



## Region-Specific Appendix (RSA): Japan

# **REMAP-CAP: Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia**

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REMAP-CAP Japan Region-Specific Appendix Version 3.0 dated 24 April, 2021

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## 1. ABBREVIATIONS

|           |  |
|-----------|--|
| CAP       | Community-acquired pneumonia   |
| CRF       | Case Report Form   |
| CTA       | Clinical Trial Agreement   |
| DSA       | Domain-Specific Appendix   |
| DSMB      | Data Safety and Monitoring Board   |
| DSWG      | Domain-Specific Working Group  |
| eCRF      | Electronic Case Report Form  |
| HREC      | Human Research Ethics Committee  |
| IIG       | International Interest Group   |
| ISIG      | International Statistics Interest Group  |
| ITSC      | International Trial Steering Committee   |
| REMAP     | Randomized, Embedded, Multifactorial Adaptive Platform trial                                     |
| REMAP-CAP | Randomized, Embedded, Multifactorial Adaptive Platform trial for<br>Community-Acquired Pneumonia |
| RCC       | Regional Coordinating Center   |
| RMC       | Regional Management Committee  |
| RSA       | Region-Specific Appendix   |
| SAE       | Serious Adverse Event  |

## 2. PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design. While all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both and commencement of the trial in new geographical regions.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study), a Statistical Analysis Appendix (details of the current statistical analysis plan and models) and Simulations Appendix (details of the current simulations of the REMAP), multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain), and multiple Regions-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the interventions within each domain, because one of the trial adaptations is that domains and interventions will change over time. Information about interventions, within each domain, is covered in a DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be subject to a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analysis model will change overtime in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis and Simulations Appendices. These Appendices are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the International Statistics Interest Group (ISIG) and the Data Safety and Monitoring Board (DSMB).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase over time. Information that is specific to each region that conducts the trial is contained within a RSA. This

includes information related to local management, governance, and ethical and regulatory aspects. It is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

The current version of the Core Protocol, DSAs, RSAs and the Statistical Analysis Appendix is listed on the study website ([www.remapcap.org](http://www.remapcap.org)).

### ***2.1. Region-Specific Protocol version***

The version of the Japan RSA is available in the header and on the front cover of this document.

### ***2.2. Version History***

Version 1.1: Developed and approved by the Japan RMC on 18 September, 2020.

Version 2.0: Amended and approved by Japan RMC on 20 January, 2021

Version 3.0: Amended and approved by Japan RMC on 24 April, 2021

## **3. JAPAN REGION**

The Japan region comprises of sites in the country of Japan.

## **4. JAPAN'S STUDY ADMINISTRATION STRUCTURE**

### ***4.1. Regional Coordinating Center (RCC)***

Regional Coordinating Center (RCC) of REMAP-CAP in Japan is Department of Emergency and Critical Care Medicine of St. Marianna University School of Medicine, where the REMAP-CAP Japan Research Center (Japan RC) has been established. The department has a predominant responsibility for the region plus management of the sites in Japan.

#### 4.1.1. Responsibilities

Department of Emergency and Critical Care Medicine of St. Marianna University School of Medicine is responsible for the following aspects of study management in Japan:

- Liaison with the ITSC and other RCCs in relation to data management, Case Report Forms (CRFs), and site management
- CRF design for any region-specific data collection
- Development, maintenance, and administration of the regional database
- Recruitment and selection of sites
- Data management
- Protocol training of site investigators and research coordinators
- Preparation and arrangement of investigator payments
- Management of study set up including assistance with Human Research Ethics Committee (HREC) applications
- Monitoring and close-out site visits
- Organization of investigator meetings
- Serious adverse event notification to DSMB
- Coordination of data entry and feedback of data enquiries
- Administrative assistance to the Regional Management Committee (RMC), Domain-Specific Working Groups (DSWG), Interest Groups (IIG), and the ITSC, as required
- Liaison with other RMCs to develop study documents and materials that are standardized as much as possible
- Management of study budget
- Application and communication to Japanese funding organizations
- Management of regulatory affairs
- Public relations for the study

### **4.2. Regional Management Committee (RMC)**

#### 4.2.1. Responsibilities

Japanese institutions are managed by REMAP-CAP Japan RMC (newly established), and are responsible for the following aspects of managing studies in Japan:

- Liaison with the staff of Japan RCC

- Approval of the RSA
- Development and approval of the RSA and study materials for the region
- Development and approval of data management systems for the region
- General study management issues
- Liaison with the ITSC, DSWGs, IIGs, and other RCCs with regard to analysis and interpretation of results, and collaboration on publications and presentations
- Funding applications, negotiations, and communication with funding bodies to funding bodies that are funded to support research activities in the Japanese local
- Approval and establishment of feasibility of domains and interventions in the region
- Consumer-engagement in Japan

The representative of the Japan RMC will be cordially invited to join the REMAP-CAP International Trial Steering Committee (ITSC).

#### 4.2.2. Members

**Chief Investigator in Japan**      Professor Shigeki Fujitani

#### **RMC members**

Shigeki Fujitani (Chairman), Department of Emergency and Critical Care Medicine, St. Marianna University School of Medicine

Hitoshi Honda, Division of Infectious Diseases, Tokyo Metropolitan Tama Medical Center

Kazuaki Jindai, Department of Healthcare Epidemiology, Kyoto University

Naoaki Ichihara, Healthcare Quality Assessment, The University of Tokyo

Hideaki Kato, Infection Prevention and Control Department, Yokohama City University Hospital

Kazuhiro Kamata, Fukushima Medical University Aizu Medical Center

Hiroyuki Kunishima, Division of Infection Diseases, St. Marianna University School of Medicine

Jun Makino, Department of Critical Care Medicine, Tokyo Metropolitan Bokutoh Hospital

Kenichi Nakazono, Department of Pharmacy, St. Marianna University School of Medicine, Yokohama City Seibu Hospital

Hiroki Saito, Department of Emergency and Critical Care Medicine, St. Marianna University School of Medicine, Yokohama City Seibu Hospital

Ayumi Shintani, Department of Medical Statistics, Osaka City University

Chizuru Yamashita, Department of Anesthesiology and Critical Care Medicine, Fujita Health University School of Medicine



### **4.3. Senior Advisory Committee**

#### 4.3.1. Responsibilities

The operation of REMAP-CAP in Japan, led by REMAP-CAP Japan RMC, will be supervised by the Senior Advisory Committee, and the Senior Advisory Committee is responsible for the following aspects:

- Confirmation of matters decided by the REMAP-CAP Japan RMC
- Advice and recommendation on matters to be examined in relation to the operation of REMAP-CAP in Japan pursuant to requests from the REMAP-CAP Japan RMC

#### 4.3.2. Members

Senior Advisory Committee Members

Osamu Nishida, The Japanese Society of Intensive Care Medicine

Norio Ohmagari, Center Hospital of the National Center for Global Health and Medicine

Kazuhiro Tateda, The Japanese Association for Infectious Diseases

### **4.4. Contact details**

#### **Chief Investigator in Japan**

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#### 4.4.1. Coordinating Center

#### **REMAP-CAP Japan Research Center, Japan RC**

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## 5. JAPAN REGIONAL MANAGEMENT COMMITTEE AUTHORIZATION

The Japan RMC have read the appendix and authorize it as the official Japan Region Specific Appendix for the study entitled REMAP-CAP. Scheduled to be signed by on behalf of the committee,

**Chief Investigator in  
Japan**

Shigeki Fujitani



Date April 24, 2021

## **6. TRIAL REGISTRATION**

Participation in this trial and involvement of sites is registered in ClinicalTrials.gov. The registration number NCT02735707 and was registered on 12 April 2016.

The Universal Trial Number is: U1111-1189-1653.

## **7. FUNDING OF REGION**

### ***7.1. Source of funding***

In Japan, this study was funded 6,500,000 Japanese Yen (JPN) (May 28, 2020 to March 31, 2021) and 15,000,000 JPN (April 23, 2021 to March 31, 2022) from the "Research Project for Promotion of Development of Innovative Drugs for Emerging and Re-emerging Infections" by Japan Agency for Medical Research and Development (AMED)

Additional funding will be sought in Japan. Local resources for research coordination may also be provided by existing infrastructure.

### ***7.2. Site costs***

Per-patient and any other project-related payments to sites will be as specified in the Clinical Trial Agreement (CTA) between the Sponsor and each site.

### ***7.3. Sponsors***

The sponsor in Japan is St. Marianna University School of Medicine.

### ***7.4. Role of the sponsor***

The role of the sponsor is to act as the legal entity for those trial related activities that can only be undertaken by a legal entity. CTAs will be between the sponsor and participating sites. All other activities, including but not limited to trial design, conduct, safety monitoring, and reporting, are the responsibility of the trial steering and management committees and working groups, as specified in the Core Protocol and appendices.

### **7.5. Insurance**

The Chief Investigator shall make arrangements for insurance in accordance with the relevant legal requirements in Japan.

## **8. TRIAL BACKGROUND AND RATIONALE**

There are no anticipated Japanese-specific issues regarding the background and rationale for Core Protocol of the study. However, some interventions may not be available in all participating sites within the region.

## **9. TRIAL DESIGN**

### **9.1. Study Setting**

As described in the Core Protocol Section 7.3.

### **9.2. Interventions**

RMC will offer all interventions that are available in Japan to all participating sites in which the intervention is available and feasible. At the time of version 2.0, participation in the following domains is planned, but the domains and interventions may be modified, added or deleted according to the situation in the future.

In the following, specific issues in Japan, different from the original REMAP-CAP at global level, will be described. Items not described here are in accordance with the original DSAs.

#### **9.2.1. Core Protocol**

In Japan, the term “adult” is defined as a person who is 20 years or older at the time that his/her consent is obtained for participating in the trial.

#### **9.2.2. Antibiotic domain**

Ceftaroline, moxifloxacin, amoxicillin/clavulanate and ertapenem are not available in Japan and will not be offered in this region.

#### 9.2.3. Macrolide duration domain

The macrolide duration domain will be offered to any site in this region.

#### 9.2.4. Mechanical ventilation domain

The mechanical ventilation domain will be offered to any site in this region.

#### 9.2.5. Pandemic appendix to the core protocol

While the selection criteria for the study is "pandemic infection is either suspected or proven (PISOP)" in the global protocol, only adult patients with confirmed COVID-19 infection will satisfy the selection criteria for domains that are specific to the PISOP stratum. In other words, at the stage where pandemic infection is only suspected, such patients will not satisfy the selection criteria.

#### 9.2.6. COVID-19 therapeutic anticoagulation domain

Only unfractionated heparin intravenous injection will be used for therapeutic anticoagulation in Japan.

#### 9.2.7. Immune modulation-2 domain

In Japan, apremilast will not be included, and only eritoran and placebo will be used. Accordingly, only confirmed COVID-19 cases in moderate state will be enrolled in this domain.

Since this domain will be implemented in Japan based on the framework of investigator-initiated trials, measures will be taken for procedures of adverse events by observing the GCP ministerial ordinances upon consulting with the Ethics Committee and regulatory authorities (PMDA).

### **9.3. Endpoints**

Data will be collected as set out in the Core Protocol and DSAs. It is mandated that trial endpoints that occur after day 90 are collected at sites in Japan.

### **9.4. Co-enrollment**

As described in the Core Protocol Section 7.9.

## **10. TRIAL CONDUCT**

### **10.1. Recruitment and embedding**

As described in the Core Protocol Section 8.3.

### **10.2. Treatment allocation**

Central randomization will occur online and be managed and operated by Spiral Web Solutions Ltd (New Zealand) at <https://remapcap.spinnakersoftware.com> except eSOCDAT operated by SOCAR Research SA (Switzerland) will be used for immune modulation-2 domain at <https://www.socar-research.com/eSOCDAT>.

### **10.3. Distribution of study drug**

The processes and management of distribution of any drug provided by the study will be outlined in operational documents and, as required, specified in the CTA.

### **10.4. Data Collection**

Data collection will be as outlined in the Core Protocol Section 8.9. The collection of data from time-points after day 90 will be mandatory in this region.

### **10.5. Data management**

Data will be entered into a secure, password protected web based CRF designed by Spiral Web Solutions Ltd (New Zealand) or SOCAR Research SA (Switzerland). Data entry and data management will be coordinated by RCC including programming and data management support.

## **10.6. Site start up and initiation**

A site initiation teleconference or visit will be conducted before site activation; at least one routine monitoring visit will be conducted during the recruitment period; and a close out visit. Additional monitoring visits will be planned based on patient inclusion rate or indication. Email and telephone communication will supplement site visits.

Standardized procedures will be in place to educate sites on the trial and trial procedures before site initiation. These include printed material, face-to-face start up meetings, webinars, and on-line study materials.

## **10.7. Quality assurance and monitoring**

### 10.7.1. Quality assurance

As described in Section 8.11 of the core protocol.

### 10.7.2. Monitoring

The study will be monitored by a representative of Department of Emergency and Critical Medicine, St. Marianna University School of Medicine (RCC), and a Contract Research Organization (CRO). Monitoring will be conducted by quality control reviews of protocol compliance, data queries and safety reporting. The study will use a monitoring plan that is developed on a risk-based approach. Details can be found in the REMAP-CAP Monitoring Plan (Section 8.11 of the core protocol).

A monitoring report will be prepared following each visit and reviewed by the RMC if appropriate. A follow up letter will be sent to the principal investigator and research coordinator at the site and will be filed in the site investigator file.

Medical records, any other relevant source documents and site investigator files must be made available to Department of Emergency and Critical Medicine, St. Marianna University School of Medicine (RCC) and the CRO for these monitoring visits during the course of the study and at the completion of the study as needed.

## **10.8. Safety report**

Safety reporting will occur as outlined in the Core Protocol Section 8.13.

All Serious Adverse Events (SAEs) will be recorded in the electronic case report form (eCRF). All SAEs must be reported to the coordinating center via the trial website within 72 hours of the investigators becoming aware of the event.

The investigator should notify the Institutional / Ethics Committee of the occurrence of the serious adverse event in accordance with local requirements.

Web address <https://remapcap.spinnakersoftware.com>  
<https://www.socar-research.com/eSOCDAT> (for Immune modulation-2 domain)

For serious adverse events, contact the following telephone number:

Department of Emergency and ++81-44-977-8111  
Critical Medicine, St. Marianna  
University School of Medicine:

Akiko Hosoyama

A 24 hour per day contact number for Japan will be provided to all sites before recruitment commences.

## **11. ETHICAL CONSIDERATIONS**

### **11.1. Ethical and Regulatory Issues**

The trial will be conducted in accordance with legislation in Japan. Approval of study ethics will be obtained from the relevant HREC prior to start of research at each institution. The investigator is responsible for ensuring that all study approvals are met and that any protocol amendments or serious adverse events are also reported to HREC as required by the committee.

#### **11.1.1. Japan**

Each participating site will submit this study protocol and other relevant study documentation to their responsible institutional review board (IRB). This study shall be carried out in compliance with all the local applicable law in Japan and the international standards applicable for conducting research including, but not limited to, the Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants, the provisions of the Declaration of Helsinki, the Guideline for Good Clinical Practice of the International Conference on Harmonization (ICH-GCP), and the requirement of the Japanese Ministry of Health, Labour and Welfare.