From Basic Research to Practical Use In Life Sciences
—Current Situation and Future Prospects In Japan

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Government Measures to Accelerate the Application of the Newest Medical Technologies

MEXT

- Life Science Division
  - TR Support and Promotion Program
    - TR Accelerating Network Program

MHLW

- Health Policy Bureau
  - Early phase, exploratory clinical trial center development project
    - Clinical research core hospital development project
      - National highly specialized medical research center (NC)
        - Japan-driven global clinical research development project
          - Highly Advanced Medical Treatment System
            - Advanced Medical Treatment System
              - Highly Advanced Medical Treatment Evaluation System (Category 3 Advanced Medical Treatment System)
                - Advanced Medical Treatment System (Category 2 Advanced Medical Treatment System)
                  - Advanced Medical Treatment System
                    - Advanced Medical Treatment Council
                      - Advanced Medical Treatment Council

- Health Insurance Bureau
  - Highly Advanced Medical Treatment System
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      - National highly specialized medical research center (NC)
        - Japan-driven global clinical research development project
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                      - Advanced Medical Treatment Council

Clinical trials

To be covered by the health insurance
Highly Advanced Medical Treatment System is a system developed by MHW (now MHLW) in 1984, for the purpose of accelerating the delivering of the most advanced medical technologies and treatments to the Japanese citizens.

It is a verification system for the inclusion of the newly developed advanced medical technologies or treatments to the coverage of health insurance, on condition that the treatments will be administered in the advanced treatment hospitals with the necessary equipments.

It is acknowledged that the treatments will be a combination with self-pay and health insurance.
Specified Medical Care Coverage

Medical treatments which are allowed to apply the use of health insurance

<table>
<thead>
<tr>
<th>Evaluated Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatments which require evaluation for the application of insurance</strong></td>
</tr>
<tr>
<td>Advanced medical treatments</td>
</tr>
<tr>
<td>Clinical Trial for drugs and medical devices</td>
</tr>
<tr>
<td>After approval by Pharmaceutical Affairs Law but not listed as insurance yet</td>
</tr>
<tr>
<td>Use of drugs or medical devices which are out of the application, but already applied in public</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Selected Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatments which do not require insurance as prerequisite</strong></td>
</tr>
<tr>
<td>A bed incurring an extra charge</td>
</tr>
<tr>
<td>Dental casting gold alloys</td>
</tr>
<tr>
<td>Metal base denture</td>
</tr>
<tr>
<td>Treatments with appointment</td>
</tr>
<tr>
<td>Treatments (After hours visit)</td>
</tr>
<tr>
<td>First treatment (in large hospital)</td>
</tr>
<tr>
<td>Re-Examination (in large hospital)</td>
</tr>
<tr>
<td>Others</td>
</tr>
</tbody>
</table>
Transition from Highly Advanced Medical Treatment System to Advanced Medical Treatment System

Application of highly advanced medical treatment used to be only available in advanced treatment hospitals, and approval process took more than one year.

Moreover, insurance application process itself was difficult to be understood. Therefore, in 2007, highly advanced medical treatment system was established for the improvement of the above.

In this system, from the application to the approval of advanced medical treatment is set to be within three months. Advanced technologies which are not "highly" advanced are also admitted. Application is also available from the hospitals which are correspondent with advanced treatment hospitals.

In this system, committee evaluates the new medical technology from science perspective and approves the standard of medical facilities which are able to apply the treatment by each medical technology
Evaluation Process for Advanced Medical Treatment and Highly Advanced Medical Treatment

**Advanced Medical Treatment**

- Technologies *without using* drugs and medical equipments *unapproved* by the Pharmaceutical Affairs Law

**Highly Advanced Medical Treatment**

- Technologies *using* drugs and medical equipments *unapproved* by the Pharmaceutical Affairs Law

**Authorized insurance medical institutions** (hospitals・clinics)

- **Advanced Medical Treatment Council**
  - (In case of Advanced) •Investigate on efficacy, safety, efficiency, social adequacy, necessity of the coverage by the health insurance •Set the standards for safe implementation

- **Highly Advanced Medical Treatment Council**
  - (In case of Highly Advanced) •Investigate on efficacy, safety, efficiency, social adequacy, necessity of the coverage by the health insurance

**Possible to be paid by the health insurance** (the cost of the surgery will be paid by the patients)
1. Radical cystectomy by laparoscopic surgery
2. Robot-supported endoscopic radical prostatectomy
3. Measurement of minimal residual disease using quantitative PCR method utilizing immune gene recombination of acute lymphocytic leukemia cells
4. minimally invasive irrigation of vertebra disc curettage
5. Treatment of intractable skin ulcer with platelet-rich plasma
6. Partial small intestine transplantation from living donor for short bowel syndrome and irreversible small intestine dysfunctionSpinal cord regeneration with olfactory mucosa autografts
Technologies Included in the Medical Insurance from Advance Medical Treatment in 2009

1. Fetal ultrasonography (for suspected heart disease cases)
2. HPV-DNA diagnosis for cervical cancer precancerous lesion
3. Laparoscope-assisted lower hepatectomy (for liver cancer only)
4. Excimer lazer phototherapeutic keratectomy
5. Genetic diagnosis of neurodegenerative diseases (for Huntington’s chorea etc)
6. Hydrodistension of the bladder in patients with interstitial cystitis
7. Intensity-modulated radiation therapy for local solid tumor
8. Pre-administration KRAS gene mutation tests for EGFR antibody drugs
9. Examination for sentinel lymph node identification and biopsy for axillary lymph dissection
10. Examination for sentinel lymph node identification and biopsy for malignant melanoma
Acknowledged Advanced Medical Technologies (Category 3 Advanced Medical Treatments)

1. Examination for sentinel lymph node identification and metastasis for malignant melanoma
2. Examination for sentinel lymph node identification and metastasis for breast cancer
3. Fetus urinary tract-amniotic shunt
4. Radiofrequency ablation treatment for chest malignant tumor
5. Computed tomography guided percutaneous radiofrequency ablation treatment for bone tumor
6. Laparoscopy-assisted hepatectomy
7. Robot-supported endoscopic radical proctectomy
8. Intraperitoneal Paclitaxel administration for peritoneal metastasis of stomach cancer
9. Photodynamic diagnosis using fluorescence systoscopy with oral administration of 5-aminolevulinic acid (5-ALA) for bladder cancer
<table>
<thead>
<tr>
<th></th>
<th>No. of Technologies</th>
<th>No. of Implementing Facilities</th>
<th>No. of Patients</th>
<th>Total Amount (billion Yen)</th>
<th>Total Amount for Specified Medical Care Coverage (billion Yen)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006-2007</td>
<td>117</td>
<td>373</td>
<td>14179</td>
<td>~9.8</td>
<td>~4.9</td>
</tr>
<tr>
<td>2007-2008</td>
<td>91</td>
<td>448</td>
<td>9579</td>
<td>~10.2</td>
<td>~5.4</td>
</tr>
<tr>
<td>2008-2009</td>
<td>107</td>
<td>519</td>
<td>20013</td>
<td>~17.3</td>
<td>~10.7</td>
</tr>
<tr>
<td>2009-2010</td>
<td>110</td>
<td>488</td>
<td>9775</td>
<td>~13.2</td>
<td>~5.4</td>
</tr>
<tr>
<td>2010-2011</td>
<td>123</td>
<td>522</td>
<td>14505</td>
<td>~17.3</td>
<td>~7.5</td>
</tr>
</tbody>
</table>
Flowchart for the evaluation of advanced medical treatment

1. Medical institutions → Administration Office → Advanced medical treatment council
2. Decide whether to assign advanced medical treatment A or B or C (C is for exceptional case)

- **Advanced medical treatment A**
  - Mainly for the new technology which use the approved drugs (Expert: 1, Tech committee: 1)
  - Review of social validity of the new technology as Advanced medical treatment B (Ethics, adaptability, return on costs) (Expert: 1)

- **Advanced medical treatment B (Advanced medical treatment technology discussion council)**
  - Medical technology accompanied with unapproved, off-label use drugs and medical devices. Also new technology like regenerative medicine (Main staff: main:1, sub: 2, tech committee: 1 (as necessary))
  - This council reviews the validity of the technology, clinical trial plan

- **Advanced medical treatment C (cancer treatment)**
  - Technology evaluated by external institution
  - External institution which have high level of knowledge evaluates the validity of technology, clinical trial plan
<table>
<thead>
<tr>
<th></th>
<th>Well-implemented Advanced Medical Technologies So Far (A)</th>
<th>Annual Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cataract surgery with multifocal intraocular lens</td>
<td>4023</td>
</tr>
<tr>
<td>2</td>
<td>3D image analysis for anterior eye segment</td>
<td>3593</td>
</tr>
<tr>
<td>3</td>
<td>Proton therapy</td>
<td>1628</td>
</tr>
<tr>
<td>4</td>
<td>Ancillary differential diagnosis using optical topography scan for depression patients</td>
<td>1237</td>
</tr>
<tr>
<td>5</td>
<td>Heavy ion radiotherapy</td>
<td>1053</td>
</tr>
<tr>
<td>6</td>
<td>Prediction and evaluation of the interferon treatment effect by IL28β genetic diagnosis</td>
<td>351</td>
</tr>
<tr>
<td>7</td>
<td>Bio-regeneration in periodontal surgical therapy</td>
<td>263</td>
</tr>
<tr>
<td>8</td>
<td>Activated self-lymphocytes introduction therapy using self-tumor tissue and dendritic cells</td>
<td>166</td>
</tr>
</tbody>
</table>
Relatively Well-implemented Advanced Medical Technologies So Far (B)

1. Combined therapy of intravenous Paclitaxel and intraperitoneal Carboplatin administration (for ovarian cancer, fallopian tube cancer, etc) 89
2. Robot-supported endoscopic radical prostatectomy 79
3. Percutaneous radiofrequency ablation for primary lung cancer or metastatic lung cancer 77
4. Neck endoscopic surgery, follicular carcinoma of thyroid, adenomatoid goiter, Basedow disease and primary hyperparathyroidism 61
5. Caffeine combined chemotherapy for malignant bone tumor or soft tissue sarcoma 53
Technologies Included In the Insurance By the Advanced Medical Treatment System in 2013 (8 out of 66 applications)

1. Amniotic membrane transplantation for refractory eye diseases
2. Laparoscopic surgery for endometrial cancer
3. Crown prosthesis with hybrid resin using dental CAD·CAM system
4. Laparoscopic sleeve gastrectomy
5. Ancillary differential diagnosis using optical topography scan
6. Subfascial endoscopic perforator vein surgery
7. Thoracoscopic patent ductus arteriosus surgery
8. Apicotomy based on CT image using operation microscope
Application Flow for Commercial Realization of the Advanced Medical Technology Cases in MHLW

Highly Advanced Medical Treatment Council

- Including technologies that use unapproved drugs or medical devices
  - Advanced Medical Treatment Council (Health Insurance Bureau)
    - Technologies that do not use unapproved drugs or medical devices
      - Highly Advanced Medical Treatment Council (Health Policy Bureau)
        - Technologies that use unapproved drugs or medical devices
          - Regenerative medicine
          - Gene therapy, etc
  - Technologies that do not use unapproved drugs or medical devices
    - Advance Medical Treatment Council
      - Central Social Insurance Medical Council
        - Advanced Medical Technology Council (Health Policy Bureau • Health Insurance Bureau)
          - Technologies that use unapproved/off-label drugs or unapproved medical devices
          - Highly difficult technologies
            - Regenerative medicine
            - Gene therapy
            - Anticancer drug
Japan’s Action in Translational Research (TR)

Based on the 3rd “Science and Technology Basic Plan” (cabinet approval on March 28, 2006), it was decided by the Council for Science and Technology Policy in the “Strategy for Promotion By Scientific Fields” for Life Sciences that one of the strategic priority sciences and technologies is Clinical Translational Research.

As a result, MEXT (Ministry of Education, Culture, Sports, Science and Technology) has decided to start the “Translational Research Support and Promotion Program” in 2007 in order to promote the practical use in medical care for the results of the basic research in life sciences such as genomics and regenerative medicine.
Goal of the Translational Research (TR) Promotion Program

Selectively establishes institutes as the supporting TR in order to support developing R&D strategy and developing centers based on Pharmaceutical Affairs Law, targeting research institutes which develop the fundamental research result which can be potentially used for the practical medical treatment.

Realizing the current capability of these institutes, establishes network among institutes in order to strengthen TR support at each location.

(Mar, 2007)
Outline of the Translational Research (TR) Center Development Project

• System for the development of the new drugs and medical devices in research institutes and universities
  1. Development strategy proposal for test candidates; acquisition and practical use of the strategic intellectual properties
  2. Enrichment of the data center functionality
  3. Non-clinical trials, manufacturing of the test candidates

• TR talent management and training
  Development planning and management experts, intellectual property and license specialists, formulation specialists, regulatory affairs experts, toxicity experts, clinical trial management experts, clinical trial data managers, biostatisticians
Translational Research Project Centers in Japan (MEXT)

Phase I Program (2007-2011)
1. Hokkaido Universities (Sapporo Medical Univ, Hokkaido Univ, Asahikawa Medical Univ)
2. Tohoku Univ
3. The Univ of Tokyo
4. Kyoto Univ
5. Osaka Univ
6. Foundation for Biomedical Research and Innovation (Kobe)
7. Kyushu Univ

Phase II Program (2012-2017)
1. Hokkaido Organization for Translational Research (Sapporo Medical Univ, Hokkaido Univ, Asahikawa Medical Univ)
2. Tohoku Univ
3. The Univ of Tokyo
4. Nagoya Univ
5. Kyoto Univ
6. Osaka Univ
7. Kyushu Univ

The Translational Research Informatics Center of the Foundation for Biomedical Research and Innovation will be the support organization for both phases (Prof. Masanori Fukushima and others)

- Program Director
  Takao Saruta
- Program Officer
  Teiichiro Koga (Daiichi-Sankyo)

- Program Director
  Takao Saruta
- Program Officer
  Shigeru Kageyama (Prof@Jikei Univ)
  Osamu Inagaki (Industry expert)
MEXT Translational Research Support and Promotion Program Centers
**Track Records of Translational Research Center Development Project**  
**（August 2007 ~ August 2013）**

<table>
<thead>
<tr>
<th>No. of Cases</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator initiated clinical trials</td>
<td>16</td>
</tr>
<tr>
<td>Sponsor initiated clinical trials</td>
<td>6</td>
</tr>
<tr>
<td>License out</td>
<td>23</td>
</tr>
<tr>
<td>Approval by Advanced Medical Treatment</td>
<td>10</td>
</tr>
<tr>
<td>Approval for manufacture and sales</td>
<td>4</td>
</tr>
<tr>
<td>Included in the Medical Insurance</td>
<td>4</td>
</tr>
</tbody>
</table>
Track Record of the TR Project (Aug, 2007 – Jan, 2013)

Registration of New Treatment (18 cases)

<table>
<thead>
<tr>
<th>No.</th>
<th>Treatment</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Artificial wrist joint</td>
<td>Hokkaido</td>
</tr>
<tr>
<td>2</td>
<td>Artificial hip</td>
<td>Hokkaido</td>
</tr>
<tr>
<td>3</td>
<td>SVN-2B peptide vaccine</td>
<td>Hokkaido</td>
</tr>
<tr>
<td>4</td>
<td>N-acetylneuraminic acid</td>
<td>Tohoku</td>
</tr>
<tr>
<td>5</td>
<td>HGF</td>
<td>Tohoku</td>
</tr>
<tr>
<td>6</td>
<td>Trehalose</td>
<td>Tokyo</td>
</tr>
<tr>
<td>7</td>
<td>Tachycardia drugs</td>
<td>Tokyo</td>
</tr>
<tr>
<td>8</td>
<td>Auxiliary artificial heart for children</td>
<td>Tokyo</td>
</tr>
<tr>
<td>9</td>
<td>Artificial dermis</td>
<td>Kyoto</td>
</tr>
<tr>
<td>10</td>
<td>Leptin</td>
<td>Kyoto</td>
</tr>
<tr>
<td>11</td>
<td>Antibodies for cancers</td>
<td>Kyoto</td>
</tr>
<tr>
<td>12</td>
<td>Myoblast sheets</td>
<td>Osaka</td>
</tr>
<tr>
<td>13</td>
<td>WT1 peptide vaccine</td>
<td>Osaka</td>
</tr>
<tr>
<td>14</td>
<td>Cell segregation device</td>
<td>Foundation</td>
</tr>
<tr>
<td>15</td>
<td>Knee joint cartilage regeneration</td>
<td>Foundation</td>
</tr>
<tr>
<td>16</td>
<td>PLGA nanoparticle</td>
<td>Kyushu</td>
</tr>
<tr>
<td>17</td>
<td>Fetal electrocardiography</td>
<td>Tohoku</td>
</tr>
<tr>
<td>18</td>
<td>BK-SE36/CpG-ODN</td>
<td>Osaka</td>
</tr>
</tbody>
</table>

Approved by the Advanced Medical Treatment System (8 cases)

<table>
<thead>
<tr>
<th>No.</th>
<th>Treatment</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Islet transplantation</td>
<td>Tohoku • Kyoto</td>
</tr>
<tr>
<td>2</td>
<td>ultra-red ray dry process waon device</td>
<td>Tokyo</td>
</tr>
<tr>
<td>3</td>
<td>bFGF+GHG</td>
<td>Kyoto</td>
</tr>
<tr>
<td>4</td>
<td>Leptin</td>
<td>Kyoto</td>
</tr>
<tr>
<td>5</td>
<td>γδT cell</td>
<td>Kyoto</td>
</tr>
<tr>
<td>6</td>
<td>Epoetin β</td>
<td>Osaka</td>
</tr>
<tr>
<td>7</td>
<td>Spinal cord injury treatment technology</td>
<td>Osaka</td>
</tr>
<tr>
<td>8</td>
<td>Cultivated autologous oral mucosal cell sheet</td>
<td>Osaka</td>
</tr>
</tbody>
</table>
Track to Practical Use for Academia Basic Research in Life Sciences

- **MEXT** (PR Support and Promotion Program)
  - Seeds for development strategy
  - Acquisition and practical use of the intellectual property
  - Manufacturing of the test candidate
  - Non-clinical trial
  - System development for clinical trials

- **MHLW**
  - Early phase exploratory clinical trial center
  - First in Man trial etc
  - Aim at POC

- Clinical trial core hospital center
  - System to enable clinical trials based on ISH-GCP standard

- Investigator initiated trial
  - Sponsor initiated trial

- Out of Clinical trial
  - Highly advanced medical treatment
  - Advanced medical treatment

- **Popularization as medical technology**
  - **Commercialization**
Early Phase・Exploratory Clinical Center Development Project

In order to be the leading country to perform first-in-human trials and achieve POC (Proof of Concept) for innovative drugs and medical devices, medical institutions that satisfy the following requirements can be selected as the candidates for Early phase • Exploratory Clinical Center.

(Requirements)
1. Advanced treatment hospital, National Center for Global Health and Medicine or equivalent hospitals with advanced treatment hospital from the viewpoint of medical delivery system
2. Have doctors with expertise in cancer, psycho-neurologic disease, cerebrovascular disease, cardiovascular disease
3. Have experts with deep expertise in clinical trial research such as doctors, biostatistitians, data managers, people who previously worked in drug regulatory offices
Establishment of Clinical Research Core hospital

MHLW will establish a clinical research core hospital as a facility to have global standard clinical research and investigator initiated clinical trial in order to generate first innovative medicine and medical devices in Japan

(Required functionality)

1. Ability to develop appropriate research plan and execute the research based on ICH-GCP guideline
2. Ability to conduct appropriate review with transparency from Ethics, Scientific, Safety, Reliability standpoint
3. Ability to manage intellectual property and migration of technology for every seed
4. Ability to develop high quality collaborative research plan with multiple facilities and execute the research plan with other medical institutes
# Most Advanced Research Practical Realization Center Project in MHLW

## Early phase clinical trial center development project

1. National Cancer Center  
   Cancer center
2. Osaka University Hospital  
   Cerebrovascular and cardiovascular disease center
3. National Cerebral and Cardiovascular Center  
   Medical device for cerebrovascular and cardiovascular disease center
4. The University of Tokyo Hospital  
   Psycho-neurologic disease center
5. Keio University Hospital  
   Refractory autoimmune disease center

## Clinical research core hospital development project

1. Hokkaido University Hospital
2. Chiba University Hospital
3. Nagoya University Hospital
4. Kyoto University Hospital
5. Kyushu University Hospital
6. Tohoku University Hospital
7. Gunma University Hospital
8. National Center for Child Health and Development
9. National Hospital Organization Nagoya Medical Center
10. Okayama University Hospital
Japan-Driven Global Clinical Research System Development Project

In order to achieve global cooperation and global market expansion

• Promote the development of Japan-driven global clinical research system and the cooperation with the drug regulatory offices in US, Europe, and Asia.

• Promote the global market entry for medical technologies and services
  1. Promotion of global trials and global clinical research
  2. Collaboration with US, Europe, and Asia drug regulatory offices
  3. Global market expansion with medical services and medical technologies

(Project centers)

• Kitasato Institute Hospital
• Foundation for Biomedical Research and Innovation
Current System For Practical Realization of Basic Research in Life Sciences
—Trend for Translational Research (TR)—

**MEXT**

TR Support and Promotion Program
2007～2011年

**MHLW**

Early phase・exploratory research center project
2011～

Clinical research core center project
2012～

Japan-driven global clinical research system development project
2012～

Clinical trial

Advance medical treatment

Global clinical trial

Health insurance
Innovational Medical Technology Development Center Project

**Collaboration between MEXT and MHLW**

Establish the organizational structure which enables to make the innovative result of fundamental research in academia into the practical use, and execute / support high quality clinical research / treatment at global standard level for the seeds at each development stage.

- **MEXT**
  - Grow seeds from fundamental research stage to the practical use
  - TR Accelerating Network Program (2014 6.5 billion JPY)

- **MHLW**
  - Clinical research by global standard • clinical trial environment setup
  - Clinical Research Core Hospital Development Project (2014 5.6 billion JPY)

Integration

Innovational Medical Technology Development Center
Innovational Drugs and Medical Devices Development Center

1. Reinforcement and enrichment of the center functionality
   • Center’s self-reliance; have fixed resources, apply self-income
   • Preparation of CPC or Phase1 beds · data center

2. Build up the TR network functionality
   • Mutual monitoring system
   • Center resource sharing system

3. Improve the clinical research and clinical trial environment
   • High quality ethnics review committee
   • Education and training opportunities