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Section Editor-in-Chief

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K.A. Timonin Institute of Plant Physiology RAS, 35 Botanicheskaya St., 12 7276 Moscow, Russia
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Interests: photosynthesis; plant physiology; environmental stress; abiotic stress; UV radiation; cyanobacteria; algal; ROS; nonphotochemical quenching (NPQ); chlorophyll fluorescence; salt stress; hydrogen energy; artificial photosynthesis

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Section Editor-in-Chief

Department of Biomedical Sciences, University of Padova, Via Ugo Bassi 58/B, I-35131 Padova, Italy

Interests: mitochondria; calcium; channels; permeability transition; ATP synthase; cell death

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Editor-in-Chief

Biotech Research & Innovation Centre, The University of Copenhagen, Copenhagen, Denmark

Interests: Rho GTPases; keratinocytes; mouse disease models

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Prof. Dr. Christoph Englert

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Section Editor-in-Chief

Leibniz Institute on Aging - Fritz Lipmann Institute, 07745 Jena, Germany

Interests: regulation of gene expression; development; organogenesis; cellular and organismic aging

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Section Editor-in-Chief

Biomedical Sciences and Neurosurgery, Regenerative Medicine Institute Eye Program, Cedars-Sinai Medical Center, Medicine, UCLA School of Medicine, Los Angeles, CA, USA

Interests: cornea; nanomedicine; wound healing

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Section Editor-in-Chief

Director of Genitourinary Pathology, University of Rochester Medical Center, Rochester, NY, USA

Interests: nuclear hormone receptors; androgen receptor; glucocorticoid receptor; antiandrogens; glucocorticoids; urothelial cancer; prostate cancer; genitourinary pathology

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Section Editor-in-Chief

Unit of Molecular Oncology and Angiogenesis, IRCCS Ospedale Policlinico San Martino, 16132 Genoa, Italy

Interests: mesenchymal stromal cells; NK cells; innate immunity; leukemia and lymphoma; anti-tumor immunity

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Department of Cell Biology, University of Groningen, University Medical Center Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands

Interests: autophagy; endosomal traffic; infection; yeast; virus; subversion

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Section Editor-in-Chief

Reader in Biomedical Science, Hull York Medical School, University of Hull, Hull HU6 7RX, United Kingdom

Interests: actin cytoskeleton; actin-binding proteins; Rho GTPases; cyclase-associated protein; coronin; plastin; cell motility; platelet biology; endothelial cell biology

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Section Editor-in-Chief

Department of Cell Biology and Anatomy, Hotchkiss Brain Institute, Alberta Children's Hospital Research Institute, Cumming School of Medicine, University of Calgary, Calgary, AB T2N 1N4, Canada

Interests: neurodevelopment; synapse formation; synaptic plasticity; anesthetics; neurodegeneration; neurite outgrowth; brain-chip interfacing



Dr. Bor Luen Tang

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Associate Editor

Department of Biochemistry, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Interests: membrane trafficking; neuronal death and regeneration; Sir1 and aging

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Prof. Dr. Ritva Tikkanen

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Section Editor-in-Chief

Institute of Biochemistry, Medical Faculty, Justus-Liebig University of Giessen, Friedrichstrasse 24, D-35392, Giessen, Germany

Interests: lysosomal storage disorders; vesicular trafficking; endosomal sorting; lysosome biogenesis; mitochondrial diseases; autoimmune disorders

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Dr. Stephen Yarwood

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Section Editor-in-Chief

Institute of Biological Chemistry, Biophysics, and Bioengineering; School of Engineering and Physical Sciences; William Perkin Building; Heriot-Watt University; Edinburgh EH14 4AS, UK

Interests: cell signalling; cyclic AMP; gene expression

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Universitätsklinikum des Saarlandes Medizinische Fakultät der Universität des Saarlandes disabled, Homburg, Germany

Interests: Echocardiography; Heart Failure; Congenital Heart Disease; Heart; Heart Transplantation; Pulmonary Hypertension; Pacemakers; Cardiomyopathies; Cardiac Echocardiography; Hypertension



Prof. Dr. Soman Ninan Abraham

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Department of Pathology, Duke University Medical Center (DUMC), Durham, NC 27710, USA

Interests: mast cell biology; host-pathogen interactions; bladder immunology; urinary tract infections; adjuvants and vaccine design



Dr. Isabel A. Abreu

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Proteome Regulation in Plants Lab, GPlantS Unit, Instituto de Tecnologia Química e Biológica, Av. da República, 2780-157 Oeiras, Portugal

Interests: plant response to environmental changes; post-translational modifications; model plants and crops; photosynthesis, quantitative proteomics; mass spectrometry

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Special Issue in *Proteomes*: *Proteomics in Plant-Environment Interactions* (/journal/proteomes/special_issues/plant%E2%80%93environment_interactions)



Dr. Colin Adrain

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Membrane Traffic Lab, Instituto Gulbenkian de Ciência (IGC), Rua da Quinta Grande 6, 2780-156 Oeiras, Portugal

Interests: membrane trafficking; endoplasmic reticulum; ERAD (ER-associated degradation); inflammation; cell signalling; lipid droplets; metabolism



Prof. Dr. Wado Akamatsu

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Genomic and Regenerative Medicine, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan

Interests: Neural stem cells; iPSC cells; Neural development; Parkinson's disease



Dr. Seiji Akimoto

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Department of Chemistry, Graduate School of Science, Kobe University, 1-1 Rokkodai-cho, Nada-ku, Kobe, Hyogo 657-8501, Japan

Interests: primary processes of photosynthesis; chlorophyll; carotenoid; phycobilin; time-resolved spectroscopy



Dr. Moulay Alaoui-Jamali

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Departments of Medicine and Oncology, Faculty of Medicine, McGill University, Montreal QC H3A 0G4, Canada

Interests: tyrosine kinase receptor signaling; tumor microenvironment; cell chemotaxis; metastasis; drug resistance; drug discovery; breast cancer; HNSCC



Prof. Dr. Anthony Albert

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University of London, Vascular Biology Research Centre, London, United Kingdom

Interests: TRP channels; calcium-sensing receptor; PIP2-binding proteins; G-protein-coupled receptors; cell signalling; Ca signalling; vascular smooth muscle; endothelium

Special Issues and Collections in MDPI journals

Special Issue in *Cells*: *Calcium-Permeable Cation Channels in Cardiovascular Function and Disease*

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Dr. Hakan Aldskogius

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Department of Neuroscience, Uppsala University, 75124 Uppsala, Sweden
Interests: neurons; microglia; peripheral nerve or dorsal root injury; injured spinal cord

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Special Issue in *Cells*: **Cellular and Molecular Mechanisms of Dorsal Root Injury and Injured Spinal Cord**
([/journal/cells/special_issues/Cellular_Molecular_Mechanisms_Dorsal_Root_Injury_Injured_Spinal_Cord](#))



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University Medical Center of Montpellier, IURC, Laboratory of Rare Human Circulating Cells (LCCRH), 641 avenue du Doyen Gaston Giraud, 34093 Montpellier, France

Interests: circulating tumor cells (CTCs); liquid biopsy; biomarkers, metastasis-competent CTCs

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Special Issue in *Cancers*: **Circulating Tumor Cells in Cancers** ([/journal/cancers/special_issues/circulating-tumor-cells](#))

Special Issue in *Cells*: **Circulating Tumor Cells: Finding Rare Events for A Huge Knowledge of Cancer Dissemination** ([/journal/cells/special_issues/CTCs_cancer](#))

Special Issue in *Cancers*: **Liquid Biopsy: Latest Advances and Future Challenges** ([/journal/cancers/special_issues/4th_ACTC](#))

Dr. Richard Allsopp

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Institute for Biogenesis Research, Department of Anatomy, Biochemistry and Physiology, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI 96813, USA

Interests: telomeres; telomerase; stem cells; aging



Dr. Maria Teresa Alonso

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Instituto de Biología y Genética Molecular (IBGM), University of Valladolid, CSIC-UVA, Valladolid, Spain

Interests: calcium signalling; Ca²⁺ transport; Ca²⁺ channels; endoplasmic reticulum Ca²⁺; mitochondria Ca²⁺; development of Ca²⁺ sensors for organelle; organelle crosstalk; Ca²⁺ and aging

Prof. Dr. Manfred Alsheimer

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Department of Cell and Developmental Biology (Zoologie I), Biocenter, University of Wuerzburg, Wuerzburg, Germany

Interests: nuclear envelope; nuclear lamina; LINC-complexes; nuclear shaping; nuclear architecture; germ cell development and differentiation; meiosis; spermiogenesis; evolutionary aspects of meiosis

Prof. Fiorella Altruda

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Director of the Molecular Biotechnology Center, Department of Molecular Biotechnology and Health Sciences, University of Turin, via Nizza 52, 10126 Torino, Italy

Interests: regenerative medicine; cell therapy; liver; mouse models



Dr. Ezequiel Álvarez

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Departamento de Medicina, Universidad de Santiago de Compostela, Servicio de Cardiología, Complejo Hospitalario Universitario de Santiago de Compostela, Galicia, Spain

Instituto de Investigación Sanitaria de Santiago, Galicia, Spain

Interests: COVID-19; endothelial cells; Oxidative Stress; erythrocytes; heart failure; cardiovascular



Prof. Javier Alvarez

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Department of Biochemistry and Molecular Biology and Physiology, Faculty of Medicine, University of Valladolid, and Institute of Biology and Molecular Genetics (IBGM), University of Valladolid and CSIC. C/Ramón y Cajal 7, 47005 Valladolid, Spain

Interests: Ca²⁺ signalling; Ca²⁺ transport; mitochondria; endoplasmic reticulum; C. elegans; aging; longevity; neurodegeneration



Dr. Cristine Alves Da Costa

Website (<http://cvs-science.aviesan.fr/cv/1094/cristine-alves-da-costa>) **SciProfiles** (<https://sciprofiles.com/profile/824988>)

Université Côte d'Azur, INSERM, CNRS, IPMC, team labeled "Laboratory of Excellence (LABEX) Distal2", 660 route des Lucioles, 06560, Sophia-Antipolis, Valbonne, France

Interests: Parkinson's disease; brain tumor; transcription; autophagy; cell death; unfolded protein response

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Special Issue in *Cells*: **Hallmarks of Parkinson's Disease** ([/journal/cells/special_issues/HallmarksOf_Parkinson](#))

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Department of Molecular Medicine, University of Padua, 35121 Padua, Italy

Interests: nucleo-cytoplasmic shuttling; protein-protein interactions; antiviral drug discovery; viral replication

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Special Issue in *Cells*: **Vesicular Trafficking Meets Nuclear Transport** ([/journal/cells/special_issues/vesicular_trafficking](https://journal/cells/special_issues/vesicular_trafficking))

**Dr. Giovanni Amabile**

Website (https://www.researchgate.net/profile/Giovanni_Amabile) **SciProfiles** (<https://sciprofiles.com/profile/334188>)

Chief Executive Officer, Entera, Milano, Italy

Interests: induced pluripotent stem cells; epigenetics; hematopoiesis; neurogenesis; early and late stage clinical trials

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Special Issue in *Cells*: **Ten Years of iPSCs: Current Status and Future Perspectives** ([/journal/cells/special_issues/ipscs](https://journal/cells/special_issues/ipscs))

Special Issue in *Cells*: **DNA Methylation in Health and Disease** ([/journal/cells/special_issues/DNA_epigenetics](https://journal/cells/special_issues/DNA_epigenetics))

**Dr. Giuseppina Amadoro**

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1. Institute of Translational Pharmacology (IFT)-CNR, Via Fosso del Cavaliere 100, 00133 Rome, Italy;

2. European Brain Research Institute (EBRI), Viale Regina Elena 295, 00161 Rome, Italy.

Interests: tau protein; Alzheimer's disease (AD); amyloid beta; Amyloid Precursor Protein (APP); synapse; non-AD tauopathies; neurodegeneration

**Prof. Fernanda Amicarelli**

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Department of Life, Health and Environmental Sciences, University of L'Aquila, via Vetoio – Coppito, 67100 L'Aquila, Italy

Interests: reactive oxygen species; oxidative stress; redox-responsive pathways; dicarbonyl stress; glycation; methylglyoxal; aging; adaptive response; hormesis; stress response

Special Issues and Collections in MDPI journals

Special Issue in *Cells*: **Glycation and Dicarbonyl Stress in Aging and Disease** ([/journal/cells/special_issues/Glycation_Dicarbonyl_Stress](https://journal/cells/special_issues/Glycation_Dicarbonyl_Stress))

Dr. Claudia D. Andl

Website (<https://med.ucf.edu/biomed/person/dr-claudia-andl/>)

Burnett School of Biomedical Sciences, University of Central Florida, Orlando, Florida, USA

Interests: receptor-mediated cell signaling; TGF β signaling; epithelial cell migration and invasion; gastrointestinal cancers

**Prof. Dr. István Andó**

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Laboratory of Innate Immunity, Institute of Genetics, Biological Research Centre Szeged, 6726 Szeged, Hungary

Interests: cellular immunity; innate immunity; insect immunity; insect physiology; molecular biology

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Institute of Biochemistry and Molecular Cell Biology, Medical Faculty, RWTH Aachen University, Pauwelsstraße 30, 52074 Aachen, Germany

Interests: nuclear pore complex; nuclear envelope; chromatin decondensation; mitotic exit

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Special Issue in *Cells*: **Lipid and Protein Dynamics at the Nuclear Envelope** ([/journal/cells/special_issues/lipid_nuclear](https://journal/cells/special_issues/lipid_nuclear))

Prof. Dr. Smaragdi Antonopoulou

Website (<https://www.ddns.hu/g/en/smaragdi-antonopoulou/>) **SciProfiles** (<https://sciprofiles.com/profile/1387157>)

Department of Nutrition-Dietetics, School of Health Science and Education, Harokopio University, 70 Eleftheriou Venizelou Avenue, 176 71 Kallithea, Greece

Interests: lipids; phospholipids; platelet-activating factor; platelets; monocytes; leukocytes; platelet aggregation; lipoprotein associated phospholipase-A2; lyso-PAF acetyltransferases; cytidine 5-diphospho-choline:1-alkyl-2-acetyl-sn-glycerol cholinephosphotransferase; platelet activating factor acetylhydrolase; mediterranean diet; inflammation; thrombosis; haemostasis; fibrinolysis; by-products; phospholipases; phenolic compounds

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Department of Microbiology and Immunology, Faculty of Medicine, Université Laval, Quebec, Canada

Interests: T cells; autoimmunity; cancer immunology; leukaemia; immunomodulation; signalling; adhesion; migration; apoptosis



Prof. Rami Aqeilan

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Interests: genomic instability; DDR signalling; DSBs; Common Fragile Sites; osteosarcoma; triple-negative breast cancer; early-onset epilepsy

Special Issues and Collections in MDPI journals

Special Issue in *Cells*: [WVVOX: A Fragile Tumor Suppressor with Pleotropic Functions](#)

(/journal/cells/special_issues/WVVOX_A_Tumor_Suppressor_with_Pleotropic_Functions)

Dr. Toshiyuki Araki

Website (https://www.ncnp.go.jp/nin/guide/r5/member/t-araki_e.html)

National Institute of Neuroscience, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan

Interests: neurodegenerative diseases; axonal degeneration; Schwann cells; myelination



Dr. Javier Conde Aranda

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Molecular and Cellular Gastroenterology, Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain

Interests: inflammation; immune-mediated diseases; inflammatory bowel disease; colorectal cancer, resolution of inflammation

Special Issues and Collections in MDPI journals

Special Issue in *International Journal of Molecular Sciences*: [Inflammation in Health and Disease: New Insights and Therapeutic Avenues](#)

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Special Issue in *Cells*: [Innate Immune System in Immune-Mediated Inflammatory Diseases \(IMiDs\)](#)(/journal/cells/special_issues/cells_IMiDs)

Special Issue in *International Journal of Molecular Sciences*: [Inflammation in Health and Disease: New Insights and Therapeutic Avenues 2.0](#)
(/journal/ijms/special_issues/inflammation_in_disease_2)



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Department of Microbiology and Immunology, Geisel School of Medicine at Dartmouth, 621 Ruben Building - HB7936, 1 Medical Center Dr. Lebanon, NH 03756, USA

Interests: inflammatory Breast Cancer; triple-negative breast cancer in young women; patient-derived xenograft models; canine mammary tumors; prognostic and predictive biomarkers



Dr. Jane Armstrong

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Interests: autophagy; autophagy biomarkers; cell death; cancer biology; lysosome/mitochondria signalling



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Department of Physiology, Anatomy & Microbiology, School of Life Sciences, La Trobe University, Melbourne Campus, VIC 3086, Australia

Interests: dementia; stroke; stroke (brain attack) care and prevention



Dr. Anthony Ashton

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Division of Cardiovascular Medicine, Lankenau Institute for Medical Research, Wynnewood, PA 19096, USA

Interests: G-protein coupled receptors; Angiogenesis; Cardiac remodeling; Pregnancy; Placentation

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Interests: androgen receptors; prostate cancer; anti-androgens; kinase signalling; synthetic lethality; transcription/translation regulation

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Special issue in [Cells: Understanding and Targeting Androgen Receptor Signalling in Prostate Cancer \(journal/cells/special_issues/Androgen_Receptor_Prostate\)](#)



Dr. Peter Askjaer

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Interests: nuclear envelope; nuclear pore complex; laminopathies; aging; nuclear organization; chromatin structure and function; gene regulation; chromosome segregation; nucleocytoplasmic transport; live microscopy

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Special issue in [Cells: Nuclear Organisation \(journal/cells/special_issues/Nuclear_Organisation\)](#)

Special issue in [Cells: Heterochromatin Formation and Function \(journal/cells/special_issues/Heterochromatin\)](#)

Special issue in [Cells: Regulation of Nuclear Organization and Function \(journal/cells/special_issues/nuclear_organization_function\)](#)

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Interests: longevity; gene; genome; epigenetic; epigenome; aging

[Special Issues and Collections in MDPI journals](#)

Special issue in [Cells: Epigenetic Mechanisms of Longevity and Aging \(journal/cells/special_issues/Epigenetic_Mechanisms_Longevity_Aging\)](#)



Dr. George Augustine

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Interests: neurotransmitter release; membrane trafficking; brain circuitry; optogenetics



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Department of Biological Sciences, University of Toledo, Toledo, OH 43607, USA

Interests: centriole; centrosome; cilium in sperm and male fertility

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Special issue in [Cells: Centrosome \(journal/cells/special_issues/centrosome\)](#)

Special issue in [Cells: Origin and Evolution of Sperm Cells—An Issue in Honor of Geoff A. Parker \(journal/cells/special_issues/honorary_sperm\)](#)

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Laboratory of Veterinary Pharmacology, Division of Veterinary Science, Osaka Prefecture University Graduate School of Life and Environmental Sciences, 1-58 Rinku-ohraikita, Izumisano, Osaka 598-8531, Japan

Interests: macrophage; dendritic cell; T cell; microglia; cytokine; interleukin; gastrointestinal immunology; liver fibrosis; inflammation; etc

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Special issue in [Cells: The Increasingly Fascinating World of Interleukins \(journal/cells/special_issues/increasingly_fascinating_world_interleukins\)](#)



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Interests: mast cells; MRGPRX2; pseudo-allergy; IgE receptor; allergy; skin; atopic dermatitis; anaphylaxis; food allergy; keratinocytes; cytokines

Accepted Article





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Department of Biology, University of Pisa, 56127 Pisa, Italy

Interests: animal models; ocular diseases; retinal function; neurodegeneration; neuroprotection; angiogenesis; inflammation; anti-angiogenic and anti-inflammatory compounds; dietary supplementation; eye health

Special Issues and Collections in MDPI journals

Special Issue in *Cells*: **Advances in Adrenergic Receptor Biology** ([/journal/cells/special_issues/Adrenergic_Receptor](#))

Special Issue in *Nutrients*: **Nutrition for Eye Health** ([/journal/nutrients/special_issues/Nutrition_for_Eye_Health](#))

Special Issue in *Cells*: **Angiogenesis and Inflammation in the Eye** ([/journal/cells/special_issues/angiogenesis_eye](#))



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Interests: mitochondrial function; mitochondrial dysfunction; oxidative phosphorylation dynamics

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Special Issue in *Cells*: **Intraorganellar Cross-Talks, Signal Exchanges, Protein Import, and Networks** ([/journal/cells/special_issues/intraorganellar_Cross-Talks](#))



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Dr. Sabine Bailly

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Special Issue in *Cells*: **Renin–Angiotensin–Aldosterone System** ([/journal/cells/special_issues/renin_angiotensin_aldosterone](#))

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Cells. 2021 Jul; 10(7): 1564. Published online 2021 Jun 22. doi: 10.3390/cells10071564

PMCID: PMC8305746

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Yong-Xiao Yang, Peng Li, Pan Wang, Bao-Ting Zhu

Cells. 2021 Jul; 10(7): 1566. Published online 2021 Jun 22. doi: 10.3390/cells10071566

PMCID: PMC8304645

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Cells. 2021 Jul; 10(7): 1569. Published online 2021 Jun 22. doi: 10.3390/cells10071569

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Cells. 2021 Jul; 10(7): 1570. Published online 2021 Jun 22. doi: 10.3390/cells10071570

PMCID: PMC8303224

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Anna Kieronska-Rudek, Agnieszka Kij, Patrycja Kaczara, Anna Tworzydło, Marek Napiorkowski, Katarzyna Sidoryk, Stefan Chlopicki

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Emre Bektik, Yu Sun, Adrienne T. Dennis, Phraew Sakon, Dandan Yang, Isabelle Deschênes, Ji-Dong Fu

Cells. 2021 Jul; 10(7): 1572. Published online 2021 Jun 22. doi: 10.3390/cells10071572

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Leszek Gromadziński, Łukasz Paukszto, Agnieszka Skowrońska, Piotr Holak, Michał Smoliński, Elżbieta Łopieńska-Biernat, Ewa Lepiarczyk, Aleksandra Lipka, Jan Paweł Jastrzębski, Marta Majewska

Cells. 2021 Jul; 10(7): 1576. Published online 2021 Jun 22. doi: 10.3390/cells10071576

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Manuel Schmitz-Elbers, Gražvydas Lukinavičius, Theodoor H. Smit
Cells. 2021 Jul; 10(7): 1578. Published online 2021 Jun 22. doi: 10.3390/cells10071578
PMCID: PMC8303455

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PMCID: PMC8303988

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PMCID: PMC8305080

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[Morphological and Calcium Signaling Alterations of Neuroglial Cells in Cerebellar Cortical Dysplasia Induced by Carmustine](#)

Cynthia Alejandra Rodríguez-Arzate, Marianne Lizeth Martínez-Mendoza, Israel Rocha-Mendoza, Yryx Luna-Palacios, Jacob Licea-Rodríguez, Ataúlfo Martínez-Torres
Cells. 2021 Jul; 10(7): 1581. Published online 2021 Jun 23. doi: 10.3390/cells10071581
PMCID: PMC8304447

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[Proteogenomics Reveals Orthologous Alternatively Spliced Proteoforms in the Same Human and Mouse Brain Regions with Differential Abundance in an Alzheimer's Disease Mouse Model](#)

Esdras Matheus Gomes da Silva, Letícia Graziela Costa Santos, Flávia Santiago de Oliveira, Flávia Cristina de Paula Freitas, Vinícius da Silva Coutinho Parreira, Hellen Geremias dos Santos, Raphael Tavares, Paulo Costa Carvalho, Ana Gisele da Costa Neves-Ferreira, Andrea Siqueira Haibara, Patrícia Savio de Araujo-Souza, Adriana Abalen Martins Dias, Fabio Passetti
Cells. 2021 Jul; 10(7): 1583. Published online 2021 Jun 23. doi: 10.3390/cells10071583
PMCID: PMC8303486

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[Pathophysiological Roles of Neuro-Immune Interactions between Enteric Neurons and Mucosal Mast Cells in the Gut of Food Allergy Mice](#)

Tomoe Yashiro, Hanako Ogata, Syed Faisal Zaidi, Jaemin Lee, Shusaku Hayashi, Takeshi Yamamoto, Makoto Kadowaki
Cells. 2021 Jul; 10(7): 1586. Published online 2021 Jun 23. doi: 10.3390/cells10071586
PMCID: PMC8305700

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[Age-Dependent Hippocampal Proteomics in the APP/PS1 Alzheimer Mouse Model: A Comparative Analysis with Classical SWATH/DIA and directDIA Approaches](#)

Sophie J. F. van der Spek, Miguel A. Gonzalez-Lozano, Frank Koopmans, Suzanne S. M. Miedema, Iryna Paliukhovich, August B. Smit, Ka Wan Li
Cells. 2021 Jul; 10(7): 1588. Published online 2021 Jun 24. doi: 10.3390/cells10071588
PMCID: PMC8304546

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[Novel Mutations in X-Linked, USP26-Induced Asthenoteratozoospermia and Male Infertility](#)

Chunyu Liu, Ying Shen, Qunshan Shen, Wen Zhang, Jiaxiong Wang, Shuyan Tang, Huan Wu, Shixiong Tian, Jiangshan Cong, Xiaojin He, Li Jin, Feng Zhang, Xiaohui Jiang, Yunxia Cao
Cells. 2021 Jul; 10(7): 1594. Published online 2021 Jun 25. doi: 10.3390/cells10071594
PMCID: PMC8307012

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[Impact of Progerin Expression on Adipogenesis in Hutchinson—Gilford Progeria Skin-Derived Precursor Cells](#)

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Cells. 2021 Jul; 10(7): 1598. Published online 2021 Jun 25. doi: 10.3390/cells10071598
PMCID: PMC8306773

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Targeted Drug Delivery Technologies Potentiate the Overall Therapeutic Efficacy of an Indole Derivative in a Mouse Cystic Fibrosis Setting

Matteo Puccetti, Marilena Pariano, Giorgia Renga, Ilaria Santarelli, Fiorella D'Onofrio, Marina M. Bellet, Claudia Stincardini, Andrea Bartoli, Claudio Costantini, Luigina Romani, Maurizio Ricci, Stefano Giovagnoli
Cells. 2021 Jul; 10(7): 1601. Published online 2021 Jun 25. doi: 10.3390/cells10071601

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UNC-45A Is Highly Expressed in the Proliferative Cells of the Mouse Genital Tract and in the Microtubule-Rich Areas of the Mouse Nervous System

Valentino Clemente, Asumi Hoshino, Joyce Meints, Mihir Shetty, Tim Starr, Michael Lee, Martina Bazzaro
Cells. 2021 Jul; 10(7): 1604. Published online 2021 Jun 26. doi: 10.3390/cells10071604

PMCID: PMC8303485

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Keratinocytes Regulate the Threshold of Inflammation by Inhibiting T Cell Effector Functions

Peter Seiringer, Stefanie Eyerich, Kilian Eyerich, Daniela Dittlein, Anna Caroline Pilz, Emanuele Scala, Johannes Ring, Heidrun Behrendt, Andrea Cavani, Claudia Traidl-Hoffmann
Cells. 2021 Jul; 10(7): 1606. Published online 2021 Jun 26. doi: 10.3390/cells10071606

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Honokiol Affects Stem Cell Viability by Suppressing Oncogenic YAP1 Function to Inhibit Colon Tumorigenesis

Dharmalingam Subramaniam, Sivapriya Ponnurangam, Satish Ramalingam, Deep Kwatra, Prasad Dandawate, Scott J. Weir, Shahid Umar, Roy A. Jensen, Shrikant Anant

Cells. 2021 Jul; 10(7): 1607. Published online 2021 Jun 26. doi: 10.3390/cells10071607

PMCID: PMC8303768

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Cancer Stem-Like Phenotype of Mitochondria Dysfunctional Hep3B Hepatocellular Carcinoma Cell Line

Yu-Seon Han, Eui-Yeun Yi, Myeong-Eun Jegal, Yung-Jin Kim

Cells. 2021 Jul; 10(7): 1608. Published online 2021 Jun 27. doi: 10.3390/cells10071608

PMCID: PMC8307994

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Gene Expression Profile in Different Age Groups and Its Association with Cognitive Function in Healthy Malay Adults in Malaysia

Nur Fathiah Abdul Sani, Ahmad Imran Zaydi Amir Hamzah, Zulikry Hafiz Abu Bakar, Yasmin Anum Mohd Yusof, Suzana Makpol, Wan Zurinah Wan Ngah, Hanafi Ahmad Damanhuri

Cells. 2021 Jul; 10(7): 1611. Published online 2021 Jun 27. doi: 10.3390/cells10071611

PMCID: PMC8304476

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Cytogenetic Evidence for Sex Chromosomes and Karyotype Evolution in Anguimorphans Lizards

Barbora Augstenová, Eleonora Pensabene, Lukáš Kratochvíl, Michail Rovatsos

Cells. 2021 Jul; 10(7): 1612. Published online 2021 Jun 28. doi: 10.3390/cells10071612

PMCID: PMC8304200

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Long-Term Suppression of c-Jun and nNOS Preserves Ultrastructural Features of Lower Motor Neurons and Forelimb Function after Brachial Plexus Roots Avulsion

Prince Last Mudenda Zilundu, Xiaoying Xu, Zaara Liaquat, Yaqiong Wang, Ke Zhong, Rao Fu, Lihua Zhou

Cells. 2021 Jul; 10(7): 1614. Published online 2021 Jun 28. doi: 10.3390/cells10071614

PMCID: PMC8307634

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Cockayne Syndrome-Associated CSA and CSB Mutations Impair Ribosome Biogenesis, Ribosomal Protein Stability, and Global Protein Folding

Mingyue Qiang, Fatima Khalid, Tamara Phan, Christina Ludwig, Karin Scharffetter-Kochanek, Sebastian Iben

Cells. 2021 Jul; 10(7): 1616. Published online 2021 Jun 28. doi: 10.3390/cells10071616

PMCID: PMC8306422

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Indole-3-Carboxaldehyde Restores Gut Mucosal Integrity and Protects from Liver Fibrosis in Murine Sclerosing Cholangitis

Fiorella D'Onofrio, Giorgia Renga, Matteo Puccetti, Marilena Pariano, Marina Maria Bellet, Ilaria Santarelli, Claudia Stincardini, Paolo Mosci, Maurizio Ricci, Stefano Giovagnoli, Claudio Costantini, Luigina Romani

Jonas Cornelius, Klemens Rottner, Martin Korte, Kristin Michaelsen-Preusse
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Article

Indonesia-Based Study of the Clinical and Cost-Saving Benefits of Subcutaneous Allergen Immunotherapy for Children with Allergic Rhinitis in Private Practice

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Abstract: Background: Until now, the cost of allergy treatment in the insured public health care system and the non-insured self-financing private health care system in Indonesia has not been well documented and published, as well as the cost of allergy treatment with subcutaneous immunotherapy. Objective: To evaluate the clinical and cost benefits of allergic rhinitis treatment in children with subcutaneous immunotherapy in a non-insured self-financing private health care system. Methods: A retrospective cohort study conducted from 2015 until 2020 that compared the clinical improvement and health care costs over 18 months in newly diagnosed AR children who received SCIT versus matched AR control subjects who did not receive SCIT, with each group consisting of 1098 subjects. Results: A decrease in sp-HDM-IgE level (kU/mL) from 20.5 + 8.75 kU/mL to 12.1 + 3.07 kU/mL was observed in the SCIT group. To reduce the symptom score of allergic rhinitis by 1.0 with SCIT, it costs IDR 21,753,062.7 per child, and for non-SCIT, it costs IDR 104,147,878.0 per child. Meanwhile, to reduce the medication score (MS) by 1.0 with SCIT, it costs IDR 17,024,138.8, while with non-SCIT, it costs IDR 104,147,878.0. Meanwhile, to lower combination symptoms and medication score (CSMS) by 1.0, with SCIT, it costs IDR 9,550,126.6, while with non-SCIT, it costs IDR 52,073,938.9. Conclusions: In conclusion, this first Indonesia-based study demonstrates substantial health care cost savings associated with SCIT for children with AR in an uninsured private health care system and provides strong evidence for the clinical benefits and cost-savings benefits of AR treatment in children.

Keywords: allergic rhinitis; subcutaneous immunotherapy; clinical benefit; cost-saving benefit

1. Introduction

Allergic rhinitis (AR) is one of the most important diseases of the natural course of allergic disease [1]. There is a tendency for less-than-optimal AR treatment by health workers [2]. AR that is not well controlled will burden patients, nurses, employers, and the health care system [3,4]. Children with uncontrolled AR have a greater risk of developing asthma, recurrent otitis media, chronic rhinosinusitis, and other comorbid conditions [5,6]. Children with AR also face a decreased quality of life, which manifests as sleep disturbances, poor school performance, decreased energy, a depressed mood, and low frustration tolerance [7,8]. The economic costs of poorly controlled AR include: the cost of non-prescription drugs to treat symptoms, prescription drug costs, and the cost of medical care for comorbid complications, such as asthma and acute sinusitis [9]. Indirect costs of uncontrolled AR include absenteeism from school, decreased productivity of children and their parents, loss of parents' daily wages, and injuries resulting from fatigue [3,9,10]. In 2011, the estimated total US direct AR costs exceeded USD14 billion, with 60% of the spending on prescription drugs [11]. In Indonesia, the highest prevalence of allergies in big cities is AR, followed by asthma and atopic dermatitis [12–15]. The majority of AR

patients in Indonesia are school-age children [12,14,15]. The main cause of AR in children in Indonesia is house dust mite allergen [12,14,15]. AR sufferers in Indonesia are dominated by school age children [12,14,15]. AR that is not managed properly will lead to asthma and disrupt children's quality of life [3,9]. Allergen Immunotherapy (AIT) is an effective and safe therapeutic method for curing AR. AIT is an underutilized treatment for AR both in the USA and elsewhere in the world including Indonesia. Only 3–5% of US children and adults with AR, asthma, or both have received AIT [16].

Until now, the cost of allergy treatment in the insured public health care system and the non-insured self-financing private health care system in Indonesia has not been well documented and published, as well as the cost of allergy treatment with AIT. It has not been required to apply AIT as an allergy treatment option in the public or private health care system in Indonesia. The AIT commonly used in Indonesia is subcutaneous immunotherapy (SCIT). For the public health care system in Indonesia, AIT with the SCIT method has been routinely carried out in Dr. Soetomo General Academic Hospital, Surabaya, and the costs can be covered by health insurance organized by the Indonesian government. For the private health care system in Indonesia, there is only one private allergy clinic that provides special services for allergic children that is equipped with SCIT services and accepts special referrals for allergic children who require SCIT from general practitioners, paediatrician, and other specialists from all areas in Indonesia. We conducted an Indonesian-based study with the aim of evaluating the clinical and cost benefits of AR treatment in children with SCIT in a non-insured self-financing private health care system.

2. Materials and Methods

2.1. Ethical Approval

This observational research procedure has received approval from the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (2021), with reference number 0297/LOE/301.4.2/I/2021. Subjects and their parents were briefed on the study before they agreed to provide clinical data and cost-of-treatment data for this observational study. Implied consent was obtained from parents and caregivers. General data—including name, address, age, gender, weight, height, and telephone number—were collected and recorded for all subjects. Likewise, specific data, for example, comorbid allergic asthma and its duration, as well as details about other allergies and their medications, were also recorded.

2.2. Subjects

Subjects in this study were children diagnosed with allergic rhinitis. Subjects' inclusion criteria included children aged 3–18 years with complete clinical and cost-of-treatment data [16]. The diagnosis and treatment of AR and asthma are consistent with allergic rhinitis and its impact on asthma (ARIA) [17] and the New Global Initiative for Asthma (GINA) [18] and results of reactive skin tests using HDM allergens. Exclusion criteria for subjects included abnormal shape in the anatomy of the nose and paranasal sinuses, patients diagnosed with cancer, autoimmune disease, cerebral palsy, and Down syndrome. Parents or legal guardians first received an explanation of the purpose of the study before they agreed that their child's clinical data belonged to us as our study data. They must complete and sign the consent form if they agree to provide clinical data and cost-of-treatment data for this observational study.

2.3. Study Design

A retrospective cohort study (2015–2020) compared the clinical improvement and health care costs over 18 months in newly diagnosed AR children who received SCIT versus matched AR control subjects who did not receive SCIT. The SCIT group and the non-SCIT group consisted of 1098 subjects each (Figure 1). The SCIT group was the group that received AR therapy plus SCIT HDM, while the non-SCIT group only received AR therapy. The AR therapy given includes antihistamines, intranasal steroids, and systemic steroids,

and subjects will be given bronchodilators, skin care, and physiotherapy according to the symptoms of other accompanying allergic diseases [17,19]. The study examined data from Children's Allergy Consultant Private Clinic in Surabaya, Indonesia, from 1 January 2015 to 31 March 2020. HDM SCIT was given once a week for 14 weeks and then continued once every 3 weeks until the 18th month. Data on weight, height, family allergy history, symptom score, treatment score, symptom-treatment combination score, and comorbid atopic conditions (asthma, conjunctivitis, and atopic dermatitis) before and after presenting SCIT were recorded. Data on the frequency of consultations with physicians (family physicians and specialists), hospitalizations (including emergencies), and rehabilitation care or physiotherapy during the 18 months of SCIT indicated. Likewise, data regarding the use of resources and funding for laboratory examinations, consultations with physicians (family physicians and specialists), prescribed drugs, emergency care, outpatient care, hospitalization, and travel costs for physician and medical examinations were documented for 18 months. observation. All clinical data and cost-of-treatment data from patients and physicians were documented by the research team into the study database.

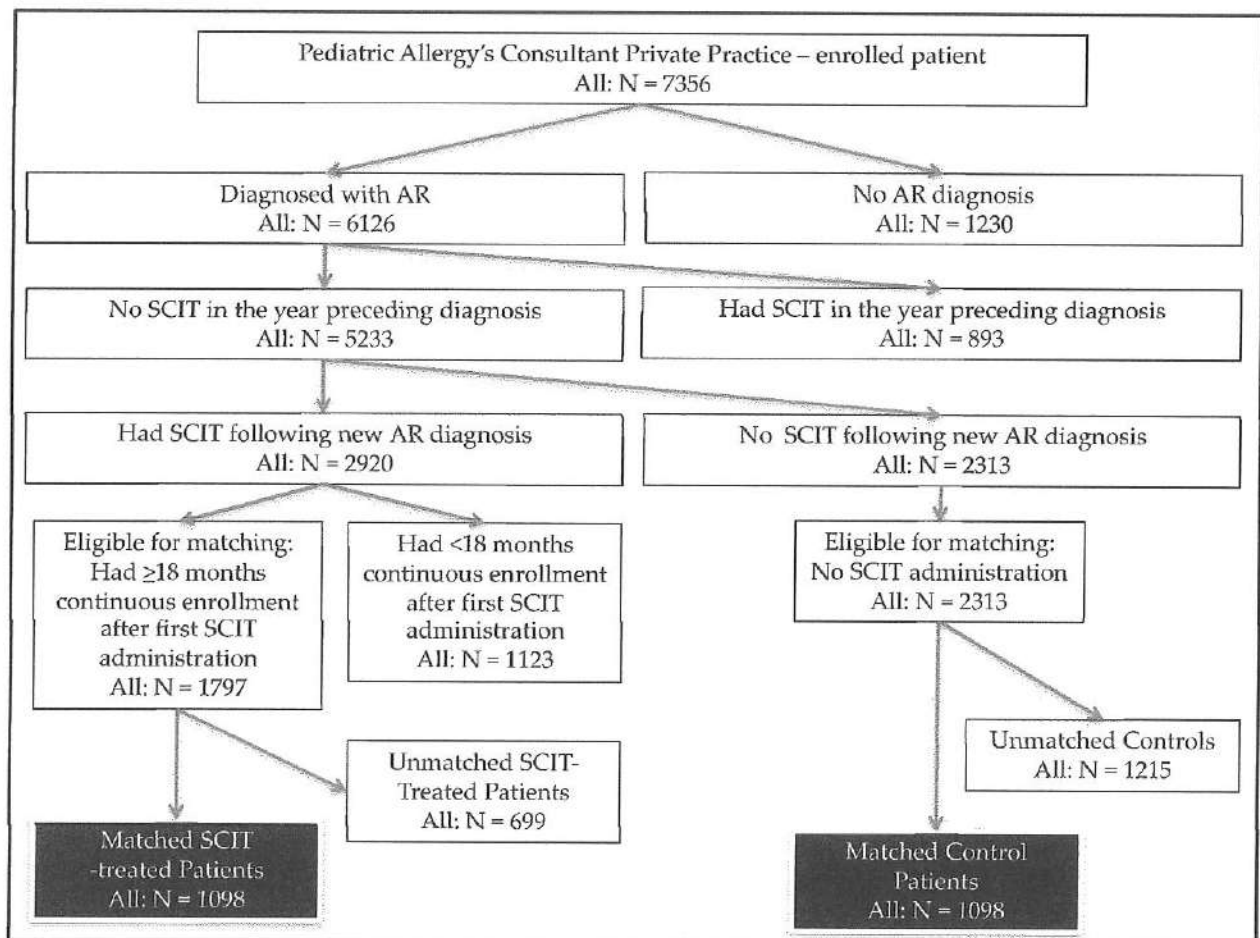


Figure 1. The identification of matched samples. Note: The 8 matching variables were: age, sex, body weight, body height, family history of allergy, symptoms, and medication scores at the SCIT initiation and comorbid atopic conditions (asthma, conjunctivitis, and atopic dermatitis) during the year prior to the SCIT initiation.

2.4. Study Procedure

SCIT is given to patients whose symptoms have not been controlled by medical treatment and symptomatic therapy. In accordance with the Indonesian Paediatric Society's treatment strategy, SCIT therapy can be given to patients whose symptoms cannot be controlled with normal allergy medical treatment for at least 3 months. Subjects included AR patients who experienced wheezing, coughing, and/or shortness of breath. In sub-

jects with asthma, spirometry tests were performed. After proper treatment and their asthma was well controlled as well as normal spirometry tests, SCIT was started. Adverse reactions to SCIT are classified into 2 categories: local reactions and systemic reactions. Local reactions were defined as erythema, pruritus, and swelling at the injection site. A systemic reaction was defined as a life-threatening range from mild to very severe anaphylaxis [20]. The house dust mite allergen immunotherapy (Teaching Industry Allergen by Dr. Soetomo Hospital-Airlangga University, Surabaya, Indonesia) used was an extract of *Dermatophagoides pteronyssinus* with 11.3–26.6 ng/mL via subcutaneous injection [21–23]. The dose of immunotherapy used every week varies: 0.1 cc (first week), 0.15 cc (second week), 0.22 cc (third week), 0.32 cc (fourth week), 0.48 cc (week fifth), 0.72 cc (sixth week), 1 cc (seventh week), 0.1 cc (eighth week), 0.15 cc (ninth week), 0.22 cc (tenth week), 0.32 cc (eleventh week), 0.48 cc (twelfth week), 0.72 cc (thirteenth week), and 1 cc (fourteenth week) [22]. The use of HDM immunotherapy is based on previous studies in Indonesia that stated that the most common types of HDM were *Dermatophagoides pteronyssinus* (87%), *Dermatophagoides farinae* (7%), and *Bromia tropicalis* (6%) [24]. Another study also states that the most common HDM found in Indonesia is *Dermatophagoides pteronyssinus*, which can be found in various places such as beds, floors, and sofas, while *Dermatophagoides farinae* is most commonly found on sofas. *Bromia tropicalis* was the least compared to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* [25].

2.5. Outcomes

2.5.1. Allergic Rhinitis Symptoms

AR and asthma symptoms were monitored according to allergic rhinitis and its impact on asthma (ARIA) [17] and the Global Initiative for Asthma (GINA) guidelines [18]. Signs and symptoms of AR include itchy nose, sneezing, rhinorrhea, or nasal congestion, as well as itching of the roof of the mouth, post-nasal drip, and cough.

2.5.2. Measurement of SPT (Skin Prick Test) and Serum Specific IgE Levels

The skin prick test (SPT) was applied to all patients to check their sensitivity to the following HDM allergens (Allergopharma, Reinbek, Germany). Their reactivity to HDM allergens in SPT was identified through allergen-induced wheals equal to or larger in diameter than histamine-induced wheals. The measurement of serum-specific IgE levels used an enzyme-linked immunosorbent assay/ELISA (Euroline TM; Euroimmun AG, Lübeck, Germany). Not all subjects were examined for spHDM IgE levels but were randomly selected by 10% of the total sample. An indirect ELISA examination was conducted by taking up to 6 mL of the subject's blood serum from the vein, which was then rotated at 3000 rpm for 15 min. The serum was stored at $-20\text{ }^{\circ}\text{C}$ to keep the condition stable. Specific ring allergens for certain allergens were inserted in the wells and then incubated with the patient's sample. Should the patient's sample be positive, the specific IgE in the subject's serum would bind to the allergen. This antibody–gene binding could be detected by adding a monoclonal anti-human IgE conjugate. The length of time to check serum IgE levels was 3.5 h. The serum IgE determination was in the range of 0.35–100 kU/L.

2.5.3. Measurement of Symptom Scores and Drug Scores

The measurement of symptom scores, drug scores, and symptom and drug combined scores is a form of clinical evaluation in addition to measuring SPT for household dust mites and specific IgE (for HDM). Clinical evaluations were carried out during the study period, which began on 1 January 2014 and ended on 31 March 2020. Subject diary cards recorded symptoms (nose, eyes, mouth, and lungs) and treatment scores (antihistamines, local steroid drugs, systemic steroids), including symptoms in the nose (sneezing, stuffiness and runny nose), eyes (itching, redness, tears and swelling), mouth and throat (itching and dryness), and chest (shortness of breath, coughing, wheezing, and tightness), on a scale of 0–3 (with a score of '0' indicating no symptoms and '1,' '2,' and '3' showing mild, moderate, and severe symptoms, respectively). The daily treatment score is scored

based on the type and amount of rescue medication used each day. In addition, each dose of decongestant, antihistamine, and inhaled corticosteroid used was marked as 1 [26]. Asthma symptoms were recorded daily for the entire treatment period on the scorecard. Daytime symptom scores included: 0—no symptoms; 1—wheezing; 2—temporary asthma attacks; 3—permanent asthma. Overnight symptom score included: 0—no symptoms; 1—wheezing; 2—1–2 asthma attacks; 3—more than 3 asthma attacks. Any additional medication required for the treatment of asthma was also recorded on a daily basis [27]. The level of asthma control was recorded in each patient's standard hospital record according to the GINA guidelines. Subject diary cards recorded symptom scores and treatment scores, including daytime symptoms, activity limitations, night time symptoms or awakening, need for relief or rescue medication, lung function, and history of exacerbations. All patients were evaluated on symptom scores, drug scores, and symptom and drug combined scores per period (trimester 1, trimester 2, semester 2, semester 3) after starting the observation.

2.5.4. Measurement of AR and SCIT Treatment Costs

The medical costs associated with each treatment are calculated as the total costs associated with the following categories of resource use: all-cause admissions, SCIT-related outpatient visits, and non-SCIT-related outpatient visits. The total cost per period (trimester 1, trimester 2, semester 2, semester 3) is calculated based on the cost per unit usage and data usage accordingly. The AR care expense calculated here is due to medical costs (e.g., medical services used for treatment) and travel costs for travel for physician and medical examinations. Direct non-medical costs (e.g., caregiver costs and household modifications), as well as indirect costs of disability, early retirement, and parent's job loss due to childcare activities, were not documented in this study. The cost is calculated by multiplying the frequency of diagnostic and treatment services by the cost of each activity. The unit cost at the 2020 price is used to estimate the use of health care resources to determine the cost of managing patients in Indonesia in both groups (SCIT and non-SCIT). The cost for private outpatient services for a specialist or family doctor is IDR 150,000. The prescribed medication is documented from patient records. Hospitalization costs are calculated using the daily average rate for accommodation (IDR 850,000), medical services (IDR 200,000), and rehabilitation therapy (IDR 775,000). The following direct costs are noted, based on clinical studies: medications (antihistamines, corticosteroids, and bronchodilators), skin care, physiotherapy, allergen immunotherapy, and hospital health care. The time horizons in the cost analysis were set to 3, 6, 9, and 18 months (trimester 1, trimester 2, semester 2, semester 3). The reason is that the SCIT outcome will provide valuable information after 3, 6, 9, and 18 months. Cost per patient for drugs is based on prices from pharmacies in Indonesia and is calculated assuming the intake of antihistamines based on cetirizine (0.25 mg/kg/dose every 12–24 h and a price of IDR 14,730 per 5 mg/mL 60 mL bottle syrup), pseudo ephedrine (0.25–1.0 mg/kg/dose every 3 to 4 h and priced at IDR 77,000 per 60 mL bottle), intranasal corticosteroids (based on fluticasone or mometasone, 50 mcg, 2 puffs/day, and a price of IDR 240,000 per puff package), fluticasone/mometasone-based inhaled corticosteroid, 125 mcg, 2 puffs/day, and a price of IDR 225,000 per 120 puff package), a salbutamol-based bronchodilator (0.1 mg/kg/dose every 8 h and a price of IDR 120,521 per 2 mg/5 mL bottle syrup 60 mL), oral corticosteroid based on oral methylprednisolone (0.5–1.0 mg/kg/dose every 12 to 24 h with a maximum dose; 60 mg/4 h and a price of IDR 7163 per 8 mg tablet). Treatment of oral H1 antihistamines and intranasal corticosteroids were prescribed to all patients for a minimum of 3 months. Oral antihistamines H1 and intranasal corticosteroids are prescribed for AR, and inhaled corticosteroids are prescribed for patients with asthma. Laboratory costs that are calculated specifically are costs for diagnosing allergic rhinitis and its comorbidities with allergic causes, including costs for radiological examinations, SPT and HDM-specific IgE. Travel costs for travel for physician and medical examinations are based on geographic location and the distance between the patient's residence and the doctor's practice. This travel cost calculation uses the standard cost of taxis, flights, hotels,

and other travel costs adjusted to the rates that apply at the location where the patient lives. The unit cost at the 2020 price is used to estimate the use of travel costs.

2.6. Statistical Analysis

A sample size of 2196 patients provided sufficient strength (90%) with a Minimum Detectable Effect (MDE) of 0.125 between the 1098 subjects in the SCIT group and the 1098 subjects in the control group ($p = 0.01$). Each patient in the group treated with SCIT matched at least 1 patient in the control group on all 8 of the following variables: age group, gender, physician specialist at referral, family allergy history, symptom score, treatment score at the initiation of SCIT, and comorbid atopic conditions (asthma, conjunctivitis, and atopic dermatitis) as long as they are worn before the initiation of SCIT. Control patients who were matched for these variables must also have at least 18 months of data after their match date. If patients treated with SCIT could not be matched on all 8 variables for at least 1 control patient, then patients treated with SCIT were excluded from further analysis. The data were first tested using Kolmogorov–Smirnov. Furthermore, data on participant's characteristics were analysed using independent *t*-test or the Mann–Whitney test. In addition, other measurement results were analysed using an independent *t*-test or Mann–Whitney test and a dependent *t*-test or Wilcoxon test. The statistical test results were declared significant if $p < 0.05$. Data analysis used IBM SPSS Statistics software version 23.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Characteristics of Study Participant

Figure 1 displays the results of the sample identification procedures. Among all Paediatric Allergy Immunology Consultant' patients enrollees ($n = 7356$), among whom there were 83.7% (6126/7356) received a diagnosis of AR; among the 6126 enrollees with newly diagnosed AR, 47.8% (2920) received de novo SCIT. Overall, there were 1797 SCIT-treated patients and 2313 control subjects eligible for matching; from this pool, 1098 SCIT-treated patients were matched to 1098 control subjects.

The distribution of the children with allergic rhinitis that were recruited as subjects of this study based on geographic area in Indonesia, as shown in Figure 2. A total of 2196 children with allergic rhinitis from 92 Districts in the Republic of Indonesia were recruited as subjects of this study, they came from (District and number of children): Surabaya 879, Sidoarjo 425, Jombang 135, Kupang 95, Lamongan 77, Gresik 40, Kediri 31, Pamekasan 31, Sampang 31, Jember 30, Sumenep 29, Mataram 28, Lumajang 27, Tulungagung 24, Mojokerto 21, Tuban 20, Balikpapan 18, Pasuruan 17, Bangkalan 16, Bojonegoro 14, Madiun 12, Nganjuk 12, Samarinda 12, Probolinggo 11, Denpasar 9, Lumajang 9, Sampit 6, Banjarmasin 5, Banyuwangi 5, Kertosono 5, Magetan 5, Malang 5, Palangkaraya 5, Pamekasan 5, Bondowoso 4, Nabire 4, Situbondo 4, Sorong 4, Mataram 3, Martapura 3, Maumere 3, Merauke 3, Muaratewe 3, Porong 3, Tarakan 3, Trenggalek 3, Waingapu 3, Bandung 2, Batulicin 2, Blitar 2, Cepu 2, Jakarta 2, Jayapura 2, Manado 2, Mojokerto 2, Palu 2, Pandaan 2, Pangkalan Boen 2, Semarang 2, Sumbawa 2, Alor 1, Ambon 1, Bandar Lampung 1, Bangil 1, Batu 1, Baubau 1, Berau 1, Besuki 1, Bima 1, Blega 1, Blora 1, Ende 1, Flores 1, Jambi 1, Kavamenano 1, Kotabaru 1, Kutai 1, Lawang 1, Makasar 1, Palembang 1, Parigi 1, Prigen 1, Sangata 1, Saumlaku 1, Sepanjang 1, Singaraja 1, Soe 1, Solo 1, Tanah Grogot 1, Timika 1, Timor 1, Tobelo 1, and Wonosobo 1. Subjects come from almost all islands in the Republic of Indonesia, consisting of (Name of Island or Islands and Number of children): Java 1956, islands in Nusa Tenggara 142, Kalimantan 68, islands in Papua 13, Bali 10, islands in Maluku 3, Sulawesi 2, and Sumatra 2.

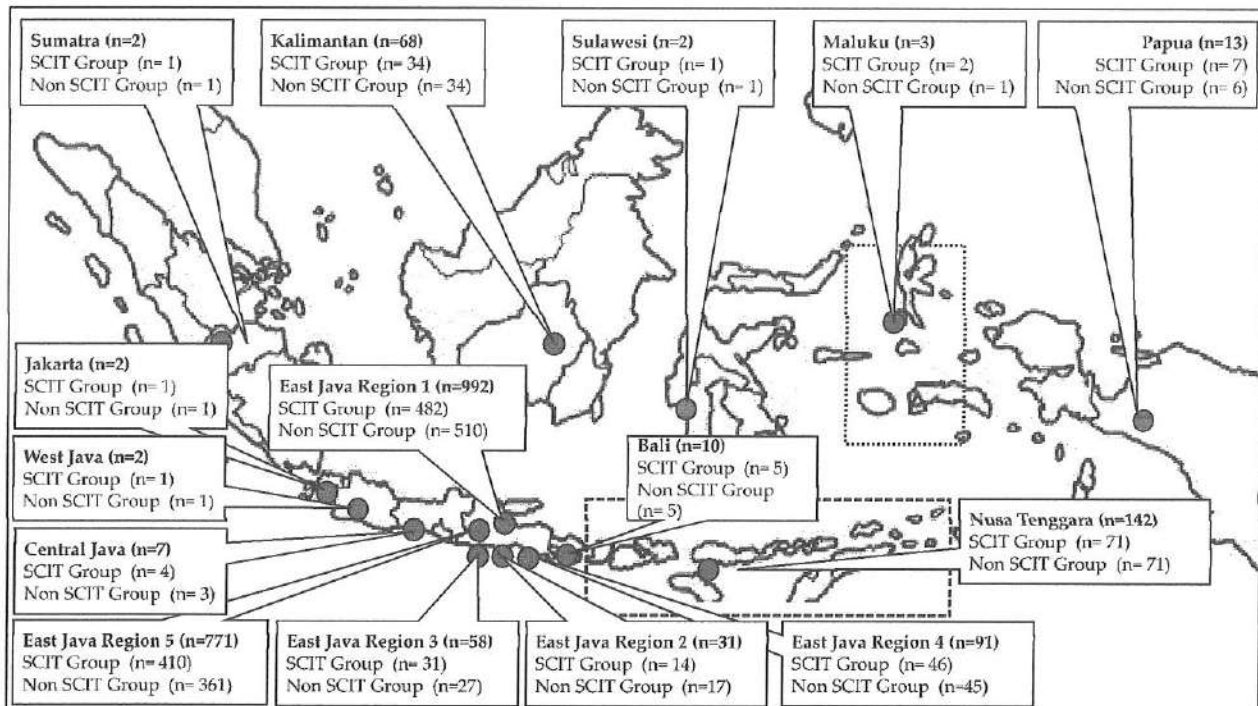


Figure 2. The distribution of the 2196 children with allergic rhinitis that were recruited as subjects of this study based on geographic area in Indonesia (Island, Province or Area).

Table 1 shows stratification according to sex, age, body weight/height, comorbid illness, and illness severity. The 1098 children in the SCIT-treated matched sample were predominantly male (63.4%); the mean age at the initial AR diagnosis was 5.5 (SD 3.51) years; mean body weight at the initial AR diagnosis was 12.8 (SD, 2.35) kilograms; the mean body height at the initial AR diagnosis was 84.7 (SD, 19.83) centimetres. In the year before their initial AR diagnoses, the majority (87.3%) of these children experienced one comorbid disease burden, and the rates of: asthma, atopic dermatitis, sinusitis, and conjunctivitis were 54.0%, 9.1%, 1.1%, and 0.3%, respectively. In total, 88.6% of our subjects were previously treated by a paediatrician, whilst those previously treated by family doctors, ENT specialists, and dermatologists, were 2.5%, 2.6%, and 6.3%, respectively. The majority of severity at the initial AR diagnosis was moderate, and the rate of the severity of mild, moderate, and severe were 46.6%, 46.6%, and 6.7%, respectively. Children originated equally from East Java Region 1 (Surabaya) 43.9%, East Java Region 5 (Bojonegoro) 37.1%, East Java Region 4 (Jember) 4.2%, East Java Region 3 (Madiun) 2.8%, and East Java Region 2 (Malang) 1.3%, as well as from outer Province (0.4%) and outer Java Island (10.1%). As shown in Table 1 compared with matched control subjects, children who subsequently received SCIT experienced significantly more overall comorbid disease burden in the year before SCIT initiation. Whereas asthma and atopic eczema occurred significantly less frequently among matched controls, rates of other diseases of the upper respiratory tract, such as sinusitis and other respiratory system diseases, such as bronchitis, were significantly higher among SCIT-treated patients.

Table 1. Characteristics Subjects.

| Characteristics | SCIT Group (n = 1,098) | | Control Group (n = 1,098) | | p |
|--|---------------------------|---------|------------------------------|---------|-------|
| Age category (years), n (%) | | | | | |
| 0–1 | 44 | (4.0) | 48 | (4.4) | 0.199 |
| 2–5 | 542 | (49.4) | 538 | (49.0) | |
| 6–12 | 432 | (39.3) | 458 | (41.7) | |
| 13–18 | 54 | (4.9) | 36 | (3.3) | |
| 18+ | 26 | (2.4) | 18 | (1.6) | |
| Sex, n (%) | | | | | |
| Male | 696 | (63.4) | 704 | (64.1) | 0.722 |
| Female | 402 | (36.6) | 394 | (35.9) | |
| AR-associated conditions, n (%) | | | | | |
| Asthma, n (%) | 593 | (54.0) | 396 | (36.1) | 0.000 |
| Bronchitis, n (%) | 431 | (39.3) | 700 | (63.8) | 0.000 |
| Atopic dermatitis, n (%) | 100 | (9.1) | 85 | (7.7) | 0.249 |
| Sinusitis, n (%) | 12 | (1.1) | 106 | (9.7) | 0.000 |
| Conjunctivitis, n (%) | 3 | (0.3) | 0 | (0.0) | 0.083 |
| GI Problem, n (%) | 7 | (0.6) | 3 | (0.3) | 0.205 |
| Urticaria, n (%) | 14 | (1.3) | 20 | (1.8) | 0.300 |
| Nutrition Status | | | | | |
| BW (kgs), mean (SD) | 12.8 | (2.35) | 12.7 | (2.33) | 0.761 |
| BH (cm), mean (SD) | 84.7 | (19.84) | 84.2 | (19.24) | 0.530 |
| % BW / Age | 82.3 | (3.29) | 82.3 | (3.26) | 0.938 |
| % BH / Age | 77.9 | (4.11) | 77.9 | (4.07) | 0.938 |
| Number of comorbidity, n (%) | | | | | |
| 0 | 40 | (3.6) | 11 | (1.0) | 0.000 |
| 1 | 959 | (87.3) | 870 | (79.2) | |
| 2 | 96 | (8.7) | 211 | (19.2) | |
| 3 | 3 | (0.3) | 6 | (0.5) | |
| Physician specialty of referral, n (%) | | | | | |
| Primary care/general practitioner | 27 | (2.5) | 27 | (2.5) | 0.277 |
| Paediatrician | 973 | (88.6) | 952 | (86.7) | |
| ENT specialists | 69 | (6.3) | 74 | (6.7) | |
| Dermatologist | 29 | (2.6) | 45 | (4.1) | |
| Geographic region, n (%) | | | | | |
| East Java Region 5 (Bojonegoro) | 410 | (37.3) | 361 | (32.9) | 0.325 |
| East Java Region 4 (Jember) | 46 | (4.2) | 45 | (4.1) | |
| East Java Region 3 (Madiun) | 31 | (2.8) | 27 | (2.5) | |
| East Java Region 2 (Malang) | 14 | (1.3) | 17 | (1.5) | |
| East Java Region 1 (Surabaya) | 482 | (43.9) | 510 | (46.4) | |
| Outer Province | 4 | (0.4) | 7 | (0.6) | |
| Outer Island | 111 | (10.1) | 131 | (11.9) | |
| Baseline Symptom Score (SS), mean (SD) | 2.7 | (0.48) | 2.7 | (0.45) | 0.398 |
| Baseline Skin Prick Test Diameter (Mite) (mm), mean (SD) | 9.3 | (4.17) | 9.3 | (4.15) | 0.807 |
| Level of sptHDM IgE (kU/mL), mean (SD) (Checked randomly by 10% of the total sample) | 20.5 | (8.75) | 20.3 | (8.66) | 0.685 |

3.2. Symptom Scores, Drug Scores, SPT of House-Dust-Mite Diameter, IgE-Specific House-Dust-Mite

Table 2 shows the effect of SCIT on symptom scores, drug scores, SPT of house-dust-mite diameters, and IgE-specific house-dust-mites. The mean symptom score (SS) of the children in the first trimester (0–3 months) in the SCIT group was 2.4 (SD 0.61), similar to

that in the non-SCIT group. Likewise, the medication score (MS) and combination symptom and medication score (CSMS) are the same in the first trimester. The decline in SS to 1.7 in 4–6 months, to 0.8 in 7–12 months, and a slight increase to 1.2 in 13–18 months occurred with SCIT. Meanwhile, in the non-SCIT group, scores did not decrease at 4–6 months, fell slightly to 2.2 at 7–12 months, and to 2.0 at 13–18 months. There was a significant difference in SS reduction with SCIT from 4–6 months to 13–18 months. The reduction in SS score on SCIT was 1.8 (SD 0.45) significantly different ($p = 0.000$) from the reduction in SS score on non-SCIT (0.4 (SD 0.48)).

Table 2. The effect of SCIT on symptom scores, drug scores, SPT of house-dust-mite diameter, IgE-specific house-dust-mite.

| Variable | SCIT Group (<i>n</i> = 1.098) | | Control Group (<i>n</i> = 1.098) | | <i>p</i> |
|---|-----------------------------------|--------|--------------------------------------|--------|----------|
| Symptom Score (SS), mean (SD) | | | | | |
| • 0–3 months | 2.7 | (0.48) | 2.7 | (0.45) | 0.390 |
| • 4–6 months | 1.7 | (0.53) | 2.4 | (0.48) | 0.000 |
| • 7–12 months | 0.8 | (0.61) | 2.2 | (0.69) | 0.000 |
| • 13–18 months | 1.2 | (0.39) | 2.0 | (0.46) | 0.000 |
| • Difference before-after | 1.8 | (0.45) | 0.4 | (0.48) | 0.000 |
| Medication Score (MS), mean (SD) | | | | | |
| • 0–3 months | 2.6 | (0.48) | 2.6 | (0.48) | 0.860 |
| • 4–6 months | 1.7 | (0.53) | 2.4 | (0.48) | 0.000 |
| • 7–12 months | 0.8 | (0.61) | 2.2 | (0.69) | 0.000 |
| • 13–18 months | 0.4 | (0.59) | 2.2 | (0.69) | 0.000 |
| • Difference before-after | 2.3 | (0.59) | 0.4 | (0.49) | 0.000 |
| Combination Symptom & Medication Score (CSMS), mean (SD) | | | | | |
| • 0–3 months | 5.0 | (0.76) | 5.0 | (0.76) | 0.955 |
| • 4–6 months | 3.5 | (1.07) | 4.7 | (0.96) | 0.000 |
| • 7–12 months | 1.6 | (1.23) | 4.4 | (1.38) | 0.000 |
| • 13–18 months | 1.5 | (0.74) | 4.2 | (0.68) | 0.000 |
| • Difference before-after | 4.1 | (0.80) | 0.8 | (0.84) | 0.000 |
| Skin Prick Test Diameter (Mite) (mm), mean (SD) | | | | | |
| • before | 9.3 | (4.17) | 9.3 | (4.15) | 0.807 |
| • after | 6.2 | (1.14) | 7.6 | (3.91) | 0.000 |
| • Difference | 2.4 | (1.26) | 1.7 | (0.71) | 0.000 |
| Level of sPHDM IgE (kU/mL), mean (SD) (Checked randomly by 10% of the total sample) | | | | | |
| • before | 20.5 | (8.75) | 20.3 | (8.66) | 0.685 |
| • after | 12.1 | (3.07) | 16.4 | (9.58) | 0.000 |
| • Difference | 8.4 | (8.93) | 3.9 | (1.73) | 0.000 |

The mean medication score (MS) of the first trimester (0–3 months) in the SCIT group was 2.6 (SD 0.48), the same as in the non-SCIT group. The decline in MS to 1.7 at 4–6 months, to 0.8 at 7–12 months, and to 0.4 at 13–18 months occurred in the SCIT group. Meanwhile, for non-SCIT, the MS score decreased to 2.4 at 4–6 months, to 2.2 at 7–12 months and remained 2.2 at 13–18 months. There was a significant difference in the decline in MS at SCIT from 4–6 months to 13–18 months. The reduction in MS score on SCIT was 2.3 (SD 0.59) significantly different ($p = 0.000$) from the reduction in MS score on non-SCIT

(0.4 (SD 0.49)). The mean combination symptom and medication score (CSMS) in the first trimester (0–3 months) in the SCIT group was 5.0 (SD 0.76), similar to that in the non-SCIT group. The decrease in CSMS to 3.5 in 4–6 months, to 1.6 in 7–12 months, and to 1.5 in 13–18 months occurred in the SCIT group. Meanwhile, for non-SCIT, the CSMS score decreased to 4.7 in 4–6 months, to 4.4 at 7–12 months, and to 4.2 at 13–18 months. There was a significant difference in the decrease in CSMS at SCIT from 4–6 months to 13–18 months. The reduction of the CSMS score on SCIT was 4.1 (SD 0.80) and significantly different ($p = 0.000$) from the reduction of the CSMS score on non-SCIT (0.8 (SD 0.84)).

The mean SPT mite diameter (mm) and sp-HDM-IgE level (kU/mL) in the SCIT group were 9.3 (SD 4.17) mm and 20.5 (SD 8.75) kU/mL, respectively, which were not significantly different from the non-SCIT group at the beginning of observation (0 months). The decrease in SPT mite diameter (mm) from 9.3 (SD 4.17) mm at the beginning of observation (0 months) to 6.2 (SD 1.14) mm at the end of the observation (18 months) occurred in the SCIT group. Meanwhile, in the non-SCIT group, there was also a decrease in SPT Mite diameter (mm) from 9.3 (SD 4.15) mm at the beginning of the observation to 7.6 (SD 3.91) mm at the end of the observation (18 months). There was a significant difference in SPT Mite diameter (mm) between the SCIT and non-SCIT groups after 18 months of observation. The reduction diameter of SPT Mite (mm) on SCIT was 2.4 (SD 1.26) and significantly different ($p = 0.000$) from the reduction diameter of SPT Mite (mm) in non-SCIT (1.7 (SD 0.71)).

The decrease in sp-HDM-IgE level (kU/mL) from 20.5 (SD 8.75) kU/mL at baseline of observation (0 months) to 12.1 (SD 3.07) kU/mL at the end of observation (18 months) occurred in the SCIT group. Meanwhile, in the non-SCIT group, there was also a decrease in the sp-HDM-IgE level (kU/mL) from 20.3 (SD 8.66) kU/mL at the beginning of the observation to 16.4 (SD 9.58) kU/mL at the end of the observation (18 months). There was a significant difference in sp-HDM-IgE levels (kU/mL) between the SCIT and non-SCIT groups after 18 months of observation. Reduction level of sp-HDM-IgE (kU/mL) on SCIT was 8.4 (SD 8.93) kU/mL significantly different ($p = 0.000$) with reduction of sp-HDM-IgE level (kU/mL) in non-SCIT (3.9 (SD 1.73)).

Table 3 shows each effect of SCIT on points of symptoms (nasal, eye, and lung symptoms).

Table 3. The effect of SCIT on points of symptoms (Nasal, Eye, and Lung Symptoms).

| Points of Symptom | | Baseline | 0–3 Months | 4–6 Months | 7–12 Months | 13–18 Months |
|--|-----------|-------------|------------|------------|-------------|--------------|
| Total Points of Symptom, mean (SD) | | | | | | |
| SCIT Group | Mean (SD) | 16.2 (2.75) | 7.2 (1.84) | 5.2 (1.60) | 2.5 (1.84) | 3.5 (1.18) |
| Non SCIT (Control) Group | Mean (SD) | 16.3 (2.70) | 7.2 (1.84) | 7.1 (1.44) | 6.6 (2.07) | 6.1 (1.39) |
| | <i>p</i> | 0.398 | 0.944 | 0.000 | 0.000 | 0.000 |
| Nasal Symptom Points of Itchy Nose, mean (SD) | | | | | | |
| SCIT Group | Mean (SD) | 2.7 (0.44) | 1.2 (0.87) | 1.6 (0.48) | 0.8 (0.56) | 1.1 (0.39) |
| Non SCIT (Control) Group | Mean (SD) | 2.8 (0.43) | 1.3 (0.78) | 1.8 (0.42) | 1.7 (0.46) | 1.54 (0.88) |
| | <i>p</i> | 0.374 | 0.010 | 0.000 | 0.000 | 0.000 |
| Nasal Symptom Points of Sneezing, mean (SD) | | | | | | |
| SCIT Group | Mean (SD) | 2.9 (0.28) | 1.4 (1.03) | 1.7 (0.61) | 0.8 (0.58) | 1.1 (0.41) |
| Non SCIT (Control) Group | Mean (SD) | 2.9 (0.28) | 1.5 (1.00) | 2.4 (0.68) | 1.9 (0.64) | 1.7 (1.01) |
| | <i>p</i> | 0.818 | 0.001 | 0.000 | 0.000 | 0.000 |
| Nasal Symptom Points of Runny Nose (rhinorrhea), mean (SD) | | | | | | |
| SCIT Group | Mean (SD) | 2.7 (0.44) | 1.0 (0.63) | 1.6 (0.49) | 0.8 (0.55) | 1.1 (0.39) |
| Non SCIT (Control) Group | Mean (SD) | 2.8 (0.43) | 1.2 (0.67) | 1.8 (0.43) | 1.6 (0.49) | 1.5 (0.88) |
| | <i>p</i> | 0.374 | 0.000 | 0.000 | 0.000 | 0.000 |

Table 3. Cont.

| Points of Symptom | | Baseline | 0–3 Months | 4–6 Months | 7–12 Months | 13–18 Months |
|--|-----------|------------|------------|------------|-------------|--------------|
| Nasal Symptom Points of Blocked Nose (nasal congestion), mean (SD) | | | | | | |
| SCIT Group | Mean (SD) | 2.6 (0.89) | 1.9 (1.43) | 0.2 (0.64) | 0.1 (0.37) | 0.0 (0.36) |
| Non SCIT (Control) Group | Mean (SD) | 2.7 (0.86) | 1.9 (1.45) | 0.9 (1.17) | 1.0 (1.44) | 1.1 (1.44) |
| | <i>p</i> | 0.508 | 0.953 | 0.000 | 0.000 | 0.000 |
| Points of Eye Symptom, mean (SD) | | | | | | |
| SCIT Group | Mean (SD) | 2.7 (0.44) | 0.2 (0.55) | 0.0 (0.00) | 0.0 (0.13) | 0.0 (0.00) |
| Non SCIT (Control) Group | Mean (SD) | 2.8 (0.43) | 0.2 (0.64) | 0.0 (0.00) | 0.0 (0.00) | 0.0 (0.00) |
| | <i>p</i> | 0.374 | 0.007 | 0.000 | 0.000 | 0.000 |
| Points of Lung Symptom, mean (SD) | | | | | | |
| SCIT Group | Mean (SD) | 2.1 (1.30) | 1.6 (1.48) | 0.0 (0.36) | 0.0 (0.21) | 0.0 (0.18) |
| Non SCIT (Control) Group | Mean (SD) | 2.1 (1.31) | 1.1 (1.43) | 0.3 (0.94) | 0.3(0.94) | 0.3 (0.92) |
| | <i>p</i> | 0.769 | 0.000 | 0.000 | 0.000 | 0.000 |

3.3. Frequencies of Resources Utilization

Table 4 shows resource utilization, such as physician and medical prescription. The average number of times SCIT group children visited a physician in 0–3 months (the first trimester), 4–6 months (second trimester), 7–12 months (second semester), 13–18 months (third semester), and in total, 18 months was 9.1 (SD 2.69) times, 9.1 (SD 0.50) times, 8.1(SD 0.44) times, 3.5 (SD 1.18) times, and 29.8 (SD 3.34) times, respectively, and at the same time, the average number of medical prescriptions required was 29.7 (SD 10.87) times, 15.9 (SD 5.26) times, 6.7 (SD 4.96) times, 1.4 (SD 3.02) times, and 53.7 (SD 17.79) times, respectively.

Table 4. Frequencies of resources utilization.

| Health Care Use | | 0–3 Months | 4–6 Months | 7–12 Months | 13–18 Months | Total | |
|----------------------|--------------------------|------------|------------|-------------|--------------|--------|---------|
| Physician Visit | SCIT Group | Mean | 9.1 | 9.1 | 8.1 | 3.5 | 29.8 |
| | | SD | (2.69) | (0.50) | (0.44) | (1.18) | (3.34) |
| | Non SCIT (Control) Group | Mean | 9.5 | 8.2 | 7.6 | 6.1 | 31.4 |
| | | SD | (2.42) | (1.99) | (1.64) | (1.39) | (7.07) |
| | <i>p</i> | 0.220 | 0.000 | 0.000 | 0.000 | 0.000 | |
| Medical Prescription | SCIT Group | Mean | 29.7 | 15.9 | 6.7 | 1.4 | 53.7 |
| | | SD | (10.87) | (5.26) | (4.96) | (3.02) | (17.79) |
| | Non SCIT (Control) Group | Mean | 30.0 | 19.8 | 17.1 | 14.0 | 80.9 |
| | | SD | (10.41) | (4.86) | (5.73) | (5.46) | (20.70) |
| | <i>p</i> | 0.537 | 0.000 | 0.000 | 0.000 | 0.000 | |
| Hospitalizations | SCIT Group | Mean | 0.00 | 0.01 | 0.01 | 0.00 | 0.03 |
| | | SD | (0.09) | (0.19) | (0.17) | (0.03) | (0.27) |
| | Non SCIT (Control) Group | Mean | 0.01 | 0.01 | 0.01 | 0.01 | 0.04 |
| | | SD | (0.16) | (0.19) | (0.19) | (0.30) | (0.43) |
| | <i>p</i> | 0.317 | 1.000 | 0.811 | 0.371 | 0.313 | |

The average number of times non-SCIT group children visited a physician in 0–3 months (the first trimester), 4–6 months (second trimester), 7–12 months (second semester), 13–18 months (third semester), and in total, 18 months was 9.5 (SD 2.42) times, 8.2 (SD 1.99) times, 7.6 (SD 1.64) times, 6.1 (SD 1.39) times, and 31.4 (SD 7.07) times, respectively, and at the same time, the average number of medical prescriptions required was 30.0 (SD 10.41) times,

19.8 (SD 4.86) times, 17.1 (SD 5.73) times, 14.0 (SD 5.46) times, and 80.9 (SD 20.70) times, respectively.

The average number of times children visited a physician in 4–6 months (second trimester) and 7–12 months (second semester) in the SCIT group were higher than the non-SCIT group but, in the past 13–18 months (third semester), were lower than the non-SCIT group. The average number of medical prescriptions required in 0–3 months (the first trimester) was not significantly different between the SCIT group and the non-SCIT group. However, from since second trimester (4–6 months), the average number of medical prescriptions in the SCIT group were lower than the non-SCIT group.

The most common agents of medical prescriptions used by AR patients were anti-histamine/decongestant combinations w/or w/o analgesic or cough suppressant 42.8% (7731 times), followed by local (nasal) corticosteroids, w/or w/o inhaled corticosteroids 33.4% (6032 times); systemic corticosteroids 14.7% (2663 times); inhaled long-acting β_2 agonists, w/or w/o short-acting β_2 agonists 7.6% (1379 times); and emollient 1.4% (259 times). Drug agents were used more by the non-SCIT group (11,251 times) than by the SCIT group (6828 times). AR patients were mainly treated with oral antihistamines. Patients suffering from both illnesses often received intranasal agents (e.g., beclomethasone dipropionate or disodium cromoglycate) and inhaled disodium cromoglycate/nedocromil. The use of prescribed inhaled sympathomimetics and corticosteroids increased proportionately to illness severity.

Children in the SCIT group decreased the average number of medication episodes over 18 months from 1.0 to 0.66 (34.0%) for antihistamine/decongestant combinations w/or w/o analgesic or cough; from 1.0 to 0.44 (56.3%) for local (nasal) corticosteroids, w/or w/o inhaled corticosteroids; from 0.63 to 0.19 (70.4%) for systemic corticosteroids; from 0.45 to 0.01 (87.3%) for inhaled long-acting β_2 agonists, w/or w/o short-acting β_2 agonists; from 0.08 to 0.01 (87.0%) for emollient. Children in the non-SCIT decreased the average number of medication episodes over 18 months from 1.0 to 1.0 (0.0%) for antihistamine/decongestant combinations w/or w/o analgesic or cough; from 1.0 to 0.84 (15.7%) for local (nasal) corticosteroids, w/or w/o inhaled corticosteroids; from 0.63 to 0.19 (70.4%) for systemic corticosteroids; from 0.36 to 0.11 (69.2%) for inhaled long-acting β_2 ; from 0.08 to 0.02 (73.0%) for emollient.

A few hospitalizations occurred during the study. Overall, 1.3% ($n = 30$) were treated as inpatients, for an average of 2.3 days (SD 0.83) in the SCIT Group ($n = 14$) and for an average of 3.1 days (SD 1.91) in the non-SCIT Group ($n = 16$). In terms of the number of inpatient stays over the 18-month period, SCIT-treated children had significantly fewer inpatient stays than their matched counterparts. A few hospitalizations occurred during the study. Overall, 1.3% ($n = 30$) were treated as inpatients, for an average of 2.3 days (SD 0.83) in the SCIT group ($n = 14$) and for an average of 3.1 days (SD 1.91) in the non-SCIT group ($n = 16$). In terms of the number of inpatient stays over the 18-month period, SCIT-treated children had significantly fewer inpatient stays than their matched counterparts. The average number of hospitalizations required in all periods of observations was not significantly different between the SCIT group and the non-SCIT group.

3.4. Medical Costs

Table 5 shows pharmacotherapy and physiotherapy costs. For antihistamine/decongestant combinations w/or w/o analgesic or cough, the total average cost was IDR 3,061,626.6 (SD 1,490,628.18) in the SCIT group and IDR 33,699.2 (SD 1,566,519.59) in the non-SCIT group. For local (nasal) corticosteroids, w/or w/o inhaled corticosteroids, the total average cost was IDR 7,543,623.5 (SD 4504589.31) in the SCIT group and IDR 11,432,952.5 (SD 5,268,534.95) in the non-SCIT group. For systemic corticosteroids, the total average cost was IDR 941,928.0 (SD 919,279.26) in the SCIT group and IDR 1,787,334.1 (SD 1,700,252.88) in the non-SCIT group. For inhaled long-acting β_2 agonists, w/or w/o short-acting β_2 agonists, the total average cost was IDR 262,012.8 (SD 284,388.49) in the SCIT group and IDR 271,779.07 (SD 444,767.99) in the non-SCIT group.

Table 5. Pharmacotherapy and physiotherapy costs.

| Pharmacotherapy (X IDR 1000) Costs | | 0–3 Months | 4–6 Months | 7–12 Months | 13–18 Months | Total |
|---|----------|------------|------------|-------------|--------------|----------|
| Antihistamine/decongestant combinations w/or w/o analgesic or cough suppressant (X IDR 1000) | | | | | | |
| SCIT Group | Mean | 1102 | 1104 | 721 | 135 | 3062 |
| | SD | (569.4) | (459.4) | (577.8) | (258.2) | (1490.6) |
| Non SCIT (Control) Group | Mean | 1017 | 880 | 818 | 655 | 3370 |
| | SD | (496.0) | (418.4) | (378.7) | (297.5) | (1566.5) |
| | <i>p</i> | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| Local (nasal) corticosteroids, w/or w/o Inhaled corticosteroids (X IDR 1000) | | | | | | |
| SCIT Group | Mean | 3975 | 2774 | 315 | 480 | 7544 |
| | SD | (1973.6) | (2252.8) | (1131.6) | (898.9) | (4504.6) |
| Non SCIT (Control) Group | Mean | 3601 | 3120 | 2389 | 2323 | 11,433 |
| | SD | (1744.6) | (1480.3) | (1565.4) | (1067.1) | (5268.5) |
| | <i>p</i> | 0.220 | 0.000 | 0.000 | 0.000 | 0.000 |
| Systemic corticosteroids (X IDR 1000) | | | | | | |
| SCIT Group | Mean | 858 | 57 | 15 | 13 | 942 |
| | SD | (757.8) | (268.9) | (127.5) | (110.4) | (919.3) |
| Non SCIT (Control) Group | Mean | 820 | 344 | 331 | 292 | 1787 |
| | SD | (694.6) | (475.1) | (457.8) | (405.4) | (1700.3) |
| | <i>p</i> | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| Inhaled long-acting β_2 agonists, w/or w/o Short-acting β_2 agonists (X IDR 1000) | | | | | | |
| SCIT Group | Mean | 254 | 6 | 1 | 1 | 262 |
| | SD | (269.4) | (50.8) | (20.4) | (17.5) | (284.4) |
| Non SCIT (Control) Group | Mean | 166 | 37 | 37 | 32 | 272 |
| | SD | (237.0) | (107.7) | (105.0) | (92.2) | (444.8) |
| | <i>p</i> | 0.160 | 0.001 | 0.000 | 0.000 | 0.379 |
| Skin Care (X IDR 1000) | | | | | | |
| SCIT Group | Mean | 123 | 3 | 2 | 1 | 129 |
| | SD | (431.5) | (67.6) | (57.5) | (49.3) | (487.0) |
| Non SCIT (Control) Group | Mean | 98 | 19 | 18 | 16 | 151 |
| | SD | (374.3) | (143.3) | (136.9) | (122.6) | (652.4) |
| | <i>p</i> | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |

Table 5. Cont.

| Pharmacotherapy (X IDR 1000) Costs | | 0–3 Months | 4–6 Months | 7–12 Months | 13–18 Months | Total |
|--|----------|------------|------------|-------------|--------------|----------|
| Physiotherapy (X IDR 1000) | | | | | | |
| SCIT Group | Mean | 85 | 5 | 5 | 4 | 99 |
| | SD | (822.3) | (163.7) | (163.7) | (140.3) | (1033.3) |
| Non SCIT (Control) Group | Mean | 748 | 63 | 59 | 53 | 923 |
| | SD | (2373.4) | (563.4) | (524.6) | (478.3) | (3137.0) |
| | <i>p</i> | 0.000 | 0.001 | 0.001 | 0.001 | 0.000 |
| Total Pharmaco-physiotherapy (X IDR 1000) | | | | | | |
| SCIT Group | Mean | 6396 | 3948 | 1058 | 635 | 12,037 |
| | SD | (3103.4) | (2561.3) | (1490.9) | (1245.3) | (6699.0) |
| Non SCIT (Control) Group | Mean | 6450 | 4464 | 3651 | 3371 | 17,935 |
| | SD | (3483.7) | (1945.5) | (2024.5) | (1538.9) | (7661.5) |
| | <i>p</i> | 0.703 | 0.000 | 0.000 | 0.000 | 0.000 |

In the SCIT group, the average costs of antihistamine/decongestant combinations w/ or w/o analgesic or cough suppressant in 0–3 months (the first trimester) and 4–6 months (second trimester) but, from 7–12 months (second semester), was lower than the non-SCIT group. The average costs of systemic corticosteroids and skin care in 0–3 months were higher than the non-SCIT group but from 4–6 months (second trimester) was lower than the non-SCIT group. The average costs of local (nasal) corticosteroids, w/ or w/o inhaled corticosteroids, inhaled long-acting β_2 agonists, w/ or w/o short-acting β_2 agonists, in the SCIT group were not different with the non-SCIT group but after 4–6 months (second trimester) until 13–18 months (third semester) were lower than the non-SCIT group.

Physiotherapy was prescribed for 7.4% ($n = 163$) of all patients. In the SCIT group, the rate of rehabilitation prescription in 0–3 months (the first trimester), 4–6 months (second trimester), 7–12 months (second semester), and 13–18 months (third semester) was 1.1%, 0.1%, 0.1%, and 0.1%, respectively. In the non-SCIT group, the rate of rehabilitation prescriptions in 0–3 months (the first trimester), 4–6 months (second trimester), 7–12 months (second semester), and 13–18 months (third semester) was 9.7%, 1.3%, 1.3%, and 1.3%, respectively. For skin care (emollient), the total average cost was IDR 129,207.7 (SD 487,025.11) in the SCIT group and IDR 150, 831.5 (SD 652,406.98) in the non-SCIT group. The average costs of physiotherapy in the 18-month period evaluation were lower than the non-SCIT group. The mean total cost for all types of pharmacotherapies given to AR children in this study during the 18 months of observation in the SCIT group was lower than that in the non-SCIT group. SCIT-treated children incurred significantly lower total pharmacotherapy costs than their matched counterparts.

The average of total pharmaco-physiotherapy costs in 0–3 months (IDR 6,396,033.2 (SD IDR 3,483,707.81)) in the SCIT group was no different from the non-SCIT group (IDR 6,449,759.4 (SD IDR 33,103,405.56)), but from 4–6 months (second trimester), the average of total pharmaco-physiotherapy in the SCIT group was lower than the non-SCIT group. The average of total pharmaco-physiotherapy given to AR children in this study during the 18 months of observation in the SCIT group (IDR 12,037,214.6 (SD IDR 6,699,040.21)) was lower than that in the non-SCIT group (IDR 17,935,392.6 (SD IDR 7,661,506.27)). The mean 18-month per-patient cost savings for outpatient visits achieved by the SCIT group was almost 1.5 times greater (IDR 12,037,215 vs. IDR 17,935,393 $p < 0.0001$) than that achieved by the non-SCIT group compared with matched control subjects, patients who received SCIT incurred significantly lower mean per-patient total health care costs within 3 months of treatment initiation; this significant effect persisted over the 18-month follow-up period.

Significant differences ($p < 0.0001$) in mean total health care costs occurred at 3-, 6-, 12-, and 18-month follow-up.

In the SCIT group, the average of physician costs in 0–3 months (the first trimester) and in 13–18 months (third semester) were lower than the non-SCIT group, but in 4–6 months (second trimester) and in 7–12 months (second semester), the average was higher. The average of physician costs in this study during the 18 months of observation in the SCIT group was lower than that in the non-SCIT group.

The average of laboratory costs in 0–3 months (the first trimester) in the SCIT group, was no different from the non-SCIT group, but in 13–18 months (third semester), it was higher. The average of laboratory costs in this study during the 18 months of observation in the SCIT group (IDR 6,491,463.5 (SD IDR 204,254.75)) was a little bit higher (1002 more higher) than in the non-SCIT group (IDR 6,501,985.8 (SD IDR 186,589.33)). By adding travel costs to the total pharmaco-physiotherapy costs, the total medical costs were obtained. The average of medical costs in 0–3 months (the first trimester) in the SCIT group was higher than in the non-SCIT group, and in 4–6 months (second trimester), it was not different from the non-SCIT. From 7–12 months (second semester), the total medical costs in the SCIT group were lower. The average of medical costs in this study during the 18 months of observation in the SCIT group (IDR 26,574,651.3 (SD 6,926,884.04)) was lower than in the non-SCIT group (IDR 28,548,577.4 (SD IDR 8,099,994.40)).

By adding travel costs to total medical costs, as seen in Table 6, we get total health care costs. The average of total health care costs in 0–3 months (the first trimester) in the SCIT group was higher than in the non-SCIT group. From 4–6 months (second trimester), the total health care costs in the SCIT group were lower. The average of total health care costs in this study during the 18 months of observation in the SCIT group (39,155,519.2 (SD 7,671,303.08)) was 0.93 times lower than that in the non-SCIT group (IDR 41,659,151.1 (SD 10,031,917.63)). However, in the non-SCIT group, the symptom score (SS) was still 1.4 times higher than in the SCIT group, the medication score (MS) was still 5.5 times higher than in the SCIT group, and the combination symptoms and medication score (CSMS) was still 2.8 times higher than in the SCIT group.

Table 6. Health care costs.

| Health Care Costs | | | 0–3 Months | 4–6 Months | 7–12 Months | 13–18 Months | Total |
|--------------------------------------|-----------------------------|----------|------------|------------|-------------|--------------|----------|
| Medical Care Costs | | | | | | | |
| Physician Costs (X IDR 1000) | SCIT Group | Mean | 1163 | 1161 | 1035 | 443 | 3802 |
| | | SD | (423.6) | (236.3) | (210.6) | (177.1) | (880.8) |
| | Non SCIT (Control) Group | Mean | 1228 | 1064 | 989 | 793 | 4073 |
| | | SD | (399.1) | (334.0) | (289.5) | (236.4) | (1219.5) |
| | | <i>p</i> | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| Laboratory Costs (X IDR 1000) | SCIT Group | Mean | 2933 | | | 3569 | 6502 |
| | | SD | (55.4) | | | (156.7) | (186.6) |
| | Non SCIT (Control) Group | Mean | 2928 | | | 3564 | 6491 |
| | | SD | (64.5) | | | (163.7) | (204.3) |
| | | <i>p</i> | 0.076 | | | 0.000 | 0.000 |
| Hospitalization Cost (X IDR 1000) | SCIT Group | Mean | 3 | 16 | 14 | 1 | 33 |
| | | SD | (108.6) | (219.2) | (195.1) | (31.7) | (313.4) |
| | Non SCIT (Control) Group | Mean | 9 | 16 | 15 | 10 | 49 |
| | | SD | (164.5) | (217.4) | (206.5) | (316.9) | (464.4) |
| | | <i>p</i> | 0.371 | 1.000 | 0.861 | 0.371 | 0.361 |

Table 6. Cont.

| Health Care Costs | | | 0–3 Months | 4–6 Months | 7–12 Months | 13–18 Months | Total |
|--|--------------------------|----------|------------|------------|-------------|--------------|------------|
| Total Pharmacotherapy Costs (X IDR 1000) | SCIT Group | Mean | 6396 | 3948 | 1058 | 635 | 12,037 |
| | | SD | (3103.4) | (2561.3) | (1490.9) | (1245.3) | (6699.0) |
| | Non SCIT (Control) Group | Mean | 6450 | 4464 | 3651 | 3371 | 17,935 |
| | | SD | (3483.7) | (1945.5) | (2024.5) | (1538.9) | (7661.5) |
| | | <i>p</i> | 0.703 | 0.000 | 0.000 | 0.000 | 0.000 |
| SCIT Costs (X IDR 1000) | SCIT Group | Mean | 2100 | 600 | 1200 | 300 | 4200 |
| | | SD | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Total Medical Care Cost (X IDR 1000) | SCIT Group | Mean | 12,595 | 5724 | 3307 | 4948 | 26,575 |
| | | SD | (3340.1) | (2582.5) | (1519.2) | (1301.4) | (6926.9) |
| | Non SCIT (Control) Group | Mean | 10,614 | 5543 | 4655 | 7737 | 28,549 |
| | | SD | (3680.3) | (2076.8) | (2054.4) | (1660.5) | (8100.0) |
| | | <i>p</i> | 0.000 | 0.070 | 0.000 | 0.000 | 0.000 |
| Travel Costs | | | | | | | |
| Travel Costs (X IDR 1000) | SCIT Group | Mean | 3948 | 3424 | 3181 | 2557 | 13,111 |
| | | SD | (1187.4) | (991.9) | (848.0) | (709.1) | (3601.2) |
| | Non SCIT (Control) Group | Mean | 3844 | 3844 | 3428 | 1464 | 12,581 |
| | | SD | (1257.5) | (541.1) | (480.9) | (529.8) | (2165.8) |
| | | <i>p</i> | 0.047 | 0.000 | 0.000 | 0.000 | 0.000 |
| Total Health Care Costs | | | | | | | |
| Total Health Care Cost (X IDR 1000) | SCIT Group | Mean | 16,439 | 9568 | 6735 | 6413 | 39,156 |
| | | SD | (4204.3) | (2633.8) | (1557.1) | (1549.6) | (7671.3) |
| | Non SCIT (Control) Group | Mean | 14,562 | 8967 | 7836 | 10,294 | 41,659 |
| | | SD | (4394.9) | (2619.7) | (2291.9) | (2054.2) | (10,031.9) |
| | | <i>p</i> | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |

For children with AR, to reduce the symptom score (SS) by 1.0 with SCIT, it costs IDR 21,753,062.7 per child, and for non-SCIT, it costs IDR 104,147,878.0 per child. Meanwhile, to reduce the medication score (MS) by 1.0 with SCIT, it costs IDR 17,024,138.8, while with non-SCIT, it costs IDR 104,147,878.0. Meanwhile, to lower the combination symptoms and medication score (CSMS) by 1.0 with SCIT, it costs IDR 9,550,126.6, while with non-SCIT, it costs IDR 52,073,938.9.

4. Discussion

In this retrospective, matched cohort study, we compared matched groups of children with newly diagnosed AR who either did or did not receive SCIT after their first AR diagnosis. Even after matching groups by age, sex, body weight, body height, family history of allergy, symptom and medication scores at SCIT initiation, and comorbid atopic conditions (asthma, conjunctivitis, and atopic dermatitis) during the year prior to SCIT initiation, SCIT-treated children incurred 32.9% (IDR 12,037,215 vs. IDR 17,935,393 $p < 0.0001$) lower mean 18-month drugs costs, 31.6% (IDR 33,470 vs. IDR 48,907 $p < 0.0001$) lower mean 18-month total inpatient costs, and 9.5% (IDR 39,155,519.2 vs. IDR 41,659,151.1 $p < 0.0001$) lower mean 18-month total health care costs, respectively, after SCIT initiation. Furthermore, these significant reductions were evident as early as 3 months after immunotherapy initiation and increased during the 18-month follow-up period. Our study demonstrated savings in reducing symptom scores (SS), medication scores (MS), and combination symptoms and

medication scores (CSMS). To reduce SS by 1.0, SCIT saved IDR 82,394,815.3 per child (IDR 21,753,062.7 per child with SCIT vs. IDR 104,147,878.0 per child without SCIT). Meanwhile, to reduce MS by 1.0, SCIT saved IDR 87,123,739.2 per child (IDR 17,024,138.8 per child with SCIT vs. IDR 104,147,878.0 per child without SCIT). Meanwhile, to reduce CSMS by 1.0, SCIT saved IDR 42,523,812.3 per child (IDR 9,550,126.6 per child with SCIT vs. IDR 52,073,938.9 per child without SCIT).

Another study [28,29] found that the cost of immunotherapy was offset by the cost savings gained 3 months [28] and 6 months [29] after the completion of immunotherapy. Our study found that SCIT costs could be offset by total cost savings in the 2nd semester (SCIT cost IDR 1,200,000.0 vs. total-health-care-cost savings of IDR. 2,788,540.0 per child), and in the 3rd semester (SCIT cost IDR 300,000.0 vs. total-health-care-cost savings of IDR 1,973,926.1 per child). An Italian retrospective study [30] compared the average direct health care costs of 135 children and adolescents with AR and asthma, asthma alone, or AR, asthma, and conjunctivitis during the year before starting immunotherapy with those obtained during 3 years of immunotherapy. Compared to the year prior to the initiation of immunotherapy, the average annual total healthcare costs per patient were 56% lower over the 3 years of immunotherapy. The investigators also found no significant difference in the mean direct healthcare costs per annual patient (>4 years) for the subset of asthmatic patients who had received immunotherapy ($n = 41$) and a matched sample of asthma patients who had not received immunotherapy. Our study found that compared to the first semester of SCIT initiation, the average total health care cost per patient in semester 3 was 73% lower during 18 months of SCIT, while those who were not immunotherapy were only 52% lower. Ariano et al. [31] conducted a 6-year prospective study in which 30 patients with seasonal rhinitis and asthma were randomly assigned to receive 3 years of immunotherapy or pharmacological treatment and then followed up for an additional 3 years after completion of treatment. Although no significant cost difference was seen in the first year of treatment, patients treated with immunotherapy had 15% ($p < 0.001$) and 48% ($p < 0.001$) lower health care costs in the second and third years of treatment, respectively. In our study, a significant cost difference was seen in the second and third semesters of treatment, and patients treated with SCIT had 29% ($p < 0.001$) and 36% ($p < 0.001$) lower health care costs in the second semester, and to the third semester, respectively. In Ariano et al.'s [31] study, this statistically significant cost difference was maintained for 3 years after discontinuation of immunotherapy and peaked at 80% ($p < 0.001$ in the sixth year of the study (the third year after discontinuation of immunotherapy)). The mean annual net savings the average over 6 years was USD830. In addition to these retrospective and prospective cost studies, several European economic modelling studies have provided support for the cost-effectiveness of immunotherapy [32].

In the most interesting study demonstrating the cost-effectiveness of AIT, Ariano et al. [33] examined the pharmacoeconomics of SCIT with SDT versus standard therapy alone among 30 patients with at least 2 years of history of AR and Parietaria-induced asthma. Patients were treated for 3 years and followed for an additional 3 years after discontinuation of treatment. In addition to tracking symptom scores and drug use, the researchers calculated the costs of patients' health care, including scheduled and unscheduled clinic visits and prescription medications. In the first year of the study, those receiving SCIT experienced significant improvement in symptoms and reduced drug use compared with patients receiving standard therapy alone. In the second year of treatment, SCIT provided a cost savings of 48% compared to standard therapy alone. At the end of the study, the investigators reported that SCIT provided an annual net savings per patient of USD 830, representing an 80% cost reduction compared to the standard therapy group without SCIT. In our study, since the first 3 months, those who received SCIT experienced significant improvement in symptoms and reduced drug use (Table 2) compared to patients who received standard therapy alone. Our study found that compared to the first semester of SCIT initiation, the average total health care cost per patient in semester 3 was 73% lower during 18 months of immunotherapy, while those who were not immunotherapy were only 52% lower. At the

end of the study (3rd year) in Ariano et al.'s study [31], the investigators reported that SCIT provided annual net savings per patient of USD830, representing an 80% cost reduction compared to the standard therapy group without SCIT, whereas, at the end of the in our study (18 months), SCIT has provided annual net savings of IDR 4,136,199.2 (equivalent to USD289) per patient representing a 73% cost reduction. Similar to Ariano et al.'s study [31], our study was also designed to cover not only the direct costs of SCIT but also the total health care costs (i.e., all prescribed medications, scheduled and unscheduled medical clinic visits, and so on), but with subjects, our study was much larger ($n = 2198$ AR children).

Another study of savings due to SCIT can be seen in a 2-year double-blind placebo-controlled trial (DBPC) comparing SCIT-administered ragweed allergen extract with a placebo for the treatment of 77 adolescents and adults with ragweed-induced asthma. The investigators reported significant improvement in clinical and economic outcomes in the patient population receiving SCIT compared to the placebo group [32]. The costs of asthma medications and allergen extracts used during the 2-year study period were considered. Over the course of the study (24 months), the cost of asthma treatment for those receiving SCIT was USD 840 versus USD 1194 for those receiving placebo; this represents the 30% cost savings benefit provided by SCIT. However, these cost savings were offset by the USD 527 spent on supplies and SCIT-related administrative costs. During our study (18 months), the cost of treating allergic rhinitis for those receiving SCIT was IDR 12,037,214 (equivalent to USD 842) versus IDR 17,935,392.6 (equivalent to USD 1255) for those receiving non-SCIT; this represents the 32% cost savings benefit provided by SCIT. The cost savings in our study were also offset by IDR 4,200,000 (equivalent to USD 293) spent on supplies and SCIT-related administrative costs. A 2005 Danish study examining the direct and indirect costs of AIT for seasonal grass pollen allergy and house dust mite (HDM) allergy patients revealed significant savings associated with AIT [34]. Prior to the initiation of AIT, the direct annual cost per patient for allergy treatment is 2580 Danish Krone (equivalent to IDR 6,044,802.6 or USD 422). In the years following discontinuation, the direct annual cost per patient fell to DKK 1072 (equivalent to IDR 2,518,407.1 or USD 176), representing 60% savings. When direct and indirect costs are considered, the annual cost per patient is significantly less with SCIT than standard therapy without SCIT. This study further supports the cost-saving benefits of SCIT for patients with allergic respiratory conditions. In a claims-based analysis of Florida Medicaid patients, Hankin and colleagues [28] compared the direct costs (pharmaceutical, outpatient and inpatient services for any reason) incurred by paediatric patients newly diagnosed with AR in the 6 months prior to the initiation of SCIT with direct costs. This patient parallel occurred within 6 months of discontinuation of SCIT. The investigators found a significant reduction in costs ($p < 0.001$) in the 6-month period following SCIT, even after SCIT costs were included.

In an extension of the previously mentioned data, Hankin and colleagues [29] performed a retrospective, matched cohort analysis of 10 years of claims data (1997–2007) to examine whether children with newly diagnosed AR who received SCIT expended less health care utilization and fewer costs over the 18-month follow-up period compared to the group of AR-matched children who did not receive SCIT. Children treated with SCIT incur significantly lower total health care costs of 18 months per patient even after including allergen immunotherapy (IT)-related costs (USD 3247 vs. USD 4872), outpatient costs excluding SCIT-related care (USD 1107 vs. USD 2266), and pharmaceutical costs (USD 1108 vs. USD 1316) compared with matched control subjects ($p < 0.001$ for all). In our study children treated with SCIT incur lower mean total health care costs of 18 months per patient even after including costs associated with SCIT (IDR 39,155,519.2, which equates to USD 2739 vs. IDR 41,659,151.1, which equates to USD 2908), costs outpatient care excluding SCIT-related care (IDR 34,922,049.3, which equates to USD 2438 vs. IDR 41,610,244.0, which equates to USD 2905), and pharmaceutical costs (IDR 12,037,214.6, which equates to USD 842 vs. IDR 17,935,392.6, which equates to USD 1255) compared to matched control subjects ($p < 0.001$ for all). Consistent with previous studies, a significant difference in Cost-Effectiveness of SCIT in total health care costs was evident in the first 3 months of starting immunotherapy

in our study. Our study shows that the initial cost savings associated with SCIT persist and, more importantly, increase over the 18-month study period.

In a retrospective large-scale, matched cohort claims analysis evaluating 12 years of Florida Medicaid data, Hankin and colleagues [3] found comparable cost savings in adults with newly diagnosed AR treated with SCIT. In this study, researchers compared the average 18-month health care costs (pharmaceutical, outpatient and inpatient) of adult and paediatric patients with newly diagnosed AR who received SCIT with those who did not. Specifically, SCIT treatment was associated with savings in children of a 30% reduction in total 18-month health care costs (USD 5253 SCIT vs. matched control subjects USD 9118; $p < 0.0001$). These savings in health care costs, including costs associated with SCIT, were evident in the first 3 months of treatment and continued throughout the 18 months of follow-up. In contrast to Hankin et al.'s study, which analysed claims from Medicaid insurance subjects, our study analysed the costs incurred by patients from private practice with non-insurance self-financing. In our study, when we compared the average 18-month health care costs (after we added pharmaceutical, outpatient and inpatient costs, and of course no travel costs), SCIT treatment was associated with savings (in paediatric AR patients) of 7% reduction in total 18-month health care costs (IDR 26,574,651.3 or USD 1855 SCIT vs. matched control subjects IDR 28,548,577.4 or USD 1992; $p < 0.0001$). The overall cost savings (7%) shown in our research seem low, but the progress of savings increased significantly when viewed from the progress in the 3-month, 6-month, 12-month, and 18-month period, which was -19% , respectively, -3% , 29% , and 36% .

From a systematic review conducted by the National Institute for Health Research Health Technology Assessment (HTA) program identifying 14 economic evaluations and two economic evaluation reviews [35]. It was concluded that on a GBP 20,000–30,000 per QALY basis, SCIT is cost-effective compared to therapeutics. The standard course is 6 years of initiation of SCIT treatment. From a National Health Service perspective, SCIT is cost-effective after 7 years, and SCIT is also found to be cost-effective compared to SLIT after 5 years. Limited evidence suggests SCIT may be more useful and less expensive than SLIT. The authors note that the studies used different outcome measures making it difficult to compare and combine results. Our study did not evaluate beyond 18 months, but at the end of 18 months, SCIT was superior to non-SCIT in reducing symptom scores (SS), medication scores (MS), and combination symptom and medication scores (CSMS). To reduce SS by 1.0, SCIT saved IDR 82,394,815.3 per child, to reduce MS by 1.0, SCIT saved IDR 87,123,739.2, henceforth, to reduce CSMS by 1.0, SCIT saved IDR 42,523,812.3 per child.

Strength and Limitations

Several limitations should be mentioned about this study, although we have attempted to match patients with potentially confounding variables but may have been unable to control for other important characteristics, such as patient adherence to pharmacological treatment and allergen avoidance. Allergen avoidance in the allergy guidelines of the Indonesian Paediatric Society is recommended as the first step in allergy treatment, but there is no guarantee that all families will comply, so we cannot determine whether SCIT and non-SCIT matched patients are equally likely to comply with instructions on allergen avoidance. In addition, we also do not have information regarding the implementation of the avoidance measures that we recommend to his parents. Because our study subjects were enrolled in care through a non-insured self-financing private health care system, these findings may not be generalizable to individuals receiving care through an insurance-financed public health care system. Although several studies, including this study, have found that SCIT-related cost savings increase over time, the duration of follow-up (18 months) was generally limited by subjects dropping out of SCIT (not following up until 18 months after SCIT initiation).

This is the first study in Indonesia to show a significant comparison of AR patients on standard therapy with SCIT with patients on standard therapy without SCIT as a matched control in health care costs as early as 3 months after initiation of treatment. With these

results, it is hoped that the use of SCIT is more frequent in Indonesia because SCIT is proven to not only improve clinical outcomes but also reduce medical expenses early and consistently in children with AR.

5. Conclusions

In conclusion, this first Indonesia-based study demonstrates substantial health care cost savings associated with SCIT for children with AR in an uninsured private health care system and provides strong evidence for the clinical benefits and cost-savings benefits of AR treatment in children.

Patient and Public Involvement Statement

- How was the development of the research question and outcome measures informed by patients' priorities, experience, and preferences? Yes, parents and advisers had been informed about research questions and outcomes measured.
- How did you involve patients in the design of this study? Patients were not involved.
- Were patients involved in the recruitment to and conduct of the study? Patients were not involved.
- How will the results be disseminated to study subjects? The results will be disseminated to study subjects and parents.

Author Contributions: A.E. conceived and planned the experiments, carried out the experiments, planned and carried out the simulations, and contributed to sample preparation. R.A.N. contributed to the interpretation of the results and initially wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved for exempt review by the Research Ethics Committee of Dr. Soetomo General Academic Hospital (protocol code 0389/105/XI/1/2020 version 4 and date of approval 25 January 2021). The Research Ethics Committee of Dr. Soetomo General Academic Hospital stated that the research protocol document above complies with The Office for the Human Research Protection (OHRP) under the requirements of the U.S. Department of Health and Human Services (HHS) Regulation 45 CFR section 46 for exempt review.

Informed Consent Statement: Written informed consent was waived due to this research was restricted to the use of clinical and cost-of treatment from existing medical records.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviation

| | |
|------|--|
| AIT | allergen immunotherapy |
| AR | allergic rhinitis |
| ARIA | allergic rhinitis and its impact on asthma |
| CSMS | combination symptom and medication scores |
| GINA | global initiative for asthma |
| HDM | house dust mites |
| IDR | Indonesian rupiah |
| IgE | immunoglobulin E |

| | |
|------|---|
| MS | medication scores |
| SCIT | subcutaneous immunotherapy |
| SD | standard deviation |
| SPSS | statistical package for the social sciences |
| SPT | skin prick test |
| SS | symptom scores |

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**SURAT EXEMPTION
(“ LETTER OF EXEMPTION ”)**

Ref. No. : 0297/LOE/301.4.2/I/2021

Judul Protokol Penelitian : MANFAAT IMUNOTERAPI DALAM MENURUNKAN GEJALA KLINIS,
FREKUENSI BEROBAT, DAN BIAYA PENGOBATAN ANAK RHINITIS
ALERGI AKIBAT TUNGAU DEBU RUMAH

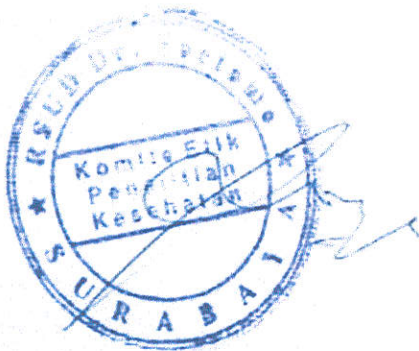
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Instalasi/Tempat Penelitian : SMF Ilmu Kesehatan Anak
RSUD Dr. Soetomo

Komite Etik Penelitian Kesehatan RSUD Dr Soetomo menyatakan bahwa dokumen diatas sesuai dengan The Office for Human Research Protections (OHRP) dibawah persyaratan the U.S. Department of Health and Human Services (HHS) Regulasi 45 CFR bagian 46 untuk exempt review.



Dr. Dominicus Husada dr., SpA(K)
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