# INA-RESPOND

**INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE**

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

December 2021


**The 3rd INA-RESPOND Webinar Series titled "One Year Living With SARS-CoV-2: Progress on Prevention & Treatment" about COVID-19 treatment was successfully held on December 4, 2021 with more than 500 people registered and attended the webinar. The aim of the webinar is to provide current updates on COVID-19 treatment and trial and discuss strategies and experiences from other countries that regarded successfully controlling the COVID-19 pandemic. We have received positive feedbacks from the participants and eager to hold more webinars in 2022. Thank you for all the parties (sponsors, organizers, speakers, moderators, etc.) and all participants involved in the success of this event. Resources for this webinar can be accessed on the INA-RESPOND network's website: https://ina-respond.net/2021/11/18/inarespond-3rd-webinar/ Thank you, and see you in the next webinar!**

**Sincerely Yours,**
**M. Karyana / Head of INA-RESPOND Steering Committee**


**NATIONAL INSTITUTE OF HEALTH RESEARCH AND DEVELOPMENT**
**MINISTRY OF HEALTH REPUBLIC OF INDONESIA**
**2021**

MASTHEAD

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**newsletter**

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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

## INA102

After the site closure in November, the TRIPOD team is now finalizing the Study report for NIHRD. Meanwhile, 2 manuscripts from baseline data are still being reviewed by the TRIPOD team and the US team. We are analyzing clinical and laboratory data for the 3rd manuscript on clinical TB and preparing concept plans to utilize specimens for further sub-studies.

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 were done (DST). The next 30 isolates for subculture are in 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 discusses Performance comparison of AFB microscopy and Xpert compared to AFB culture is being prepared by the Manuscript writing team.
4. Working on TRIPOD sub-study, using specimens 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 use.

Status for Repository specimens is provided in figure 1.

| Site | Specimen Type | Whole blood (EDTA) - DNA | Whole blood (Heparin) - PBMCs | Whole blood (Heparin) – Plasma | 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. Repository Specimens and Aliquots per Oct 2021*

## INA104

As of November 30, 2021, from 4,336 subjects enrolled, 1161 subjects had ended their study due to some reasons: 827 subjects completed the study, 221 subjects died, 33 subjects moved away to a city where no PROACTIVE site is available, 29 subjects withdrew, 46 subjects were lost to follow up and five subjects had negative HIV test result. The list of participants with "end of study" status in all sites is shown in Table 1. On the other hand, participant retention status in all sites reached the percentage of 93.5%, with the lowest number in site 600 (79.6%) and the perfect number in site 640 as well as site 700 (Table 2).

Table 1. List of participants with "end of study" status in all sites

**Table 1.** List of participants with "end of study" status in all sites

| No | Site | Death | *Lost to follow up* | Participants moved to other healthcare | Participants with HIV negative | Withdrew consent | End of study duration | Total |
|---|---|---|---|---|---|---|---|---|
| 1. | 530 – RSUPN Dr. Cipto Mangunkusumo | 17 | 4 | 0 | 0 | 0 | 111 | 132 |
| 2. | 550 – RSUP Dr. Wahidin Sudirohusodo | 19 | 18 | 5 | 0 | 0 | 99 | 141 |
| 3. | 560 – RSUP Dr. Kariadi | 27 | 0 | 5 | 3 | 1 | 54 | 230 |
| 4. | 570 – RSUD Dr. Soetomo | 19 | 3 | 3 | 0 | 13 | 109 | 147 |
| 5. | 580 – RSUP Dr. Sardjito | 3 | 0 | 3 | 0 | 0 | 0 | 6 |
| 6. | 590 – RSUP Persahabatan | 31 | 1 | 0 | 1 | 0 | 56 | 89 |
| 7. | 600 – RSUP Dr. H. Adam Malik | 19 | 10 | 2 | 0 | 3 | 118 | 152 |
| 8. | 610 – RSU Kabupaten Tangerang | 19 | 8 | 3 | 0 | 6 | 120 | 156 |
| 9. | 630 – RSUD Dr. M. Ansari Saleh | 7 | 2 | 2 | 0 | 0 | 50 | 61 |
| 10. | 640 – RS St. Carolus | 1 | 0 | 0 | 0 | 0 | 47 | 48 |
| 11. | 650 – RSU Budi Kemuliaan Batam | 8 | 0 | 5 | 0 | 3 | 39 | 55 |
| 12. | 660 – RSU A. Wahab Sjahranie | 4 | 0 | 2 | 0 | 0 | 5 | 11 |
| 13. | 510 – RSUP Dr. Hasan Sadikin | 4 | 0 | 2 | 0 | 1 | 0 | 7 |
| 14. | 540 – RSPI Dr. Sulianti Saroso | 5 | 0 | 0 | 0 | 0 | 7 | 12 |
| 15. | 670 - RSUD Zainoel Abidin | 11 | 0 | 0 | 0 | 0 | 11 | 22 |
| 16. | 680 - RSUD Soedarso | 10 | 0 | 0 | 0 | 0 | 0 | 10 |
| 17. | 690 - RSUD Abepura | 6 | 0 | 1 | 1 | 1 | 0 | 9 |
| 18. | 700 - RSUD TC Hillers | 10 | 0 | 0 | 0 | 1 | 0 | 11 |
| 19 | 520 - RSUP Sanglah | 1 | 0 | 0 | 0 | 0 | 1 | 2 |
| **Total** | | **221** | **46** | **33** | **5** | **29** | **827** | **1161** |

**Table 2.** Participant retention status in all sites

| No | Site # | Hospital's Name | Enrolled | Total Missed Visit | Total SID > 1 Missed Visit | Retention (%) |
|---|---|---|---|---|---|---|
| 1 | 510 | Hasan Sadikin | 208 | 31 | 5 | 97.6% |
| 2 | 520 | Sanglah | 143 | 10 | 3 | 97.9% |
| 3 | 530 | Cipto Mangunkusumo | 310 | 64 | 14 | 95.5% |
| 4 | 540 | Sulianto Saroso | 182 | 100 | 15 | 91.8% |
| 5 | 550 | Wahidin Soedirohusodo | 337 | 224 | 57 | 83.1% |
| 6 | 560 | Kariadi | 230 | 50 | 8 | 96.5% |
| 7 | 570 | Soetomo | 313 | 33 | 3 | 99.0% |
| 8 | 580 | Sardjito | 220 | 124 | 29 | 86.8% |
| 9 | 590 | Persahabatan | 249 | 61 | 18 | 92.8% |
| 10 | 600 | Adam Malik | 338 | 187 | 69 | 79.6% |
| 11 | 610 | Kabupaten Tangerang | 327 | 25 | 2 | 99.4% |
| 12 | 630 | Ansari Saleh | 245 | 32 | 8 | 96.7% |
| 13 | 640 | St. Carolus | 225 | 2 | 0 | 100.0% |
| 14 | 650 | Budi Kemuliaan Batam | 229 | 21 | 2 | 99.1% |
| 15 | 660 | A.W. Sjahranie | 222 | 11 | 0 | 100.0% |
| 16 | 670 | Zainoel Abidin | 126 | 35 | 8 | 93.7% |
| 17 | 680 | Soedarso | 115 | 70 | 17 | 85.2% |
| 18 | 690 | Abepura | 137 | 63 | 22 | 83.9% |
| 19 | 700 | T.C. Hillers | 180 | 0 | 0 | 100.0% |
| **Total** | | | 4,336 | 1143 | 280 | 93.5% |

## INA107 PARTICIPANT STATUS

Based on uploaded CRFs per 8 December 2021, 148 participants were enrolled in the ORCHID-COVID-19 study, which consisted of 105 participants from site 610 (RSU Kabupaten Tangerang, Tangerang) and 43 participants from site 521 (RS Universitas Udayana, Denpasar). There were 141 participants (95%) who had already completed this study, 2 participants passed away during the study, and 5 participants decided not to continue the study categorized as other (figure 1).

Up to 8 December 2021, a total of 132 participants (89%) were identified as positive COVID-19, and only 16 participants (11%) identified as negative COVID-19. In site 610, the number of participants identified as positive COVID-19 was 95 participants (90%) and 10 participants as negative COVID-19. While in site 521, there were 37 participants (86%) identified as positive COVID-19, and 6 participants (14%) identified as negative COVID-19 (figure 2).

In site 521, SARS-CoV-2 was identified in 33 participants (77%) based on pathogen identification data. SARS-CoV-2 and influenza B (confirmed by RDT Antigen Influenza) co-infections were identified in 5 participants (12%). Dengue (confirmed by RDT Dengue NS-1) was also identified in 1 participant (2%). While in site 610, SARS-CoV-2 was identified in 94 participants (90%). SARS-CoV-2 and dengue (confirmed by RDT Dengue NS-1) co-infection were identified in 1 participant (1%). The pathogen cannot be identified within 14 participants (9%), 4 in Site 521, and 10 in site 610 (figure 3).

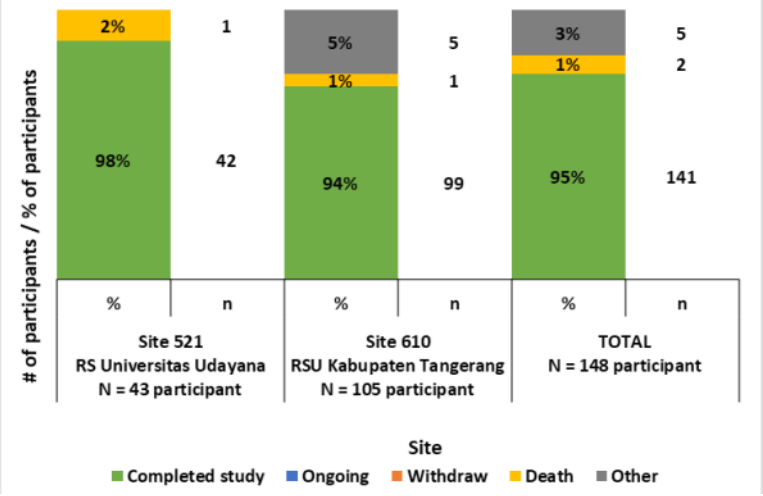


*Figure 1. Participant status per site based on uploaded CRF as of 8 Dec 2021*

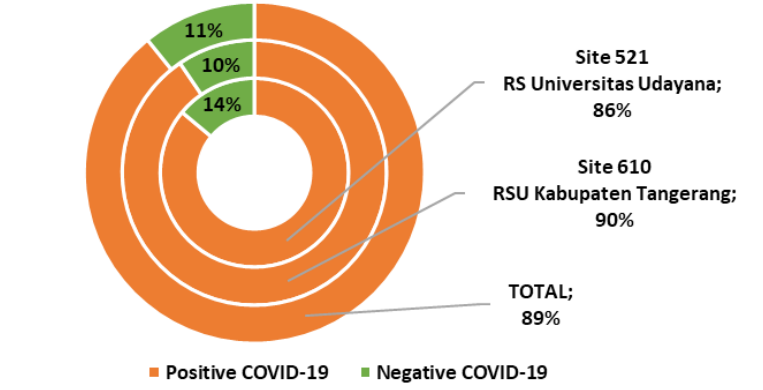


*Figure 2. COVID-19 identification at enrolment based on uploaded CRF per 8 December 2021*

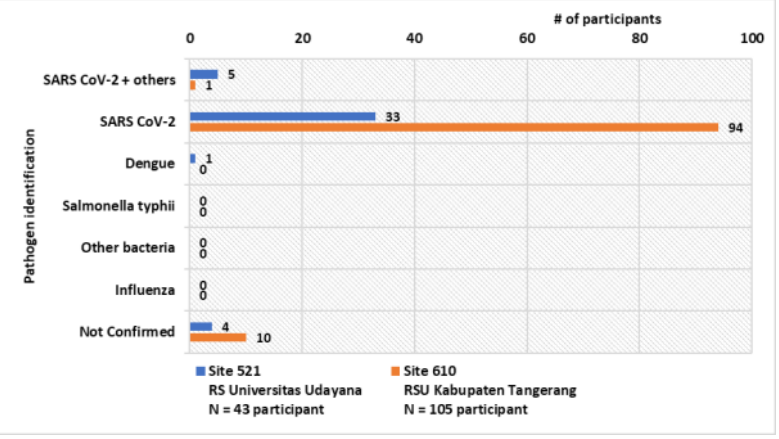


*Figure 3. Pathogen identification based on uploaded CRF per 8 December 2021*

INA-RESPOND Newsletter

# ORAL ANTIVIRUS FOR COVID-19 (PART 2)

By: Yan Mardian

SCIENCE CORNER

In last month's newsletter, we mainly talked about oral antiviral drugs' principal mechanisms and an in-depth overview of Molnupiravir. In this 2nd part, we will explain the other candidates of oral antiviral drugs for covid, and the summary is presented in a table below (page 10).

**PAXLOVID™ (PF-07321332; ritonavir)**

PAXLOVID™ is an investigational SARS-CoV-2 protease inhibitor antiviral therapy, specifically designed to be administered orally to be prescribed at the first sign of infection, potentially helping patients avoid severe illness, hospitalization, and death. Pfizer developed PF-07321332 in early 2000s as a potential treatment for SARS caused by the coronavirus SARS-CoV. At the start of the Covid-19 pandemic, they retooled it to work against SARS-CoV-2, which has similar biology with SARS-CoV. In addition, they modified the drug, originally designed to be given intravenously, as a pill. Pfizer's PF-07321332 is designed to block the activity of the SARS-CoV-2-3CL protease (Mpro) (Fig.4), thus inhibit proteolysis, which occurs before viral RNA replication. Co-administration with a low dose of HIV antiviral ritonavir helps slow the metabolism, or breakdown, of PF-07321332 to remain active in the body for longer periods at higher concentrations to help combat the virus. In pre-clinical studies, PF 07321332 did not demonstrate evidence of mutagenic DNA interactions (1).

PAXLOVID™, as the drug is now known, went into clinical trials in March 2021, followed by a larger Phase 3 trial in July. On November 5, based on an interim analysis of the Phase 2/3 EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) a randomized, double-blind study of non-hospitalized adult patients with COVID -19, the administration of this drug showed an 89% reduction in risk of COVID-19-related hospitalization or death from any cause compared to placebo in patients treated within three days of symptom onset (primary endpoint); 0.8% of patients who received PAXLOVID™ were hospitalized through Day 28 following randomization (3/389 hospitalized with no deaths), compared to 7.0% of patients who received placebo and were hospitalized or died (27/385 hospitalized with seven subsequent deaths). The statistical significance of these results was high ($p<0.0001$). Similar reductions in COVID-19-related

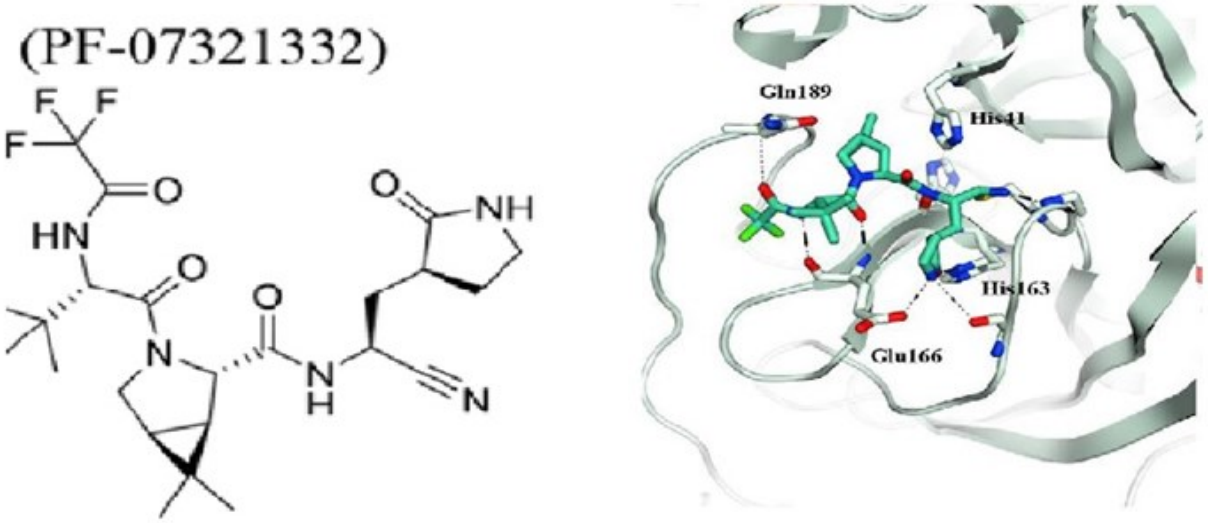


Figure 4. Cristal Structure of PF-07321332 and binding site with SARS-CoV-2 Mpro

hospitalization or death were observed in patients treated within five days of symptom onset; 1.0% of patients who received PAXLOVID™ were hospitalized through Day 28 following randomization (6/607 hospitalized, with no deaths), compared to 6.7% of patients who received a placebo (41/612 hospitalized with ten subsequent deaths), with high statistical significance ($p<0.0001$). In addition, in the overall study population through Day 28, no deaths were reported in patients who received PAXLOVID™ as compared to 10 (1.6%) deaths in patients who received placebo (2). At the recommendation of an independent Data Monitoring Committee and in consultation with the U.S. FDA, Pfizer will cease further enrollment into the study due to the overwhelming efficacy demonstrated in these results and plans to submit the data as part of its ongoing rolling submission to the U.S. FDA for EUA as soon as possible. Similar with Molnupiravir, PAXLOVID™ needs to be given within the first five days of symptoms onset, at about $700 per treatment course (twice daily for five days).

**AT-527**

An oral direct-acting antiviral, AT-527, is being co-developed by Atea Pharmaceuticals in partnership with Roche. AT-527, a double prodrug of a guanosine nucleotide analog, was previously shown to be highly efficacious and well-tolerated in hepatitis C virus (HCV)-infected subjects. Its unique mechanism of action, with dual targets including chain termination of RdRp and nidovirus RdRp associated nucleotidyltransferase (NiRAN), which serves to prime the RdRp for RNA synthesis inhibition, and thus has the potential to create a high barrier to resistance with broad antiviral coverage to different variants of SARS -CoV-2 (Fig. 5). Atea has completed a comprehensive nonclinical program to characterize the potency and safety profile of AT-527. In vitro analysis showed potent antiviral activity against flaviviruses and coronaviruses, including SARS-CoV-2 (EC90=0.5 μM). Results from these non-clinical studies demonstrate that AT-527 is non-mutagenic and has no effects on fertility and reproduction (3).

Atea Pharmaceuticals in its October press release provided update and topline results for Phase 2 MOONSONG Trial Evaluating AT-527 in the outpatient setting. The randomised, multicentre, double-blind, placebo-controlled Phase II trial assessed the safety, antiviral activity and pharmacokinetics of twice-daily (BID) doses of 550 mg and 1,100 mg AT-527 in adult subjects with mild or moderate Covid-19 against placebo. Findings showed that AT-527 failed to meet the primary goal versus placebo in the overall trial population, which had two-thirds of subjects with mild symptoms at reduced risk. A decline of viral load of nearly $0.5\log_{10}$ at day seven was reported in increased risk subjects with underlying health conditions when administered with BID 550 mg and 1,100 mg AT-527 against placebo. Nearly 20% in the placebo arm and AT-527 550mg BID arm reported adverse event (AE) versus 27% in the AT-527 1100 mg BID arm. Furthermore, the most common AEs observed in the trial were gastrointestinal-related (4). "Based on the totality of the results for AT-527 to-date, the current level of understanding of the virus and the evolving COVID-19 environment, we are assessing the Phase 3 MORNINGSKY trial for modifications to ensure the best possible outcome for the program," said Janet Hammond, MD, PhD, Chief Development Officer of Atea Pharmaceuticals. "We, along with our partner Roche, are continuing to advance multiple studies in parallel to provide further clinical evidence as well as outcome data to support AT-527 as an oral, potent, direct -acting antiviral treatment for COVID-19." Possible changes to the international Phase III MORNINGSKY trial, including its primary goal and subject population, will be analyzed by Atea and Roche. Results from this trial are anticipated in the second half of next year (2022).

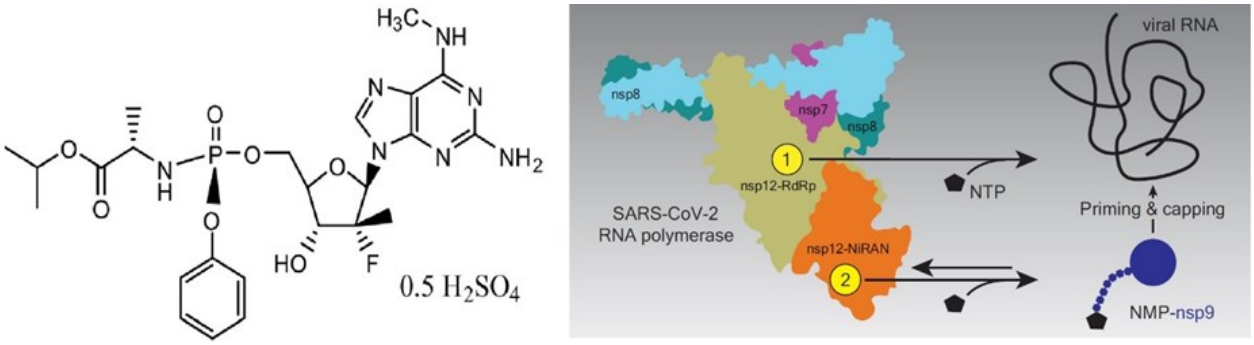


Figure 5. At-527 chemical structure and SARS-CoV-2 RdRp associated nucleotidyltransferase (NiRAN)

**Favipiravir**

Favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide) also known as T-705, avigan, or favilavir, is an antiviral agent that was first developed by the Japanese Toyama Chemical Co., a subsidiary of Fuji Film. It was originally designed to beat against the flu, as reported initially by Furuta in 2002. In 2014, it was approved in Japan as a backup choice for resistant influenza infection. Favipiravir is a pyrazinecarboxamide derivative that can inhibit the RdRp of influenza virus and has also been shown to have antiviral activities beyond the flu. In animals, favipiravir has shown activity against viruses such as Influenza, West Nile, Yellow fever, Foot and Mouth Disease, and Rift Valley as well as other Flaviviruses, Arenaviruses, Bunyaviruses, Alphaviruses (e.g., Chikungunya [CHIKV]; Sindbis [SINV]; Western equine encephalitis [WEEV]; and Semliki Forest [SFV] viruses), and Enteroviruses. Favipiravir has been shown to have an effect in vitro and in vivo against Zaire Ebola, Rabies (RABV), and Zika viruses. Favipiravir was described to reduce the morbidity and mortality associated with RABV infection in mice. In a Syrian hamster model that mirrors the human disease, favipiravir reduced encephalitis, hemorrhagic fever, respiratory difficulties, and mortality rate caused by Nipah virus infection (a Bat virus) (5).

Favipiravir is structurally similar to ribavirin (antiviral drug used to treat Respiratory Syncytial Virus [RSV] infection, Hepatitis C, and some viral hemorrhagic fevers). Favipiravir and ribavirin share a carboxamide (C-[O]-NH2) moiety. However, favipiravir is a more specific version of ribavirin. Both drugs target the viral RNA polymerase; ribavirin primarily targets the Inosine-5′-monophosphate dehydrogenase (IMPDH), while favipiravir interacts with RNA polymerase. Mechanistically, favipiravir is a prodrug that does not inhibit influenza RNA polymerase activity until it is phosphoribosylated in cells forming favipiravir-ribofuranosyl-50-triphosphate (favipiravir-RTP). Favipiravir -RTP then binds to the active site of RdRp to stop RNA replication (6). It has been suggested that the human hypoxanthine guanine phosphoribosyl-transferase (HGPRT) plays a role in the favipiravir activation. The active form of favipiravir is recognized by the catalytic domain of the viral RNA-dependent RNA polymerase and blocks its enzymatic activity. This results in inhibition of the RNA-dependent RNA polymerase and effectively ending the infectious cycle of SARS-CoV-2 (Fig. 6). Note that favipiravir is not toxic to mammalian cells and does not inhibit RNA or DNA synthesis within these cells (5,7).

Previous favipiravir trials, albeit small, had suggested that in mild to moderate hospitalized COVID-19 patients, the drug could clear SARS-CoV-2 in their noses and throats, leading to a number of countries, including Japan, Kenya, Russia, Saudi Arabia, and Thailand, to approve favipiravir for Covid-19. But a February review of favipiravir trials suggested that it has only negligible impact on mortality in patients with serious symptoms. Nine studies encompassing 827 patients were included the meta-analysis (PROSPERO (CRD42020180032)) to determine the efficacy and safety of Favipiravir against COVID-19. The results revealed a significant clinical improvement in the Favipiravir group versus the control group during seven days after hospitalization (RR = 1.24, 95% CI: 1.09–1.41; P = 0.001). Viral clearance was more in 14 days after hospitalization in Favipiravir group than control group, but this

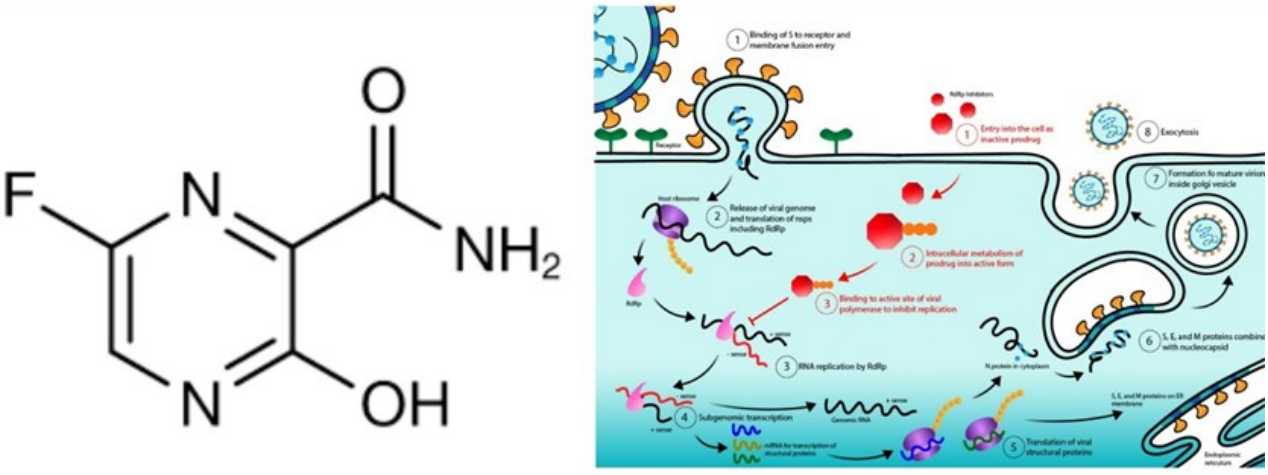


Figure 6. Favipiravir Chemical Structure and its binding to RdRP to block RNA replication

finding was marginally not significant (RR = 1.11, 95% CI: 0.98–1.25; P = 0.094). Requiring supplemental oxygen therapy in the Favipiravir group was 7% less than the control group, (RR = 0.93, 95% CI: 0.67–1.28; P = 0.664). Transferred to ICU and adverse events were not statistically different between the two groups. The mortality rate in the Favipiravir group was approximately 30% less than the control group, but this finding was not statistically significant (8). Favipiravir possibly exerted no significant beneficial effect in terms of mortality in the general group of patients with mild to moderate COVID-19. Other trials are still underway to see if it can be useful for early treatment for people recently diagnosed with Covid-19, such as PRINCIPLE trial lead by University of Oxford UK (https://www.principletrial.org/news/favipiravir-to-be-investigated-as-a-possible-covid-19-treatment-for-at-home-recovery-in-the-principle-trial)

**S-217622**

S-217622, a therapeutic drug for COVID-19, is a 3CL protease inhibitor created through joint research between Hokkaido University and Shionogi & Co., Ltd. (Head Office: Osaka, Japan; President and CEO: Isao Teshirogi, Ph.D.; hereafter "Shionogi"). The new coronavirus (SARS-CoV-2) has an enzyme called 3CL protease, which is essential for the replication of the virus. S-217622 suppresses the replication of SARS-CoV-2 by selectively inhibiting 3CL protease. During at the International Society for Influenza and Other Respiratory Virus Diseases (ISIRV)-World Health Organization (WHO) Virtual Conference., the results of non-clinical drug efficacy and pharmacokinetic studies, and a summary of the results from the Japanese Phase 1 clinical trial1 which started in July 2021, were presented. The information presented is outlined below:

Non-clinical studies using SARS-CoV-2 infected animals:

S-217622 showed in vitro antiviral activity against a broad range of strains, including the δ strain.

A dose-dependent viral reduction effect of S-217622 was observed in multiple animal studies.

S-217622 showed a good drug metabolism and pharmacokinetics profile supporting oral dosing.

The Japanese Phase 1 clinical trial (a single ascending dose study), began in July 2021:

Single oral administration of S-217622 to healthy Japanese subjects was safe and well-tolerated.

The once-daily oral dosing of S-217622 was predicted to exceed the target concentration required for the viral reduction effect from the non-clinical studies.

Based on these results, S-217622 has the potential to reduce SARS-CoV-2 viral load with once-daily oral administration. Phase 2/3 clinical trial of S-217622 is currently underway in mild or asymptomatic COVID-19 patients. The Phase 2/3 clinical trial will evaluate the efficacy and safety of oral administration of this drug once daily for five days in patients with mild COVID-19 or asymptomatic SARS-CoV-2 infection compared to placebo (9).

**EDP-235**

In August 2021, Enanta Pharmaceuticals, Inc. a clinical stage biotechnology company, announced that it had nominated EDP-235, its lead oral protease inhibitor specifically designed for the treatment of COVID-19. The preclinical data for EDP-235 were presented in a poster titled "EDP-235, A Potential Oral, Once-Daily Antiviral Treatment and Preventative for COVID-19," during the International Society for Influenza and Other Respiratory Virus Diseases (ISIRV)–World Health Organization (WHO) Virtual Conference 2021. In a biochemical assay, EDP-235 inhibited the SARS-CoV-2 3CLpro protease with an IC50 of 5.8 nM. Importantly, this activity was retained against proteases from SARS-CoV-2 variants. EDP-235 potently blocked the replication of SARS-CoV-2 in multiple cellular models, including primary human airway epithelial cells, where an EC90 of 33 nM was observed. Additionally, EDP-235 was shown to have potent antiviral activity across other human coronaviruses. Mutations in the spike protein aren't expected to significantly affect the activity of EDP-235. Compared to preclinical data from other direct-acting antivirals in development for COVID-19 today, EDP -235 appears to be among the most potent against SARS-CoV-2 in cellular assays. EDP-235 showed good human Caco-2 cell permeability and a low plasma clearance in human liver microsomes. Consistent with this in vitro data, EDP-235 had robust plasma exposure with an oral bioavailability of 95% in rats. Moreover, EDP-235 had favorable in vivo penetration into multiple target tissues, including lung, kidney, liver, and heart. These results indicate that EDP-235 has good oral bioavailability and target tis-

sue distribution compared to other antivirals in development for SARS-CoV-2 today. Based on allometric scaling, EDP-235 is projected to have a long half-life of 16 hours with an efficacious dose of 100 to 500 mg once daily in humans. Taken together, these data indicate that EDP-235 has the potential for once-daily oral dosing with a low pill burden. Enanta has completed IND-enabling preclinical studies of EDP-235 and plans to advance the candidate into the clinic in early 2022 (10).

All this emerging evidence has brought new hope of a turning point in the pandemic: a not-too-distant future when a simple pill could keep infected people from dying or falling severely ill. However, will new covid treatments be elusive for developing countries, or will these treatments remain largely with nations able to pay for early access, as they have done with vaccines? It requires coordinated global action, grounded in full transparency in the procurement and delivery process as a commitment for equity and defeating the pandemic together. The summary of promising oral drugs is presented in the table below.

Summary of Investigational oral antiviral drugs for COVID -19

| | **Molnupiravir** | **Paxlovid™** | **AT-527** | **Favipiravir** | **S-217622** | **EDP-235** |
|---|---|---|---|---|---|---|
| **Developer** | Merck & Co Inc.& Ridgeback Biotherapeutics LP | Pfizer Inc. | Atea Pharmaceuticals & Roche | Toyama Chemical Co., Fujifilm, Japan | Hokkaido University and Shionogi & Co., Ltd. | Enanta Pharmaceu-ticals, Inc. |
| **Repurposed** | Yes, originally designed to treat influenza | No | Yes, originally designed against HCV | Yes, originally designed to treat influenza | No | No |
| **Mechanism** | Nucleoside Analogs / RdRp inhibitor, induces mutations | SARS-CoV-2-3CL protease ($M^{pro}$) inhibitor | Nucleoside Analogs / RdRp inhibitor, non-mutagenic | Nucleoside Analogs / RdRp inhibitor, non-mutagenic | SARS-CoV-2-3CL protease ($M^{pro}$) inhibitor | SARS-CoV-2-3CL protease ($M^{pro}$) inhibitor |
| **Dose** | Orally 800 mg (4 x 200 mg capsules) taken twice daily (BID) for 5 days. | Orally twice daily (BID) for 5 days | Orally 550 mg twice daily (BID) for 5 days | Orally 1600 mg twice daily on the 1st day followed by 600 mg twice daily (BID) for 5 days | Once daily for five days | Once-daily, oral dosing |
| **Given with co-drug** | No | Yes, Ritonavir to promote half-life | No | No | No | No |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Published Result/ Efficacy in Trial** | **Phase III.**<br><br>Efficacy 50% to reduce hospitalization or death risk<br><br>Update on Final Analysis: Efficacy lowered to just 30% effective | **Phase III.**<br><br>Efficacy 89% to reduce hospitalization or death risk | **Phase II.**<br><br>Failed to meet the primary goal.<br><br>Possible protocol modification to the Phase III trial, including its primary goal and subject population | **Phase III.**<br><br>Modest impact on mortality in patients with serious symptoms. Other trials are still underway to assess efficacy on early treatment. | **Phase 1.**<br><br>Single oral administration of S-217622 to healthy subjects was safe and well-tolerated. Pharmacokinetic analyses confirm that blood drug concentrations meeting or exceeding the target concentration required for the viral reduction effect from the non-clinical studies. | **Pre-Clinical.**<br><br>Preclinical studies showed potent antiviral activity and a favorable pharmacokinetic profile |
| **Possible Risk** | Off-target coding for mutation catastrophe | Not yet defined | Not yet defined | May cause teratogenic effect | Not yet defined | Not yet defined |
| **Cost** | ~ $700 / treatment course | ~ $700 / treatment course | Unknown | Unknown | Unknown | Unknown |

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INA-RESPOND Newsletter

# ETHICAL CONSIDERATIONS IN CLINICAL TRIALS IMPORTANCE OF DIVERSITY IN CLINICAL TRIAL PARTICIPANTS (PART 1)

By: Louis Grue



FROM OUR PARTNER

Note: "minority" in this article refers specifically to the US minority populations.

Brief Overview of Clinical Trial Inclusion and Exclusion Criteria

Inclusion criteria are the characteristics that prospective participants must have if they wish to join the study.

Exclusion criteria are the characteristics that disqualify prospective participants from joining a study.

During drug development, the inclusion of broad patient populations in clinical trials helps provide evidence that the investigational medical products will be safe and effective in the full range of patients likely to use the product if the product is approved. Eligibility criteria determine who can participate in clinical trials and, at times, this results in the enrollment of study populations that may not represent the broader patient populations that will use the approved products. There was a time, not that long ago, when clinical trial study participants were predominantly white males. This left a lot of unanswered questions about the safety and efficacy of these medications in women, children, and people of other ethnic or racial backgrounds. Much of the important data obtained during the modern biomedical research revolution, came from men. This includes aspirin for the prevention of heart attacks and migraine headaches, studies on aging, even studies on HIV/AIDS omitted women.

There are a lot of reasons for this and mostly it reflects the history of medical care In the US and who had access to it. Other issues also added to this problem. Over the past few decades, there have been policy initiatives to increase the inclusion of subgroups in clinical trials, including women and older adults, and to ensure that all

eligibility criteria are scientifically justified. This includes initiatives by the U.S. Food and Drug Administration (FDA) and the National Institutes of Health (NIH) that emphasize the importance of inclusive eligibility criteria. Despite these efforts, challenges and barriers that limit participation in clinical trials remain.

NIH 1994 Inclusion Guidelines

In 1979, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research produced the Belmont Report which set out three basic principles to guide the conduct of human subject research: respect for persons, beneficence, and justice. The principle of justice as articulated in the Belmont Report was concerned with the protection of vulnerable populations from exploitation. In the interim, the principle of justice has been re-framed to promote equitable access to the benefits of research. Advocates used this re-framed principle of justice to advocate for the inclusion of women, minorities, and children in clinical research, focusing on the limited generalizability of results from research conducted with heterogeneous subject populations and on the potential ethical harms of failing to address the systematic exclusion of various categories of people. Efforts to increase the number of women enrolled in clinical research began with recommendations by the NIH Women's Advisory Committee in the 1985 and culminated in 1994 with a Congressional mandate that NIH funded biomedical and behavioral research (with special emphasis on Phase III clinical trials) include women and minorities.

In March of 1994, the National Institutes of Health (NIH) released guidelines mandating the inclusion of women and minorities in clinical research. Four years later, the NIH released similar guidelines mandating the inclusion of children. These "inclusion guidelines" were created to increase the representation of women, minorities, and children in clinical research to address potential harms (real and perceived) created by their exclusion or omission. As designated in the guidelines, Institutional Review Board (IRB), NIH Scientific Review Groups (SRG) and NIH program staff all have responsibility for the evaluation of Principal Investigator (PI) adherence to the inclusion guidelines.

Building on the momentum generated regarding the inclusion of women and minorities, Congressional hearings were held in 1995 regarding the inclusion of children in research culminating in the adoption of the 'Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects' in 1998.

National Institutes of Health Minority Health and Health Disparities Strategic Plan 2021–2025

The mission of NIH, as part of HHS, is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. This strategic plan was created with the input of several NIH working groups, including teams of staff and researchers. To ensure that stakeholders at multiple levels were involved in this strategic planning process, input was gathered from experts within and outside of NIH. The NIH defines health disparity populations as racial and ethnic minority populations, less privileged socioeconomic status populations, underserved rural populations, sexual and gender minorities, and any subpopulations that can be characterized by two or more of these descriptions. opportunities and needs to advance the research. This plan lays out a focused vision for the next 10 years, specifying short-, intermediate-, and long-range research strategies and activities that will facilitate progress toward long-term goals.

Why is Diversity in Clinical Trials So Important?

Even with a concerted emphasis on attracting a wide range of participants, researchers still struggle to recruit diverse populations. For example, in 2018, Black participants accounted for 7.7% of US and Canadian clinical oncology trials, but only 2.6% of global oncology drug trials. Cancer clinical drug trials have become more inclusive of Asian participants; however, other racial and ethnic minority groups remain under-represented. As clinical trials migrate globally, researchers need to make their efforts reflective of, and applicable to, the populations they are serving. Clinical trials, and the people who volunteer to participate in them, are essential to help the development of ways to fight illnesses. To make sure that the FDA has a full picture of the risk or benefit of a medical product, patients enrolled in a trial should be representative of the types of patients who are likely to use the medical product if it is approved or cleared by the FDA. Certain populations can be more at risk for certain diseases—such as

diabetes and heart disease—than others. It is important for patients in those populations who are more likely to be treated for a condition to be included in a trial.

Researchers have found that one in five new drugs approved within a recent six-year period yielded differences in response among racial and ethnic groups. In some cases, these differences were so drastic that they necessitated population-specific dosing recommendations. One can find a primary example of race affecting drug tolerance in the case of Plavix. Post-marketing studies for this blood-thinning medication identified that people with certain alleles (one of two or more alternative forms of a gene that arise by mutation and are found at the same place on a chromosome) of the CYP2C19 liver enzyme poorly metabolized Plavix, rendering it ineffective. People of Chinese background proved to be seven times more likely than Caucasians to be poor metabolizers, putting them at higher risk of fatal cardiac events. Additionally, the U.S. Food and Drug Administration (FDA) has found that females have between a 1.5 and 1.7% higher risk of experiencing an adverse drug event. The FDA has ultimately withdrawn several medications because of glaring sex-based adverse events.

Defining Diversity

The operative word in clinical trial recruitment is "representative." If a trial population does not adequately represent the overall patient population for the condition being studied, the trial findings lose relevance. Worse, they can do harm. Incorporating patient populations of varying racial and ethnic identities is essential to ensuring high-quality research. Other variables factor into a research study's level of true diversity, including diversity of sex, gender identity, sexual orientation, socioeconomic status, geographic distributions, physical ability, and age. For example, if city-dwellers get over-recruited compared to those living in rural communities, that may significantly impact clinical research outcomes. These two patient populations can differ markedly in their occupational and environmental exposures and, therefore, their disease processes and responses to therapies. It is important for clinical trials to have participants of different ages, sexes, races, and ethnicities. When research involves a group of people who are similar, the findings may not apply to or benefit everyone. When clinical trials include diverse participants, the study results may have a much wider applicability. Researchers need the participation of older people in their clinical trials so that scientists can learn more about how the new drugs, therapies, medical devices, surgical procedures, or tests will work for older people. Many older people have special health needs that are different from those of younger people. For example, as people age, their bodies may react differently to drugs. Older adults may need different dosages of a drug to have the right result. Also, some drugs may have different side effects in older people than younger people. Having seniors enrolled in drug trials helps researchers get the information they need to develop the right treatment for older people.

Some U.S. patients also may not trust medical research due to historical mistreatment of study subjects, such as those involved in the Tuskegee Study, which began in 1932 and continued for 40 years. That study's serious flaws led to major changes in how clinical trials are conducted in order to protect the rights, safety, and welfare of patients in clinical trials. Today, participants' rights are protected by law and by committees such as "institutional review boards." These ethics committees, also known as "IRBs," are independent from the people conducting the study. IRBs carefully review plans for research involving people before research can be conducted and at least once a year while research is conducted. The FDA is working with a variety of stakeholders, including federal partners, medical product manufacturers, medical professionals, and health advocates. For example, the FDA has a dedicated section on its website for patients that provides information and tools to encourage clinical trial participation. This section includes information that focuses on people of different ages, races, ethnic groups, and genders. The FDA's Office of Women's Health, along with the National Institutes of Health (NIH) Office for Research on Women's Health, launched an initiative to raise awareness among women and share best practices for clinical trials. The FDA's Office of Minority Health also has tools to encourage people and their health care providers to learn about trials, including public service announcements (PSAs). (You can view PSAs on the FDA's "Minorities in Clinical Trials" webpage.) The FDA offers guidance for researchers as appropriate, including recent recommendations to industry and agency staff on how race and ethnicity data should be collected.

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**Why Are Older and Diverse Participants Important in Clinical Trials?**

https://www.nia.nih.gov/health/what-are-clinical-trials-and-studies#older

**EVALUATING INCLUSION AND EXCLUSION CRITERIA IN CLINICAL TRIALS**

**PUBLIC WORKSHOP: WORKSHOP REPORT**

The National Press Club • Washington, DC • April 16, 2018

https://www.fda.gov/media/134754/download

**Inclusion and exclusion criteria in research studies: definitions and why they matter**

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**Wanted Single, White Male for Medical Research, Rebecca Dresser**

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INA-RESPOND Newsletter

# ALL ABOUT FLEXIBILITY

By: Marco Ariono



Flexibility is the range of motion (ROM) in a joint or series of joints that reflects the ability of the musculotendon structures to elongate within the physical limitations of the joint. There are two basic types of flexibility, static and dynamic. Static flexibility is the range of motion about a joint without considering how easily or quickly the range of motion is achieved. Dynamic flexibility is the resistance to motion in a joint that affects how easily and quickly a joint can move through its range of motion.1

In 2013, the American College of Sports Medicine (ACSM) defined that "flexibility exercise training is a type of exercise that focuses on improving or maintaining the range of motion in muscles and joint structures by holding or stretching the body in specific positions." A historical tradition says that stretching has been practiced for thousands of years, primarily by warriors before combat.2,3

Flexibility is essential for our daily life, such as putting on shoes or reaching the top shelf. It is also important for muscle relaxation and proper posture. Flexibility is also important for sports performance. But it depends on the type of sport. Gymnasts need to be more flexible than runners and cyclists. There aren't scientific studies that directly link selected flexibility values with performance in athletes who can move through the required range of motion. For example, a bicyclist with a normal range of motion in the ankle, knee, hip, and trunk will not become a better cyclist just by increasing flexibility in those joints.1

**Measuring Flexibility**

The flexibility measurement is not an exact, standardized procedure with a well-established criterion test. Direct measurement in the laboratory usually measures angular displacement between adjacent segments or from a reference point. Such measurements are typically performed with a goniometer or flexometer.1

Variations of the stand or sit-and-reach test are the most popular field test of flexibility. Because of its widespread use as the only flexibility test in physical fitness test batteries, the sit-and-reach test has often been misinterpreted as a measure of total body flexibility. It is often assumed that if individuals have good flexibility in this test, they will be equally good in other joint muscle units. Although this idea is appealing for simplicity and ease of testing, it is not accurate.1

**The Influence of Sex on Flexibility**

One study has shown that across the entire age spectrum from 10 to 75 years, males exhibited greater anterior trunk flexion (also called lumbar mobility or low-back flexibility) than females. Conversely, females showed greater right lateral trunk flexibility across most of the same age span than males. Females also had greater left lateral flexibility than males, at least in adults. 1 These observations contradict the usual assumption that females are more flexible than males.

**The Influence of Age on Flexibility**

Figure 1 illustrates specificity through the pubertal growth years. The general trend is for lumbar flexibility to decrease between 10 and 15 years of age, while lateral flex-

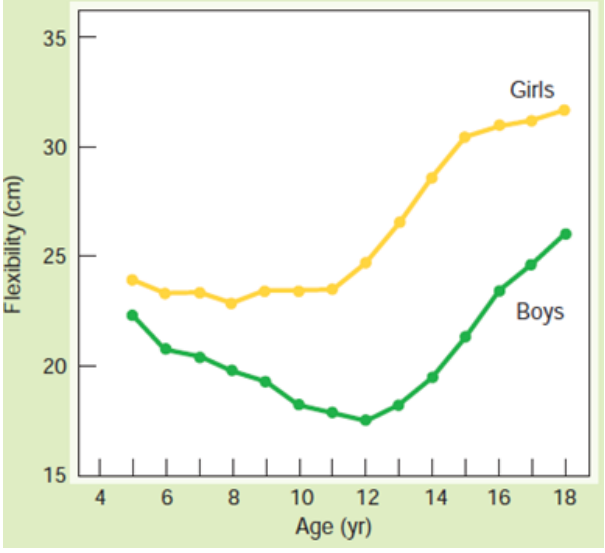


Figure 1. Flexibility as Measured by the Sit and Reach Test1

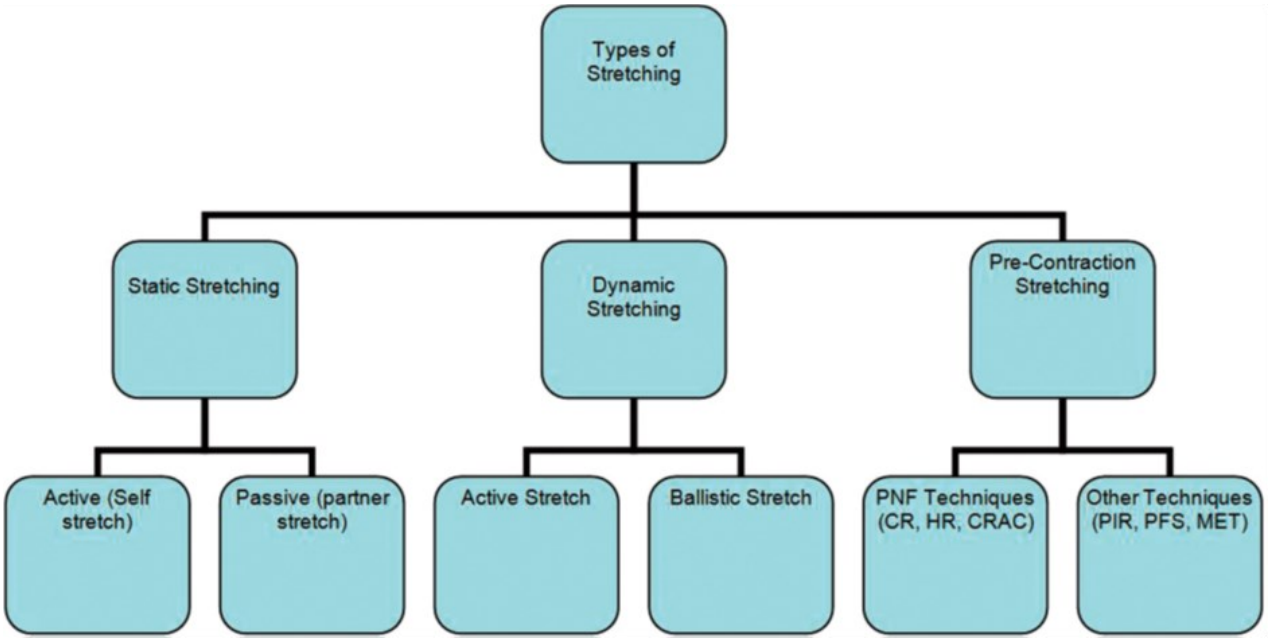


Figure 2. Techniques of Muscle Stretching. HR=Hold relax; CR=Contract relax; CRAC= Contract relax, agonist contract; PIR= Post-isometric relaxation; PFS=Post-facilitation stretching, MET= Medical exercise therapy5

ion generally increases during the same period. Basically, girls show a consistent improvement from age 5 to 18 years, while boys show a U-shaped response—that is, a gradual decline from age 5 to 13 years and then an improvement from 13 to 18 years, such that they are more flexible in the hip and posterior thigh by adulthood.

Flexibility either declines or stays the same through the adult years. But, all ages appear to be trainable to improve their flexibility. This adaptation may be significant to the elderly. Flexibility exercise in the elderly effectively increases joint range of motion in various joints, and other functional outcomes can be improved.4

**Stretching Techniques**

Stretching is a common activity used by athletes, older adults, rehabilitation patients, and anyone participating in a fitness program.5

There are two types of dynamic stretching: active and ballistic stretching. Active stretching generally involves moving a limb through its full range of motion to the end ranges and repeating several times. Ballistic stretching, characterized by an action-reaction bouncing motion, is a form of stretching in which the joints involved are moved to the extremes of the joint range of motion by fast, active contractions of agonistic muscle groups. As a result, the antagonistic muscles are stretched quickly and forced to elongate. This type of stretching is generally not recommended. Ballistic stretching may cause muscle soreness.1,5

Static stretching is a form of stretching in which the muscle to be stretched (the antagonist) is slowly put into a position of controlled maximal or near-maximal stretch. The position is held for 10–30 seconds. Static stretch has been touted as a means of avoiding injury and relieving muscle soreness. Over the last two decades, static stretching has been considered harmful to subsequent strength and power performances. It has been recommended not to apply static stretching before strength- and power-related activities. 1,2

Proprioceptive neuromuscular facilitation (PNF) is a stretching technique in which the muscle to be stretched is first contracted maximally. The muscle is then relaxed and is either actively stretched by contraction of the opposing muscle or is passively stretched by an outside force. PNF stretching carries some risk of injury if the partner attempts to push the relaxed limb too far.1

**Benefits of Flexibility**

The main way to increase your flexibility is by stretching. As you age, your muscles gradually become shorter and tighter, reducing your overall flexibility. This restriction makes you more susceptible to muscle, tendon and joint

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INA-RESPOND Newsletter

COMIC CORNER

# THINK TWICE THINK FURTHER; A SPELL TO MAKE OUR FUTURE EASIER

By: Aly Diana


The focus of this corner is to prepare ourselves when we want to use/re-use our own data in the future, including quantitative-, qualitative-data, and tissue samples. In the future, we may find an opportunity to collaborate with more experts, secure more findings, and encounter a new invention, …. There is a lot to discuss using the 'secondary data.' However, let us discuss it from the ethical perspective, to be more specific.

It is often believed that the use of secondary data relieves the researcher from the burden of applying for ethical approval – and sometimes, from thinking about ethics altogether. But the whole research process involves ethical considerations, whether or not any primary data collection is involved. Usage of secondary data is, in itself, a highly ethical practice: it maximizes the value of any (public) investment in data collection, it reduces the burden on respondents, it ensures replicability of study findings, and therefore, greater transparency of research procedures and integrity of research work. But the value of secondary data is only fully realized if these benefits outweigh the risks, notably in terms of re-identification of individuals and disclosure of sensitive information.

For this to happen, usage of secondary data must meet some key ethical conditions: data must be de-identified before release to the researcher/collaborator; consent of study subjects can be reasonably presumed; outcomes of the analysis must not allow re-identifying participants, and use of the data must not result in any damage or distress. The main keyword is de-identified. In general, data that are entirely and robustly anonymized do not contain personal data, so ethical review and approval are usually not required.

Another important thing (to make our life easier), the same design of data collection should incorporate the possibility of releasing the data for secondary use, in that informed consent includes provisions for sharing and future use of data; this also applies for the tissue

samples. When obtaining consent for the collection of samples for use in a specific research project, researchers should request consent for the use of the samples also in future studies. However, individuals must be free to consent for the use of their samples in the immediate specified research only (fully restricted consent), or for the use of these samples in the immediate specified research (partially restricted consent), and also in future research, either of a specified or unspecified nature (unrestricted consent).

A little note: some institutional review boards or ethical committees are not fully supportive with unrestricted consent; but still open to partially restricted consent. When this happens, let's try our best to predict the future and specify the use of these samples in the future. In the case of samples obtained previously without any future use provisions, researchers should try to obtain informed consent from the original donors or their proxies for the use of these materials in research studies for which they were not originally obtained. Where this is not practicable, and the research is expected to produce significant public health benefits, the researcher should request the ethics committee waive the informed consent requirement.

Good luck!

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## Sport and Lifestyle

### All about Flexibility—continued from page 17

injuries. The effectiveness of stretching is usually reported as an increase in joint ROM. While it is widely debated whether or not stretching prevents injury, it has been proven to increase circulation. Stretching has been shown to increase the range of motion in joints effectively. A better range of motion enables you to keep a better balance. Better balance means you are less susceptible to falls and the resulting injuries. Research shows that individuals suffering from LBP have less range of motion, particularly in the low-back and hamstring areas. As with the reduced strength and endurance, however, these differences are more likely the result of LBP than its cause.1,5,6

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# INA-RESPOND Newsletter

The Indonesia Research Partnership on Infectious Disease newsletter is an internal bulletin of INA-RESPOND research network intended to disseminate information related to the network's studies, activities, and interests to all members of the network as well as its sponsors and related parties.

The INA-RESPOND newsletter welcomes all network members and stakeholders to contribute by submitting articles related to the network's studies and interests. Send your articles or subscribe to our latest newsletter by sending an email to INA.Secretariat@ina-respond.net