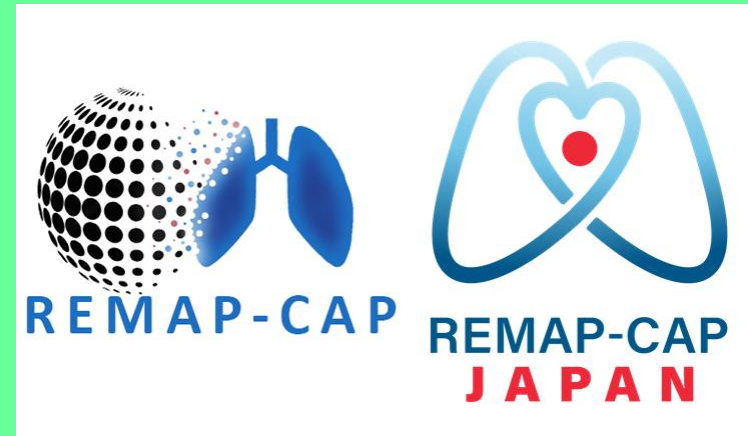


Studying influenza pneumonia in Japan through an international adaptive platform trial, REMAP-CAP

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Introduction

REMAP-CAP: Randomized, Embedded, Multi-factorial, Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP) enables the simultaneous assessment of multiple therapeutic strategies on community-acquired pneumonia, including influenza pneumonia, across domains.

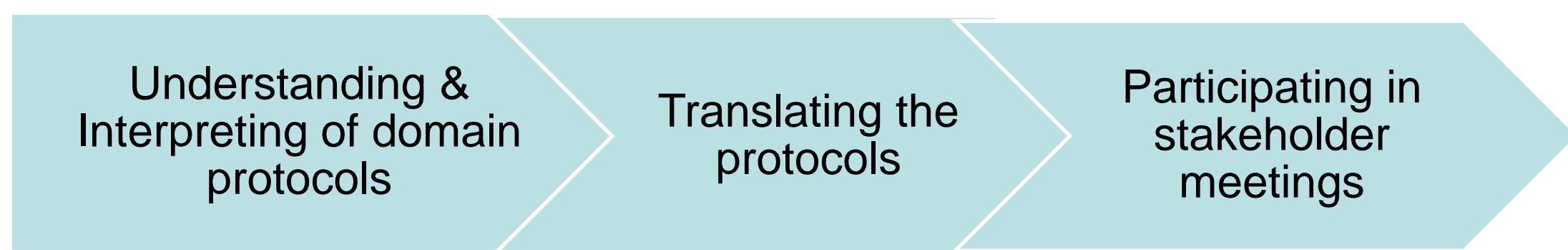
325 sites across 25 countries have participated in the trial, including 30 sites in Japan.

REMAP-CAP findings contributed to evidence regarding therapeutic options for COVID-19, such as anticoagulation, tocilizumab and sarilumab therapies.¹⁾²⁾³⁾

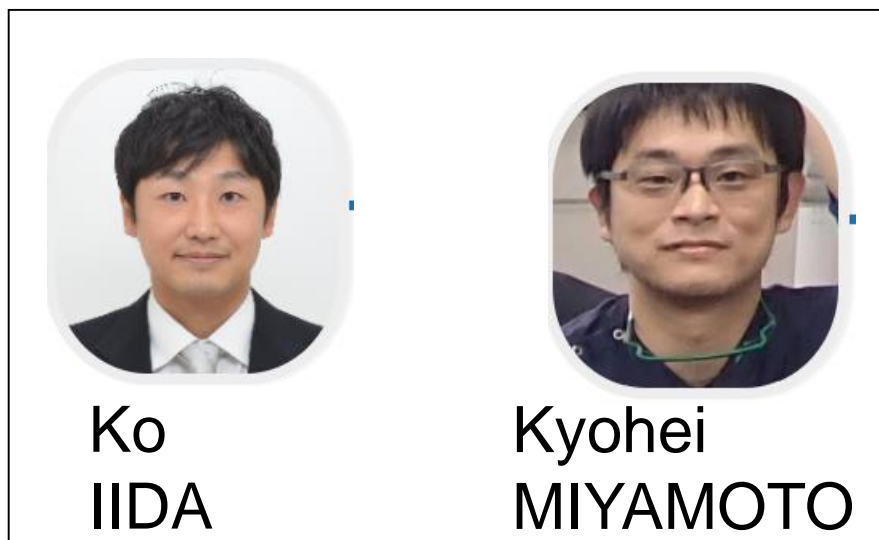
Aim

To share some experiences of practical operations when we incorporate the REMAP-CAP antiviral for influenza domain in Japan. Our findings would be helpful for further research collaboration between Thailand and Japan.

Work contents in Domain Core Team



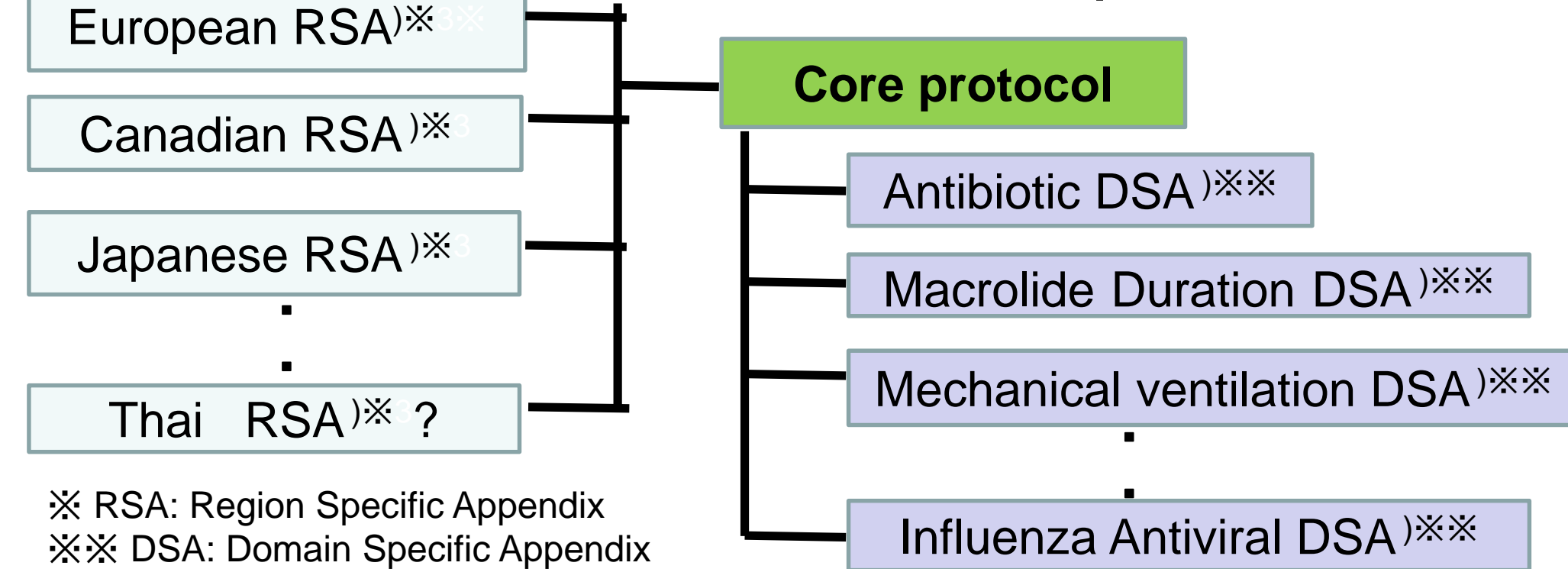
Domain Core Team



Japan Regional Management Committee (RMC)



Framework of protocol



RMC submits RSA amendments as shown below.

| Stratum | Pandemic infection suspected or proven | | Pandemic infection neither suspected nor proven | | |
|------------------------------------|--|--|--|--|--|
| | Moderate State | Severe State | Moderate State | Severe State | |
| Core protocol documents | REMAP-CAP Core Protocol + Pandemic Appendix, or REMAP-COVID Core Protocol | | REMAP-CAP Core Protocol | | |
| Illness Severity State | Moderate State | Severe State | Moderate State | Severe State | |
| Interventions offered at this site | Ward | ICU | Ward | ICU | ICU |
| | <input type="checkbox"/> No antiviral <input checked="" type="checkbox"/> 5 days oseltamivir <input type="checkbox"/> 10 days oseltamivir <input type="checkbox"/> Baloxavir on days 1 and 4 <input type="checkbox"/> 5 days oseltamivir +baloxavir on days 1 and 4 <input type="checkbox"/> 10 days oseltamivir +baloxavir on days 1 and 4 | <input type="checkbox"/> No antiviral <input checked="" type="checkbox"/> 5 days oseltamivir <input type="checkbox"/> 10 days oseltamivir <input type="checkbox"/> Baloxavir on days 1 and 4 <input type="checkbox"/> 5 days oseltamivir +baloxavir on days 1 and 4 <input type="checkbox"/> 10 days oseltamivir +baloxavir on days 1 and 4 | <input type="checkbox"/> No antiviral <input checked="" type="checkbox"/> 5 days oseltamivir <input type="checkbox"/> 10 days oseltamivir <input type="checkbox"/> Baloxavir on days 1 and 4 <input type="checkbox"/> 5 days oseltamivir +baloxavir on days 1 and 4 <input type="checkbox"/> 10 days oseltamivir +baloxavir on days 1 and 4 | <input type="checkbox"/> No antiviral <input checked="" type="checkbox"/> 5 days oseltamivir <input type="checkbox"/> 10 days oseltamivir <input type="checkbox"/> Baloxavir on days 1 and 4 <input type="checkbox"/> 5 days oseltamivir +baloxavir on days 1 and 4 <input type="checkbox"/> 10 days oseltamivir +baloxavir on days 1 and 4 | <input type="checkbox"/> No antiviral <input checked="" type="checkbox"/> 5 days oseltamivir <input type="checkbox"/> 10 days oseltamivir <input type="checkbox"/> Baloxavir on days 1 and 4 <input type="checkbox"/> 5 days oseltamivir +baloxavir on days 1 and 4 <input type="checkbox"/> 10 days oseltamivir +baloxavir on days 1 and 4 |

• The influenza antiviral domain is available for patients who have microbiologically confirmed influenza.
 • The criteria exclude patients with eGFR < 10 ml/min in Japan.

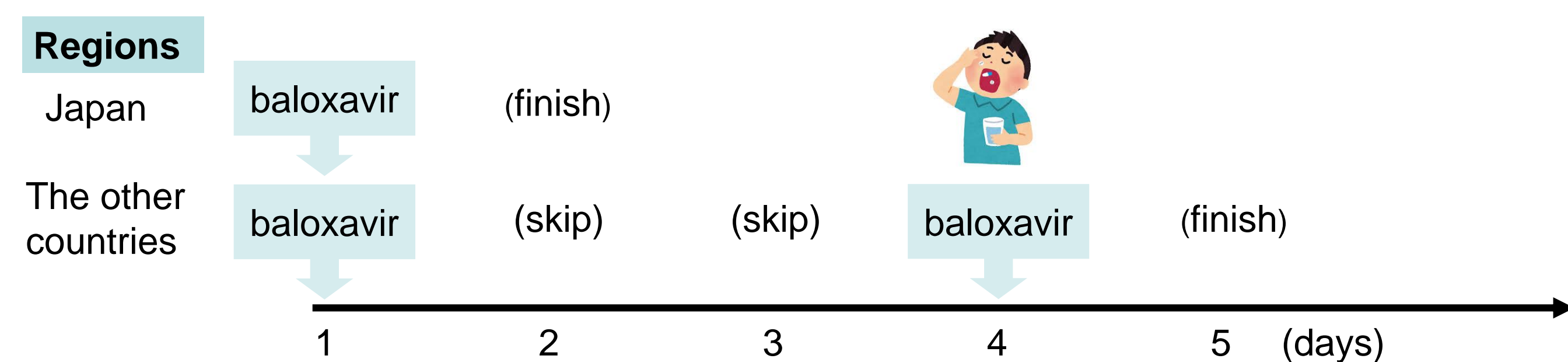
Material & methods

Differences in renal adjustment of oseltamivir between Japan and other countries

| oseltamivir | Kidney function | Japan | The other countries |
|-------------|------------------|---|-------------------------|
| | eGFR < 10 ml/min | oseltamivir is NOT officially recommended | oseltamivir: 30mg daily |

According to the original protocol, 30 mg oseltamivir should be taken daily in patients with eGFR < 10 ml/min. There is no officially recommended dose for patients with eGFR < 10 ml/min in Japan.

Differences in the approved baloxavir doses between Japan and other countries



Baloxavir is approved for day 1 administration alone in Japan.

In contrast, the second version of the antiviral domain indicates that baloxavir should be given on days 1 and 4.

Result

As for oseltamivir dose adjustment for renal dysfunction, we will modify Japan Regional Specific Appendix to exclude patients with eGFR < 10 ml/min from this domain in Japan.

Additionally, because the baloxavir protocol is not approved in Japan, we are in discussions with a suitable pharmaceutical company regarding how to include this domain under appropriate regulatory framework.

Discussion

REMAP-CAP enrolled patients very rapidly during the pandemic. A global-network clinical trial is essential to respond to future outbreaks⁴⁾ Just as the operational aspects of the influenza antiviral domain are being discussed in Japan, every country must ensure REMAP-CAP operation is aligned with local ethical guidelines and regulations.

Conclusion

When introduced to Japan, REMAP-CAP needs to be adapted to local operational issues.

This exercise would facilitate good understanding of the local adaptation of a global protocol and lead to improved pandemic preparedness.

References

- 1) N Engl J Med 2021; 385: 777
- 2) N Engl J Med 2021; 385: 790
- 3) N Engl J Med 2021; 384: 1491
- 4) Lancet Infect Dis 2022; 22: e153