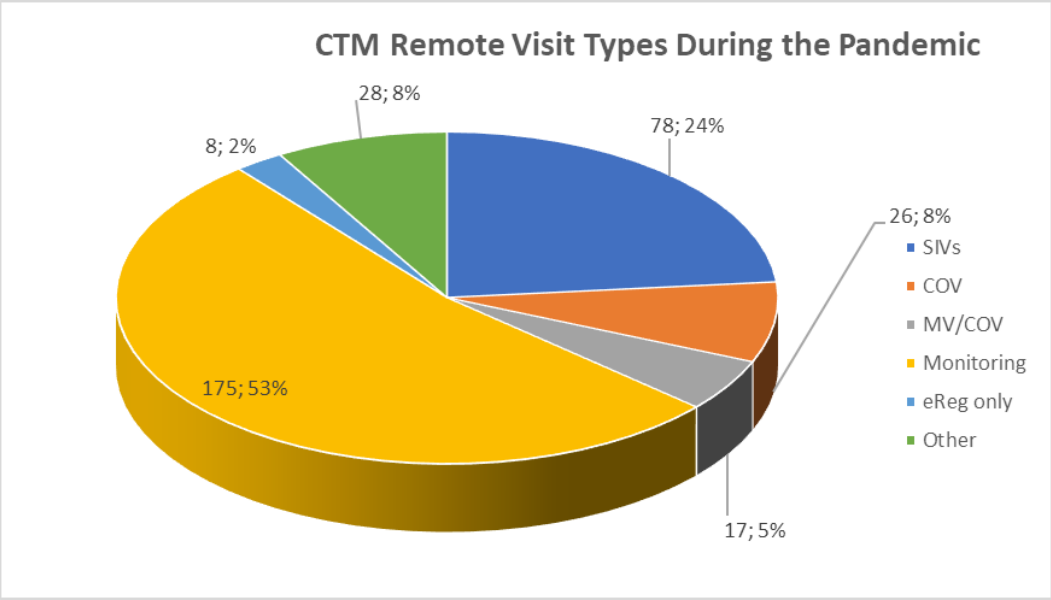
ICH Good Clinical Practice R2 (dated March 2018) describes sponsor monitoring responsibilities and includes the following statement: "The sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring. The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the monitoring plan)." So, where does "remote clinical trial monitoring" come in to play?

Remote clinical trial monitoring, or remote monitoring, has been around for years; however, the COVID -19 pandemic provided the impetus for making this the face of a changing landscape in clinical trials monitoring. Few study sponsors and clinical sites were fully prepared for a shift to primarily performing remote monitoring, but some embraced it in the wake of travel restrictions and quarantine mandates.

Remote monitoring uses a combination of data collected from study databases centrally in conjunction with a monitoring review of electronic source documents. Thanks to technology, it is easier than ever before to access and navigate data collected. Databases and electronic data capture systems have not only made data analysis more efficient, but they have also become vital to monitoring trial data remotely and maintaining the connection between study sponsors and research sites.

The National Institute of Allergy and Infectious Diseases (NIAID) Office of Clinical Research Policy and Regulatory Operations (OCRPRO) as a study sponsor and the Regulatory Compliance and Human Subjects Protection Program (RCHSPP) Clinical Trials Management (CTM), Leidos Biomedical Research, Inc., have embraced remote monitoring supplemented by on-site reviews. Since the pandemic began, RCHSPP CTM has conducted more than 300 remote monitoring visits (including study initiation and close-out visits). Procedures and templates were updated to allow for the changing technology and methods of managing remote monitoring work.

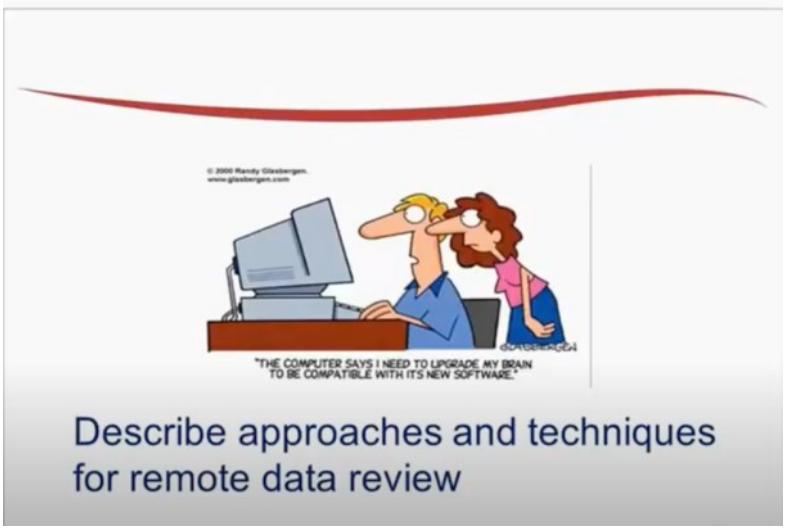
The success of RCHSPP CTM has relied on web-based data management systems that allow for remote review from various locations. In addition, RCHSPP CTM relied on sites providing either remote access to electronic medical records or scanning paper source documents. The use of tools such as Huddle, a secure server that can house copies of documents provided by study sites, and mobile devices with video capabilities can make remote monitoring possible. RCHSPP CTM has conducted pharmacy visits via video conferencing and by scanning copies of pharmacy files into Huddle for monitors to review.



Monitoring encompasses more than just source data verification. Access to centralized data reviews by safety oversight groups, including data and safety monitoring boards and safety monitoring committees, and review of site-essential documents and study drug accountability files for investigational study agents are also key to ensuring proper sponsor oversight. Remote monitoring involves sending regulatory files to the sponsor in an electronic format that allows the sponsors' Electronic Trial Master Files to be updated on time.

To ensure a smooth remote monitoring visit, it is helpful for clinical sites to have staff readily accessible to meet with clinical research associates/monitors. RCHSPP CTM has found that this helps to address questions and makes the visit go more efficiently.

There are benefits to having remote monitoring visits, such as the ability to schedule the visit soon after a site begins enrolling participants. Having the data reviewed early on helps to reduce poor documentation practices at the site level. In addition, data management systems could be more inclusive to "clean data" sooner rather than later with centralized and remote data review and by verifying data from participants' medical records. Although remote monitoring has several benefits for sponsors and sites, there are also potential drawbacks to consider. For sites with resource limitations related to internet connectivity, technology, scanner availability, and staffing, remote monitoring has been challenging to implement. Another drawback has been the amount of additional work for study staff due to the large quantities of paper documentation needed for successful remote monitoring. However, RCHSPP CTM has found that even these obstacles can be overcome with a little flexibility and advance planning, including the use of secure systems like Huddle and establishing process flows early on with sites.



INA-RESPOND Newsletter

EXERCISE AND OSTEOARTHRITIS: FRIENDS OR FOES?

By: Edrick Purnomo Putra

Have you ever heard people say that doing exercise is bad for your knees? Exercise and sports are common physical activities that people do in their leisure time. Studies have shown that exercise give a lot of positive health benefits such as weight control, increase physical fitness, cardiovascular health, metabolic health, and also mental health.1 However, there are some concerns in the community that doing exercise will bring negative effects on the joints especially the knee. And for those who already had knee problems, they are reluctant to move their joints because they feel that their joints are stiff and painful. They are also afraid that exercise will worsen the symptoms of the disease. In contrast, recent studies have shown the opposite. Exercise is used as a part of the management for knee osteoarthritis to decrease pain and increase function.2 So, are they actually friends or foes?

Osteoarthritis is one of the most common joint problem in the world. It is a chronic and progressive degenerative disease of the joint that is characterized by the loss of joint cartilage. Without the cartilage, the bones will rub against each other and cause irritation and inflammation. Even though cartilage is the main problem in osteoarthritis, the whole joint is affected by this. The bones will try to repair itself, but instead, abnormal growth of the bone happened, and it causes more problem.1 The narrowing of the joint space is also observed in those with osteoarthritis.2 Therefore, signs and symptoms like pain, swelling, stiffness, limited range of motion, joint instability, and muscle weakness will occur, and, in the end, it will lead to decrease of physical function, and quality of life.3 Even though osteoarthritis is related to aging, there are some other factors that might increase the risk of developing osteoarthritis at younger age. Previous history of injury and biomechanical factors, such as excessive body weight or anatomic abnormality, might be the risk factors.1 Osteoarthritis is considered as one of the leading causes of disability. Knee, hip, wrist and spine are the most common site of osteoarthritis.4

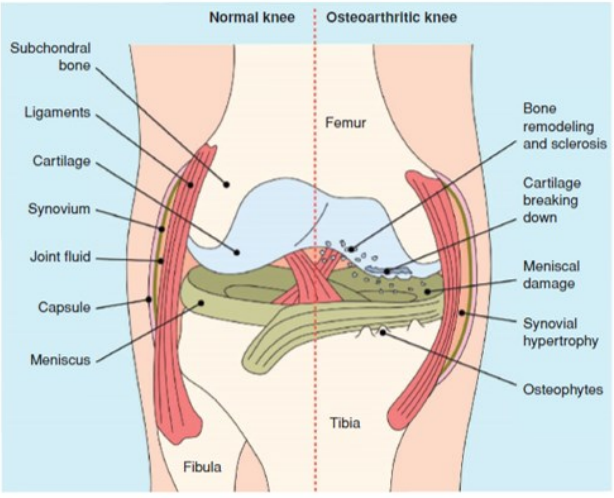


Figure: Pathological features of osteoarthritis.

While previous history of injury is one of the risk factors of developing osteoarthritis, what about those who participate in regular exercise and sports? People with normal joints might ask whether their exercise and sport program will increase their risk of developing osteoarthritis in the future. A case control study with men and women aged 55 to 75 years old who received knee arthroplasty in Finland found out that a history of moderate recreational physical exercise is associated with a decreased risk of developing knee osteoarthritis.5 In contrast, a cohort study with men and women who participated in ski race in Sweden found out that participants with multiple and fast races have an increased risk of subsequent arthroplasty of knee and hip due to osteoarthritis suggesting that intensive exercise may increase the risk.6 A study review concluded that there is no deleterious effect of exercise and sports participants on the joints in individuals with normal and healthy joints who participated in moderate physical activity. In the level of elite athletes who performed their activities with high impact and high stress to the joints, it appears to have an increased risk of developing osteoarthritis.1 A case control study of older

female in Bangladesh suggest not to continue a high level of physical activities and continue with moderate and low level of physical activity to impede knee osteoarthritis and for general health well-being.7 This increased risk however, is actually a result of participation which make people with high exercise participation susceptible to injury.1 On the contrary, a newer study in older adults indicates that long term strenuous physical activity participation showed no association with the incident of radiographic knee osteoarthritis in 10 years. This finding suggests that older adults with high risk of developing knee osteoarthritis may safely engage in strenuous physical activity in moderation.8

Other studies also find that sports and exercise participation as a weight bearing activity for the joints may give a protective effect against the development of osteoarthritis. Articular cartilage is mechano-adaptive tissue. It is responsive to mechanical stimuli, and it may alter the morphology and composition of cartilage.1 Previous studies in animal and human show that the absence of mechanical stimulation on articular cartilage due to prolonged immobilization leads to reduction of articular cartilage thickness.9 However, the results of human studies investigating the influence of physical activity on cartilage thickness is still unclear. A cross sectional study in runners found that cartilage proteoglycan is increased in those who exercised compared to sedentary control observed in results of MRI with contrast agent. This indicates that glycosaminoglycan distribution within cartilage is increased in those participating in exercise, therefore indicating a promising protective factor against osteoarthritis.1

What about those who already suffered from osteoarthritis? Since it is a degenerative disease, there is no exact cure for it.10 However, there are things that can be done to slow its progression and maintain function. Management of osteoarthritis includes pharmacological, non-pharmacological, and surgery. NSAID is commonly used for pain and inflammation control.11 Surgery might be suggested if conservative treatment is not successful, and at end stage of osteoarthritis, arthroplasty might be done by doing total knee replacement especially in older patient.12 Non-pharmacological treatment includes weight reduction, walking aids, braces, modalities, footwear, and insole.11 Exercise is one of the non-pharmacological treatments that is proven to be effective in reducing pain, stiffness, and increase quality of life.11

There are many types of exercises that can be utilized to manage patients with osteoarthritis, such as aerobic exercise, strengthening exercise, flexibility, Tai Chi, and water-based exercise. A systematic review and meta-analysis on exercise for knee osteoarthritis indicates high-quality evidence that a land based therapeutic exercise provide short term benefit in terms of reducing pain that is sustained for at least two to six months after cessation of formal treatment and comparable with estimates reported for those treated with NSAID. The study also indicates moderate quality evidence that shows improvement in physical function in patients with knee osteoarthritis.2 Even though exercise may improve pain and physical function, few studies shows that exercise does not attenuate the structural disease progression.3

General recommendation of exercise for patient with osteoarthritis according to American Geriatric Society is to do flexibility, strengthening, and endurance exercises. Flexibility exercise with static stretching should be done daily in moderate intensity. Strengthening training should be done especially for muscles that support the joints. It is advised to do it two or three times a week with moderate intensity. Endurance exercise should be done three to five times a week with low to moderate intensity for an accumulation of 150 minutes weekly. Exercise program should be tailor-made according to each patient's condition. Long-term effects of exercise in patients with osteoarthritis includes decreased pain,

increased muscle strength and activation, improved physical function, better joint stability, improved postural control and proprioception. Exercise will also improve cardiovascular capacity and body composition, which is beneficial for health in longer term.4

However, it is challenging for patient to maintain adherence to an exercise program. There are many factors that may contribute to patient's adherence, such as physiological status, symptoms and signs of the disease itself, previous experience, exercise preference, motivation and personality, knowledge, social support, time restraint, socioeconomic status, and physical environment.10 Multi-aspect strategy should be applied to maximize patient's adherence. Using supervised exercise sessions in a class format for initial exercise followed by home exercises may enhance adherence. Monitoring by intermittent consultation or attending a "refresher" session may also assist a long-term adherence and improve outcomes. Encouraging healthy lifestyle habits combined with education and behavioral strategies will help patient to increase overall physical activity level.3

As a conclusion, we can see that exercise takes a particularly important part in promotive, preventive, curative, and rehabilitative aspects of osteoarthritis management. People should not fear that exercise will bring harm to their joints' health. In fact, if trauma is avoided, exercise does not lead to acceleration of developing osteoarthritis when done in moderate intensity and even give protective effect compared to sedentary control. Individuals with normal and healthy joints should be actively encouraged to exercise regularly both for the benefits for joints and other health benefits. Exercise is also proven to be an excellent treatment for osteoarthritis management. Even though exercise does not improve structural disease progression, exercise is excellent for symptom management, improving physical function, improving general health and well-being. Sadly, exercise intervention is often overlooked in osteoarthritis management. Therefore, we should encourage exercise as a part of holistic management for our patients.

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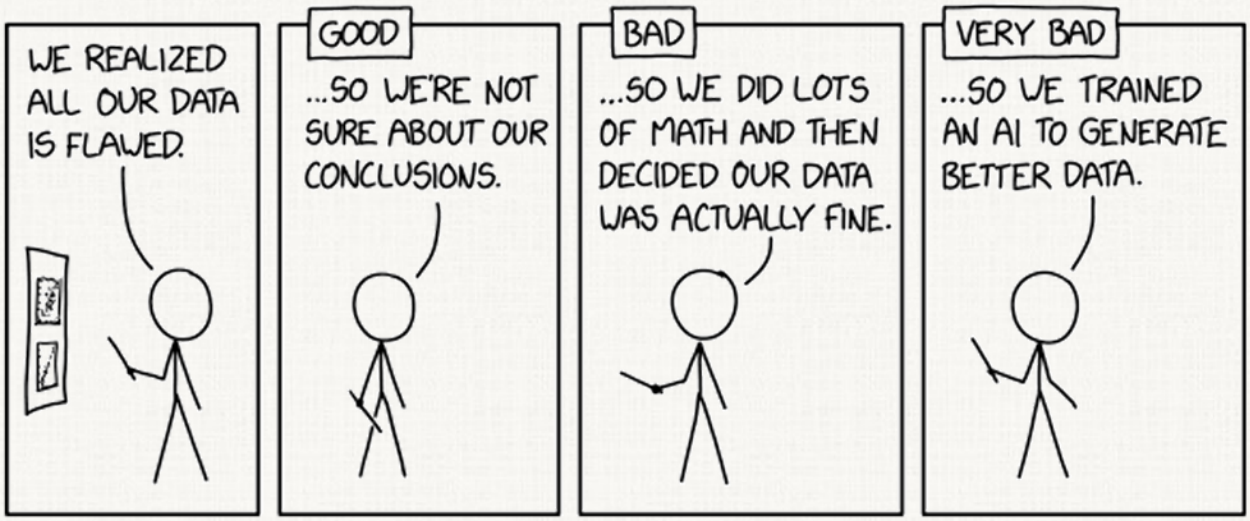
INA-RESPOND Newsletter

MISSING DATA – GOOD, BETTER, AND THE BEST

By: Aly Diana

COMIC CORNER



Source: https://xkcd.com/2494/

We usually put all of our mind, blood, and sweat in collecting the best data possible. Nevertheless, truth be told, missing data are unavoidable in epidemiological and clinical research. We (some of us) usually address missing data by including in the analysis only complete cases —those individuals who have no missing data in any of the variables required for that analysis. However, results of such analyses can be biased. Furthermore, the cumulative effect of missing data in several variables often leads to exclusion of a substantial proportion of the original sample, which in turn causes a substantial loss of precision and power. Oh no!!!

First thing first, let us remind ourselves about what kind of missing data we have; as the risk of bias due to missing data depends on the reasons why data are missing. Reasons for missing data are commonly classified as: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR). MCAR: There are no systematic differences between the missing values and the observed values. For example, blood pressure measurements may be missing because of breakdown of an automatic sphygmomanometer. MAR: Any systematic difference between the missing values and the observed values can be explained by differences in observed data. For example, missing blood pressure measurements is higher among younger people, but only because doctor more likely only examine blood pressure among older people. MNAR: Even after the observed data are taken into account, systematic differences remain between the missing values and the observed values. For example, people with high blood pressure may be more likely to miss clinic appointments because they have headaches.

MCAR causes enlarged standard errors due to the reduced sample size but does not cause bias

('systematic error' that is overestimation of benefits and underestimation of harms). When it is plausible that data are missing at random, but not completely at random, analyses based on complete cases may be biased. Such biases can be overcome using methods such as multiple imputation that allow individuals with incomplete data to be included in analyses.

Multiple imputation allows for the uncertainty about the missing data by creating several different plausible imputed data sets and appropriately combining results obtained from each of them. The most popular algorithm used is Multivariate Imputation by Chained Equation (MICE); which is available in most statistical package (including R). MICE assumes that data are MAR. It pretends the probability of a missing variable depends on the observed data. MICE provides multiple values in the place of one missing value by creating a series of regression (or other suitable) models, depending on its 'method' parameter. In MICE, each missing variable is treated as a dependent variable, and other data in the record are treated as an independent variable.

Multiple imputation has potential to improve the validity of medical research. However, the multiple imputation procedure requires the user to model the distribution of each variable with missing values, in terms of the observed data. The validity of results from multiple imputation depends on such modelling being done carefully and appropriately—whenever possible specialist statistical help should be obtained. If it is not possible, then let's learn the theories and then seek consultation from statisticians or some experts (advice for beginners only)!

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