# THE APPLICATION OF INDICATION BASED PRICING TO REGENERATIVE MEDICINE THERAPIES: AN INTERACTIVE WORKSHOP

*DISCUSSION LEADER: DIANA I. BRIXNER, RPH, PHD*

PROFESSOR, DEPARTMENT OF PHARMACOTHERAPY, UNIVERSITY OF UTAH, SALT LAKE CITY, UNITED STATES, DIANA.BRIXNER@UTAH.EDU.

ISPOR
Improving healthcare decisions

# PANELISTS

- Masayuki Yamato, PhD, Professor, Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University, Tokyo, Japan
- Michael Drummond, PhD; Professor, Center for Health Economics, University of York, York, United Kingdom
- Mime Egami, BA, Adjunct Professor, Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, United States; Executive Director, Cell Sheet Tissue Engineering Regenerative Medicine Initiatives, Tokyo, Japan
- Diana Brixner, RPh, PhD, FAMCP, Executive Director, Pharmacotherapy Outcomes Research Center; Professor, College of Pharmacy, University of Utah, Salt Lake City, United States

# PRESENTATION OVERVIEW

- Understand production, treatment and evidence generation for regenerative therapy (Yamoto)
- Pricing challenges in regenerative medicine under newly established Regenerative Medicine Promotion Act in Japan (Egami)
- Describe how indication pricing has been used in other disease areas and indications (Drummond)
- Discuss the application of indication based pricing to the application of regenerative medicine in the heart and knee. (Panel)

# MEETING THE NEEDS[1]

- Value-engineered translation of regenerative therapies is necessary to set regulatory frameworks, policy, and tie investment decisions to value-based criteria of health systems.
- Attention needs to be paid to applying novel economic modeling methods to better inform investment decisions.



1. Bubela T, McCabe C *et al*. Value-Engineered Translation for Regenerative Medicine: Meeting the Needs of Health Systems. Stem cells and development. 2013, 22: 1.

# THE FUTURE FOR REGULATION AND REIMBURSEMENT[1]

- Therapies that receive conditional approval are eligible for reimbursement by the Japanese health system, but Japan's universal health insurance system requires up to 30% copayment from patients depending on age and type of condition (unpublished observations).

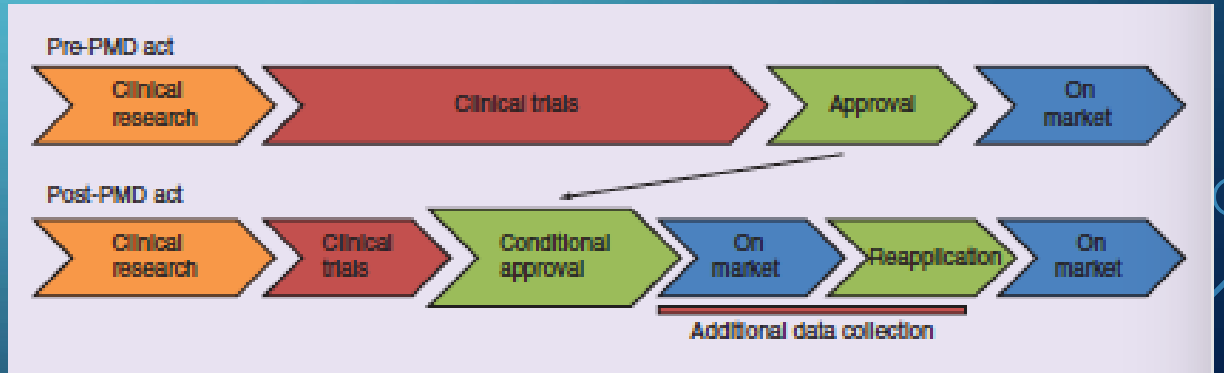



**Figure 2. Market access in Japan before and after the Pharmaceutical and Medical Device Act.** The conditional approval of the PMD act allows for market access in Japan earlier in product development [81].
PMD: Pharmaceutical and medical device.

1. Bubela T, McCabe C, Archibald P, Atkins H, Bradshaw, SE *et al.* Bringing regenerative medicines to the clinic: the future for regulation and reimbursement. Regenerative medicine. 2015, 10: 7.

# THE FUTURE FOR REGULATION AND REIMBURSEMENT[1] CONT'D

- The scheme transfers the economic and health risks of experimental regenerative medicine technologies to the Japanese health system.
- The scheme may negatively impact the ability to collect meaningful efficacy data for final regulatory and reimbursement decisions, because patients with access to therapies have no incentive to enroll in well-designed clinical.
- Conditional licensing and reimbursement regimes are being discussed cautiously on both sides of the Atlantic.



1. Bubela T, McCabe C, Archibald P, Atkins H, Bradshaw, SE *et al*. Bringing regenerative medicines to the clinic: the future for regulation and reimbursement. Regenerative medicine. 2015, 10: 7.

# PRODUCTION, TREATMENT AND EVIDENCE GENERATION FOR REGENERATIVE MEDICINE

*MASAYUKI YAMATO, PHD;*

PROFESSOR, INSTITUTE OF ADVANCED BIOMEDICAL ENGINEERING AND SCIENCE, TOKYO WOMEN'S MEDICAL UNIVERSITY, TOKYO, JAPAN, YAMATO.MASAYUKI@TWMU.AC.JP.

ISPOR
Improving healthcare decisions

# REGULATORY APPROVAL AND NHI PRICING OF REGENERATIVE MEDICINE PRODUCTS IN JAPAN

**Mime Egami, BA**;

ADJUNCT PROFESSOR, DEPARTMENT OF PHARMACEUTICS AND PHARMACEUTICAL CHEMISTRY, UNIVERSITY OF UTAH, SALT LAKE CITY, UNITED STATES / EXECUTIVE DIRECTOR, CELL SHEET TISSUE ENGINEERING REGENERATIVE MEDICINE INITIATIVES, TOKYO, JAPAN MIME.EGAMI@UTAH.EDU.



ISPOR
Improving healthcare decisions

# REGENERATIVE MEDICINE PRODUCT IN JAPAN UNDER PHARMACEUTICALS AND MEDICAL DEVICES ACT (PMD ACT)

◆ New category " Regenerative Medicine Products"

New category is created to regulate Regenerative Medicine Product (incl. gene therapy products), while reimbursement system does not reflect this change – Pricing committee of either drug or medical device is appointed by each **regulatory profile (major mode of action).**

◆ Expedited approval system and provisional reimbursement pricing

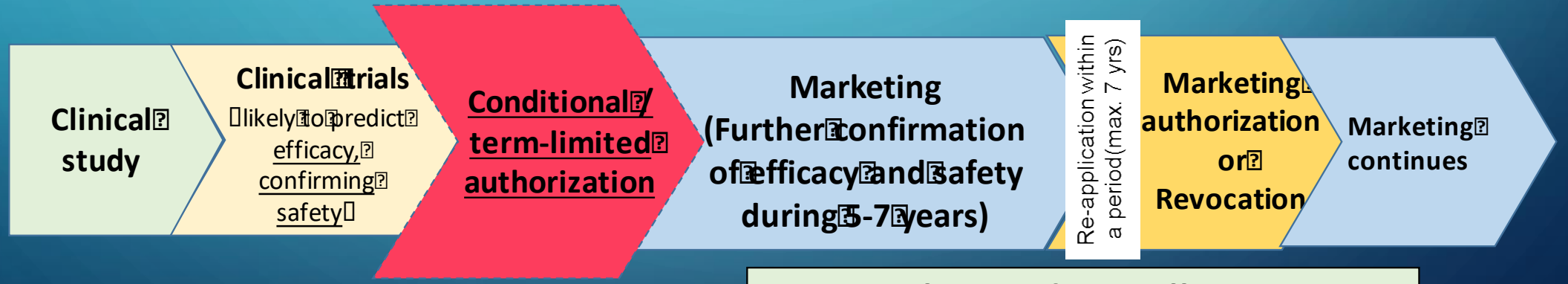
After the safety is confirmed by small size clinical trial and its efficacy is scientifically predicted, conditional and term-limited (provisional) marketing authorization (5-7 years) with reimbursement is provided for timely access to the patients (full outcome report is required )

Regenerative Medicine product will be re-approved after provisional period with the updated reimbursement price

# EXPEDITED APPROVAL SYSTEM UNDER PMD ACT

**[Conventional approval process before PMD Act]**


**[Current regulatory scheme for regenerative medicine products under PMD Act]**




**Post-marketing data collection is required for safety and efficacy**

# BASIC STRUCTURE OF NHI PRICING IN JAPAN

- Newly listed (approved) NHI drug prices are investigated by specific committee and officially determined by Chuikyo.

  - "Comparative Method" for new drugs/devices that have listed product(s) in the comparative category
    - NHI pricing will be;

    Current comparative NHI price + "premium"

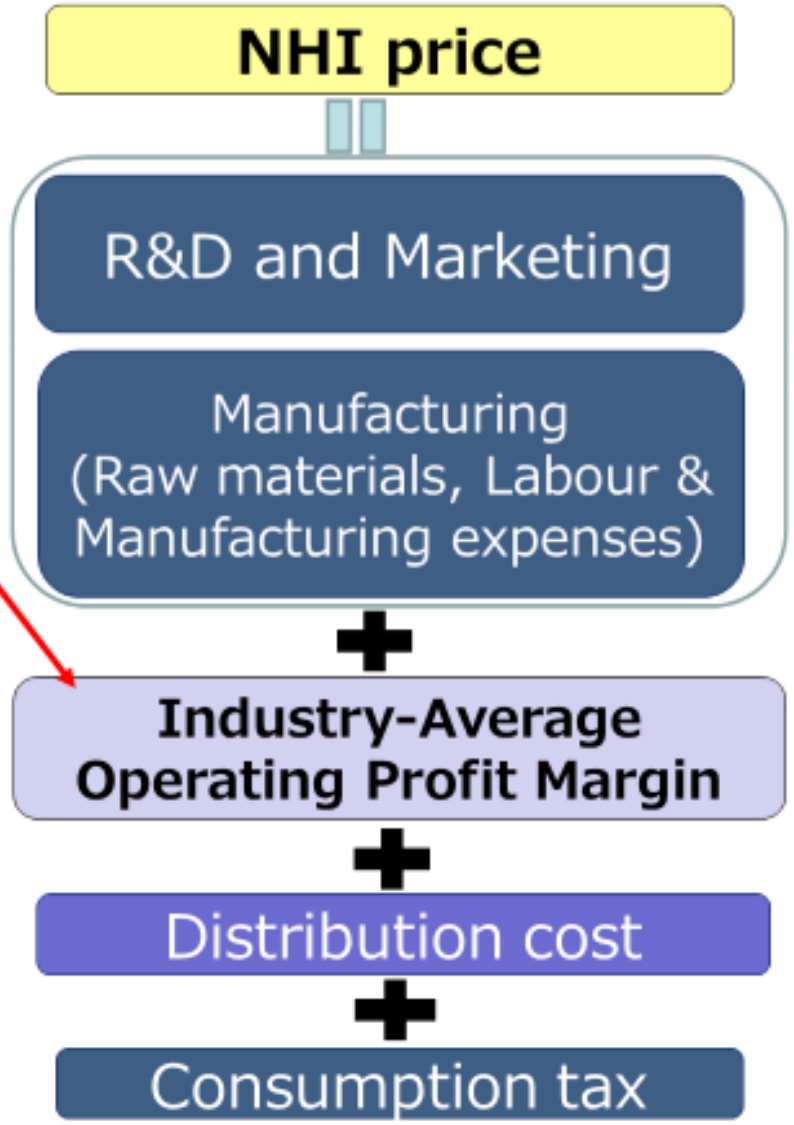
  - "Cost Calculation Method" for innovative drugs/ devices with no comparative products on the list
    - NHI price is determined by cost data provided by company and industry average margin (incl. orphan)

# "COST CALCULATION METHOD"

- Sum of product costs & margins

Price adjustment is applied to the profit as "premium", depending on novelty, efficacy & safety, versus existing standard treatment; this premium assessment is judged by "clinical trial" data

Premium evaluation for RM product is not feasible as small trial case to judge efficacy, impact of training period for physicians until standard therapy (technology) is established.



# GMP MANUFACTURING COST AND SCALE-UP ANALYSIS FOR CELL-BASED THERAPIES

Scale-Up and Manufacturing of Cell-Based Therapies IV
January 18-22, 2015

## A LIFE CYCLE COST ASSESSMENT OF THE CELL PRODUCTION FOR CLINICAL ORGANIZATIONS IN JAPAN

**Takuro KAMIYA[1], Manabu MIZUTANI[2], Mime EGAMI[3], Teruo OKANO[3], and Masahiro KINO-OKA[2]**

[1]Waseda University Academic Solutions Corporation, 5 Babashita-cho, Shinjyuku-ku, Tokyo, Japan
[2]Division of Science and Biotechnology, Graduate School of Engineering, Osaka University, Japan
[3]Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University, Japan

### Introduction

The Japanese Diet approved an amended law under Pharmaceutical Affairs Law (PAL) for regenerative medicine and a new law under Act on Safety of Regenerative Medicine (ASRM) in 2013. They were enforced on 25 November 2014. Noteworthy, under ASRM, companies can be consigned to operate the cell processing work from hospitals or medical institutes. Due to the entry of Industry in this field, promotion of a novel treatment in regenerative medicine is expected.

We investigated reality of the current practices to assess potentials of commercialization and industrialization by comparing the manufacturing costs between PAL and ASRM. Here, we mainly deal with the Life Cycle Costs (LCC) under ASRM.

### Method

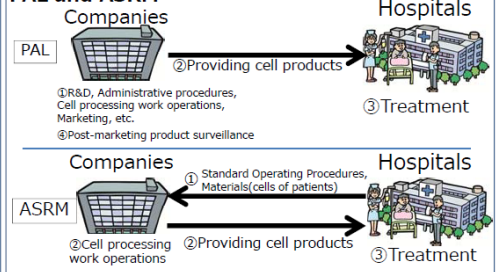
Life Cycle Costing refers to "the process of economic analysis to assess the total cost of acquisition, ownership and disposal of a product".*(IEC 60300-3-3)*

In this investigation, we calculated the LCC of the autologous cell production model for clinical organizations by using the given data on initial and running costs of the cell processing facilities (CPFs) that have clean rooms with safety cabinets.

In addition, we calculated administrative and financial costs of a company that accepts cell processing work operations from hospitals or medical institutes by benchmarking an existing office and financial services.

We compiled all these costs mentioned above in the income statement format.

### Fig.1 : Difference of business models under PAL and ASRM

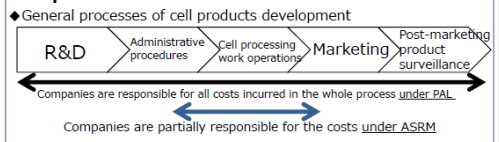



This figure shows difference of business models under PAL and ASRM. Under PAL, companies are responsible for R&D, administrative procedures, processing, and marketing related to cell products.

Under ASRM, companies follow relevant SOPs to receive Materials from hospitals and manufacture cell products. Doctors are responsible for their treatment by using cell products.

Medical expenses incurred under PAL are covered by public health insurance but the ones under ASRM are not.

### Fig.2 : Difference of cost range for companies under PAL and ASRM




This figure shows difference of cost range for companies between under PAL and ASRM. Under PAL, companies have to bear the costs in the all cell products development processes. Under ASRM, companies have to mainly bear the costs in the cell processing work operations.

### Table.1 : Result

This table shows two sets of test calculation based on the model we have proposed for cost assessment of cell production.
- Accumulated LCC from 10years operation
- The number of cell products processed per year : 60 cell products or 500 cell products

(Unit: US dollars in thousands)

| ◆Life Cycle Costs | 60/year | 500/year |
|---|---|---|
| Total Running costs | 17,496 | 81,566 |
| Total Initial costs | 1,793 | 6,566 |
| Life Cycle Costs | 19,289 | 88,132 |
| Life Cycle Costs per one product | 40 | 22 |
| ◆Running costs | 60/year | 500/year |
| Manufacturing cost | 9,994 | 48,415 |
| Selling, G&A Expenses | 7,217 | 32,044 |
| Other loss | 284 | 1,106 |
| Total | 17,496 | 81,566 |
| ◆Initial costs | 60/year | 500/year |
| Land acquisition Expenses | 343 | 1,716 |
| Facilities Expenses | 1,000 | 3,400 |
| Machines Expenses | 450 | 1,450 |
| Total | 1,793 | 6,566 |

### Conclusion

In this investigation, we constructed a prototype model for cost assessment of the cell production for clinical organizations in Japan. By Using this model, companies will be able to easily assess their feasibility of regenerative medicine in Japan.

We will improve this model for the companies to assess their business feasibility regardless of the country and region of the production, types of treatment, number of cell products processed and manufacturing processes.

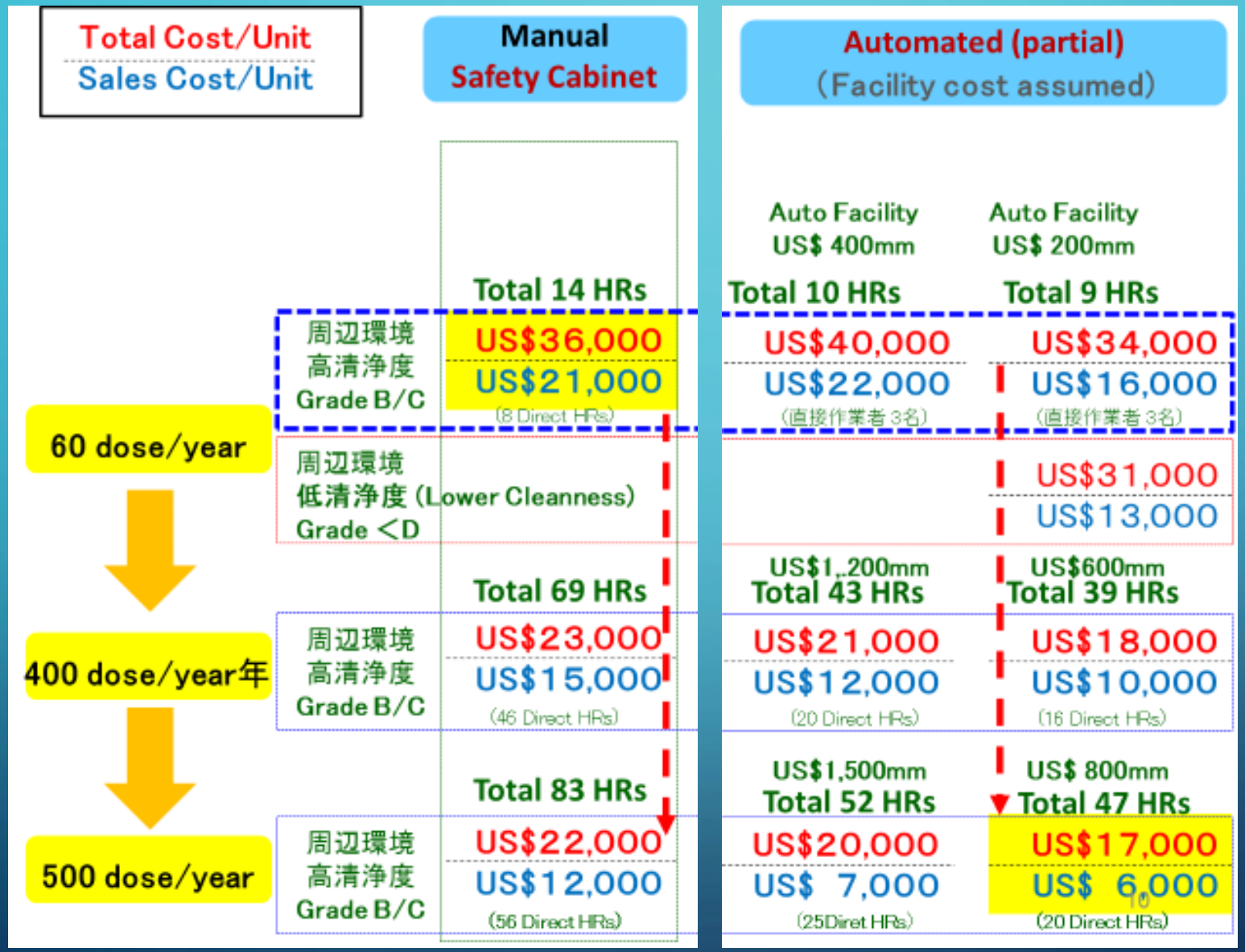
We will contribute to development of regenerative medicine industry not only in Japan, but also around the world to save many patients who suffer from incurable diseases under conventional treatments.

**Acknowledgment :** This research is funded by grants from Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST), and New Energy and Industrial Technology Development Organization (NEDO), grant number P14006.



**If constant large scale production is available for 10 years, GMP man. Cost of cell-sheet may be reduced from $40,000(60/yr) to $22,000(500/yr).**

# ACADEMIC SURVEY: GMP CELL CULTURE COST SIMULATION






Manual or Partial automation cannot realize scale merit. ( as a sample case, 3 week culture is assumed)
Data provided by FIRST project at Tokyo Women's Medical University TWIns

# REGENERATIVE MEDICINE PRODUCT LAUNCHED AND INSURED IN JAPAN BY NOW

| Brand Name | Type | Company | Listing date (regulatory approval date) |
|---|---|---|---|
| JACE | Autologous Cultured Epidermis cell (sheet) | Japan Tissue Engineering Co. | Jan.2009 (Oct.2007) |
| JACC | Autologous Cultured Chondrocyte cells in Atelocollagen | Japan Tissue Engineering Co. | Apr.2013 (Jul.2012) |
| Heart Sheet | Autologous Skeletal Myoblast Sheets | Terumo Co. | Nov.2015 (Sep.2015) |
| TEMCELL HS | Mesenchymal Stem cells for GVHD (allogeneic) | JCR Pharmaceuticals | Nov.2015 (Sep.2015) |

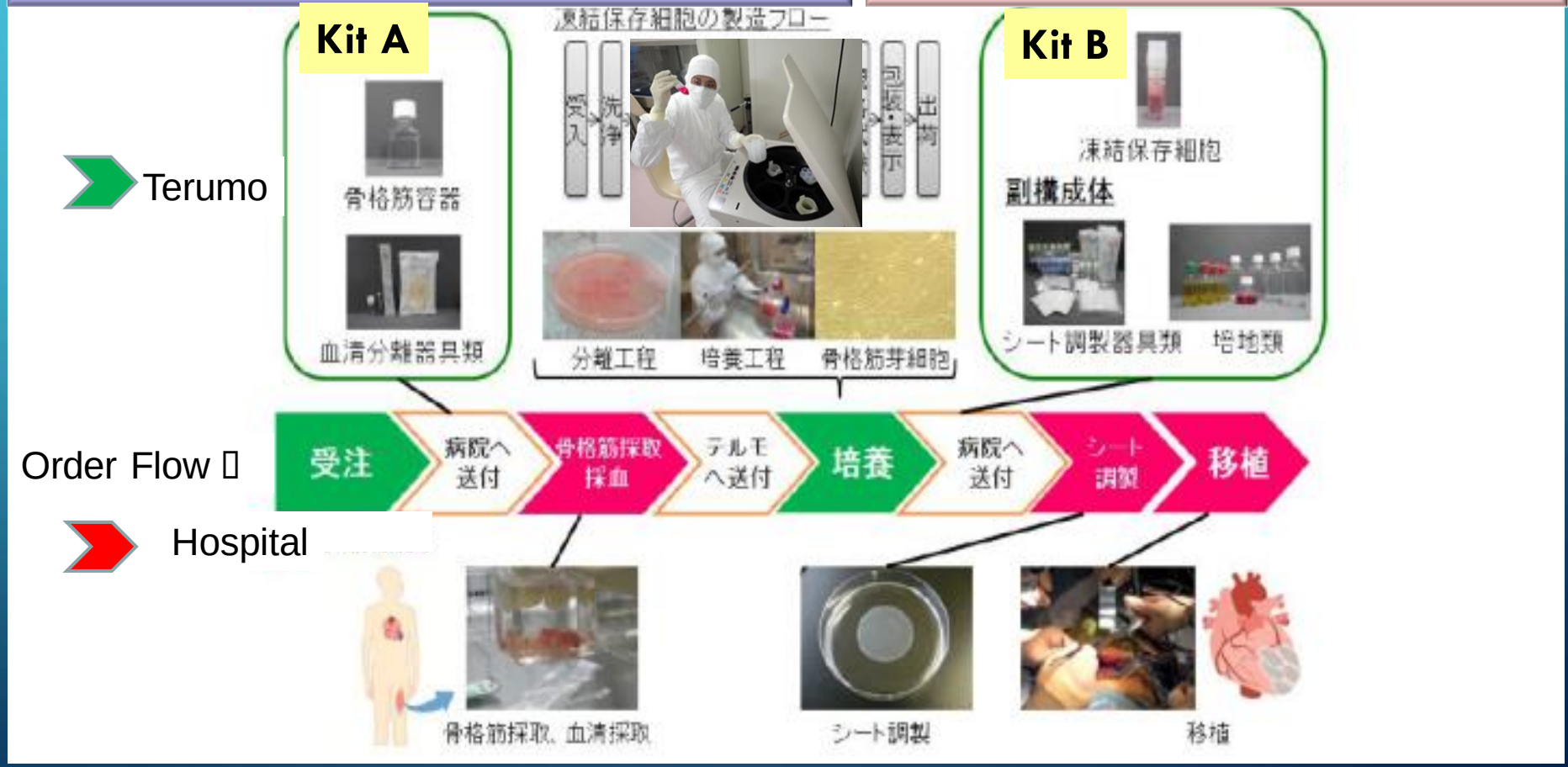


Time lag between regulatory approval and listing is significantly improved

# HEART SHEET PRODUCT OUTLINE

**Kit A: for biopsy of skeletal myoblast tissue and serum at hospital, send back to Terumo to subculture and expand**

**Kit B: ship frozen cell to hospital**
**+ cell sheet preparation kit**
**+ culture media pack per sheet**



# NHI: ORIGINAL REIMBURSEMENT PRICING

| Brand Name | NHI Price<br>A kit: Biopsy/Culture<br>B kit: Man./Transplant. | Pricing method | Profit Margin<br>Industry average |
|---|---|---|---|
| JACE | ¥ 306,000 per sheet<br>2016/4 pricing revised | Not Announced | |
| JACC | ¥ 2,080,000<br>2016/4 pricing revised | Cost Calculation Method | 5.8%<br>(Medical device) |
| Heart Sheet (Cond. A) | A kit ¥ 6,360,000<br>B Kit ¥ 1,680,000 | Cost Calculation Method | 5.8%<br>(Medical device industry margit) |
| TEMCELL HS | ¥868,680 per bag (10.8ml) | Cost Calculation Method | 15.9%<br>(Pharmaceutical industry margin) |



"Heart Sheet" is under expedited approval , while other 3 products received full approval .

# NHI: REVISED REIMBURSEMENT PRICING

| Brand Name | NHI current price<br>A kit: Biopsy/Culture<br>B kit: Man./Transp. | Comparison to Original Pricing | Budget Impact per treatment |
|---|---|---|---|
| JACE | A kit ¥ 4,380,000<br>B kit ¥ 151,000 ps<br>¥10,420,000(40sts) | ¥ 306,000 x<br>max. 40 sheets<br>¥ 12,240,000 | 25→200+hospital<br>20→40 sheets<br><br>△ ¥1,820,000 |
| JACC | A kit ¥ 879,000<br>B kit ¥ 1,250,000<br>¥ 2,190,000 | ¥ 2,080,000<br>per treatment | 240+ hospital<br><br>+ ¥49,000 |
| Heart Sheet | A kit ¥ 6,360,000<br>B kit ¥ 1,680,000ps<br>¥14,760,000( 5sts) | No change | |
| In case of autologous RM, reimbursement by the process is becoming standard pricing. | | | |

# ISSUES ON NHI SYSTEM FOR RM PRODUCTS

- Japan applies its own HTA by Government, not QALY/ICER.
- All approved drugs are "automatically" covered and reimbursed by NHI system. "Budget Impact" is the top consideration point.
  - No "Threshold" argument even on "mediocre" products
  - Conditions of 1)Regulatory + 2) Reimbursement = modified budget impact acceptable for NHI system.
  - Companies hesitate to touch other than NHI pricing.
- Weak information asymmetry between "NHI pricing" and "Outcome evaluation" , previous PMS data was mainly for safety issue.

# HTA CHALLENGE FOR UPCOMING RM PRODUCTS

- What is the transparent pricing to encourage patient and industry for "Initial pricing" (CCM now) and "Repricing" (outcome data based ? Up/Down ? Budget impact ?)
  - How to reflect "established values" into Repricing ?
    - Value by physician's view point (clinical benefit/cure)
    - Value by patients' viewpoint (Improved QOL)
    - Composed Value for society (innovation appreciation and decrease in social costs)
- When global convergence and communication available ?
  - How to link with global debate on "indication-based pricing" or "differential pricing" ?
- Shall we make special evaluation if RM provides cure treatment ?

# IS INDICATION-BASED PRICING AN OPTION FOR REGENERATIVE MEDICINE THERAPIES?

*MICHAEL DRUMMOND, PHD*

PROFESSOR, CENTER FOR HEALTH ECONOMICS, UNIVERSITY OF YORK, YORK, UNITED KINGDOM, MIKE.DRUMMOND@YORK.AC.UK.

ISPOR
Improving healthcare decisions

CHE
Centre For Health Economics

THE UNIVERSITY of York

# VARIATION IN COST-EFFECTIVENESS BY INDICATION – BEVACIZUMAB

| *NICE Technology Appraisal* | *Indication* | *ICER (£/Quality-adjusted life-year)* |
|---|---|---|
| TA118 (Jan 2012) | Metastatic colorectal cancer | 60,430-88,400 |
| TA263 (Aug 2012) | First-line metastatic breast cancer | 82,000-182,000 |
| TA284 (May 2013) | First-line advanced ovarian cancer | 128,000-161,000 |

# VALUE-BASED PRICING BY INDICATION

- A number of countries in Europe based the price of a drug on its 'added value', either based on a clinical assessment or an assessment of the QALYs gained
- In the UK, 'patient access schemes', involving confidential discounts, are often negotiated to ensure that a drug meets NICE's value for money criterion in a particular indication
- However, the implications for these discounts when a drug has multiple indications is not clear
- In Italy, separate registries are created by indication, and sometimes by line of therapy, to support pricing agreements



Mestre-Ferrandiz *et al* (2015) Office of Health Economics Seminar Briefing 18, London, OHE. www.ohe.org.uk

# NICE SIMULATED TECHNOLOGY APPRAISAL OF CAR-T

- Main objective was to explore the methodological issues in undertaking appraisals of regenerative therapies
- An exploratory study estimated the costs and effects (QALYs) of CAR-T (in relapsed or refractory B-cell acute lymphoblastic leukaemia in children and young adults), as compared with current care.
- Two indications assessed: bridge to hematopoietic stem cell transplantation; curative intent
- Large amount of uncertainty in all estimations, based on current level of knowledge
- An Expert Panel with a strong understanding of NICE Technology Appraisals was then convened to discuss a range of scenarios for price discounts and payment models

# BENEFITS AND COSTS OF CAR-T IN THE TWO INDICATIONS

| | ***Bridge to HSCT*** | ***Curative Intent*** |
|---|---|---|
| Assumed incremental QALY gain per patient | 7.46 | 10.07 |
| Assumed price (acquisition cost) to be close to NICE's threshold for end-of-life therapies | £356,100 | £528,600 |

# EXPERT PANEL REACTIONS TO DIFFERENT PRICING ARRANGEMENTS

| ***Scenario*** | ***Expert Panel 'Decision'*** |
|---|---|
| One-off acquisition cost | Reject |
| One-off acquisition cost with 20% discount | Borderline |
| Lifetime leasing (£2,756 per month) | Reject |
| Payment for patients with remission only (approx. reduction of 35% in average cost) | Accept |

# CHALLENGES IN IMPLEMENTING INDICATION-BASED PRICING

- Flume et al identify barriers in terms of legal feasibility, data collection, billing arrangements and other factors in 6 European countries
- Tracking the number of patients treated in each indication can be difficult in some settings
- The need to maintain a single published price (per unit) of the drug implies the use of differential rebates by indication
- Understanding the nature of the rebates given and to whom (eg the treatment center, the health ministry/insurer, the general government budget) is important for giving appropriate incentives



Flume M, Bardou M, Capri S, Sola-Morales O, Cunningham D *et al*. Feasibility and attractiveness of indication value based pricing in key EU countries. Journal of market access and health policy 2016, 4: 30970.

# PANEL DISCUSSION

*DIANA I. BRIXNER, RPH, PHD;*

PROFESSOR, DEPARTMENT OF PHARMACOTHERAPY, UNIVERSITY OF UTAH, SALT LAKE CITY, UNITED STATES, DIANA.BRIXNER@UTAH.EDU.

ISPOR
Improving healthcare decisions

# PRICING MODELS FOR REGENERATIVE MEDICINE

- How premium is transparently reflected in CCM and Should CCM based premium vary for heart vs. knee ?
- What evidence would be needed to justify differences:
  - Values to different stakeholders
    - Patient
    - Physician
    - Payer
    - Public society
- If regenerative medicine provides cure, how does the model change?

# INPUTS FOR INDICATION BASED PRICING IN REGENERATIVE MEDICINE

- Cost:
  - Time relatively equal (2~3 weeks) or linear by manual manufacturing process
  - Quantity needed has minimal impact to price
  - Training and distribution service required by regulatory approval
- Outcomes: QoL ( heart - life threatening, Knee – Patient QOL )
  - Knees: $/QALY
  - Heart: $/QALY
- Safety: procedure risk of each
  - Heart higher risk
  - Knee lower risk

# ACKNOWLEDGEMENT


- Tianze Jiao, PhD, Postdoctoral fellow, McGill University, Montreal, Canada




ISPOR
Improving healthcare decisions