Challenges in developing devices using RWD in Japan

- Industry perspective -

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COI Disclosure

- The authors have no financial conflicts of interest to disclose concerning the presentation.

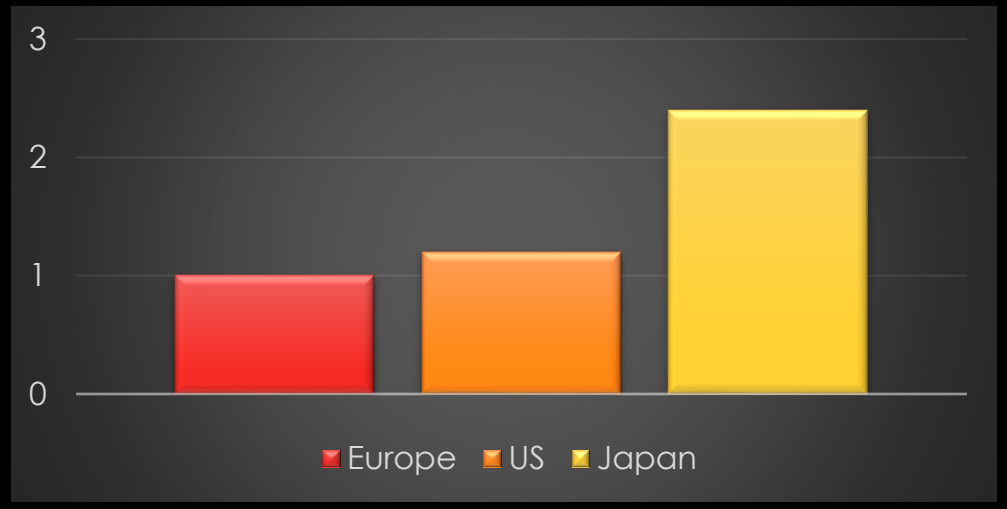
Notification

- This presentation includes the content of the individual's opinion and is not representative of the company.

Cost issue of pre-market studies in Japan

- Difference b/w Japan and US

Cost of clinical trial (per pts)



出典：治験の国際化シンポジウム

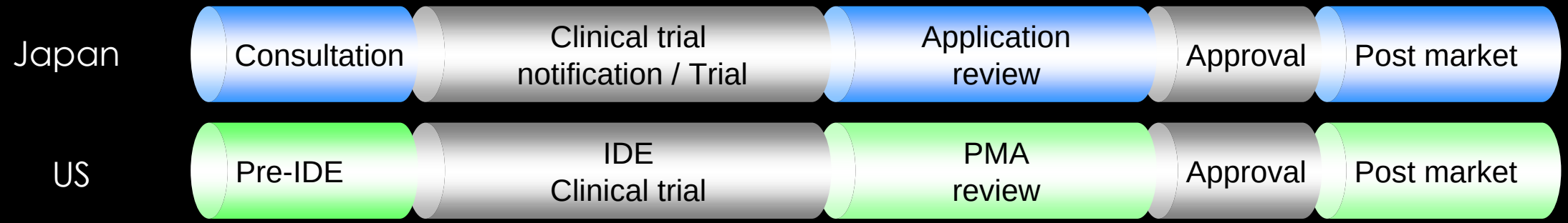
Deviation rate

- US: 0.5～5% on items
- Japan: 0.01～0.1% on items
  - Based on our experience

✓ Quality and enrollment rate are excellent in Japan, but "Japan passing" occurs due to expensive cost…

Development process

- No difference b/w Japan and US on regulation (text base)



What's "actual" difference?→actual process/operation

what industries really feel

US

Class III products (PMA)	Bimo audit
Class II products (510(k)	*Pick up audit for class II?*

- Mainly focus on system integrity
- Accuracy may not be important if there is no big impact on endpoints
- May accept even if there are some limitation at audit

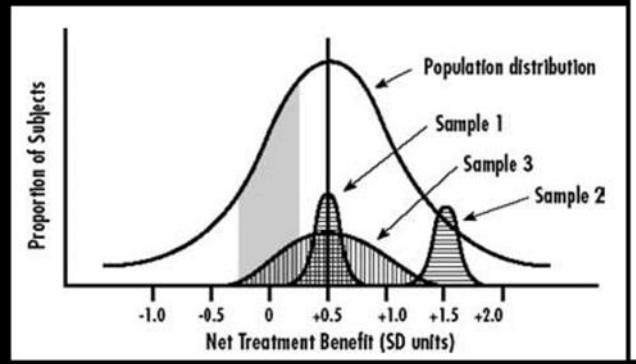
Japan

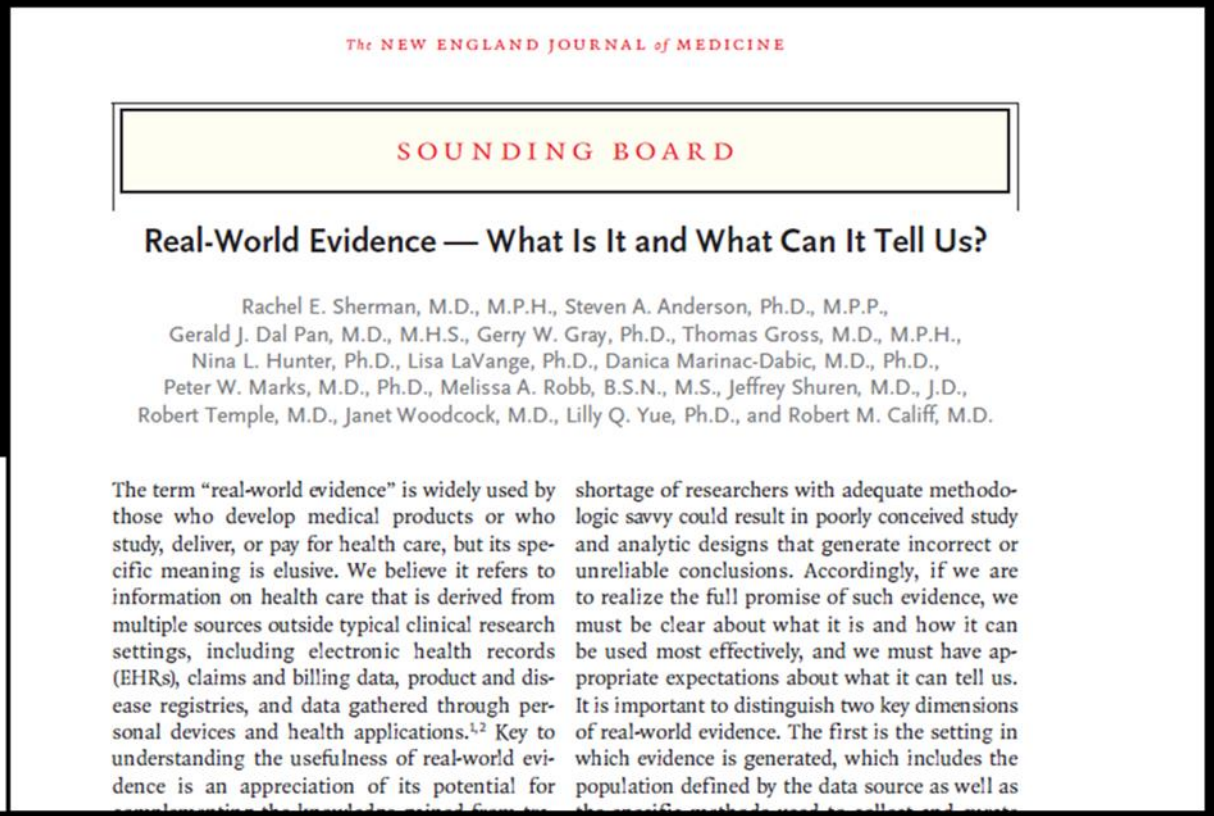
Class IV products	Same level of GCP audit
Class III products	

- Mainly focus on accuracy (requires strict accuracy)
- Confirm the system based on precedent principle
- Requires free-access to all original documents at all sites

What's RWE

- "Limitation of Chiken" for application
  - Pros.
    - controlled
    - high level evidence
  - Cons.
    - limited population
    - high cost





The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

Real-World Evidence — What Is It and What Can It Tell Us?

Rachel E. Sherman, M.D., M.P.H., Steven A. Anderson, Ph.D., M.P.P., Gerald J. Dal Pan, M.D., M.H.S., Gerry W. Gray, Ph.D., Thomas Gross, M.D., M.P.H., Nina L. Hunter, Ph.D., Lisa LaVange, Ph.D., Danica Marinac-Dabic, M.D., Ph.D., Peter W. Marks, M.D., Ph.D., Melissa A. Robb, B.S.N., M.S., Jeffrey Shuren, M.D., J.D., Robert Temple, M.D., Janet Woodcock, M.D., Lilly Q. Yue, Ph.D., and Robert M. Califf, M.D.

The term "real-world evidence" is widely used by those who develop medical products or who study, deliver, or pay for health care, but its specific meaning is elusive. We believe it refers to information on health care that is derived from multiple sources outside typical clinical research settings, including electronic health records (EHRs), claims and billing data, product and disease registries, and data gathered through personal devices and health applications.[1,2] Key to understanding the usefulness of real-world evidence is an appreciation of its potential for

shortage of researchers with adequate methodologic savvy could result in poorly conceived study and analytic designs that generate incorrect or unreliable conclusions. Accordingly, if we are to realize the full promise of such evidence, we must be clear about what it is and how it can be used most effectively, and we must have appropriate expectations about what it can tell us. It is important to distinguish two key dimensions of real-world evidence. The first is the setting in which evidence is generated, which includes the population defined by the data source as well as

"Real world data" is useful to collect data in the actual medical field

Kravitz RL et al, Milbank Q. 2:661-87(2004), Sherman RE et al, NEJM375:2293-97(2016)

Expectations for RWE from Industry

- As a control (PG) for next-generation development
- As an alternative to PMS
- As data for indication expansion
- Alternative for cases where pre-marketing studies are difficult
- Reduce scale (sample size) of clinical trials considering combination with pre/post rebalancing

- **Main target is "to submit new indication"** (including partial change)
  - ●攻めたい「本丸」はここ

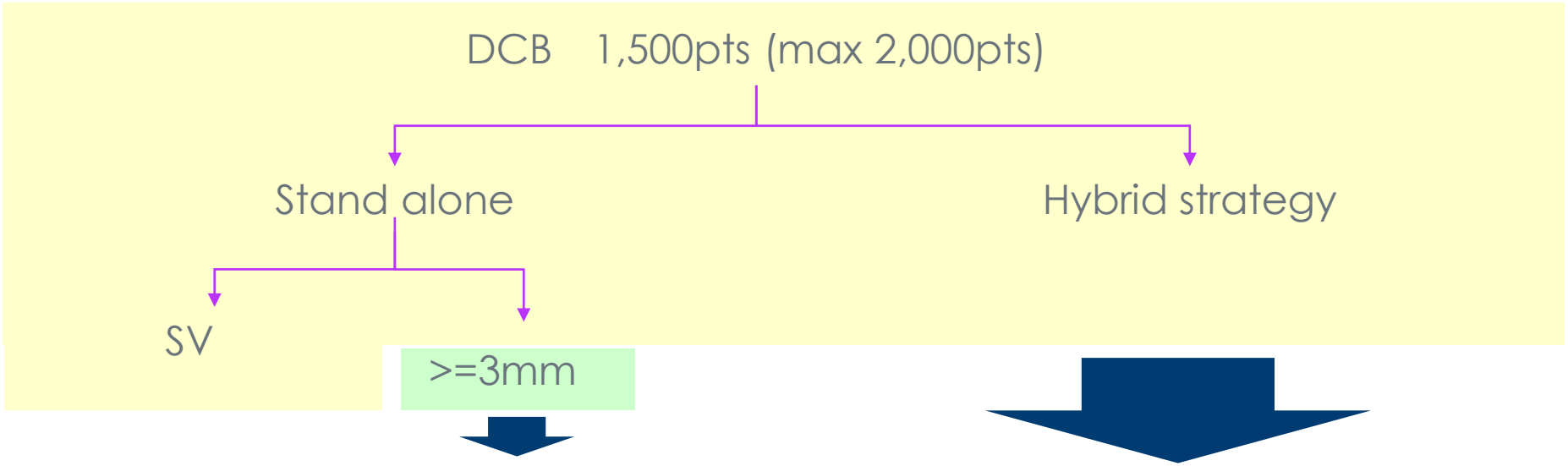
Dilemma in thinking about registry

- As mentioned previously, main target is “whether it can be used for application”
- On the other hand, it is difficult to collect "off-label" data for new application under current strict regulation and guidance
  - Protocol which includes off-label use must be conducted under “Clinical Trials Act”
    - Clinical Trials Act has another difficulties and many people think that it’s simple / better to conduct pre-market study (Chiken)

To construct of the registry in anticipation for partial change submission is inconsistent under current regulation?

Need a change of mindset!!

ALLIANCE registry



To utilize for application Expansion

To check/confirmation of DCB status in real world treatment and update guidance

Expected results

1. Contribute to the development of treatment in Japan by confirming current status of DCB usage and updating treatment guidelines
2. Promote the use of real-world data by sharing various infrastructures (SOP/WI etc.) obtained through ALLIANCE registry as educational materials for ISRs
3. Provide a part of data to industry to encourage expansion of indication, and Contribute to the proper use of medical devices.

Background of the Realization of the Alliance Registry

- Long history of discussions about real-world evidence between Academia, government and industry
  - Basic consensus: "RWE is important"
  - Input by academia: DCB statement and Consensus document
  - Suggestion by PMDA: input through consultation meeting (clinical evaluation consultations, registry utilization consultations)
  - Input based on industry experience for clinical trials

Demonstrated that industry-government-academia collaboration is necessary to take a new step forward

Quality control of ALLIANCE registry

- Establishment of plan with the following key points
  - Validity of unbiased as RWD
  - Necessary bare minimum of Quality control under clinical research

- Specific idea
  - Create and setting necessary bare minimum level
    - SOP/Wis
    - EDC including validation
    - Monitoring: Balance between cost and quality
  - Avoid case bias by continuous case registration at clinical sites
  - Appropriate consent form for future activities
  - CEC / DSMB
  - Audit: Implementation of audits based on system audits

Issues for future real world registry

- There are additional consideration based on the experience of ALLAIANCE registry
  - Financial consideration: how and who will be able to support academia registry?
  - Detailed preparation can be conducted if application purpose has been inputted in prep phase, but how we can utilize already existing evidence for future application?
  - It should be noted that on-labeling of limited use may not apply in all cases.

The concept of the ALLIANCE registry is one of the good instruction material for us, and it's important to further consider to utilize other cases.

Conclusion

- High expectations for the use of real-world evidence
- It's necessary to consider appropriate reliability assurance in clinical research based on the actual situation in Japan.
- The ALLIANCE registry is a new initiative that aims to collect and utilize real world data to expand indication.
- The knowledge from ALLIANCE registry is one of the good instruction material for us, and it's important to consider father expansion.
- Industry-government-academia collaboration is essential to promote RWE
- Quality consideration b/w Japan and US may be good next topic for HBD.

Thank you for your attention!