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A FRAMEWORK FOR INTRODUCTION OF TEMPORARY APPROVAL OF NEW HEALTH TECHNOLOGY (TANHT)

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ABSTRACT

Objectives: To suggest a framework and managing requirements for the temporary approval of new health technology (TANHT) that can meet the needs of patients who have suffered from rare diseases.
Methods: We investigated the Korean healthcare insurance and overseas policies for clinical trials and Coverage with Evidence Development (CED) through a literature review and interviews with experts. Subsequently, using these interviews and literature, we developed a frame work and a detailed procedure for the TANHT.
Results: We suggested a framework and detailed procedure for the TANHT that allows conditional approval of the research-phase health technology, which lacks clinical evidence but shows promise. We also provided related amendments of enforcement rules, a process of enacting related regulations, guidelines for patient safety, the disclosure of conflict of interest, and the authoring qualifications and ownership rights to research results.
Conclusions: This study is the first attempt to devise a framework, management requirements, and guidelines for the TANHT. Through this elaborative system, high-quality and reliable evidence necessary for new health technology assessments will be generated earlier than before.

INTRODUCTION

In South Korea, even if a newly device for rare or intractable disease is developed and approved by the regulating body, the Minister of Food and Drug Safety, doctors cannot use the newly health technology before evaluating it using a new health technology assessment (nHTA). All doctors' services (both coverage and non-coverage items) are listed in the national health insurance coverage list because the health insurance system is based on a "fee for service" model that results in lower medical insurance fees for the whole nation. The government decides on whether the technology is included in the national health insurance coverage list based on the results presented by the Medical Review Activity Committee based on its cost-effectiveness, and monitors the propriety of insurance claims by the National Health Insurance Act (http://www.law.go.kr/LSW/lsInfoP.do?lsiSeq= 149136 #0000 (accessed 06/05/2014). Usually, nHTAs are conducted using a systematic review, which is a global methodology in evidence-based medicine. This method usually consists of gathering currently existing clinical evidence, and qualitatively or quantitatively synthesizing appropriate results to draw conclusions regarding the safety and effectiveness of the given technology. As such, systematic evaluation of newly developed health technologies is performed at the national level in order to ensure that safe and effective medical technologies are delivered to the public (Chae-Min *et al.*, 2013). On the other hand, there are many health technologies that have insufficient clinical evidence, but are very promising; these are called "research-phase health technologies." Research-phase health technologies, defined by the Committee for New Health Technology Assessment, cannot be introduced into the Korean healthcare market because the government manages the non-coverage insurance

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list using the national health insurance coverage list. Table 1 shows the definition of research-phase health technologies in the Korean healthcare system. However, patients and their families who suffer from rare of intractable diseases (e.g., pseudomyxoma peritoneum, turner syndrome, leukemia) want to receive research-phase health technologies and will do so with patient consent, the burden of the expense, and the expectation of potential. Although there is no alternative treatment option, the National Health Insurance Act regards these treatments as illegal and forbids the use of these technologies cause of a lack of clinical evidence. Consequently, a lack of clinical evidence for these kinds of health technologies is common and this causes hardship to patients who suffer from rare or intractable diseases. Furthermore, it is difficult to generate clinical evidence without support at the national level, particularly in cases of therapeutic (diagnostic) methods for rare or intractable diseases. Therefore, there has been a significant need to support the collection of clinical evidence at the national level by improving the current healthcare system (Chae-Min *et al*., 2013). To improve these kinds of limitations in the Korean healthcare system, in this study we suggest the "Temporary Approval of New Health Technology" (TANHT), a temporary approval policy for newly developed health technologies that lack sufficient evidence of their safety or effectiveness, but show promise for rare or intractable diseases or conditions without available alternative treatments or diagnostic methods. In addition, we present the necessary requirements (rules, regulations, guidelines, and official notifications) for implementing the TANHT by analyzing applicable systems in other countries (Chae-Min *et al*., 2013).

METHODS

Literature review of conditions of the Korean healthcare insurance system, overseas policies for clinical trials, and Coverage with evidence development (CED)

To make an efficient framework for the TANHT, we investigated the Korean healthcare insurance conditions of research-phase health technologies for rare diseases or those that do not have alternative health technologies currently listed within the National Health Insurance system (Chae-Min *et al*., 2013). We also investigated and analyzed overseas policies that allow for the use of research-phase health technologies with insufficient clinical evidence for a certain period of time under insurance coverage or private payment structures, after which the generated evidence can be used for assessment of the health technology for coverage decisions. We searched studies in MEDLINE and EMBASE (from 1995 to week 1 of January 2014 in both databases) that reported policies allowing the use of newly developed health technologies for evidence generation and its outcomes in advanced countries that had nHTA systems. The search terms were "conditional coverage" and "evidence generation."A total of 56 articles were searched and the articles on clinical trials and policy issues were excluded. Finally 6 articles remained (included a method or framework of CED) after the additional 50 articles were excluded. However, only one article was appropriate for our purpose; it has detailed information of similar policies for each country including UK, Germany, Canada, Spain, Australia, US, Switzerland, Sweden, Belgium, Netherlands, France, and Italy from various standpoint with mechanisms of marketing approval decisions, coverage decisions. We mainly focused on the policy framework, principles, related regulations, funding support, guidelines, responsibilities of participants, and detailed performance cases. We identified the common characteristics and management procedures of related overseas policies that are in keeping with the purpose of the TANHT system, which aims to produce objective evidence at the national level for nHTAs, unlike clinical trials on drugs and medical devices sponsored by industries for regulatory approval.

Expert interviews for devising the TANHT system

To design a rigid system for the TANHT, we conducted individual and group interviews with experts who could provide high quality advice and who had no conflict of interest with regard to the development of a TANHT system and related industries. Specifically, we included patient and consumer organizations, medical ethicists, and professionals in clinical research to ensure the rights and safety of patients, while excluding policy makers, payers, and hospital employees as a result of collecting extensive options from several advanced public hearings and open forums. Together, two interior senior researchers and two junior researchers considered the necessary requirements for TANHT in their development of interview content. The interview subjects were representatives of patient and consumer organizations (6 people), medical ethicists (3 people), and professionals in clinical research (3 people). They were recruited through recommendations from related organizations (Consumers Korea and Korea Alliance of Patients Organization) and associations (Korean Academy of Medical Sciences and The Korean Society for Medical Ethics).

Before the interviews, we confirmed that they do not have any conflicts of interest with the TANHT system or any medical device or drug industries. The interviews with representatives of patient organizations or consumer organizations were conducted one-on-one. The interview contents were as follows: (i) the detailed needs of patients or their families, (ii) opinions of paying privately for the treatment fees, and (iii) responsibilities for unexpected accidents or events (e.g., death, life-threatening illness, hospitalization, disability/capacity, congenital anomaly/birth defects). The interviews with the medical ethicists were conducted in the same manner as a group meeting. The interview contents were as follows: (i) the ethical aspects of the details of the TANHT system to be fulfilled, (ii) opinions on private payment for treatment fees, (iii) responsibilities of the government and implementing institutions, (iv) the essential contents of related rules (http://www.law.go.kr/lsInfoP.do?lsiSeq=128349#0000(accessed 06/05/2014), and (v) regulations and guidelines. Finally, as with the representatives of patient/consumer organizations, professionals in clinical research were interviewed individually. The interview contents included (i) ethical aspects of the details of the TANHT system to be fulfilled, (ii) opinions of private payment for the treatment fees, (iv) responsibilities of the government and implementing institutions, (v) the essential contents of related rules (http://www.law.go.kr/lsInfoP.do?lsiSeq=128349#0000(accessed 06/05/2014), and (vi) regulations and guidelines. We also

interviewed the CEO of the U.S. Center for Medical Technology Policy (CMTP) to obtain information on specific examples, operating systems, and achievements of the CED in the U.S. All of the interviews were conducted in a uniform manner by the 4 researchers who developed the interview content.

Preparation of the framework, detailed procedure, and requirements for operation of the TANHT system

The framework and detailed procedure for the TANHT were prepared according to the analyzed results from the literature review and expert interviews. The necessary amendments of related enforcement rules, a process for enacting related regulations, and guidelines were developed after reviewing the related the Korean insurance related rules, Acts (http://www.law.go.kr/lsInfoP.do?lsiSeq=128349#0000(accessed 06/05/2014) and overseas guidelines of health policy (http://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/CED.pdf(accessed 06/05/2014; Bernard and Field , 2009; National Patient Safety Agency, 2011; Norris *et al*., 2011; http://hms.harvard.edu/about-hms/integrity-academic-medicine/hms-policy/faculty-policies-integrity-science/authorship-guidelines (accessed 06/05/2014; http://wustl.edu/policies/authorship.html (accessed 06/05/ 2014)).

Process for designing the framework and procedure for the TANHT

We designed the framework and detailed procedure for the TANHT according to the results of the literature review of overseas policies, particularly the operation system of CED in the U.S., Only in Research (OIR) in the UK, and Conditionally Funded Field Evaluation (CFFE) in Canada. The opinions of experts were reflected by considering conditions of the Korean healthcare insurance system.

Development of amendments to concerning enforcement rules and process of enacting related regulations

In order to have legal reason for the process of the TANHT, we created a new clause for related enforcement rules ("the rules on new health technology assessment" of Ministry of Health and Welfare (MOHW)) (http://www.law.go.kr/lsInfoP.do?lsiSeq=128349#0000(accessed 06/05/2014) and developed an acting process of related regulations ("regulations on acknowledgement and enforcement of TANHT" of MOHW) based on the devised framework and the results of a literature review of "the International Conference on Harmonization of Good Clinical Practice" (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf(accessed 06/05/2014)).

Development of related guidelines and example of notification

TANHT is regional health policy improvement in South Korea. Especially there is no opportunity to provide health technology that has been evaluated as safe but has not been established as effective because this is illegal, even if that technology is for rare or intractable diseases. Therefore, interviewed ethicists requested that selected treatments have to be controlled under Guidelines such as the "International Conference on Harmonization of Good Clinical Practice," (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf(accessed 06/05/2014)) the "Nuremberg Code," (Government Printing Office, 1949) and the "Declaration of Helsinki" (http://www.ub.edu/recerca/Bioetica/doc/Declaracio_Helsinki_2013.pdf(accessed 06/05/ 2014)) to ensure patients' rights and safety. They also insisted that there have to be no conflict of interest to the researchers and healthcare professionals who concerned and TANHT have to be implemented in the well-organized clinical setting and reasonable evidence generation system.

Therefore, first, we developed 'The Guidelines for the Protection and Management of the Human Rights of Patients' based on the "International Conference on Harmonization of Good Clinical Practice," the "Nuremberg Code," and the "Declaration of Helsinki." Second, we developed 'The Guidelines for Reporting and Managing Conflicts of Interest' by referring to related documents (Bernard and Field, 2009; Norris *et al*., 2011). Third, 'The Guidelines for Management of Authoring Qualifications and Ownership Rights to Research Results' were developed by referring to related guidelines (http://hms.harvard.edu/about-hms/integrity-academic-medicine/ hms-policy/f aculty-policies-integrity-science/ authorship-guidelines (accessed 06/05/2014; http://wustl.edu/po licies/ authorship.html (accessed 06/05/2014) and considering the characteristics of the TANHT. Fourth, 'The Checklist and Grading Table for the Reviewers' was made by referring to similar domestic clinical research selection and implementation systems. One example is the National Strategic Coordinating Center for Clinical Research, which is a MOHW-affiliated organization with a mission that includes selecting and managing the implementing institutions that undertake clinical research to serve the public interests. Finally, examples of official notification for the individual TANHT were developed using the devised framework and related reports of the Committee on New Health Technology Assessment in Korea (http://neca.re.kr/nHTA/eng/report/evaluation_paper.jsp (accessed 06/05/ 2014).

RESULTS

Analysis of the Korean healthcare insurance system and overseas policies for clinical trials and CED

Condition of the Korean healthcare insurance system

In the Korean healthcare insurance system, using newly developed health technologies without a nHTA is impossible except in clinical trials. This is particularly true for research-phase health technologies classified as II-b (as described in Table 1, II-b is a kind of research phase health technology that has uncertainty for effectiveness but is for rare disease or has no alternatives that is currently listed), which refer to technologies that do not provide specific benefits to industries, government, or medical institutions; for such technologies, industries or governments are less likely to provide clinical trial funds (Chae-Min *et al*., 2013). However, II-b health technologies inevitably exist.

Currently, 9 research-phase health technologies are classified as II-b and the indications or application targets are depicted in

Table 2. Although most of them are clinically safe, they lack evidence for clinical effectiveness (Chae-Min *et al*., 2013; http://neca.re.kr/nHTA/ eng/report/evaluation_paper.jsp (accessed 06/05/ 2014)).

Overseas policies for clinical trials and CED

Foreign countries that perform evidence-based nHTAs to determine the range of benefits and insurance coverage of health technologies typically conduct clinical trials with conditional payment and have implemented policies of permitting the use of unlisted drugs and health technologies. These policies have been conducted using general guidelines and principles regarding clinical trials. The most utilized guidelines were the "International Conference on Harmonization-Good Clinical Practices," the "Nuremberg Code," and the "Belmont Report" (http:// videocast.nih.gov/pdf/ohrp_appendix_belmont_report_vol_2.pdf (accessed 06/05/ 2014)), which all emphasize the safety, voluntariness, and welfare of clinical trial subjects around the world. Furthermore, they clearly define the responsibility and function of "Institutional Review Boards (IRB)" of implementing institutions and include a detailed explanation about the role of investigators and sponsors. In the following sections (3.1.2.1–3.1.2.5), we summarize the major policies of a variety of developed countries.

United States

The U.S. permits the insurance coverage of health technologies that lack sufficient evidence for reimbursement or have low-quality clinical trials, under the condition of generating high-quality evidence to support early market introduction of promising new health technologies (15,16). The Centers for Medicare and Medicaid Services (CMS) determine the technologies from lack sufficient evidence undergo CED though the National Coverage Determination (NCD), and the National Institution of Health (NIH) proposed the clinical trials. Then, CMS performed the specific roles to accumulate sufficient evidence of the designated technologies (http://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/CED.pdf (accessed 06/05/2014; Carbonneil *et al*., 2009; Trueman *et al*., 2010; Mohr and Tunis, 2010; Tunis and Pearson, 2006). The CEO of the CMTP was interviewed and was responsible for the design and management of the CED program in CMS. The CMTP manages two or three CED items per year. To manage several CED items, the CMTP operates a specialized committee consisting of 10-15 experts for decision-making and management purposes. In addition, the CMTP pays only the CED management fee while the fee for clinical trials (including the data registry design and management fee) is paid by investigators' research funds. The investigators who want to perform the CED item of the CMTP are recruited from selected Research Coordinating Centers.

United Kingdom

In the UK, if a promising health technology does not have sufficient clinical evidence from the results of the nHTA of the National Institute for Health and Clinical Excellence (NICE), it is determined as OIR, which means that its use is recommended in the research environment but nowhere else (Claxton *et al*., 2012). If certain health technology is selected as "OIR" by the NICE, a related clinical trial is conducted according to the criteria of the National Institute of Health Research and in accordance with the Trials and Studies Coordinating Centre program (Claxton *et al*., 2012; Dhalla *et al*., 2009). The representative example was "laparoscopic surgery for colorectal cancer" (Carbonneil *et al*., 2009).

Japan

In Japan, new health technology that is expected to be safe and effective despite a lack of evidence can be used under the Advanced Health Technology Support System. This system designates two kinds technology: Advanced Health Technology A and Advanced Health Technology B. Health technology A is not accompanied by the use of unapproved or off-label drugs or medical devices according to the Pharmaceutical Affairs Act, while B is health technology that is accompanied by the use of such drugs or devices. Advanced Health Technology A is usually reviewed in terms of its safety, effectiveness, clinical validity, and the need for the corresponding technology to be covered by insurance in the future through a decision of the Committee for Advanced Health Technology; the corresponding technology can be performed in specified medical institutions so long as they satisfy the institutional criteria for safe and effective use. For Advanced Health Technology B, if the review results for the safety and effectiveness and the possibility of performance in the applying medical institution are judged appropriate at the Committee for Advanced Health Technology, it can be used in approved medical institutions (Chae-Min *et al*., 2013; Hideya, 2006; Sho *et al*., 2013).

Canada

In Ontario, Canada uses the CFFE, whereby the government selects health technologies with potential benefits that are currently lacking evidence in relation to safety, effectiveness, or cost-effectiveness, and then supports clinical trials to generate evidence for this health technology. The conducting institution is the Ontario Health Technology Advisory Committee (OHTAC) and it completed 19 performance assessments by 2011; currently, 38 research projects are being conducted (Carbonneil *et al*., 2009; Goeree *et al*., 2010).

Other countries

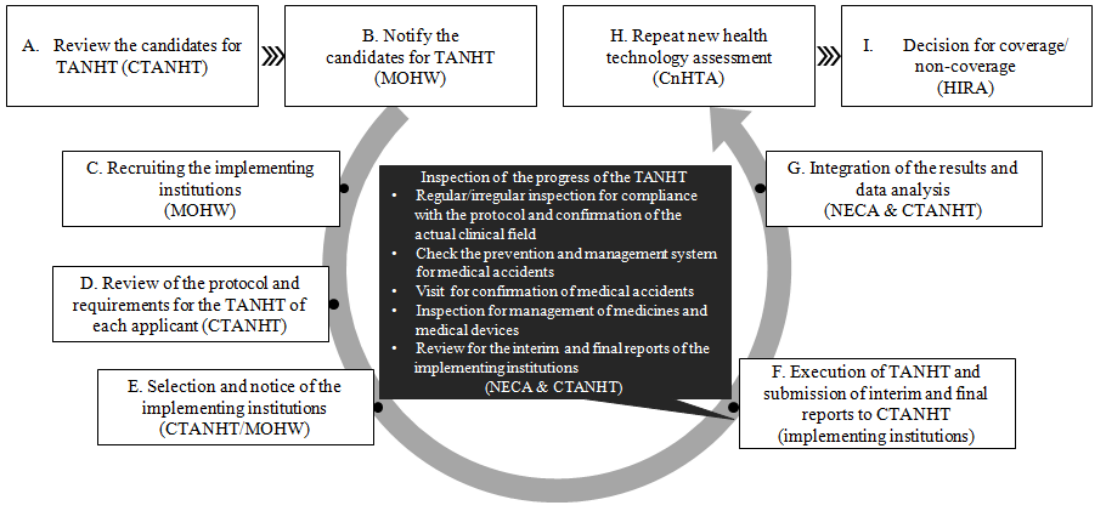
Major European countries such as Germany, Italy, the Netherlands, France, Spain, Switzerland, and Sweden also have conditional coverage systems, including a suspended coverage decision with a pilot project in Germany; independent research on medicine in Italy, conditional reimbursement in the Netherlands; Still in Clinical Research in France; monitored use in Spain; medical services under evaluation in Switzerland; and reimbursement with conditions in Sweden. Each of these systems is suitable for the environment and criteria of each government (Carbonneil *et al*., 2009). As mentioned in the systems listed above, when safety or effectiveness of health technologies is uncertain, they permit the use in the clinical environment for a certain period as a coverage item. After the generation of enough evidence, they decide whether to include the technology in the coverage list based on the accumulated evidence (Carbonneil *et al*., 2009; Willis *et al*., 2010).

Opinions of experts in designing the TANHT system and its details

The needs of patient and their families are reflected in the TANHT and the representatives of patient organizations and consumer organizations stated that if there are new policies that permit the use of promising health technologies for rare or intractable diseases, many patients and their families are willing to receive those health technologies and bear the expenses because they otherwise do not have proper treatment or diagnosis methods. This policy will ensure the rights of patients by enhancing medical options and guaranteeing the quality of treatment by monitoring and auditing the system. The opinions of medical ethicists and professionals in the area of clinical trials were that ethical review is to be considered most important for the safety and rights of patients. They also suggested that the patient informed consent form must be standardized and made to coincide with the related Korean and international ethics guidelines (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf (accessed 06/05/2014); Government Printing Office, 1949; http://www.ub.edu/recerca/Bioetica/doc/Declaracio_Helsinki_2013.pdf(accessed 06/05/ 2014; http://neca.re.kr/nHTA/ eng/ report/evaluation_paper.jsp (accessed 06/05/ 2014; http:// videocast.nih.gov/pdf/ohrp_appendix_belmont_report_vol_2.pdf (accessed 06/05/ 2014)). The experts also reported that a clarification of the confidentiality of the patient's personal record in the informed consent and notification procedures would be useful. Medical ethicists indicated that government should guarantee clinical autonomy and strengthen the function of IRBs for maintaining reliability and clarification of clinical evidence generated from TANHT. In addition, experts of clinical trials stated that the MOHW would have to give enough of an implementation period for the TANHT process and a role to implementing institutions so that proper clinical evidence for a nHTA could be generated (Chae-Min *et al*., 2013). Furthermore, they suggested that the MOHW would have to strive to secure experts with board experience related to clinical trials for auditing implementing institutions.

The framework for the TANHT system

The TANHT is a policy aimed at supporting the generation of clinical evidence for research-phase health technology that lacks sufficient evidence on safety or effectiveness, and where there are currently no alternatives for or the treatment/test is for rare or intractable diseases. Moreover, introduction of such technology is urgent and it should not have concerns for abuse. In that case, research-phase health technology that receives temporary approval would be regarded as non-covered health technologies in designated implementing institutions for a



* Temporary Approval of New Health Technology (TANHT): a temporary approval policy for newly developed health technologies that lack sufficient evidence of their safety or effectiveness, but show promise for rare or intractable diseases or conditions without available alternative treatment or diagnostic methods.

Fig. 1. The process of the Temporary Approval of New Health Technology (TANHT)

Table 1. The types and characteristics of the results of the new Health Technology Assessment (nHTA)

Classification		Definition		Legitimacy of the use in clinical field
New health technology		Its clinical safety and effectiveness is recognized through the nHTA		Allowed
Research-phase health technology	I	There is uncertainty with regard to clinical safety or effectiveness. (In the case of II-b, there is uncertainty of effectiveness)	Even if its safety and effectiveness is recognized, there will be no benefit from introduction to the clinical field.	Prohibited
	II-a		However, there is an alternative health technology that is currently listed. If its safety and effectiveness is recognized, there will be potential benefits to patients and the clinical field.	
	II-b		However, it is for rare diseases or has no alternative health technology that is currently listed. Furthermore, it must be introduced urgently; if its effectiveness is recognized, there will be potential benefit to patients and the clinical field.	

specific period under the promise of clinical evidence generation. After use for a specific period, a nHTA is conducted again with the generated evidence, and if the safety and effectiveness of the health technology is verified, it would be possible to introduce it into the Korean health care system. As Figure 1 shows, the process of the TANHT consists of the following stages: application, review, selection, performance and management, completion, and reassessment. First, the Committee for the TANHT (CTANHT), which falls under the Committee for New Health Technology Assessment, reviews the candidates for the TANHT among current research-phase health technologies. These candidates have to be safe but lack evidence for effectiveness and be a treatment or diagnosis method for rare or intractable diseases. In addition, the introduction to the Korean healthcare system of those health technologies must be urgently needed. Next, the CTANHT report the review results to the Minister of the MOHW through the supporting institution, the National Evidence-based Healthcare Collaborating Agency (NECA).

Following that, the MOHW notifies the candidates for the TANHT and recruits the implementing institutions. In this stage, doctors from the implementing institutions that are interested in the TANHT can apply to this notification with an application form.

Then, the CTANHT reviews the protocols, study design, and requirements of the applicants and select the implementing institutions equipped with the proper facilities and experienced doctors, and report the results to the Minister of the MOHW. If the Minister of the MOHW judges the selection to be appropriate, the MOHW will notify the implementing institutions and provide detailed information on the temporarily approved research-phase health technologies. Next, the implementing institutions conduct the TANHT within the scope permitted by the MOHW. While conducting the TANHT, the CTANHT will inspect the progress of the TANHT with the support from the NECA.

Table 2. List of research-phase health technology of II-b (04/24/2014)

No.	Name of health technology	Applicable patient or disease
1	Photodynamic therapy for lung cancer	Progressive lung cancer accompanied by airway obstruction and for which surgery is not possible
2	CD4 lymphocyte activity [bioluminescent assay]	Heart, lung, pancreas, small intestine, and hematopoietic stem cell transplantation
3	Wide-field scanning laser ophthalmoscopy in retinal disease	Patients for whom choroidal tumor was confirmed
4	Autologous bone marrow stem cell treatment in musculoskeletal disease	Non-union/delay in union of fracture
5	Therapeutic use of autologous peripheral blood stem cell in myocardial infarction	Myocardial infarction
6	Autologous platelet rich plasma application	Tendinosis
7	Autologous stem cell treatment for peripheral arterial disease	Diabetic limb ischemia
8	C-11-methionine positron emission topography (PET) and C-11-methionine PET/CT	(i) Assessing the result of treating prostate cancer, (ii) diagnosing and assessing the result of treating bladder cancer, (iii) diagnosing kidney cancer
9	Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy	Pseudomyxoma peritoneum, appendiceal cancer, peritoneal mesothelioma, stomach cancer, peritoneal sarcomatosis

Table 3. Rules, regulations, guidelines for implementation of TANHT

	Title	Main contents
Enforcement rules	Rules for the New Health Technology Assessment	Legal basis: eligibility criteria/requirements, procedure, composition and role of committee, duties of the implementing institution, application form.
Regulations	Regulations on Acknowledgement and Enforcement of TANHT	Detailed procedure: glossary, application, judgment (approval), management, etc.
Guidelines	The Guidelines for the Protection and Management of the Human Rights of Patients	Patient consenting: duties of doctors and patients, procedure, form (recommended).
	The Guidelines for Reporting and Managing Conflicts of Interest	Reduce bias probability: types of valid conflicts of interest, application form, reporting procedure, document management, disclosure statement.
	The Guidelines for Management of Authoring Qualifications and Ownership Rights to Research Results	Authorship & ownership: qualification, replacement of authors, inspection procedure, and acknowledgement format.
Checklist	Checklist and Grading Table for the Reviewers	Scoring table for approval procedure: 6 categories (urgency of introduction, accuracy of the completion of the application form, capacity of implementing institutions, competence level of implementing doctors, and presence of record for untruthful research).
Official notification	Bronchial Thermoplasty (example)	General information of the selected health technology: name of the selected health technology, background, applicable patients, indications, technical explanation for the medical mechanisms, characteristics (method), available alternatives, benefits, currently available evidence. Specific information of the selected health technology: selected medical institutions, permitted methodology, follow up years, patient numbers, period of approval for evidence generation.

The primary contents of an inspection are compliance with the approved protocol, proper procedures for the prevention and management of medical accidents, and proper management of medicines and medical devices. When an identified doctor from an implementing institution provides treatment to an enrolled patient, the implementing institution submits the medical results to NECA monthly using an electronic Case Report Form. The CTANHT will review the interim and final reports written by the implementing institutions. Following that, upon completion of the implementation, the CTANHT will integrate data and analyze it with the support from the NECA. The analyzed results are then submitted to the Committee for New Health Technology Assessment, which will perform another nHTA according to the Rules on New Health Technology Assessments (Chae-Min *et al*., 2013; http://www.law.go.kr/ lsInfoP.do?lsiSeq=128349#0000 (accessed 06/05/2014).

Amendments of related enforcement rules

The procedures for the TANHT, the roles and responsibilities of the involved parties, and the CTANHT were included in the amended "Rules for the New Health Technology Assessment" as shown in Table 3 (http://www.law.go.kr/lsInfoP.do?lsiSeq=128349#0000(accessed 06/05/2014), the contents of which are as follows: (a) eligibility criteria and requirements for the TANHT; (b) procedures for the assessment and implementation of the TANHT; (c) role of the CTANHT (details of the review, process management, etc.); (d) duties of the implementing institutions (observance of protocols, periodic reporting for adverse events, submission of interim and final reports); and (e) application forms for the TANHT and the evidence generation plan (Chae-Min, 2013; http://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/CED.pdf(accessed 06/05/2014).

The process of enacting the related regulations of the MOHW

The enactment of "regulations on acknowledgement and enforcement of TANHT" requires definition of terms, a detailed procedure for the application and approval of the TANHT, the managing process of implementing institutions, and detailed implementation criteria.

The major contents of this regulation are as follows:

(a) acceptance criteria and the application form for the TANHT; (b) detailed procedure for the TANHT and announcement of the assessment results; (c) procedures for modifying the TANHT; (d) formation of the CTANHT and relevant subcommittees; (e) implementation criteria for the TANHT; (f) management process of the implementation institutions; (g) process of opinion collection; (h) process of confidentiality and non-disclosure; (i) compensation for the victims of adverse events resulting from TANHT; (j) explanation documents for patients; and (k) patient consent forms, etc. (Chae-Min, 2013; National Patient Safety Agency, 2011; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf(accessed 06/05/2014,).

Related guidelines and example of official notification

In total, 3guidelines, 1 checklist, and 1 example of an official notification were developed (see Table 3). First, "the Guidelines for the Protection and Management of the Human Rights of Patients" contains the objective, scope of application, definitions of terms, duties of implementing doctors for patient consent, and details of patient consent (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf(accessed 06/05/2014; Government Printing Office, 1949; http://www.ub.edu/recerca/Bioetica/doc/Declaracio_Helsinki_2013.pdf(accessed 06/05/ 2014; http://neca.re.kr/nHTA/eng/report/evaluation_paper.jsp (accessed 06/05/ 2014); http://videocast.nih.gov/pdf/ohrp_appendix_belmont_report_vol_2.pdf (accessed 06/05/ 2014)).

Second, "the Guidelines for Reporting and Managing Conflicts of Interest" includes the objective, scope of application, definitions of terms, types of valid conflicts of interest, the way for reporting and disclosing of conflicts of interest, principles of review, follow-up actions for conflict of interests, principles for archiving and managing related documents, and conflict of interest disclosure statements (Chae-Min, 2013; National Patient Safety Agency, 2011;Norris *et al*., 2011). Third, "the Guidelines for Management of Authoring Qualifications and Ownership Rights to Research Results" contains the objective, scope of application, definitions of terms, qualification of authors, replacement of authors, ownership and inspection procedures for research results, and standardized phrases for acknowledgement (Chae-Min, 2013; http://hms.harvard.edu/about-hms/integrity-academic-medicine/hms-policy/faculty-policies-integrity-science/ authorship-guidelines (accessed 06/05/2014); http://wustl.edu/policies/ authorship.html (accessed 06/05/2014)). Fourth, the "Checklist and Grading Table for the Reviewers" consists of 6 categories, as follows: urgency of introduction, accuracy of the completion of the application form, capacity of implementing doctors and institutions, facilities of implementing institutions, competence level of implementing doctors, and presence of record for untruthful research (Chae-Min *et al*., 2013). Finally, an example of official notification for an individual case of TANHT was prepared for "bronchial thermoplasty." This notification consists of the name of the selected health technology, background for the selection as a TANHT, applicable patients, indications, technical explanation for the medical mechanisms, and characteristics of the selected health technology including method for treatment or diagnosis, available alternatives, benefits of selected health technology over the alternatives, currently available evidence for safety and effectiveness, selected implementing institutions, permitted methodology, follow-up years, patient numbers, period of approval for evidence generation, and so on (Chae-Min *et al*., 2013).

Funding issues

The TANHT funding source consists of government funding (including subsidies) and patient charges. Government funding supported each TANHT item to up to 180,000US dollars in the initial half year, and 280,000US dollars in each subsequent year. Approved hospitals (and associated investigators)

generated income through patients' payments for treatment. Furthermore, the government recommends that approved hospitals use treatment income as a follow-up cost. Although government supports funding through subsidies for follow-up costs, it is not enough to fully cover them. The TANHT has been implemented since April 24, 2014 with 360,000US dollars.

DISCUSSION

This study was conducted to provide a framework for the TANHT and the requirements for managing its evidence-generation process, so that the high-quality evidence generated from this system could be used in subsequent nHTAs. If the system for the TANHT were to be implemented based on the results of this study under the strict clinical management system at the national level, it would not only help maintain the quality of the temporarily approved health technologies, but also facilitate the generation of clinical evidence and ensure the objectivity and transparency of the process (Chae-Min *et al*., 2013). However, the derived system for the TANHT may be considered somewhat strict in the current clinical situation in Korea, and the doctors in charge may forgo applying for the TANHT to avoid the rigorous process. That said, it must be noted that this system was developed to provide opportunities for patients to receive promising research-phase health technologies for which there are no alternatives. Furthermore, the urgency of the clinical introduction for such technologies must be acknowledged and the necessary clinical evidence for the nHTA needs to be generated. Such significance must be noticed by the doctors in charge and the leadership in implementing institutions so they can clearly understand their responsibility as healthcare professionals and institutions to produce the necessary clinical evidence in a fair and transparent manner.

In addition, the TANHT may potentially cause misunderstandings among patients regarding the effectiveness of temporarily approved technologies and it could be considered controversial from an ethical standpoint. Thus, doctors in charge must inform the patients and their families that this system offers more treatment options to the patient and improves the chances of recovery at the national level. At the same time, the patients and their families must be informed in detail of the risks and benefits involved, including the possible side effects, before being asked for their consent (6,10–14). In addition, before the introduction of this system, efforts must be made to minimize any potential misunderstandings arising from the lack of communication with the relevant patient and consumer organizations by providing sufficient explanation and information. Moreover, the implementing parties are advised to equip themselves with the necessary safety nets. Furthermore, for matters not stipulated in the Guidelines for the Protection and Management of the Human Rights of Patients, the relevant laws and regulations such as the Bioethics and Safety Act should be observed through discussions by the CTANHT (Chae-Min, 2013; http://www.ich.org/fileadmin/Public_ Web_ Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1_ _Guideline.pdf(accessed 06/05/2014); Government Printing Office, 1949; http://www.ub.edu/recerca/Bioetica/doc/ Declaracio_Helsinki_2013.pdf(accessed 06/05/ 2014); http://neca.re.kr/ nHTA/e ng/ report/ evaluation_paper.jsp (accessed 06/05/ 2014); http://videocast.nih.gov/pdf/ohrp_ appendix_belmont_report_vol_2.pdf (accessed 06/05/ 2014)). In order to implement the TANHT system efficiently, the doctors in charge must produce the necessary clinical evidence in accordance with the approved evidence generation protocol and improve the protocol of TANHT items within the verification system (e.g., Institutional Review Board, Data Safety Monitoring Board, etc.). Simultaneously, the CTANHT must dedicate its efforts to ensuring the proper management of the derived process. In addition, complex issues (e.g., the degree of risk permitted based on the patient benefit-risk ratio) arising from each of the technologies should be resolved through discussions and understanding among the relevant experts and stakeholders, including policymakers (Chae-Min *et al*., 2013).

Although evidence can be generated through this system, it might be that successive repetitions of then HTA for each temporarily approved health technology will differ. Indeed, the assessments could result in the new technology lacking sufficient evidence, or could reveal the technology to have poor clinical effectiveness (Carbonneil *et al*., 2009). For instance, lung volume reduction surgery and high-dose chemotherapy with autologous bone marrow transplant were conducted as CEDs in clinical settings in the U.S. for many years (Mohr and Tunis, 2010). After 7 to 10 years of producing clinical evidence for these technologies, overwhelming evidence indicated that these technologies were more risky than the conventional procedures and did not provide any additional benefits to the patients. Based on these results, these procedures were removed from the conditional coverage list. Despite the investment of a significant amount of time and money in order to provide conditional insurance coverage, the NIH and American society accepted the results, even though these results differed from what they expected; researchers of the NIH concluded that further unnecessary spending on these technologies should be prevented. Based on this, efforts must be made to raise awareness among patients, guardians, and implementing institutions that not all temporarily approved new health technologies will be deemed to be safe and effective after the final assessment (Chae-Min *et al*., 2013). To operate the TANHT system efficiently and increase its application, established data through this system must be released and research outcomes have to be shared across various countries performing similar health technology assessments; this will allow for discussion of required improvements for this system. However, despite great efforts, the evidence generated after performing the TANHT system might be insufficient to allow it to undergo another nHTA, and the effectiveness of the studied technology might not be supported even after repeated assessments. At this point, we will have to consider the challenges of predicting various cases of new health technologies failing to accrue evidence, and prepare specific procedures and standards for cases where a lack of evidence can be predicted. Moreover, there should be procedures for obtaining the opinions of stakeholders and discussing the matters in an official manner. Subsequently, the results of the discussion should be periodically reflected in the related rules, regulations, and guidelines. Finally, it is important to note that the lack of a procedural implementation

period and budget can be fatal to the system's operation; thus, it is necessary to constantly inform the stakeholders and policymakers of the importance of this system and attract financial assistance (Chae-Min, 2013; Carbonneil *et al*., 2009).

Conclusion

The system for the TANHT was developed to supplement the current nHTA system, which is an extension of an evidence-based decision-making system. It involves allowing the implementation of promising research-phase health technologies with reimbursement coverage for a certain period while the necessary clinical evidence is generated. In addition, the collected evidence is analyzed and managed by objective experts to be used as basic data in another nHTA. In this study, we developed an amendment of related enforcement rules, a process of enacting related regulations, an example of official notification, and guidelines to ensure that the TANHT can be implemented under a strict management system at the national level. Through these provisions, it will be possible to maintain the quality of the temporarily approved new health technologies above a certain level and to assure objectivity and transparency of the generated clinical evidence (Chae-Min *et al*., 2013). Additionally, this system would provide a legal basis and enable patients to opt for new health technologies that would otherwise not be implemented because of the restrictions of the current health insurance system, even if implementation were desired. This protects the rights and interests of patients suffering from intractable diseases who are seeking to obtain timely treatment. In addition, it will be possible to secure quality and reliable evidence necessary for establishing healthcare policies, such as the reimbursement coverage standards at the national level, by presenting a procedure for the analysis and management of clinical evidence for temporarily approved new health technologies. Through this system, new health technologies can be assessed in a timely manner and promising health technologies of possibly great benefit for the public will be introduced much earlier than before. In addition, this system will allow the efficient use of limited healthcare resources while encouraging reinvestments into the development of related health technologies. In other words, this system can contribute to the development and nurturing of new health technologies. Finally, it will lessen the ongoing controversies over the delayed introduction of newly developed health technologies (Chae-Min *et al*., 2013).

Limitations

The proposed system for TANHT is for regional health policy improvement in South Korea. In addition, every health insurance system in the world is optimized at each country's social environment. Therefore we suggest that developed TANHT is to be used as a reference of health policy improvement (allowance of health technologies that have uncertainty in effectiveness but promising), not as a CED introduction.

List of abbreviations

CED: Coverage with Evidence Development
CFFE: Conditionally Funded Field Evaluation
CMS: Centers for Medicare and Medicaid Services
CMTP: Center for Medical Technology Policy
CTANHT: Committee for the Temporary Approval of New Health Technology
IRB: Institutional Review Boards
MOHW: Ministry of Health and Welfare
nHTA: new health technology assessment
NECA: National Evidence-based Healthcare Collaborating Agency
NCD: National Coverage Determination
NIH: National Institution of Health
OHTAC: Ontario Health Technology Advisory Committee
OIR: Only in Research

Declarations

- Ethics: This manuscript does not report any studies involving human participants, human data, human tissue or animals.
- Consent to publish: This manuscript does not contain any individual person's data.
- Competing interests: The authors declare that they have no financial or non-financial competing interests.
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- Availability of data and materials: All authors allowed sharing of included data in this manuscript.

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