INA RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

Newsletter

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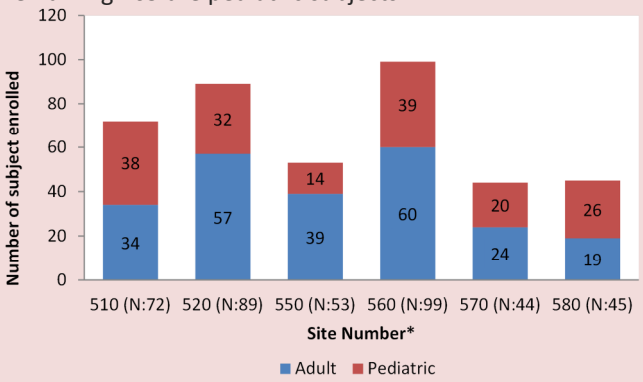
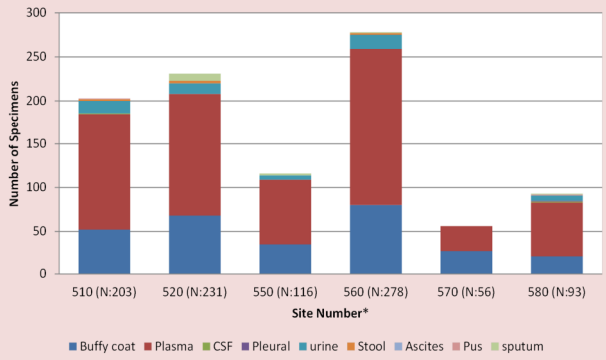
AFIRE STUDY

Enrollment progress up to 27 April 2014 can be seen in the graphic below. A total of 402 subjects have been enrolled, of which are 233 adults and the remaining 169 are pediatric subjects.



Specimens collected from the subjects were shipped to NIHRD on a monthly basis. Until March 2014 NIHRD has received a total of 977 specimens form all active sites. They consist of:



*510 – RSUP dr Hasan Sadikin, Bandung
520 – RSUP Sanglah, Denpasar
550 – RSUP dr Wahidin, Makassar
560 – RSUP dr Kariadi, Semarang
570 – RSUD dr Soetomo, Surabaya
580 – RSUP dr Sardjito, Yogyakarta

Detailed screening and enrollment progress is available in portal folder: Studies\INA101\Screening progress.pdf or go to the following link: https://ina-respond.s-3.com/EdmFile/getfile/797233

INTERIM ANALYSIS – First of all The Secretariat would like to thank site teams for submitting the CRFs, Query Forms, and ODCFs in a timely manner so that we were able to analyze data from the first 155 subjects. The analysis showed that etiological diagnoses were not yet confirmed among 53% of the analyzed subjects. We are going to submit an abstract from this interim analysis result to ICAAC that will be held in September 2014.

-UN-

NSC Meeting

The 2nd NSC meeting in 2014 was successfully conducted on April 23-24. All participants received warm welcome from the host, dr. Hussein Gasem, at RS Kariadi, Semarang. Most of the Steering Committee (SC) members came to this event, except from Surabaya. Dr. Sophia Siddiqui and dr. Clifford Lane came all the way from the USA to meet all INA-RESPOND's SC member. In this meeting, SC member thoroughly discussed about INA-RESPOND studies progress. As the AFIRE study progresses, we had enrolled 383 subjects, received 367 CRF, and stored 977 specimen. Dialogues about how to improve the quality of study conduct, specimen repository, and data management were the highlights. The Secretariat is working on the implementation plan now that TB Study is in the stage of protocol completion. Dr. Abu Tholib as one of the protocol Co-Investigators in Sepsis study shared SEAICRN meeting result in Bangkok. He suggested that INA-RESPOND participate in the study after the study protocol amendment is available. Moreover, a critical point about future study was pointed out at the meeting. All SC member agree that each site will compile a proposal to express their interest in what to do with the specimen. On the whole, the meeting was insightful and worthwhile.

Left to right front row: dr. M. Karyana (INA-RESPOND Chair), dr. Cliff Lane (Governing Board - NIAID), dr. Siswanto (Governing Board-NIHRD), Drs. Bambang (SC Member from NIHRD), dr. Abu Tholib (SC Member site 580), Prof. Pratiwi (SC Member site 530), Dr. Bachti (SC Member site 510). Left to right back row: dr. Santo (Secretariat), Prof. Emil (Central Research Team), Dr. Sophia (SC Member from NIAID), Prof. Tuti (SC Member site 520), Widoretno (Central Research Team), dr. Dewi Lokida (Central Research Team), dr. Delima (Central Research Team), dr. Nurhayana (Co-PI Site 550), dr. Indri Hapsari (RA Site 560), dr. Dewi Muliati (PI Site 540), Yanti Triswan (Secretariat), Sonia (Secretariat), Kanti (Secretariat), Frilasita (Eijkman), Mila (Secretariat), Anandika(Secretariat).

-AP-

Manuscript Writing Workshop

-NHS, SK-

Three months has gone by since the Manuscript Writing Workshop, and no, we do not forget about your manuscript. It is INA-RESPOND's commitment to help you get your manuscript published in a recognized international peer-review journal. We believe that you also have the same commitment and we are looking forward to see more manuscripts submitted in the upcoming months.

No	Author	Institution	Title	Status
1	Ni Made Dewi Dian Sukmawati	Internal Medicine Dept. Universitas Udayana	Assessing Risk For Severe Manifestation Of Dengue Virus Infection: Role Of Enzyme Metalloproteinase 9	**Submitted to International Scholarly Research Notices journal**
2	Hana Krismawati	Centre 1, NIHRD	First Reported Dengue Outbreak in Kaimana District, West Papua Province: A Report from Epidemiology and Entomology Surveys	Being revised
3	Ungke Antonjaya	Eijkman Institute	Association of two polymorphism in DC SIGN with severity of dengue disease in Indonesia	Being revised
4	Masri Sembiring Maha	Centre 1, NIHRD	First report of east central south African (ECSA) Chikungunya virus in Indonesia	To submit to a journal
5	Silvita Fitri Riswari	Health Research Unit, Universitas Padjadjaran	Cluster Investigation Methods To Identify Early Dengue Infections: Results From A Second Proof-Of-Concept Study In Bandung, Indonesia	Being revised
6	I Made Susila Utama	Internal Medicine Dept. Universitas Udayana	Associated of opportunistic infections with HIVRNA and CD4 cell count in pre ARV and ARV failure at CST Clinic Sanglah Hospital, Bali	To submit to a journal
7	Narendra Yoga Hendarta	Health Polytechnic. MoH Yogya	Simple and rapid method using dipstick for early HBV detection based on combination of Loop Mediated Isothermal Amplification (LAMP) and Lateral Flow Dipstick (LFD)	Being revised
8	Vivi Lisdawati	Centre 1, NIHRD	First Molecular Epidemiology of Mycobacterium tuberculosis and its susceptibility to anti-Tuberculous drugs in Indonesia	Being revised
9	Hana Apsari Pawestri	Centre 1, NIHRD	Genetic Characterization of Influenza A/H5N1 Viruses Isolated From Patients in Indonesia, 2008-2012	Being revised
10	Kindi Adam	Centre 1, NIHRD	Viral infections in influenza-like illness cases in Indonesia, 2012	Being revised
11	Ni Ketut Susilarini	Centre 1, NIHRD	Respiratory Viruses in Patients Presenting With Severe Acute Respiratory Infection in Indonesia, 2012	Being revised
12	Vivi Setiawaty	Centre 1, NIHRD	Evaluation of a rapid diagnostic kit for patients with influenza-like illness in Indonesia	Being revised
13	Armedy Roni Hasugian	Centre 2, NIHRD	Artemisinin-Napthoquine versus Dihydroartemisinin-Piperaquine in adult subjects with Plasmodium vivax infection in Indonesian Hospitals	To submit to a journal
14	Rita Marleta	Centre 2, NIHRD	Plasmodium knowlesi cases in Souh Kalimantan, Indonesia	Being revised
15	Nurhayana Sennang	Pathology Clinic Dept. Universitas Hasanuddin	IgG Response To Msp2, Eba175 And Rh2a Antigens Of Plasmodium Falciparum During Wet And Dry Seasons In Indonesia	Being revised
16	Hadjar Siswantoro	Centre 2, NIHRD	Safety and Efficacy of Artemisisnin-Naphtoquine and Dihydroartemisinin-Piperaquine in Patients with Uncomplicated Malaria at Health Facilities Level in Indonesia	Being revised
17	Mutiara Widawati	Centre 1, NIHRD	Preliminary Study For An Herbal Topical Repellent Of Piper Betle And Patchoulli Oil Mixture In Gel Form Against Aedes Aegypti	**Submitted to Biotropia journal**
18	Hera Nirwati	Microbiology Dept. UGM	Detection of Group A Rotavirus Strains Circulating among Children with Acute Diarrhea in Indonesia	To submit to a journal
19	Khie Chen	Internal Medicine Dept. UI	Seroprevalence of Widal Test in Healthy Jakarta's Urban Population	Being revised
20	Nur Farhanah	Internal Medicine Dept. UNDIP	Are ADAMTS13 and von Willebrand Factor levels involved in the development of thrombocytopenia and bleeding in severe leptospirosis ?	Being revised
21	Tri Wibawa	Microbiology Dept. UGM	Cyclosporine A Decreases the Fluconazole Minimum Inhibitory Concentration of *C. albicans* Clinical Isolates	Being revised

GCP Forum

Protocol Deviation

Any carefully planned clinical trial is intended to provide a proper assessment of treatment efficacy while ensuring that each patient's individual needs are catered for. No matter how meticulously one plans the trial protocol, it is almost inevitable that some patients' requirement will deviate from the protocol specifications. There are innumerable ways in which things can go wrong in a clinical trial.

Basically, any departure from the intended treatment and/or evaluation constitutes a protocol deviation. The aim should be to identify each protocol deviation, to try and explain why it occurred and more generally to prevent unnecessary deviations occurring in the future.

There is no general agreement on what constitutes appropriate thresholds for acceptable and excessive protocol violation (PV) rates. One authority on the conduct of clinical trials has suggested that PVs in more than 10% of enrolled patients is excessive and "reflect[s] a generally poor standard of trial organization which needs tightening up". Post hoc evaluation committees analyzing completed Food and Drug Administration (FDA) Phase III licensing trials have reported PVs ranging from 15.6% (88/564) to 24.9% (431/1728) of all enrolled patients, however neither committee classified these levels as excessive [2].

The repeated occurrence of protocol violations may indicate that the trial is poorly administered with low cooperation from investigators and/or patients. If major deviations are frequent, one should consider whether the protocol as specified is impractical and fails to fit in with acceptable clinical practice. Of course, some withdrawals may be unavoidable (e.g. if the patient moves away). In either case one should take steps to improve study design and execution.

The fact that some patients fail to adhere to their prescribed treatment is a common experience in general clinical practice so that it would be naïve to anticipate perfect patient compliance in clinical trials. The first step in reducing non-compliance is when patients are being entered into the trial. Careful explanation to the patient of his treatment schedule and the trial's objectives would seem essential in achieving full patient cooperation. Essentially a caring and well-organized treatment team is a valuable start to patient compliance.

All protocol violations and major deviations should be recorded as they occur and investigators should aim to provide an honest account of such events in any report of trial finding. However, should such patients with protocol deviations be included in the main treatment comparisons or should they simply be noted as being deviates and be excluded from subsequent results? In most circumstances, Pocock in his book suggests that the first approach is required; that is, all eligible patients, regardless of compliance with protocol should be included in the analysis of results whenever possible.

Statistical evaluation of a treatment effect is usually complicated by missing observations because of drop-outs (i.e. subjects who drop out of the clinical trial after some short-term follow-up visit and do not return) or by missing observations because subjects missed one or more visits even though they may have completed the trial.

Many procedures exist to deal with missing data. The most common strategy to deal with missing data is imputing missing values with some predicted values. Some strategies use multivariate analysis of the prognostic factors to predict the most likely outcome in subjects lost to follow-up. All of these strategies generally make unconfirmed assumptions that may also bias the estimates of treatment effect by imputing data. Thus, inferences from studies with a high magnitude of loss to follow-up are less accurate and therefore more questionable than those with minimal loss to follow-up or drop-outs.

None of the strategies used for dealing with missing data can minimize all bias introduced by lost of follow-up and thus they cannot be considered as the solution for all poorly conducted trials. They must be used with caution since statistical analysis and imputation techniques can never compensate for or exactly reproduce missing data [3].

Finally it should be noted that sophisticated statistical analysis cannot improve poorly designed and conducted trials. Clinical trials should always be planned and conducted with the highest methodological standards and should aim to accomplish an ideal Intention-To-Treat (ITT) analysis without missing data and with full compliance [1].

References:
1. Pocock SJ: **Protocol Deviations.** In *Clinical Trials: A Practical Approach*. New York: John Wiley & Sons; 1983:176-186
2. Sweetman and Doig. Trials 2011, 12:214 http://www.trialsjournal.com/content/12/1/214
3. Armijo-Olivo, Susan, et al. Intention to treat analysis, compliance, drop-outs and how to deal with missing data in clinical research: a review. Physical Therapy Reviews, 2009, Vol.14 No.1:36-49.

-SK-

INA RESPOND SQUAD

Site 580 – RSUP dr. Sardjito, Yogyakarta

From left to right: dr. Abu Tholib, dr. Tri, dr. Riska, dr. Mega, dr. Yan, dr. Yuli, dr. Umi, dr. Ida Safitri

This time we are going to meet research team from site 580, RS Sardjito, Yogyakarta. Yogyakarta is widely known as the city of art and education. So, it is not surprising to see and meet people with genuine passion for research such as our INA RESPOND research team. Let's meet these lovely folks!

Dr Abu Tholib, the NSC member at site. In terms of working, he is a high achiever who wants everything to be done correctly and timely. But can also be forgetful at times because of his busy schedule. Aside from work, he is a cycling enthusiast. **Dr. Tri, the Site PI.** Microbiology is his passion. As a microbiologist, he is eager to observe everything and translate his observations into scientific papers. He is a humble and cooperative man with a big heart. **Dr. Ida Safitri, SpA, the Co PI.** A friendly pediatrician who embraces life; no wonder she always looks pretty and lovely. She dislikes nothing but fatty and sugary foods. **Dr. Rizka, SpPD, the Co PI.** No one would guess that this lovely mother of 5 used to be a tomboy! She loves holiday so that she can spend more time with her children. Well, who doesn't love holidays anyway? ☺. **Dr. Yuli, the RA.** A funny fact about her is that you can guess her mood by checking the weather outside. Cloudy and rainy days make her feel gloomy, and sunny days make her shine. She has an unusual hobby for a woman: martial art… so watch out boys! **Dr. Mega, the RA.** Quiet and friendly are the impressions we get when seeing her. Don't overload dr Mega with a bunch of work because it will drain her energy and make her prone to flu. **Dr. Yan, the RA**. He is an activist who loves reading. In contrast to dr Yuli, he dislikes hot days. As the newest member of the team, he is very excited to work in INA-RESPOND studies. **Ms. Dwi, the LT.** She is a loving person and easy to get along with. Her hobby is trying new recipes in her kitchen. **Dr Umi, SpPK.** She is humble, friendly and has been a great support for the INA-RESPOND team. She serves as the coordinator of clinical pathology laboratory in RS Sardjito, and her contribution in supervising study specimen management is invaluable.

-AP-

The winner of April Quiz is dr. Linda from site 510

April Quiz Answer: Tuberculosis of the Pubis

Best Wishes for INA101 team members celebrating their birthday in April:

- 2 May – dr. Dewi Murniati, Sp.A (PI Site 540)
- 2 May – dr. Annisa Salmah (RA Site 560)
- 2 May – Maria Mila Erastuti, S.Si., Apt. (INA-RESPOND Secretariat)
- 5 May – Ni Wayan Nilawati (Lab Technician Site 520)
- 17 May – dr. Risna Halim Mubin, Sp.PD (Co-PI site 550)
- 18 May – dr. Nurhayati (INA-RESPOND Secretariat)
- 24 May – Meity H. Siahaan (INA-RESPOND Secretariat)
- 27 May – dr. Siswanto, MHP, DTM (Governing Board)

And congratulations to dr. Venty (RA Site 560) and husband on their wedding on 27 April 2014

INA-RESPOND Newsletter

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