# Going forward together with patient in Asia and beyond

**FUJIWARA Yasuhiro, M.D., Ph.D.**

**Chief Executive, PMDA**

# Today's Topics

- Transparency
- International Cooperation

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# “Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2”

**Background**

- To ensure the efficacy and safety of vaccines used in Japan and accelerate vaccine development, the first edition of a guidance summarizing principles for evaluation on non-clinical and clinical study data required for initiation of a clinical study and application for approval was issued on September 2, 2020.
- To date, Appendices 1, 2, and 3 have been issued to supplement the first version in view of the current social circumstance and findings from development of vaccines against SARS-CoV-2 .

## Time line

**September 2, 2020**

**Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (first edition) issued**

**April 5, 2021**

**Appendix 1_Evaluation of vaccines against variants issued**

■ It presents principles for evaluation of the efficacy and safety of vaccines against variants in Japan based on knowledge at present and overseas guidance on variant vaccine development in response to a statement of companies which have already granted regulatory approval or emergency use authorization of SARS-CoV-2 vaccine that they will develop vaccines against variants by modifying the existing vaccine.

**June 11, 2021**

**Appendix 2_Ethical Considerations for Subjects in Placebo-Controlled Studies issued**

■ It presents principles for the ethical consideration given to subjects assigned to a placebo group in ongoing or future clinical studies for development of vaccines against SARS-CoV-2 in view of the circumstance that the Official Vaccination Program in Japan has been initiated and an increasing number of people will be vaccinated in the future.

**October 22, 2021**

**Appendix 3_Principles for the Immunogenicity-based Evaluation of Vaccines Against the Novel Coronavirus**

■ It presents principles for design of confirmatory clinical trials to evaluate the efficacy of new vaccines against SARS-CoV-2 in unvaccinated subjects on the basis of the immunogenicity in accordance with the ICMRA consensus from an ethical viewpoint since the official vaccination programs have progressed worldwide, making it increasingly difficult to evaluate preventive effects of vaccines on the basis of clinical events (onset, etc.) in placebo-controlled trials.

# Collection and evaluation of Safety Information for COVID-19 Vaccines

**Passive Surveillance**

**<Enhancement for COVID-19 vaccines>**

○ **AEFI reporting system**
- If doctors suspect adverse reactions or specific symptoms occurring within a specific period, those information should be reported to PMDA.

➡ Enhanced by introducing **electronic reporting system**

**Active Surveillance**

○ **Early-phase health survey (by MHLW)**
- 100% follow-up survey in very early-phase of vaccination campaign.
- Symptoms and illnesses for a certain period (about 1 month) after vaccination are collected in approx. 10,000 HCPs.

➡ Special survey **specific for Covid-19 vaccines**

○ **Post-vaccination health status survey (by MHLW)**
- A questionnaire-type survey is conducted on specific symptoms and illnesses which are relatively frequent (fever, swelling at the inoculation site, etc.) in general vaccines.

➡ Enhanced by introducing **electronic reporting system**

○ **Post-marketing surveillance (by MAH)**
- Collecting safety information for general and/or specific groups (ex. pregnant women, pediatric). Surveillance plan is to be determined at the time of marketing approval.

# Special survey specific for Covid-19 vaccines

● **Evaluation**

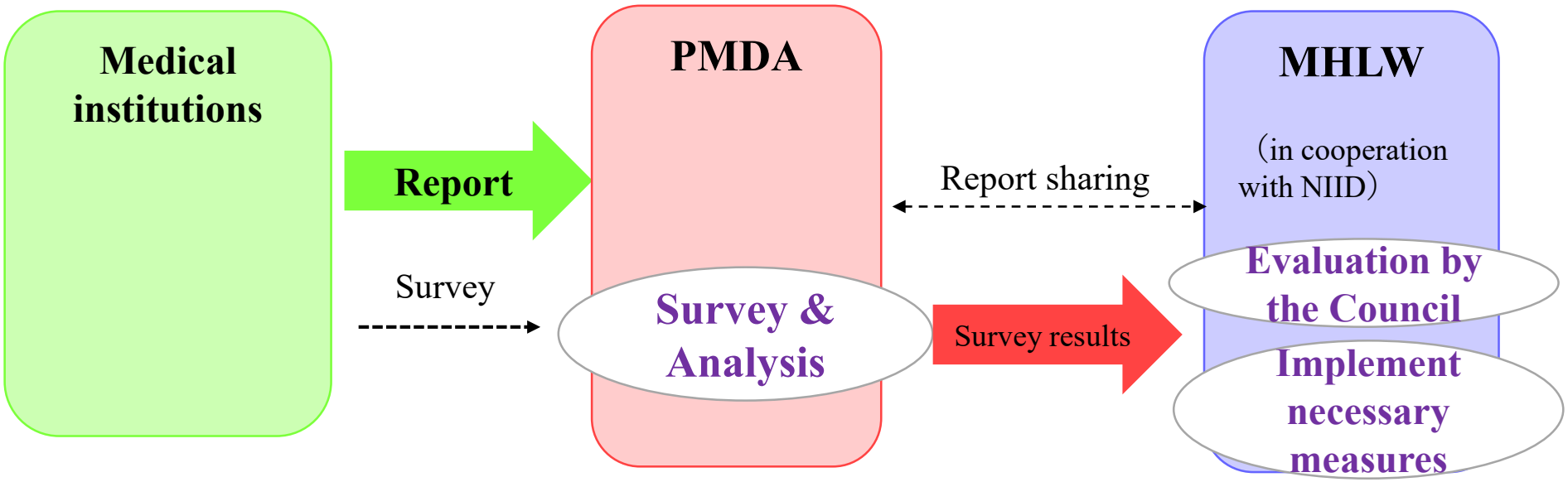
○ **Expert Advisory Council (in MHLW)**
- Monitoring the number of reports, evaluation of individual cases and considerations of necessary measures

○ **MHLW, NIID, PMDA**
- Real time monitoring of safety information reported
- Conducting field surveys on individual cases for details, if necessary

**<Enhancement for COVID-19 vaccines>**

Held **more frequently** than usual
**Ad-hoc** in an emergency

## Flow on the report and evaluation
**(in the AEFI reporting system)**



# Information sharing in a timely manner

## The Health Science Council of MHLW

18th February 2022

21st January 2022

24th December 2021

| 回数 | 開催日 | 議題等 | 議事録／議事要旨 | 資料等 | 開催案内 |
|---|---|---|---|---|---|
| 第76回 | 2022年2月18日（令和4年2月18日） | （1）新型コロナワクチンの接種及び副反応疑い報告の状況並びに接種後の健康状況に係る調査等について<br>（2）HPVワクチンの情報提供について<br>（3）その他 | ▸ 議事録 NEW 3月4日 | ▸ 資料 NEW 2月18日<br>▸ 遵守事項等資料 NEW 2月18日 | ▸ 開催案内 |
| 第75回 | 2022年1月21日（令和4年1月21日） | （1）新型コロナワクチンの接種及び副反応疑い報告の状況並びに接種後の健康状況に係る調査等について<br>（2）麻しん、風しん、おたふくかぜ、水痘、帯状疱疹、肺炎球菌（23価）、HPV、百日せき、ジフテリア、破傷風、不活化ポリオ、肺炎球菌（13価）、Hib、BCG、日本脳炎、B型肝炎、ロタウイルスのワクチンの安全性について<br>（3）その他 | ▸ 議事録 | ▸ 資料<br>▸ 遵守事項等資料 | ▸ 開催案内 |
| 第74回 | 2021年12月24日（令和3年12月24日） | （1）新型コロナワクチンの接種及び副反応疑い報告の状況等について<br>（2）新型コロナワクチンの接種後の健康状況に | ▸ 議事録 | ▸ 資料<br>▸ 遵守事項等資料 | ▸ 開催案内 |

Side Effect Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council has been held frequently to provide an overview of the status of instances of suspected adverse reactions to COVID-19 vaccines.

## Vaccine Safety

**MHLW Press Release: Report of suspected fetal cases after receiving the COVID-19 vaccine**

https://www.mhlw.go.jp/stf/newpage_17104.html

報道関係者各位

### 新型コロナワクチンの接種後の死亡事例の報告について（１例目）

新型コロナワクチンの接種後の副反応疑い報告において、死亡事例が報告されたため、情報提供します。

| No. | 事例 | ワクチン名 | 接種日時 | 発生日時 | 年代・性別 | 基礎疾患等 | 報告者の評価 |
|---|---|---|---|---|---|---|---|
| 1 | 死亡 | コミナティ筋注 | 令和3年2月26日 | 令和3年3月1日 | 60代・女性 | なし | 本剤との因果関係は評価不能 |

ワクチン接種後には、体内に異物を投与するため、様々な反応が生じます。この副反応疑い報告は、国がワクチンの安全性の評価を行うために、ワクチン接種によるものではない偶発的な症状も含めて、広く収集しているものです。
本プレスリリースは、副反応疑い報告制度の透明性の向上及び周知等のため、当面、接種後にアナフィラキシー又は死亡の報告を受けた際に公表するものです。
今後、厚生労働省では、専門家によるワクチン接種との因果関係の評価や審議会での検討を速やかに行い、ワクチン接種の安全性を評価する予定です。

Information contains:

- Status
- Vaccine Name
- Date of vaccination
- Date of occurrence
- Age
- Sex
- Health issues
- Evaluation

# Safety measures and provision of information related to measures against COVID-19

**The following safety information is posted on the PMDA website**

➢ **Safety measures for COVID-19 product**

- May 2021 Compliance with Dosage and Administration (COMIRNATY)
- June 2021 Deletion of ”Acute renal disorder” in “11.1 Clinically significant adverse reactions” etc. (VEKLURY)
- July 2021 Revision of Precautions related to myocarditis and pericarditis (COMIRNATY and SPIKEVAX)
- July 2021 Revision of Precautions related to thrombosis, capillary leak syndrome and Guillain-Barre syndrome (VAXZEVRIA)
- Sept. 2021 Revision of Precautions related to alternate vaccination (COMIRNATY, SPIKEVAX and VAXZEVRIA)
- Oct. 2021 Revision of Precautions related to myocarditis and pericarditis in male adolescents and young adults pericarditis (COMIRNATY and SPIKEVAX)
- Dec. 2021 Revision of Precautions related to anaphylaxis etc. (COMIRNATY and SPIKEVAX)

※ Also available via the PMDA medi-navi

**Provision of Safety Information regarding COVID-19 related products**

- Alert for Proper Use of Ivermectin

Information on drug safety measures


[PMDA's Efforts to Combat COVID-19]

https://www.pmda.go.jp/about-pmda/news-release/0012.html

# Sharing information through social media

- MHLW's official Twitter and Facebook share the latest information.
- Official LINE account also shares information on incidents and prevention of COVID-19.


https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/covid-19sns.html

# Today's Topics

- Transparency

- International Cooperation

# ICMRA
## (International Coalition of Medicines Regulatory Authorities)

https://www.pmda.go.jp/int-activities/int-harmony/icmra/0001.html

**A voluntary, executive-level, strategic coordinating, advocacy and leadership entity of regulatory authorities (36 regulatory authorities) that work together to**

- address current and emerging human medicine regulatory and safety challenges globally, strategically and in an on-going, transparent, authoritative and institutional manner
- provide direction for areas and activities common to many regulatory authorities' missions etc.

**Chair**
- Ms. Emer Cooke
  EMA

**Vice Chair**
- Dr. FUJIWARA
- Dr. John Skerritt
  TGA (Australia)

**Main Strategic Areas**

1. **Innovation Project** (Utilization of method and results of horizon scanning):
   **Japan serves as Co-chair**
2. **Communications**: assigned as ICMRA PR
   **Japan is responsible for website updates, and operation and maintenance management**

# ICMRA major activities for COVID-19
## -workshops-

Global regulatory workshop on COVID-19 vaccine development

#1 March 18, 2020
#2 June 22, 2020

Global regulatory workshop on COVID-19 Real-World Evidence and Observational Studies

#1 April 6, 2020
#2 May 19, 2020
#3 July 22, 2020
#4 October 13, 2020
#5 January 25, 2021
#6 May 10, 2021

Global regulatory workshop on COVID-19 therapeutic development

#1 April 2, 2020
#2 July 20, 2020

Vaccine Safety Collaboration Workshop

#1 January 13, 2021

Pregnancy and Lactation Workshop

#1 February 9, 2021

ICMRA-Industry Workshop on Enabling Manufacturing Capacity in the COVID-19 Pandemic

#1 July 7-8, 2021

COVID-19 Virus Variants Workshop

#1 February 10, 2021
#2 June 24, 2021
#3 January 12, 2022

Co-chairs:
**Dr. FUJIWARA (PMDA)**
Dr. June Raine (MHRA)

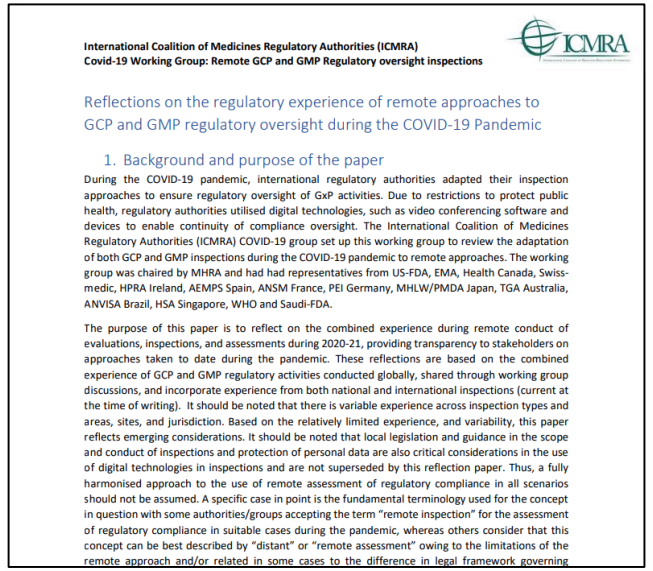
http://www.icmra.info/drupal/en/covid-19

# Regulatory Agility

## ICMRA Remote Inspections

- Many countries and regions have started remote inspections since Covid-19 pandemic. The GCP and GMP Remote Inspection methods in each region are shared, and the experience of the remote inspection is summarized in the Reflection Paper. (10th December 2021)

- Pilots project for hybrid (on-site/remote) inspections of post-approval changes is now under consideration.



International Coalition of Medicines Regulatory Authorities (ICMRA)
Covid-19 Working Group: Remote GCP and GMP Regulatory oversight inspections

Reflections on the regulatory experience of remote approaches to GCP and GMP regulatory oversight during the COVID-19 Pandemic

1. Background and purpose of the paper

During the COVID-19 pandemic, international regulatory authorities adapted their inspection approaches to ensure regulatory oversight of GxP activities. Due to restrictions to protect public health, regulatory authorities utilised digital technologies, such as video conferencing software and devices to enable continuity of compliance oversight. The International Coalition of Medicines Regulatory Authorities (ICMRA) COVID-19 group set up this working group to review the adaptation of both GCP and GMP inspections during the COVID-19 pandemic to remote approaches. The working group was chaired by MHRA and had had representatives from US-FDA, EMA, Health Canada, Swissmedic, HPRA Ireland, AEMPS Spain, ANSM France, PEI Germany, MHLW/PMDA Japan, TGA Australia, ANVISA Brazil, HSA Singapore, WHO and Saudi-FDA.

The purpose of this paper is to reflect on the combined experience during remote conduct of evaluations, inspections, and assessments during 2020-21, providing transparency to stakeholders on approaches taken to date during the pandemic. These reflections are based on the combined experience of GCP and GMP regulatory activities conducted globally, shared through working group discussions, and incorporate experience from both national and international inspections (current at the time of writing). It should be noted that there is variable experience across inspection types and areas, sites, and jurisdiction. Based on the relatively limited experience, and variability, this paper reflects emerging considerations. It should be noted that local legislation and guidance in the scope and conduct of inspections and protection of personal data are also critical considerations in the use of digital technologies in inspections and are not superseded by this reflection paper. Thus, a fully harmonised approach to the use of remote assessment of regulatory compliance in all scenarios should not be assumed. A specific case in point is the fundamental terminology used for the concept in question with some authorities/groups accepting the term "remote inspection" for the assessment of regulatory compliance in suitable cases during the pandemic, whereas others consider that this concept can be best described by "distant" or "remote assessment" owing to the limitations of the remote approach and/or related in some cases to the difference in legal framework governing

https://www.icmra.info/drupal/sites/default/files/2021-12/remote_inspections_reflection_paper.pdf

# Remote GMP Inspections in Japan

- It is difficult to grasp the actual situation of the manufacturing site only with the conventional desktop inspection.
- Deeper inspection method was required for the inspection of manufacturing sites assessed to have a high risk.

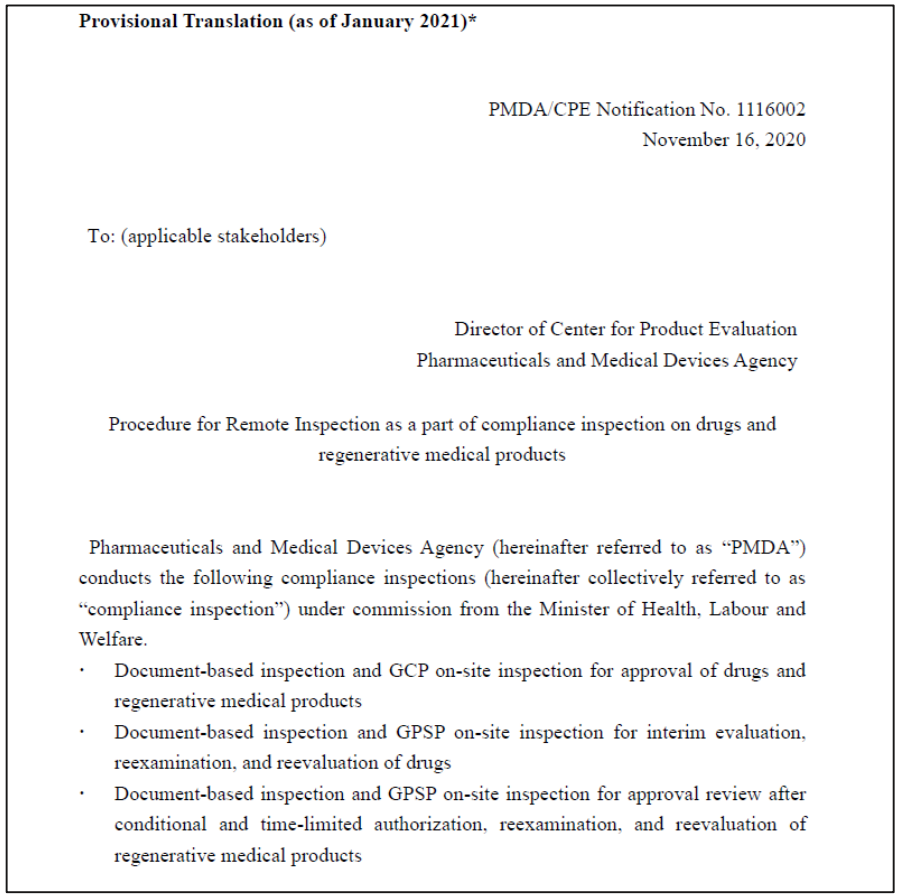
**“Remote inspection using ICT tools"**

# Remote GCP Inspections

**Remote GCP inspections have started from May 2020.**

- PMDA can conduct remote inspections to Sponsors.
- Confirmation of management on clinical trial sites by sponsor can be **done without GCP on-site inspection**
  https://www.pmda.go.jp/files/000235011.pdf
- Notification documenting the method of remote GCP inspections was published on Nov. 16, 2020.
  https://www.pmda.go.jp/files/000238733.pdf

- Implementation policy
- Procedure
- Consideration for preparing evidence material
- Consideration for web conference system



**Provisional Translation (as of January 2021)***

PMDA/CPE Notification No. 1116002
November 16, 2020

To: (applicable stakeholders)

Director of Center for Product Evaluation
Pharmaceuticals and Medical Devices Agency

Procedure for Remote Inspection as a part of compliance inspection on drugs and regenerative medical products

Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA") conducts the following compliance inspections (hereinafter collectively referred to as "compliance inspection") under commission from the Minister of Health, Labour and Welfare.

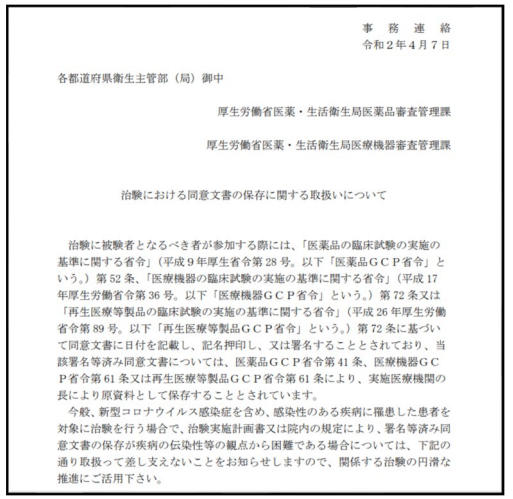
- Document-based inspection and GCP on-site inspection for approval of drugs and regenerative medical products
- Document-based inspection and GPSP on-site inspection for interim evaluation, reexamination, and reevaluation of drugs
- Document-based inspection and GPSP on-site inspection for approval review after conditional and time-limited authorization, reexamination, and reevaluation of regenerative medical products

# Electronic-Informed Consent in Clinical Trials

**“Electronic-Informed Consent” will be an option in clinical trials from April 2022.**

- To accerelate subject enrollment to clinilal trials
  - ➢Informed consent by video conference system
  - ➢Obtaining a signature to Informed consent forms by electronic methods (ex. Digital sign by tablet)

- Notification will be issued, and the following points will be explained:
  - ➢Basic concept (securing subjects’ human rights and safety, scientific quality, and reliability etc.)
  - ➢Points to consider (Identify verification, procedures etc.)



事　務　連　絡
令和２年４月７日

各都道府県衛生主管部（局）御中

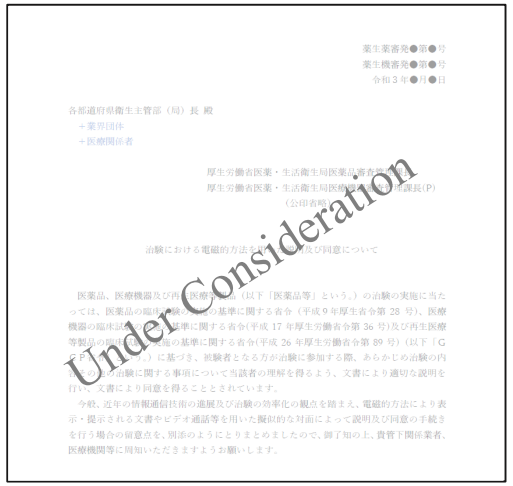
厚生労働省医薬・生活衛生局医薬品審査管理課

厚生労働省医薬・生活衛生局医療機器審査管理課

治験における同意文書の保存に関する取扱いについて

治験に被験者となるべき者が参加する際には、「医薬品の臨床試験の実施の基準に関する省令」（平成９年厚生省令第 28 号。以下「医薬品ＧＣＰ省令」という。）第 52 条、「医療機器の臨床試験の実施の基準に関する省令」（平成 17 年厚生労働省令第 36 号。以下「医療機器ＧＣＰ省令」という。）第 72 条又は「再生医療等製品の臨床試験の実施の基準に関する省令」（平成 26 年厚生労働省令第 89 号。以下「再生医療等製品ＧＣＰ省令」という。）第 72 条に基づいて同意文書に日付を記載し、記名押印し、又は署名することとされており、当該署名等済み同意文書については、医薬品ＧＣＰ省令第 41 条、医療機器ＧＣＰ省令第 61 条又は再生医療等製品ＧＣＰ省令第 61 条により、実施医療機関の長により原資料として保存することとされています。

今般、新型コロナウイルス感染症を含め、感染性のある疾病に罹患した患者を対象に治験を行う場合で、治験実施計画書又は院内の規定により、署名等済み同意文書の保存が疾病の伝染性等の観点から困難である場合については、下記の通り取扱って差し支えないことをお知らせしますので、関係する治験の円滑な推進にご活用下さい。



薬生薬審発●第●号
薬生機審発●第●号
令和３年●月●日

各都道府県衛生主管部（局）長　殿
＋業界団体
＋医療関係者

厚生労働省医薬・生活衛生局医薬品審査管理課長(P)
厚生労働省医薬・生活衛生局医療機器審査管理課長(P)
（公印省略）

治験における電磁的方法による[illegible]及び同意について

医薬品、医療機器及び[illegible]（以下「医薬品等」という。）の治験の実施に当たっては、医薬品の臨床試験の実施の基準に関する省令（平成９年厚生省令第 28 号）、医療機器の臨床試験の実施の基準に関する省令（平成 17 年厚生労働省令第 36 号）及び再生医療等製品の臨床試験の実施の基準に関する省令（平成 26 年厚生労働省令第 89 号）（以下「ＧＣＰ省令」という。）に基づき、被験者となる方が治験に参加する際、あらかじめ治験の内容その他の治験に関する事項について当該者の理解を得るよう、文書により適切な説明を行い、文書により同意を得ることとされています。

今般、近年の情報通信技術の進展及び治験の効率化の観点を踏まえ、電磁的方法により表示・提示される文書やビデオ通話等を用いた擬似的な対面によって説明及び同意の手続きを行う場合の留意点を、別添のようにとりまとめましたので、御了知の上、貴管下関係業者、医療機関等に周知いただきますようお願いします。

Under Consideration

# Acquiring and Sharing Asian Data

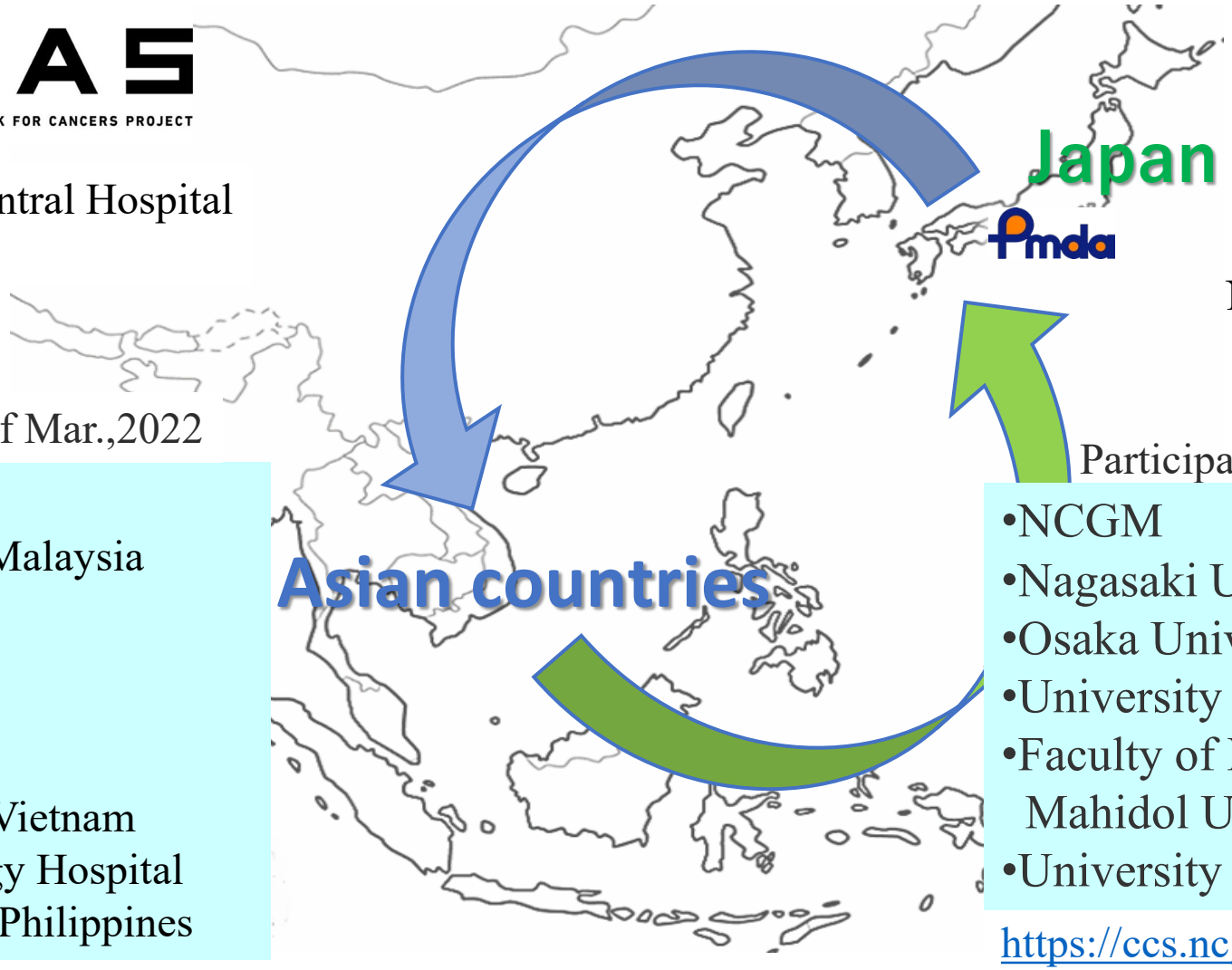
ATLAS
ASIAN CLINICAL TRIALS NETWORK FOR CANCERS PROJECT

National Cancer Center Central Hospital (NCC)

Participating facilities as of Mar.,2022

- NCC
- National Cancer Institute, Malaysia
- Sarawak General Hospital
- Hospital Kuala Lumpur
- Hospital Sultan Ismail
- Hospital Pulau Pinang
- National Cancer Hospital, Vietnam
- Ho Chi Minh City Oncology Hospital
- St. Luke's Medical Center, Philippines

https://en.atlas.ncc.go.jp/




ARISE

National Center for Global Health and Medicine (NCGM)

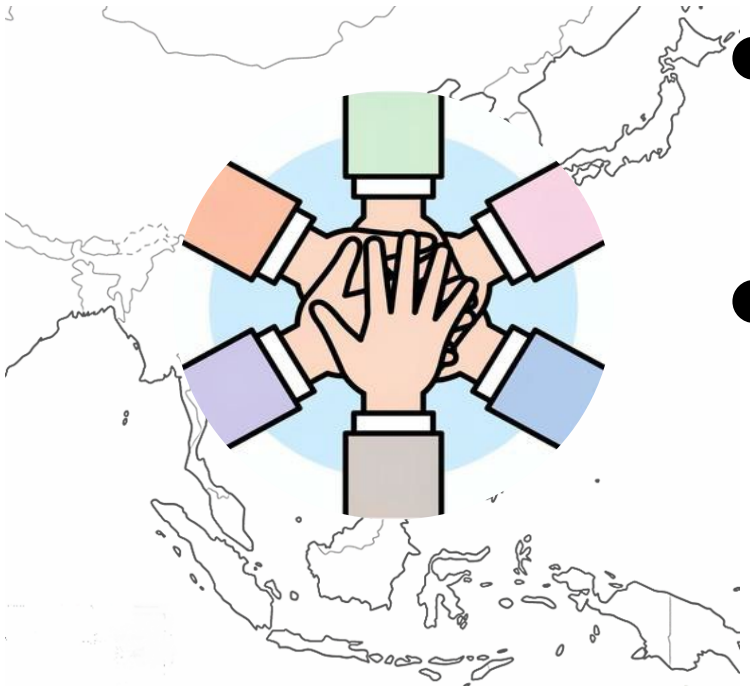
Participating facilities as of Mar.,2022

- NCGM
- Nagasaki University
- Osaka University
- University of Indonesia
- Faculty of Medicine Siriraj Hospital, Mahidol University
- University of the Philippines Manila

https://ccs.ncgm.go.jp/050/en/capacity_building/arise.html

# Working as “Team Asia” toward Asian people

➢Maximizing potential of Asia in Drug Development for the people in Asia, and the world



- Regulatory agility
- Asian studies allow
  - ✓ To develop products to meet unmet medical needs in Asia
  - ✓ To find appropriate dosage & administration for Asian people
- Challenges
  - ✓ Close cooperation of stakeholders
    -Academia, Industries and regulatory agencies among Asia
  - ✓ Regulatory convergence

**Asian Collaboration is the Key!**

Thank You!