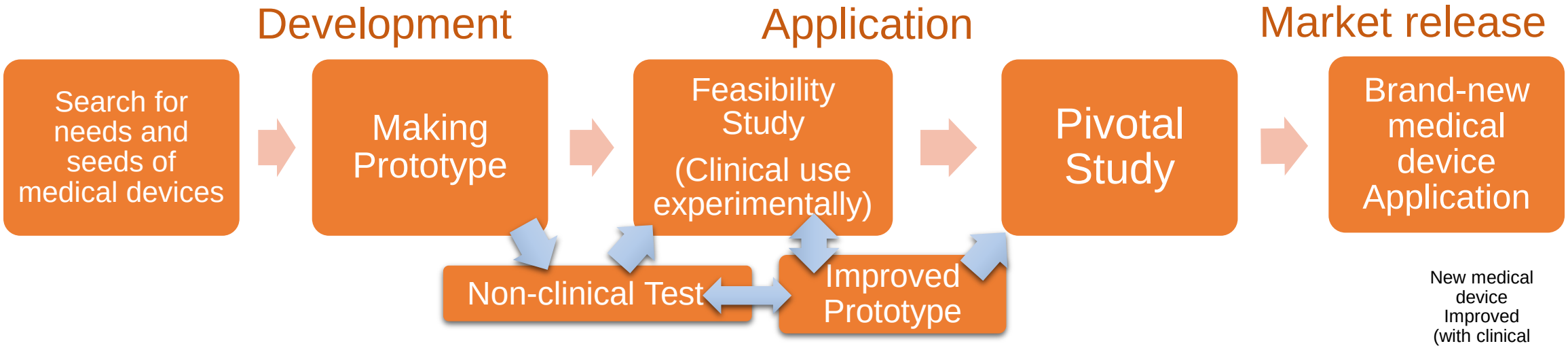
Actions to achieve fast patient access to medical devices

Principal Reviewer, Office of Medical Devices I

Pharmaceuticals and Medical Devices Agency

Moe Ohashi

Flow of Medical Device Development and Review

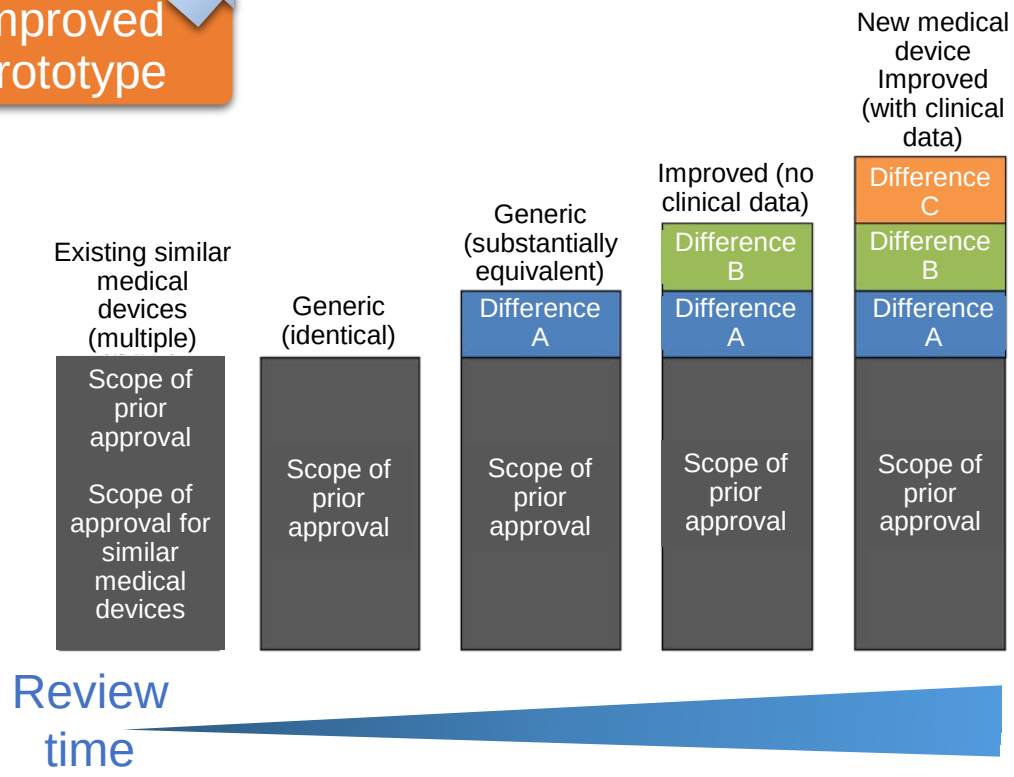


Difference A: **Within the scope of substantial equivalence**

Difference B: **The efficacy and safety are different from those of existing products but can be evaluated by methods other than clinical studies.**

Difference C: **Within the scope where evaluation in a clinical study is required**

→ If the novelty is high, the points of discussion will increase, and a longer review time will be required.



Aiming for Early Patient Access

Until now

Seeking approval for medical devices approved overseas but not in Japan.

+

From now on

Early introduction of innovative technologies with high novelty ahead of other countries

Early access to unmet medical needs for which no treatment is available anywhere in the world

= Early patient access in the true sense

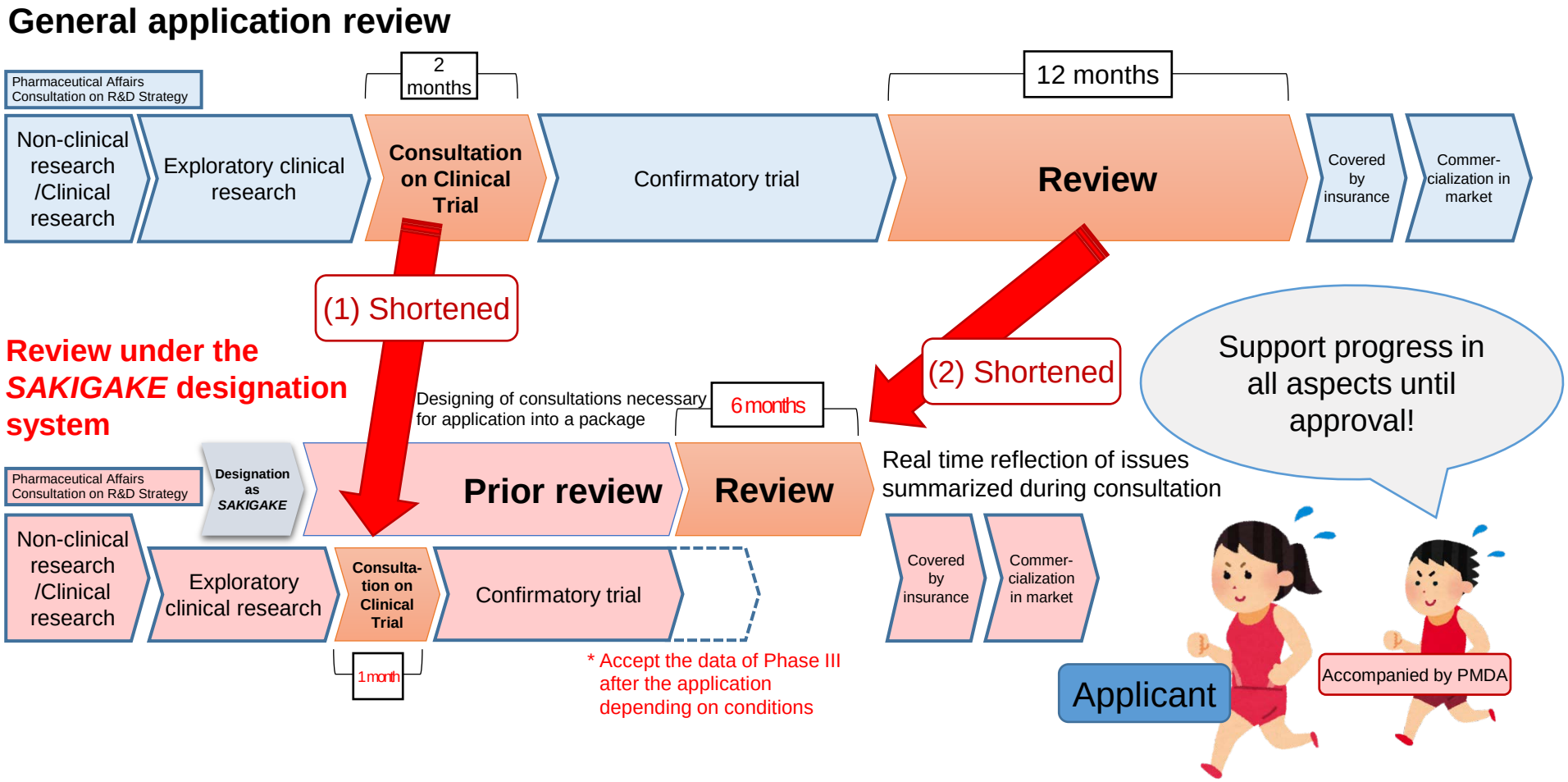
SAKIGAKE Designation System

Based on the "Japan Revitalization Strategy" revised in 2014 (June 24, 2014), the **"*SAKIGAKE* Designation System"** was established **for the designation of medical devices, etc. developed ahead of other countries and expected to have marked efficacy in an early stage of clinical trials to aim for the early practical application with various kinds of support** for the purpose of putting innovative drugs/medical devices/regenerative products into practical use in Japan ahead of other countries.

SAKIGAKE (= *Pioneer*) designation criteria

1. **Innovative medical products**
2. **For serious diseases**
3. **Prominent effectiveness expected on non-clinical and early phase clinical studies**
4. **Development and application in Japan being world's first or simultaneous with other countries**

Flow of Review under the *SAKIGAKE* Designation System



Differences from the Usual Review

Shortening of time to approval

- Review partner system (the PMDA version of concierge)
  - ➢ Designate a dedicated department manager-class staff member as a concierge.
  - ➢ Facilitate smooth development by holding meetings to confirm the progress at each milestone, giving instructions and communicating/coordinating with necessary departments.
- Enhancement of post-marketing safety measures

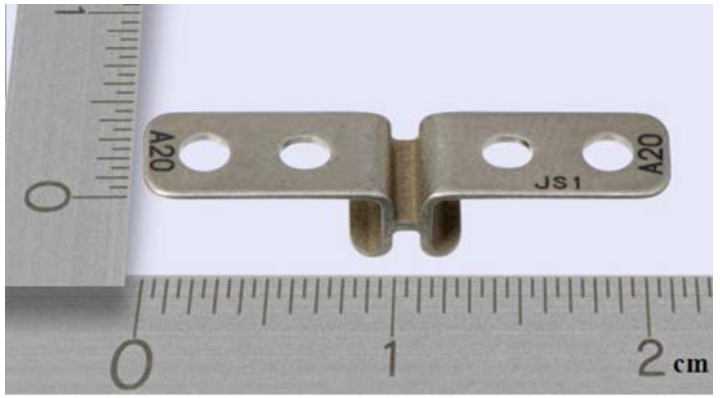
Other efforts to promote development

- Priority consultation (2 months → 1 month)
  - ➢ To be recruited as necessary and implemented in 1 month in effect
- Acceleration of the practical review schedule by improving the prior review
- Priority review (12 months → 6 months)
  - ➢ Preparation for early implementation of review, QMS/GCTP inspection, and GLP/GCP/GPSP compliance assessment

TITANBRIDGE

- Approved product name : TITANBRIDGE
- Approved Marketing Authorization Holder : Nobelpharma Co., Ltd. (Head Office: Chuo-ku, Tokyo)
- Indications : Improvement of symptoms in Adductor spasmodic dysphonia

15th December 2017 Approved*



(Source: https://nobelpark.jp)

*Review Reports:

https://www.pmda.go.jp/english/review-services/reviews/approved-information/devices/0003.html#selectT

Adductor Spasmodic Dysphonia

- A disease in which the vocal cord closes during phonation because the glottal closure muscle (the vocal cord) within the larynx contracts independently of one's own consciousness.

- This is a refractory disease of unknown cause. The patient may have depression, social withdrawal, and suicide attempt due to persistent difficulty in his/her social life.

Existing treatment

Botulinum toxin type A injection

- Invasiveness: Low
- Efficacy: Temporary (3 to 4 months)

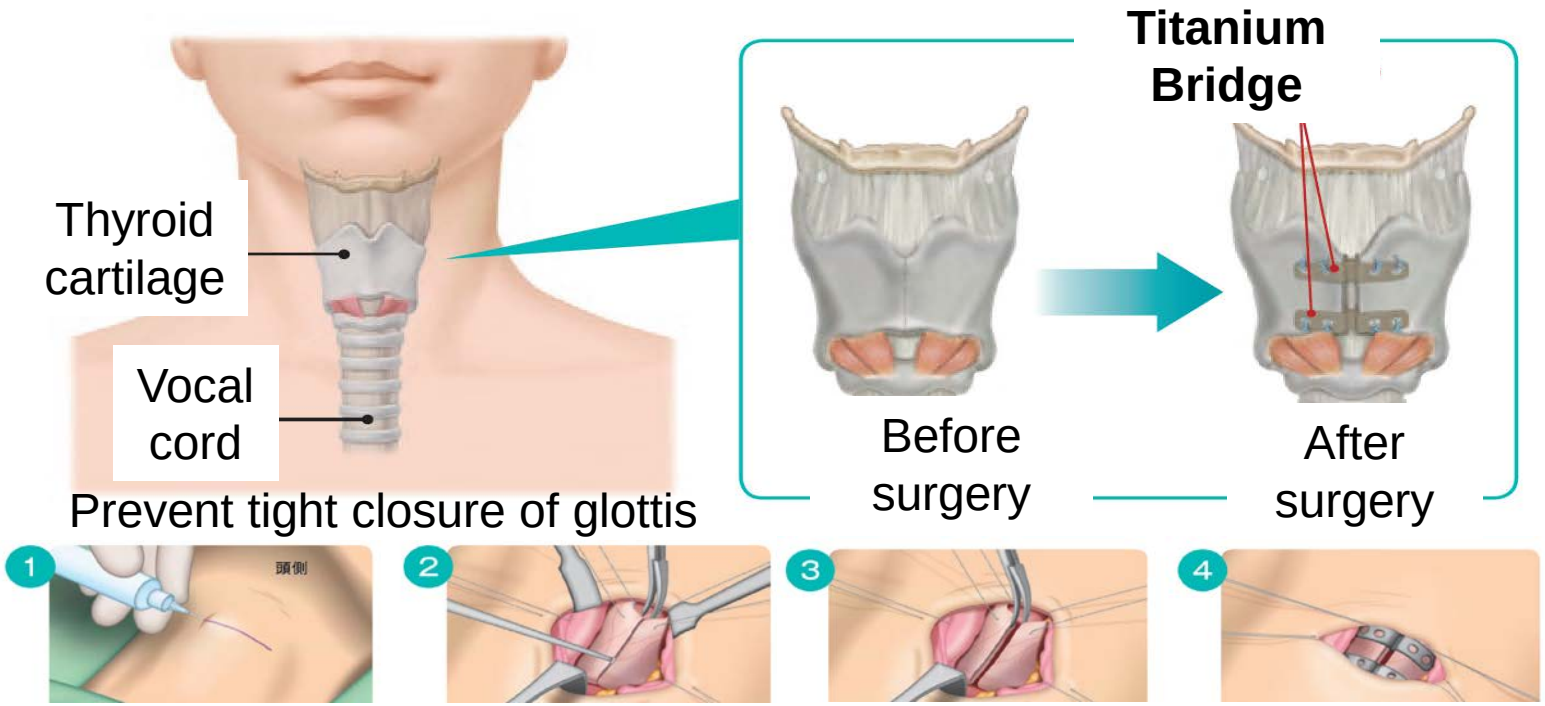
Thyroarytenoid myectomy

- Invasiveness: High (general anesthesia)
- Efficacy: Permanent

Need for new treatment

- Invasiveness: Low
- Efficacy: Permanent

Improvement in the symptoms of adductor spasmodic dysphonia



(Source:https://nobelpark.jp)

SAKIGAKE (= Pioneer) point

Type 2 thyroplasty (treatment with titanium bridge) was developed as a less invasive and permanent treatment.

Use of the *SAKIGAKE* Designation System

1 Consultation on R&D strategy

✓Clinical Trial Design (Endpoint, Number of samples)
✓The justification of using data package for the regulatory application.

2 Protocol consultation for Clinical trial

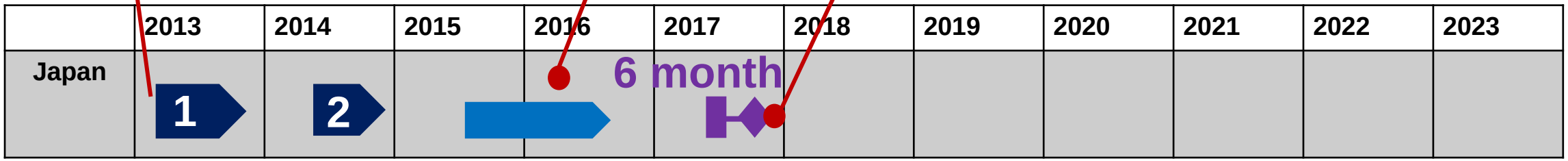
✓The outline of Clinical Trial Design
✓Study design for the mechanical stiffness study

Points of interest

Technology seeds **from universities**

Designation as ***SAKIGAKE*** device

1st approval case of ***SAKIGAKE*** device



Consultation　Clinical study　Application　Approval

Study Summary

Target) Adductor spasmodic dysphonia

Objective) To verify the efficacy and safety of type 2 thyroplasty using a titanium bridge.

Design) Uncontrolled, open-label study

Study institutions) Kumamoto University Hospital, Hokkaido University Hospital, Yokohama City University Hospital, Kyoto University Hospital

Target sample size) 20 patients

Study duration) From informed consent to 52 weeks after surgery

Primary endpoint) Comparison of the difference between pre-operation and at 13 weeks after operation, using Voice Handicap Index (VHI) -10 (degree of awareness of voice impairment)

Secondary endpoints) Speaking function, acoustic analysis, etc.

Safety endpoints) Incidence of adverse events and malfunctions

Study Summary

Efficacy evaluation
● The use of TITANBRIDGE improved VHI-10 scores and showed efficacy. ● The differences in VHI-10 scores in the clinical trial were much greater than the differences in the NHI-10 scores reported in the literature. ● There were two subjects without improvement in VHI-10 score. ● The results of secondary endpoints (e.g., Speaking function and acoustic analysis) showed a trend toward improvement.
Safety evaluation
● No adverse events for which a casual relationship to TITANBRIDGE could not be ruled out or serious adverse events. ● No malfunction occurred. ● Information regarding surgical procedure-related adverse events and procedural precautions have appropriately been included in the package insert.

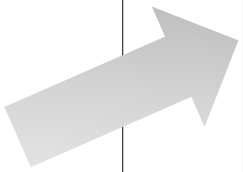
Voice Handicap Index (VHI) and VHI-10

VHI questionnaire

These are statements that many people have used to describe their voices and the effects of their voices on their lives. Circle the response that indicates how frequently you have the same experience in the past 2 weeks.

0 : never, 1 : almost never, 2 : sometimes, 3 : almost always, 4 : always

1. My voice makes it difficult for people to hear me.
2. I run out of air when I talk.
3. People have difficulty understanding me in a noisy room.
4. The sound of my voice varies throughout the day.
5. My family has difficulty hearing me when I call them throughout the house.
6. I use the phone less often than I would like to.
7. I am tense when talking to others because of my voice.
8. I tend to avoid groups of people because of my voice.
9. People seem irritated with my voice.
10. People ask, "What's wrong with your voice?"
11. I speak with friends, neighbors, or relatives less often because of my voice.
12. People ask me to repeat myself when speaking face-to-face.
13. My voice sounds creaky and dry.
14. I feel as though I have to strain to produce voice.
15. I find other people don't understand my voice problem.
16. My voice difficulties restrict my personal and social life.
17. The clarity of my voice is unpredictable.
18. I try to change my voice to sound different.
19. I feel left out of conversations because of my voice.
20. I use a great deal of effort to speak.
21. My voice is worse in the evening.
22. My voice problem causes me to lose income.
23. My voice problem upsets me.
24. I am less outgoing because of my voice problem.
25. My voice makes me feel handicapped.
26. My voice "gives out" on me in the middle of speaking.
27. I feel annoyed when people ask me to repeat.
28. I feel embarrassed when people ask me to repeat.
29. My voice makes me feel incompetent.
30. I am ashamed of my voice problem.



VHI questionnaire

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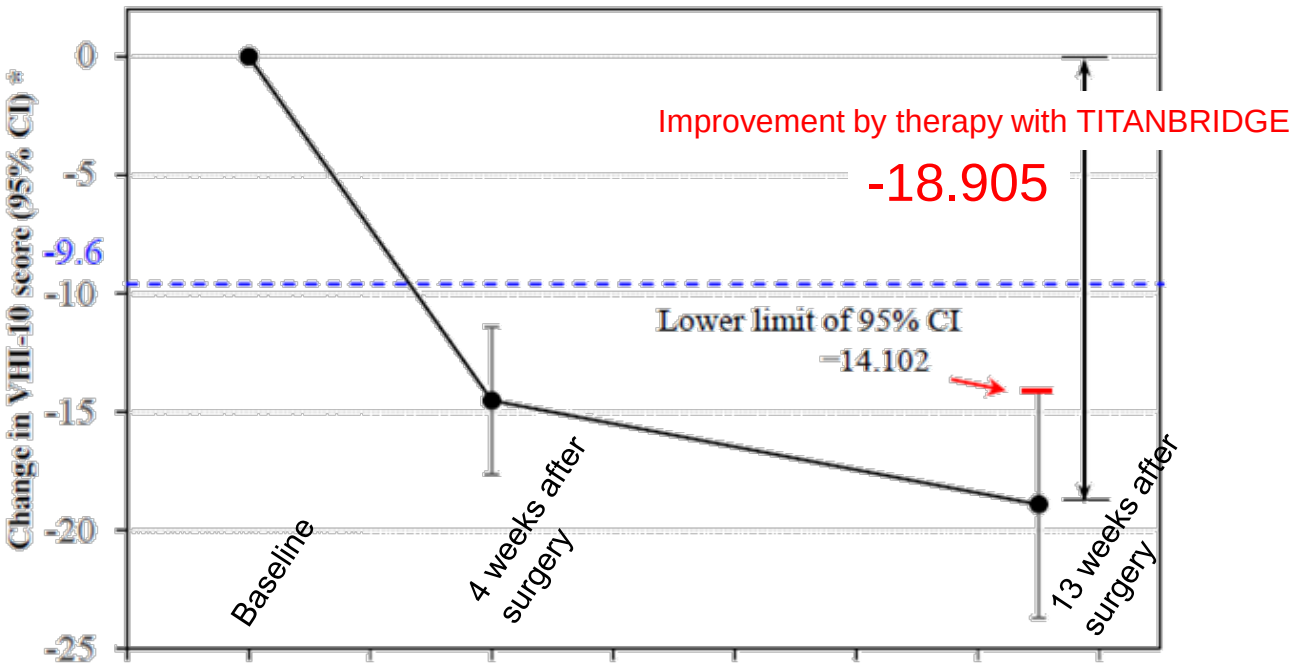
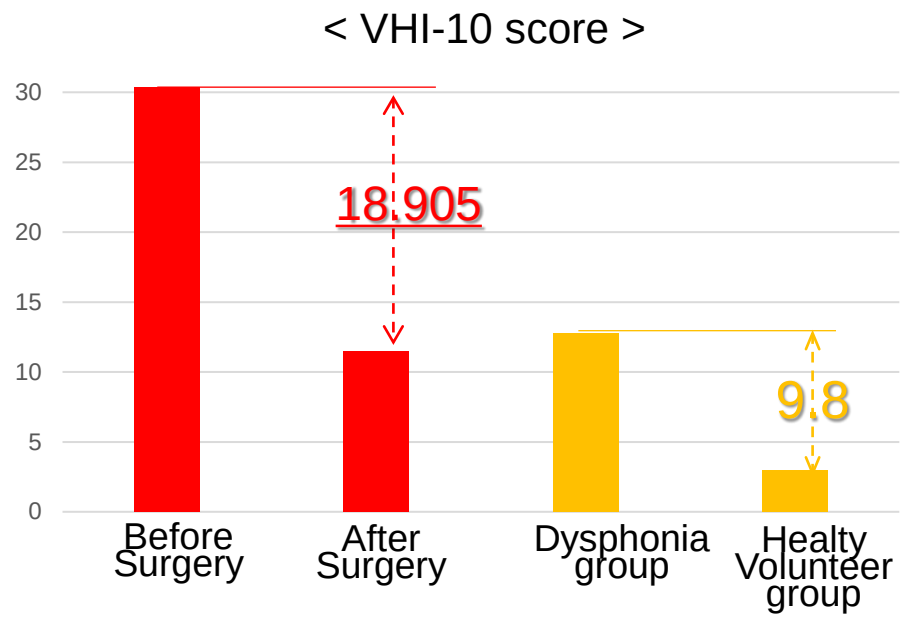
1. My voice makes it difficult for people to hear me.
2. I run out of air when I talk.

- Higher scores indicate greater voice-related handicap.
- VHI is compatible with VHI-10, simpler VHI-10 is more commonly used in clinical practice.
- VHI-10 is accepted internationally as a means to assess patients' perception of severity of their voice disorder.

1. Jacobson B. H. et al., The voice handicap index (VHI): Development and validation.; American Journal of Speech Language Pathology, 6(3), 66-70, 1997.
2. Rosen C. A. et al., Development and validation of the voice handicap index-10.; Laryngoscope, 114, 1549-56, 2004.

Efficacy evaluation

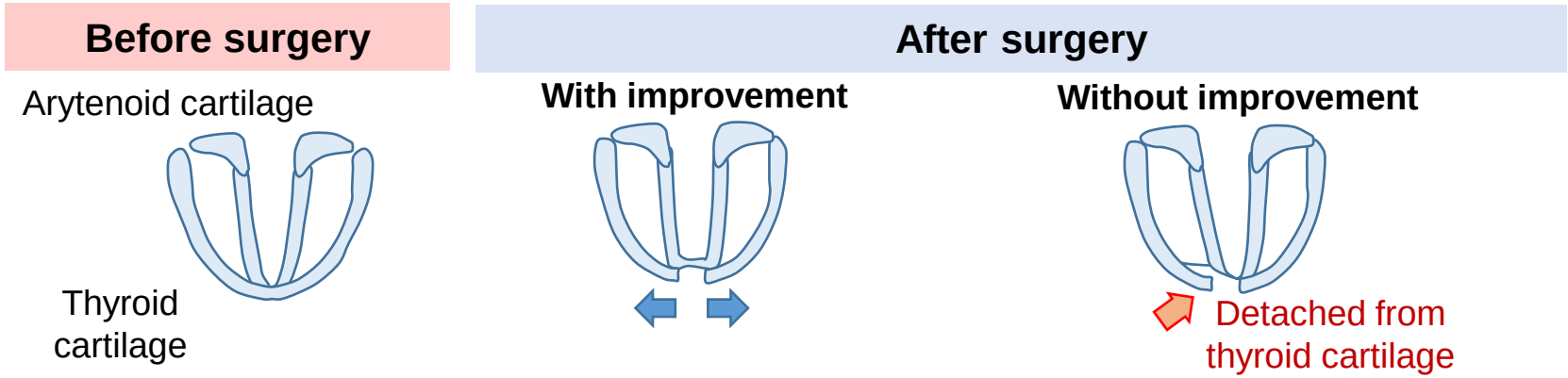




The differences in VHI-10 scores in the clinical trial were much greater than the differences in the NHI-10 scores reported in the literature.

Two subject without improvement in VHI-10 score

Subject number	A		B	
	VHI-10	Change from baseline	VHI-10	Change from baseline
Baseline	32.67	-	25.67	-
4 weeks	32.0	-0.67	22.0	-3.67
13 weeks	29.0	-3.67	20.0	-5.67
26 weeks	28.0	-4.67	23.0	-2.67
52 weeks	32.0	-0.67	29.0	3.33



To ensure the effectiveness of TITANBRIDGE used to keep the split thyroid ala apart, procedural precautions taken when splitting and separating the thyroid ala should be communicated to surgeons more specifically.

Conditions for Approval

Article 79 of the Act

Any permission, accreditation, or approval set forth in this Act may be conditional or time-limited and may be modified.

2. The conditions or time limit set forth in the preceding paragraph shall be limited to the minimum extent necessary to prevent the occurrence of health hazards and shall not impose unreasonable obligations on persons who obtain permission, accreditation or approval.

Conditions for approval of titanium bridge

The applicant is required to take necessary measures such as holding workshops in cooperation with relevant academic societies so that physicians with sufficient knowledge and experience related to type 2 thyroplasty will use this product in compliance with the intended use and the directions for use after acquiring adequate skills on the use of this product and knowledge on adductor spasmodic dysphonia.

Current Overseas Situation of Adductor Spasmodic Dysphonia Treatment

The patients group in US (NSDA)

✓The first-ever patient registry devoted to focal dystonias.
✓Over to **55000 people have registered** from over 60 countries.

NSDA
NATIONAL SPASMODIC DYSPHONIA ASSOCIATION

TITAN BRIDGE is introduced as bellow;

This procedure was developed by Dr. Isshiki and his group around 2000. The concept of this surgery is aiming to smooth the airflow by making the glottal gap wider during phonation. The titanium bridges used in this procedure are manufactured and approved for use in Japan only at the Isshiki Memorial Voice Center. They are not FDA approved and not yet available for use in the United States. ***The NSDA has been working with Nobel Pharma to bring these bridges to the US for a clinical trial for adductor spasmodic dysphonia.***

(Source: https://dysphonia.org/)

Medical devices with high social expectations, which are urgently awaited by patient groups.

English, Thai, French, etc.
Features such as the number of vowels and consonants are different depending on the language.

Expectations for early patient access by conducting global clinical trials

Summary

- The *SAKIGAKE* Designation System is a system for the designation of medical devices developed ahead of other countries and expected to have marked efficacy at an early stage of clinical trials to aim for the early practical application with various kinds of support.
- Through the use of the *SAKIGAKE* Designation System, the efficiency of the entire development can be enhanced. A review can be completed in 6 months at the shortest.
- Global clinical trials and global development may enable early patient access in other countries.