Form Section 5 - Research Plan

Complete this section in the order of all the following components: (A) Specific Aims, (B) Statement of Qualifications for Innovative Research Grant Award, (C) Background and Significance, (D) Previous and Current Studies, (E) Research Design and Methods, (F) Anticipated Results, (G) Human Subjects, (H) Gene Recombination, (I) Microbes in Risk Group 2, 3, 4, (J) Animal Investigations, (K) Potential Hazards, and (L) References. Please specify each item in separate paragraphs.

(A) Specific Aims

Overall aims: This project has two primary purposes. The first purpose is to develop a computerized adaptive knowledge and education system for testing and improving the patient's and caregiver's knowledge on both stroke and occupational therapy (OT). The second purpose is to develop a patient-centered, individual tailored OT program on the basis of the computerized adaptive knowledge and education system and examine its effect on ADL function in stroke patients.

Specific aims (as described according to the timeline of this project):

Phase 1 - First half year (0-0.5; 0.5 year):

1. To develop a 100-item pool for stroke and OT knowledge, respectively. All 200 items will be designed to be easy-to-understand for the patients and encompass the full spectrum of knowledge.
2. To develop educational materials using multimedia for stroke and OT knowledge. All the items of stroke and OT knowledge and their corresponding educational materials will be matched.

Phase 2 - Second half of the first year to the first half of the second year (0.5-1.5; 1 year):

1. To administer the 200 items on caregivers and patients with as wide a range of severity as possible. Because of the endurance/acceptability of patients, each patient will be interviewed with about 100 items randomly selected from the 200 items. Each caregiver will be interviewed for all 200 items. In addition, responses from 200 patients and 200 caregivers for each item are needed for data analysis. Thus, 400 patients and 200 caregivers will be interviewed.
2. To apply the educational materials for 100 patients and 100 caregivers. We will make sure that all the educational materials will be easy-to-understand for patients and caregivers.

Phase 3 - The second half of the second year (1.5-2; 0.5 year):

1. To examine the model-data fitting of the items and calibrate the item characteristics with Rasch modeling. The fitted and calibrated items will serve as the item bank of the computerized adaptive testing system for stroke and OT knowledge.
2. To determine the performance (i.e., number of items needed to achieve excellent reliability) of the computerized adaptive testing system via a simulation study.
3. To develop a personal computer version of the computerized adaptive knowledge and education system to be used for the subsequent data collection.

Phase 4 - The third year (2-3; 1 year):

1. To examine the effectiveness of on 50 patients and 50 caregivers.

Phase 5 - The last 3 months of the third year (3; 0.25 year):

1. To develop the treatment protocol of patient-centered, individual tailored OT on the basis of the

computerized adaptive knowledge and education system. We will ensure that the protocols are feasible.

Phase 6 - The fourth year and the fifth year (4-5; 2 years):

1. To examine the effectiveness of the treatment protocol of patient-centered, individual tailored OT on 100 patients. Both short-term and long-term effects will be determined.
2. To determine the cost effectiveness and cost utility of the protocol of patient-centered OT.

(B) Statement of Qualifications for Innovative Research Grant Award

N/A

(C) Background and Significance

The importance of ADL function for stroke patients

Stroke is the leading cause of adult disability.[1] A patient's performance of activities of daily living (ADL) is considered indicative of the level of concomitant disability (or independence), which is often an outcome measure in stroke trials.[2, 3] ADL dependence (i.e., disability) of a stroke patient often leads to burden and stress on his/her caregiver and dissatisfaction with life.[4, 5] Thus, the quality of life of both patients and caregivers is highly threatened following a stroke.[6]

ADL includes both basic ADL (i.e., self-care activities) and instrumental ADL (IADL), which is higher levels of physical function or activities that can occur and are necessary for independence in the home and community.[7, 8] Patients and caregivers often complain that they are ill-prepared for community living (i.e., ADL independence in the community) with respect to practical skills.[9] Particularly problematic is the transition from rehabilitation 'patient' to that of community-dwelling person with a disability. Once discharged from rehabilitation, patients feel isolated and abandoned and have difficulty finding out about and accessing community services. A Canadian study found that only 11% of patients with chronic stroke were fully satisfied with their level of community reintegration.[10] Thus, reducing the degree of dependence in ADL is often a central aim of rehabilitation programs for patients who have suffered a stroke.

The major challenges of ADL training

There are at least 3 major challenges for ADL training. First, most patients and caregivers lack knowledge of stroke and its resulting disability. Several studies have reported that public awareness of stroke is limited.[11-13] This lack of knowledge of stroke can greatly affect the patients and caregivers' expectations of recovery and rehabilitation. In particular, stroke patients continue to expect a full recovery, even months after their stroke onset.[9] On the other hand, clinicians are reluctant to predict outcomes and have difficulty communicating realistic information about recovery to patients. Thus, patients and their families tend to expect that rehabilitation therapy should focus on training related to motor recovery rather than ADL training. They may also believe that if motor function can be recovered, there is no need for ADL training.

Knowledge of stroke plays an important role in treatment decision-making.[11, 13, 14] If patients and their families do not accept the disability status (reflecting knowledge of stroke), they will not understand, not to mention accept, the importance of ADL training. Thus, the knowledge of stroke of the patients and family is highly associated with the acceptance and effectiveness of ADL training.

Second, because clinicians are usually very busy, they neither have sufficient time nor use efficient methods to educate the patients/caregivers on stroke and occupational therapy (OT). In particular, the profession of OT is known for and dedicated to promoting ADL function for patients.[15, 16] Thus, even patients who have been receiving rehabilitation for a while may have a limited understanding of stroke and OT.[9, 17] Because stroke patients and their families cannot understand the long-term effects of stroke, the resulting disability, and help provided by the profession of OT, the need of the patients to participate in ADL training is limited.

Third, the family members of stroke patients, in Taiwan, may employ caregivers (either foreign or domestic caregivers) who are very likely to help patients perform ADL. Thus, the patients with caregivers tend to be dependent on their caregivers. Their need for ADL training is also affected. On the other hand, because of the help of caregivers, the ADL independence of the patients is always limited.

These challenges have to be overcome to increase the motivation and need of stroke patients and their caregivers. In other words, clinicians have to improve patients' and caregivers' knowledge of stroke and OT in order to increase the motivation, need, and effect for ADL training.

The importance of the patient-centered approach

In recent decades, two major movements (the patient-centered approach and evidence-based medicine) have emerged in medicine, both intending to improve the efficiency of clinical decision-making and quality of patient care.[18] The terminology related to the patient-centered approach in the literature is inconsistent and includes a variety of terms, including client-centered practice, patient-centered care, and patient-focused care. These terms are often used interchangeably, although they may have different meanings. A widely used definition is that the patient-centered approach demonstrates respect for patients, involves patients in decision-making, advocates with and for patients in meeting patient needs/expectations, and otherwise recognizes patients' experience and knowledge.[9, 19, 20]

The patient-centered approach has contributed to the overall progress of rehabilitation for patients and their families. The patient-centered approach helps rehabilitation improve both from an ethical viewpoint and from the viewpoint of its results and efficiency.[21, 22]

From the ethical point of view, the patient-centered approach requires rehabilitation professionals to acknowledge that persons with disability are full-fledged persons, that they not only have needs but also thoughts and emotions, and that even though they come across difficulties, they possess a certain amount of ability. The patient-centered approach thus generates practices that are more respectful of each patient's needs, particularities, and preferences. This approach allows patients' voices to be heard, and their expertise and competence to be acknowledged.[9]

From the technical and practical point of view, the patient-centered approach makes it possible to break with the medical discourse monopoly on disability and allows one to acknowledge that there is a time for care, which is distinct from a time for medicine.[9] By making this possible, this approach leads to clear medical acknowledgement of the parts and know-how of other health professionals; it also allows acknowledgement that individuals are not isolated, that they are social beings who need the presence of people around them, people who must be trained and informed about their needs. The patient-centered approach also increases professional acknowledgement that persons with disability are individuals (and individuals who are different from one another) whose needs and strengths vary with time. As a result, this approach leads to improvement in intervention effectiveness/efficiency.[21, 23, 24]

There are 4 mechanisms that explain how the patient-centered approach can improve rehabilitation outcomes. First, the patient-centered approach encourages clinicians to provide information to the patients. Thus, the patients and family can understand and get used to the disease and the resulting disability. Second, the patient-centered approach encourages respect, shared decision-making, and mutual goal-

setting with patients, thereby facilitating long-term collaboration between patients and clinicians to improve the quality of long-term rehabilitation.[25-27] Third, the patient-centered approach promotes patients' and caregivers' motivation, participation, compliance (adherence), satisfaction with intervention, and thereafter, the effect of rehabilitation.[28, 29] Fourth, the evaluation of outcomes needs to incorporate the expectations of patients and consider performance areas important to patients.[9] Thus, the patient-centered approach is helpful for achieving patient-focused expectations/goals.

In brief, the patient-centered approach appears to be very useful to foster patient's and caregiver's motivation and responsibility to be ADL independent. The patient-centered approach seems to help patients and caregivers participate in ADL training and thereafter to improve the effect of ADL training. On the other hand, if the patients and caregivers do not participate in ADL training, the effect of ADL training and the goal of ADL independence will not be achieved.

In addition, the importance of individualization for the patient-centered approach from the patient's perspective has implications for evidence-based medicine. It includes the use of care pathways, treatment guidelines, and protocols that tend to be prescriptive and allow little latitude for individual patient differences.[18] Furthermore, because rehabilitation patients usually have chronic illnesses that they are learning to manage and live with in the long term, it is therefore especially important that power be shifted to the patients and caregivers so that they can assume responsibility for managing their own conditions.[9]

The major obstacles to administering the patient-centered approach

The key points of administering a patient-centered approach are providing information, communication, goal-setting, and decision-making.[9, 30] At daily busy clinics, both communication and decision-making have to be completed in a short or reasonable time. The first obstacle is philosophical. In particular, the clinicians are using a bio-medical model.[9] For patients and their families, patient-centered rehabilitation refers to active involvement in managing their health care and their rehabilitation process in partnership with rehabilitation professionals who understand and respect their individual needs.[9] This involvement requires a shift away from the expert discourse of professionals to a discourse that recognizes the value of lay and professional knowledge.

The second obstacle is the limited resources (including manpower, time, and educational materials) of the clinicians. Particularly, modern rehabilitation clinics are so busy that clinicians do not have enough time to administer the time-consuming patient-centered approach. Thus, patients and caregivers often report more difficulties when their goals do not match those of the programs or the professionals.[9]

The possible effects of stroke/OT education

Stroke patients and caregivers have a substantial need for information. Education and information are crucial to informed client participation in decision-making and goal setting.[9] As aforementioned, patients' and their family's knowledge of stroke and OT is often limited, which hampers the administration of the patient-centered approach and ADL training. Both patient and family often fail to comprehend the long-term disability following stroke. As a result, the needs of ADL training might be neglected. Thus, stroke and OT education can be viewed as a key requirement for administering the patient-centered approach and ADL training.

Providing stroke-related information can improve the patient's and caregiver's knowledge of stroke, as well as aspects of patient satisfaction.[31] However, clinical education program may not be effective for improving stroke-related knowledge in stroke patients.[32] If educational material is not repeated or reinforced, this may lead to inefficient learning.[32] Educational information should be appropriate and timely, and meet the patient's expectations. In addition, if stroke education is not individualized, that is, if

it does not address each patient's specific needs, the effect of education will be compromised. Thus, individualized and adaptive education will improve teaching efficiency.[33, 34]

OT is conceptualized as a temporary phase in the career of chronic illness and disability that is directed at helping people to function as best they can within the limitations of their conditions and prepares them to function in their homes and community. OT has proven its ability to improve patients' ADL independence and thus quality of life.[15, 16] If patients and their family can understand how OT can help them, their motivation to participate in OT intervention and ADL training will increase, and the effects of ADL training will be improved.[35]

Public education campaigns for stroke are used worldwide. However, few evaluations of such campaigns have been published, so the short-term and long-term effects of stroke and OT education remain unknown. Since the knowledge of stroke and OT is critical to administering the patient-centered approach and promoting ADL independence of stroke patients, the next step is to do more research to evaluate actual behavior changes that occur after educational interventions and to determine whether they translate into access to acute stroke therapy.[36]

Computerized adaptive testing (CAT) is efficient and precise for assessments

CAT involves the use of a computer to administer items to respondents and allows respondents' levels of function to be estimated as precisely as desired (i.e., to reach a pre-set reliability level).[37, 38] Because each assessment is tailored to the unique ability level of each respondent, CAT is adaptive to each patient. Items are administered on the basis of the patient's performance. For example, if a patient cannot stand independently, the computer 'knows' not to ask whether he/she can walk. Instead, the computer asks whether he/she can sit without assistance. The result is a decrease in administrative burden with little loss in precision.[37, 39] Thus, CAT has shown efficiency, reliability, and validity in health-related measurements.[39-42] Therefore, CAT is very promising in testing patients/caregivers' stroke/OT knowledge. Such a technique also seems promising in delivering educational materials for stroke/OT knowledge.

Summary of literature review

Stroke is the leading cause of adult disability. A person's level of independence in ADL is considered indicative of the level of disability. The effectiveness of ADL training depends greatly on the motivation of patients and their families. The patient-centered approach has been advocated for clinical practice and has the potential to increase the motivation and effectiveness of ADL training. However, the patient and his/her caregiver mostly lack knowledge of stroke (e.g., resulting long-term disability) and OT, which is professional help with ADL training. This lack of fundamental knowledge not only hampers the execution of patient-centered approach but also limits patients' motivation for ADL training and the effectiveness of ADL training.

To address these issues, our primary purpose is to develop an computerized adaptive knowledge and education system for testing and improving patients' and caregivers' knowledge of both stroke and OT. Our further purpose is to propose a patient-centered OT approach partly based on the adaptive knowledge and education system and to examine its effect on ADL function in stroke patients. Finally, we hope that our project will allow us to combine patient-centered care and evidence-based medicine while addressing the imperatives of cost effectiveness and utility. Our goal is to foster a patient-centered approach that is evidence based.

(D) Previous and Current Studies

Professor Hsieh has led a research group to develop computerized adaptive testing (CAT) systems for assessing neurobehavioral outcomes and patient-reported outcomes in stroke patients for several years. The team includes psychometricians (Drs. Kai-Ping Grace Yao and Wen-Chung Wang), experts in computerized adaptive testing (Drs. Ching-Lin Shih and Wen-Chung Wang), and stroke-related professionals (e.g., neurologist Dr. Jiann-Shing Jeng, physiatrist Dr. Wen-Hsuan Hou, physical therapist Dr. Jau-Hong Lin, and occupational therapists Professors I-Ping Hsueh and Ching-Lin Hsieh). His research group has developed 4 neurobehavioral CAT systems, which can be accessed at http://140.112.116.44/cat/.

Because the current neurobehavioral measures used in Taiwan cannot achieve precision, efficiency, and comprehensiveness simultaneously, to address these fundamental issues for clinicians, researchers, and patients, he has maintained a consistent interest in psychometrics and outcome measurements related to clinical research on patients with stroke. Since the year 2000, he has written about 60 articles regarding neurobehavioral measures and patient-reported measures in stroke patients. These articles systematically examined the psychometric properties (including reliability, validity, responsiveness, and minimal important difference) of well-known outcome measures for stroke patients, e.g., ADL/IADL, mobility, motor function, and HRQOL. Most of the articles have been published in internationally respected journals, including 6 articles in *Stroke* and more than 30 articles in top-ranking international rehabilitation-related journals (e.g., the *Archives of Physical Medicine and Rehabilitation*, *Physical Therapy*, and *Neurorehabilitation and Neuro Repair*).

We have listed some relevant publications (including advanced topics on CAT developments, the application of Rasch models, data interpretation of outcome measures, and cost-utility) completed since 2006 by the PI and Co-PIs as the primary authors. In particular, our research team has validated the utility measure (the EQ-5D)[43, 44] and applied it to calculate the quality-adjusted life expectancy in stroke patients.[45] The reprints are attached.

In addition, we have carried out a pilot study interviewing 20 patients and 10 caregivers about their understanding about stroke and OT. The results showed that patients' and caregivers' knowledge about stroke and OT is very limited. In particular, although the patients had been treated with OT for several weeks, the patients and caregivers still found it difficult to identify the difference between physical therapy and OT. The patients and caregivers also found difficulty in determining their short-term or long-term prognoses. These preliminary results imply that stroke and OT education is greatly needed by patients and caregivers.

Thus, in more than 10 years in this field, he and his team have accumulated abundant experience in the fields of psychometrics, item response theory, computerized adaptive testing, and occupational therapy for stroke patients. His research team should be well qualified to conduct this study.

(E) Research Design and Methods

The 5-year project is divided into 6 phases (Figure 1)--Phase 1: developing item pools and educational materials for stroke and OT knowledge. Phase 2: field testing of the items and educational materials on patients and caregivers. Phase 3: developing a personal computer version of the computerized adaptive knowledge and education system. Phase 4: examining the effectiveness of the computerized adaptive knowledge and education system. Phase 5: developing a patient-centered OT program. Phase 6: examining the effectiveness of the patient-centered OT program.

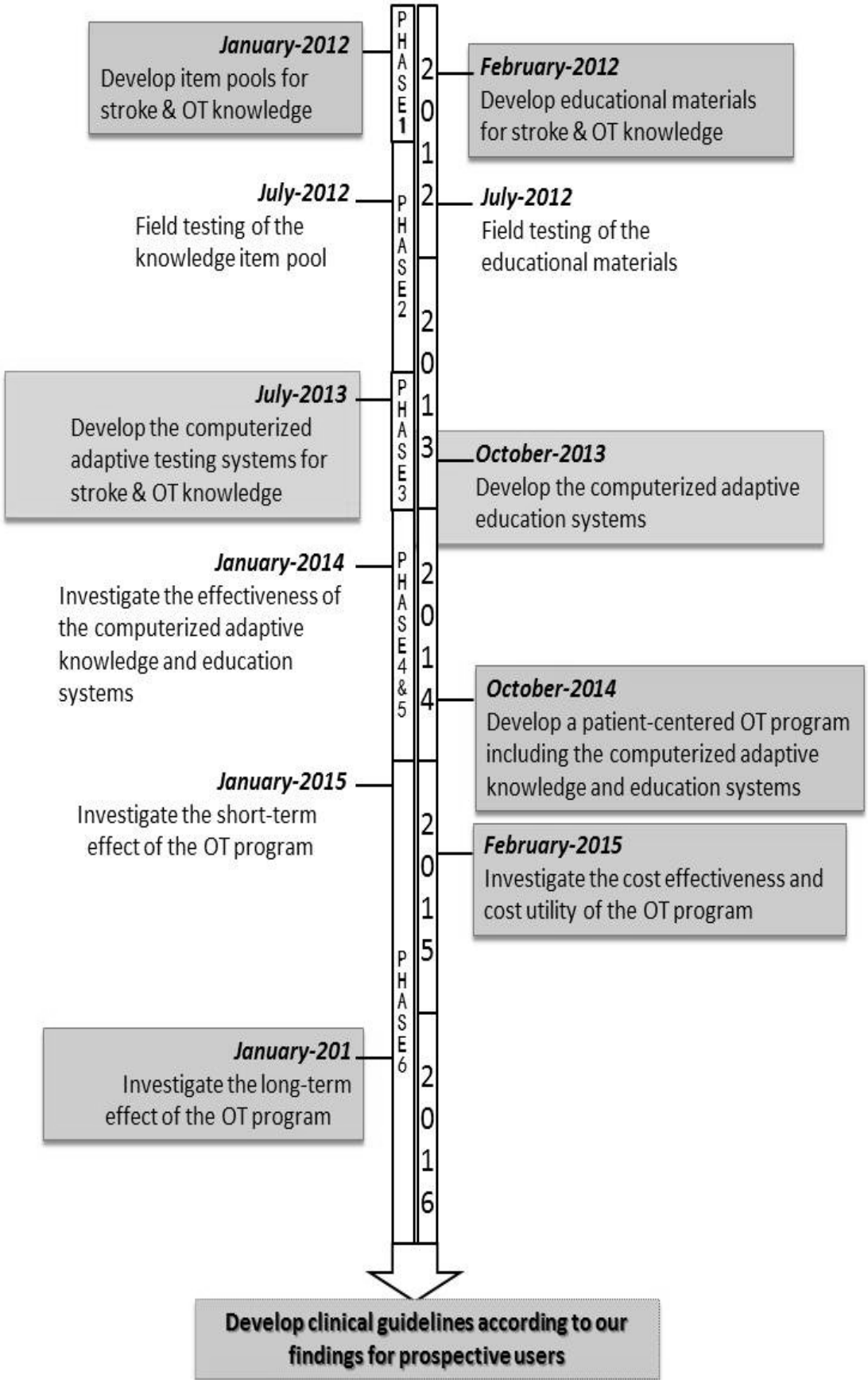

Figure 1. Timeline and procedure of the 5-year project.

Phase 1: Developing item pools and educational materials for stroke and OT knowledge.

In the first six months, we will develop item pools and educational materials for stroke and OT knowledge. The general principles and procedures of developing the item pools and educational materials are shown in Figure 2.

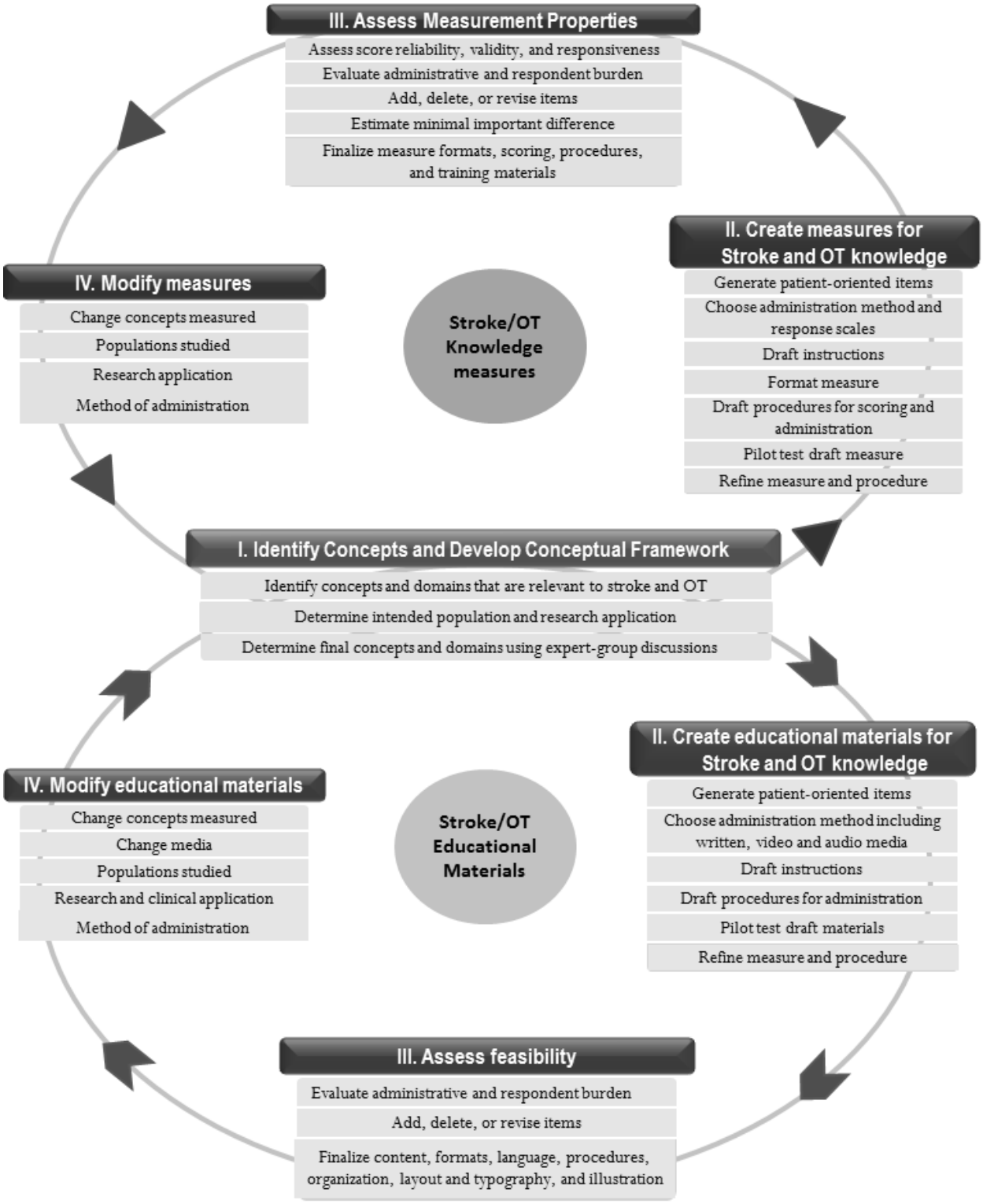

Figure 2. The steps of developing the stroke/OT knowledge items (the top part) and educational materials (the bottom part).

Procedures of Item Pool Development:

Figure 2 [the top part] shows the item generation and review procedures. Because both stroke and OT knowledge have multiple domains, we will first determine the domains for both item pools. At least 5 stroke and OT experts will be invited to participate.

We will first systematically search and examine all the existing measures to propose possible domains for stroke and OT knowledge, respectively. In addition, focus group interviews with stroke and OT experts will be conducted to examine the domain coverage and determine the final domains. We expect that 3 to 5 focus group interviews will be needed to reach final agreement on the domains of stroke and OT knowledge.

A sufficient number of items will be developed, at least 50 items for each domain. Five focus group interviews with clinicians and psychometric experts will be conducted to examine item continuum coverage in order to ensure a whole range of items for each domain (covering both bandwidth and depth).

We will recruit about 50 caregivers and 50 patients with a diverse range of severity of stroke for development and cognitive debriefing of each item. The final wordings of each item will be determined based on expert opinions and field testing on cognitive debriefing to achieve clarity, appropriateness, and relevance for each item, as perceived by the caregivers and patients.

We will employ a cognitive interviewing protocol proposed by Willis.[46] The cognitive interviewing process will ascertain: (1) comprehension of each item (i.e., what the patient/caregiver believes the item is asking; what specific words and phrases in the item mean to the patient/caregiver); (2) the processes used by the patient/caregiver to retrieve relevant information from memory (i.e., what the patient needs to recall to be able to answer the question; what strategies the patient uses to retrieve the information); (3) decision processes, such as motivation and social desirability (i.e., whether the patient/caregiver is sufficiently motivated to accurately and thoughtfully answer the question; whether the patient is motivated by social desirability in answering the question); and (4) response processes (i.e., whether the patient/caregiver can match his/her response to the question's response categories).

All items will undergo an initial set of 10 cognitive interviews. The items will be revised, if necessary, to increase clarity, appropriateness, and relevance for the patients/caregiver. If, however, after 5 interviews the item undergoes major revisions, the item will be subjected to 3 to 5 additional interviews after the revisions. When no further revisions are needed, the final versions of the items will be completed.

We expect that 200 items will be constructed for each item pool. A total of 400 items will be developed for both the stroke and OT knowledge-item pools.

Procedures of Developing Educational materials:

Figure 2 (the bottom part) also shows the content generation and review procedures. The content and design features of the educational information will be prepared according to best practice recommendations.[34] This includes features such as appropriate layout, organization, and typography; appropriate use of illustrations and media; and the incorporation of features that facilitate learning and motivation.

For the development of content, the educational materials will be fully linked with the domains and items of stroke and OT knowledge. We will use various media, including written, audio, and video media, where appropriate, to achieve ultimate learning effects. All educational materials will undergo an initial set of 5 cognitive interviews. The materials will be revised, if necessary, to increase clarity, appropriateness, and relevance for the patients/caregiver.

Phase 2: **Field testing of the knowledge items and educational materials on caregivers and stroke patients with characteristics as diverse as possible**

Subjects:

From the 6th to the 18th month, 400 patients (half inpatients and half outpatients) will be recruited if they meet the following criteria: (1) diagnosis (International Classification of Diseases, ninth revision, clinical modification [ICD-9] codes) of cerebral hemorrhage (ICD-9, 431) or cerebral infarction (ICD 9, 434), (2) absence of any other major disease affecting premorbid ADL independence and mobility (e.g., severe rheumatologic arthritis), (3) ability to follow instructions and complete the interviews, and (4) ability to give informed consent personally. We will exclude patients with cognitive impairment (Mini-Mental State Examination (MMSE)[47] scores < 20). In addition, we will invite 200 caregivers to participate in this study.

The reasons for recruiting 400 patients are described as follows, although a theory-based mathematical function to calculate sample sizes needed for IRT is largely lacking.[48] First, because of the endurance/acceptability of patients, each patient will be administered about 100 knowledge items randomly selected from the 200 items and their corresponding educational materials. In addition, at least 200 responses for each item, or responses from 200 patients, are strongly recommended for data analysis.[49, 50] Thus, about 400 patients will be interviewed.

To ensure selection of patients with a broad range of severity and days after stroke onset, we will use a stratified sampling method. Two stratifying variables will be considered. One is stroke severity (using the National Institutes of Health Stroke Scale [NIHSS][51] as 4 strata: mild [NIHSS 0-5], moderate [6-10], severe [11-20], and very severe [>20]). The other is time after stroke onset (3 strata: 0-3 months, 3-12 months, and > 12 months). We will determine whether the patients cover the entire spectrum of stroke severity and days after onset after one year of data collection. If not, we will later recruit patients who are less representative to ensure adequate representation of the stroke population.

Procedures:

All 200 items and their corresponding educational materials developed in Phase 1 will be coded and saved in personal computers (PC, a touchscreen notebook). We will randomly select items from the item pools to administer on each patient or caregiver. On average, each patient will be tested with about 100 items by face-to-face interview. After the testing, if a participant fails on some items, the corresponding educational materials will be presented. However, each session will be shorter than 1.5 hours to prevent patient/caregiver discomfort and fatigue. The patients/caregivers will be able to take a rest during the testing, if necessary. If a patient/caregiver cannot complete more than 60 items in one session, the patient will be invited to be tested again on another day, but within a week.

The data collection will be carried out by research assistants (full-time or part-time; occupational therapists or research nurses). All items will be administered by face-to-face interview. To avoid any possible interference during the interviews, all the interviews will be administered in a quiet room (e.g., individual treatment room or counseling room).

Data analysis

We will first use the Mplus software to perform a one-factor confirmatory factor analysis (CFA) to examine the unidimensionality of all items in each domain. Three indices will be employed to assess model data fit. The first is the root mean square error of approximation (RMSEA). A RMSEA lower than 0.06 is good.[52] The second and third indices are the comparative fit index (CFI) and the Tucker-Lewis

index (TLI), whose critical values are both above 0.95.[53] In addition, the item will be deleted if its factor loading is below 0.4.[54] The remaining items will be further analyzed using the Rasch analysis.

Rasch analysis (item selection for the item banks and psychometric testing):

The unidimensionality of each domain of stroke and OT knowledge, respectively, will be further examined using multidimensional Rasch analysis to select items for each domain. We will use the ConQuest computer program to perform multidimensional Rasch analysis.[55]

Both infit and outfit statistics will be used to examine whether the data fit the model's expectations. The infit mean square (MNSQ) is sensitive to unexpected behavior affecting responses to items near the person's proficiency measure (e.g., soundness of sleep, executive function); the outfit MNSQ is sensitive to unexpected responses by persons on items far from the person's proficiency measure. Items with infit or outfit MNSQs greater than 1.3 indicate potential misfits.[56]

When items fit the model's expectations, the residuals (observed scores minus expected scores) should be randomly distributed. A factor analysis will be conducted to verify whether any dominant component exists among the residuals. The assumption of unidimensionality will hold if no dominant component is found.[56] Only the items fitting the Rasch model's expectations will be selected for the item bank of each domain of stroke and OT knowledge.

When the remaining items of each domain of stroke and OT knowledge fit the Rasch model, the Rasch transformed scores for each domain will be used for the remaining data analysis. Rasch (transformed) scores are ability estimates (e.g., knowledge of stroke or OT) expressed in logits (natural log odds for succeeding on items of a measure), in which odds are defined as the ratio of the probability of a positive response over the probability of a negative response.

In addition, Rasch analysis yields a reliability coefficient, which is useful for determining the measurement precision of the measures. Furthermore, another structural equation model will be used to validate the stroke and OT knowledge measures. A CFA will be used to confirm the factor structure of the stroke and OT knowledge measures to establish its construct validity. The three indices (i.e., the RMSEA, CFI, and TLI) will be used to determine model data fit.[52-54]

To manage the possible missing data, we will first examine the patterns and frequency to determine why it is missing. If the data is missing systematically, we will exclude the data by "list-wise" deletion. For example, missing data on some particular items may be attributed to privacy issues. On the other hand, for data that is missing at random, we will use a multiple imputation method implemented in the software ConQuest to derive the estimated value of non-response items. These missing data management processes will also be applied on the remaining parts of this project.

Phase 3: Development of a personal computer version of the stroke and OT knowledge measures.

The stroke and OT knowledge measures (the personal computer version) will be developed and administered in 4 steps. First will be *item calibration*: The Rasch-calibrated item banks (every item with a specific "difficulty" parameter) will be used for developing the stroke and OT knowledge measures and the related simulations. Second will be *starting rule and initial function estimation*: We will use the maximum Fisher information (MFI) as the item selection algorithm, and the maximum a posterior (MAP) method to estimate the patient's ability (i.e., level of function or satisfaction). In administering the stroke and OT knowledge measures, the system will present an initial item with a moderate difficulty from the item banks for the participant. The participant's response to that item will give the CAT a basis for making the first tentative estimate of the tested participant's level of knowledge. Third will be *selecting further items*: The computer will select the item with the largest information gain for further testing; and

fourth, *stopping rule*: Excellent reliability (coefficient = 0.95) will serve as the stopping rule for both CATs.

We will determine the efficiency (number of items needed) of the stopping rule for the CAT-PROS via a simulation study. We will use the actual data of the stroke patients participating in the item pool testing (phase 2) for simulation. The personal-computer-based version will be developed in a later stage by our information technology personnel.

At this stage, we anticipate that the CATs for stroke and OT knowledge could reach an overall reliability above 0.95 (i.e., excellent reliability) and require less than 10 minutes to administer, or test fewer than 20 items, to ensure its efficiency.

Phase 4: Examining the effectiveness of the computerized adaptive knowledge and education system.

Subjects:

A total of 50 sub-acute patients and 50 caregivers will be recruited from the National Taiwan University Hospital. To cover all possible patients receiving rehabilitation, half of the patients/caregivers will be recruited from inpatients and the other half from outpatients. The patients will meet the following criteria: (1) diagnosis (International Classification of Diseases, ninth revision, clinical modification [ICD-9] codes) of cerebral hemorrhage (ICD-9, 431) or cerebral infarction (ICD 9, 434), (2) ability to follow instructions and complete the computerized knowledge and education system with or without the help of a research assistant, and (3) ability to give informed consent personally. We will exclude patients with other major diseases affecting premorbid ADL independence and mobility (e.g., late stage of Parkinsonism, severe rheumatologic arthritis) and patients with cognitive impairment (MMSE scores < 20).

The 50 caregivers will meet the following criteria: (1) aged 20 or above, (2) having taken care of a stroke patient for more than 1 month, (3) ability to follow instructions and complete the computerized knowledge and education system with or without the help of a research assistant.

Procedure:

The patients and caregivers will be invited and will use the system individually. To determine effect on patients and caregivers, respectively, if a patient is recruited, we will not invite his/her caregiver, and vice versa. Both patients and caregivers will be randomly assigned into an experimental group (receiving the computerized knowledge and education system) or a control group (receiving additional rehabilitation) using numbers randomly generated by a computer. Allocation concealment will be applied. All the participants will be tested by the knowledge system at the beginning of the study, 4 weeks after inception of the study, and 3 months after inception of the study. All the testing will be administered by a research assistant who will be unaware of study-group assignment.

Regarding the sample size needed for this study, a difference of 20% on stroke and OT knowledge in favor of the experimental group will be expected. In addition, we expect that about 70% of the participants will complete all assessments. Therefore, about 25 patients and 25 caregivers will be required for each arm of the trial to achieve a sufficient statistical power of 80%.

Protocols for the experimental and control groups:

The patients/caregivers assigned to the experimental group will first receive the computerized adaptive knowledge testing system. They will be then given adaptive educational materials provided by the educational system according to their testing results. The participants will be instructed to read or

watch the educational materials. A research assistant will help them use the system and offer counseling/explanations for the materials. The patient and caregiver will be given a week to learn these materials (Figure 3). Further counseling/explanations will be given, if necessary. After a week, the research assistant will ask the participants whether they have further questions on the educational materials. The research assistant will answer their remaining questions until the participants are satisfied with the explanations. Then the participants will be asked to take the computerized knowledge testing system again. Further educational materials will be offered, if necessary. The testing and educational procedures will continue until the participants' stroke and OT knowledge has reached a satisfactory level. The research assistant will make sure that the participants understand all the fundamental knowledge of stroke and OT, which will be pre-determined by our experts.

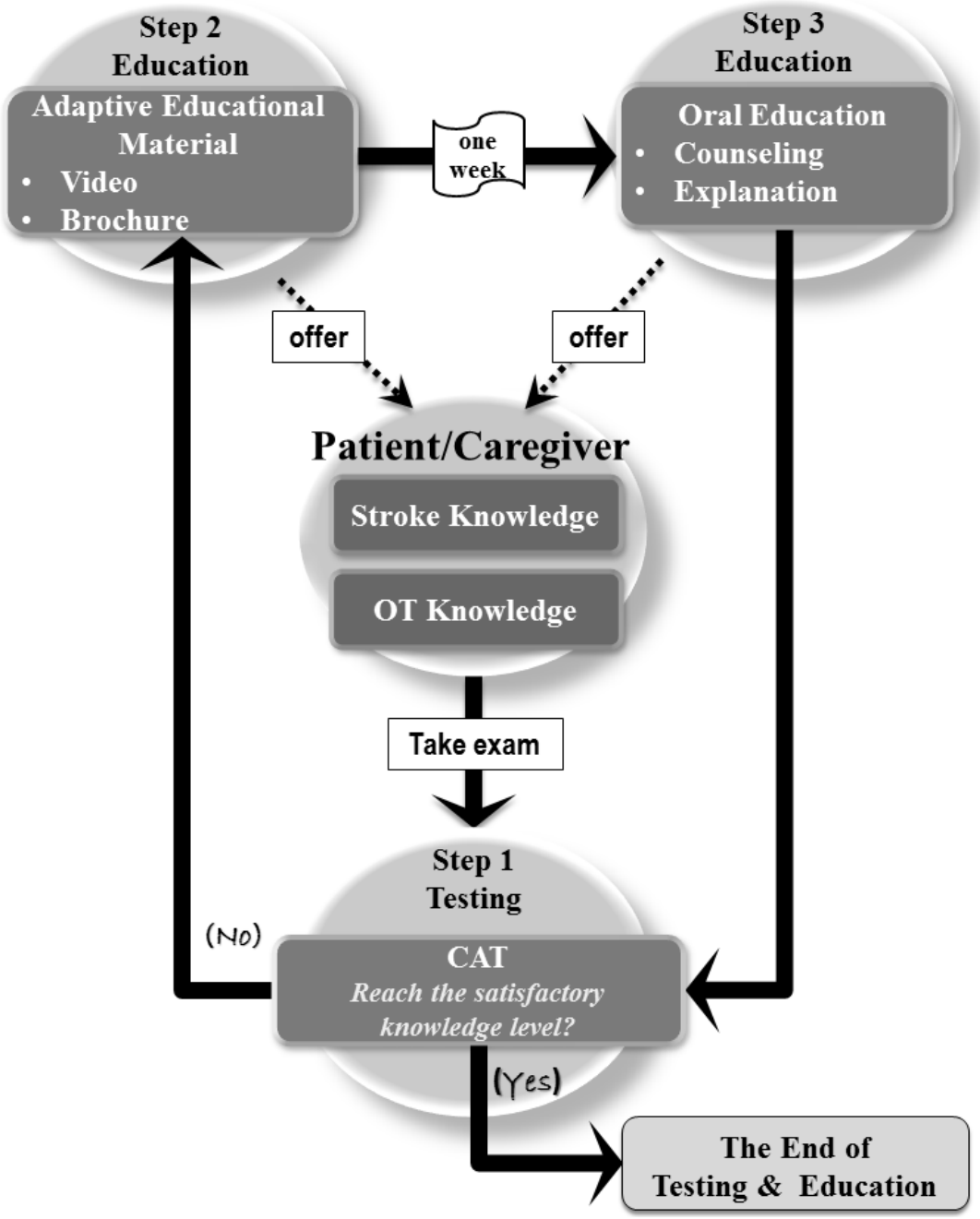

Figure 3. The procedures of testing knowledge of stroke/OT and offering educational materials and counseling.

We expect that the whole procedure will take about 2 to 3 weeks (i.e., two to three times of education). The time that the patient/caregiver devotes to learning the related materials will be recorded. We will also document the difficulties/questions raised by the participants. Such information will be useful for further improving the efficiency of the system.

The participants in the control group will not be given the results of testing. However, oral explanations will be given by the research assistant if they have questions about the testing. These participants in the control group will be offered additional rehabilitation programs to serve as a placebo. The time of the additional rehabilitation program will be similar to the time that the participants spend taking part in the experimental group, which we expect to be about 2 hours per week for 3 consecutive weeks.

Data analysis

Baseline characteristics will be reported by descriptive statistics (e.g., mean and SD for continuous variables, or frequency tabulations for categorical variables) for each group. Homogeneity of both groups at the baseline (time 1) will be examined using a Student's t test or Mann-Whitney U test where appropriate. If there are between significant differences between both groups, statistical control (e.g., analysis of covariance, ANCOVA) will be applied for further analysis of effectiveness.

The primary analysis of effectiveness (full-analysis set) will consist of a comparison of the change scores between time 2 to time 1 and time 3 to time 2 in stroke and OT knowledge. Analysis of variance (ANOVA) will be used to compare the change scores between groups. The analyses will be adjusted using ANCOVA for any significant differences at baseline. Intention-to-treat analysis will be applied. Alpha level will be set at 0.05. The statistical analyses will be done by use of SPSS (version 16.0).

Phase 5: Developing a patient-centered OT program.

We will develop a patient-centered, individual tailored OT program on the basis of both a theoretical framework and the opinions of clinical experts. We will employ Steward et al.'s model[30] to develop the patient-centered OT program. The 6 main components of Steward et al.'s model include: (1) exploring both disease and illness experience, (2) understanding the whole person, (3) finding common ground, (4) incorporating prevention and health promotion, (5) being realistic, and (6) enhancing the patient-clinician relationship.[30] We will develop detailed procedures for administering all the components, as an individual and as a whole. The computerized adaptive stroke and OT knowledge and education systems will be included in the component of "exploring both disease and illness experience." We will invite 5 occupational therapists with sufficient clinical experience and 2 physiatrists to review the procedures of the patient-centered, tailored OT program. Their comments will be used to revise the procedures until agreement has been reached.

After the procedures for the patient-centered OT program are developed, we will test the feasibility of the program. We will make revisions where necessary. The clinical experts will be consulted if necessary.

Phase 6: Examining the effectiveness the patient-centered OT program on 100 patients.

Subjects:

100 sub-acute patients (including inpatients and outpatients) will be recruited from the National Taiwan University Hospital. The patients will meet the criteria (both inclusion and exclusion criteria) mentioned in the phase 4 study. Their caregivers will also be invited to participate.

Power analysis

A difference of 2 points (about 10%) on the Barthel index in favor of the experimental group will be regarded as clinically relevant.[57] In addition, we expect that about 70% of the participants will complete all assessments. Therefore, about 50 patients will be required for each arm of the trial to achieve a sufficient statistical power of 80%.

Procedure:

The patients will be randomly assigned into an experimental group (receiving the patient-centered program) or a control group (receiving additional rehabilitation). Allocation concealment will be applied. All participants will be assessed by trained raters at the beginning of the study, 4 weeks after inception of the study, 3 months after inception of the study, and 1 year after inception of the study. The raters will be unaware of study-group assignment. The cost of each group will be recorded.

We will determine cost-effectiveness by relating the costs to the effects of the program. The effects will be expressed as quality-adjusted life years (QALYs), which are measured by the EQ-5D. The costs include the costs related to resource use of primary care clinicians, secondary care appointments, admissions to health care facilities, community-based support, and individual out-of-pocket expenditure (direct costs). The direct cost estimates will be based on the costs of hospital stay and follow-up rehabilitation care. Medication costs and costs related to assistive devices and adaptations in and around the house will also be included. The costs of productivity losses (indirect costs) will not be counted because most stroke patients are retired. The incremental cost-effectiveness ratio will be calculated by dividing the mean difference in costs by the mean difference in effect (as measured by the EQ-5D) between the two groups. Costs will be evaluated by having each patient keep a cost diary for the first 24 weeks after randomization. A research assistant will check the diary every other day to ensure the integrity of recording (including the time spent on each kind of professional care). The hourly costs of specialists (including physicians, physical therapists, occupational therapists, and speech and language therapists) will be calculated using the salary schedules at the National Taiwan University Hospital.

The patient-centered program will last for 6 weeks. We expect that the therapist will spend 2-4 hours on each patient per week. For the control group, we will provide 2-hour OT per week in addition to the original OT. The content of the original and additional OTs will be recorded for both groups.

Neurobehavioral conditions of the patients:

The NIHSS[51] will be used to indicate stroke severity in the study sample. The NIHSS is a well validated and commonly used stroke impairment scale that sums the scores from individual elements of the neurological examination to provide an overall stroke severity score.[51, 58]

The stroke rehabilitation assessment of movement (STREAM)[59] instrument consists of 30 items that are equally distributed among 3 subscales: upper-limb motor function, lower-limb motor function, and mobility. Motor function is scored on a 3-point scale (0: unable to perform the test movement; 1: able to only partially perform the test movement; and 2: able to complete the test movement). Mobility is scored on a 4-point scale similar to that used for scoring limb movements except that a category has been added to allow for independence with the help of a mobility aid. Thus, the maximum raw total STREAM score is 70, with each of the limb subscales scored out of 20 points and the mobility subscale scored out of 30 points. We have validated the STREAM thoroughly in stroke patients.[60-64]

Primary outcome measures:

The Frenchay Activities Index (FAI)[65] was developed to measure social function and instrumental activities of daily living following stroke. It comprises 15 items related to normal activities: preparing

meals, washing up, washing clothes, light housework, heavy housework, local shopping, social outings, walking outside for more than 15 minutes, actively pursuing hobbies, driving/bus travel, outings/car rides, gardening, household/car maintenance, reading books, and gainful employment. The total possible score of the FAI ranges from 0 to 45. The FAI is reliable and valid in assessing social function for patients with stroke.[65-67]

The Barthel ADL Index (BI)[68] and the FAI scores can be combined to represent comprehensive activities of daily living (CADL) function, representing the entire continuum of disability.[69] The CADL contains 10 items of the BI and 13 items of the FAI (with 2 misfit items of the FAI deleted to fit the Rasch model).[69] The Rasch-transformed interval score of the CADL proposed by Hsueh et al.[69] will be used in this study.

We will also use the computerized adaptive ADL test which was developed by our research group. The computerized adaptive ADL test is efficient and valid to assess ADL and IADL in stroke patients.[70] The computerized adaptive ADL test is particularly useful for the patients in our country because it is the only ADL/IADL measure developed for stroke patients in Taiwan. Particularly, some IADL items are specific to cultural differences.[71]

Secondary outcome measures:

The EuroQol is a generic measure of quality of life (QoL) and consists of a health status profile in five domains (EQ-5D), including two that are directly related to self-care and mobility.[72] The EuroQol has been validated for use in stroke patients.[73] The advantage of the EuroQol is that it can be transformed into a utility score, allowing cost-utility analysis.[43, 72]

The Stroke-Specific Quality of Life (SS-QOL)[1] is the first HRQOL measure designed to capture all domains meaningful for stroke patients. The original developers constructed the domains and items of the SS-QOL on the basis of patient interviews. It originally included 49 items from 12 domains. We have reported that construct validity of the 12-domain SS-QOL is well supported for measuring HRQOL in ischemic stroke patients.[74]

Treatment protocols for the experimental and control groups:

The patients assigned to the experimental group will first receive the computerized adaptive knowledge testing system. They will be then given adaptive educational materials provided by the educational system according to their testing results. The participants will be instructed to read or watch the educational materials. A research assistant will help them use the system and offer counseling/explanations for the materials. The patient and caregiver will be given a week to learn these materials. Further counseling/explanations will be given, if necessary. After a week, the research assistant will ask the participants whether they have further questions on the educational materials. The research assistant will answer their remaining questions until the participants are satisfied with the explanations. Then the participants will be asked to take the computerized knowledge testing system again. Further educational materials will be offered, if necessary. The testing and educational procedures will continue until the participants' stroke and OT knowledge has reached a satisfactory level. The research assistant will make sure that the participants understand all the fundamental knowledge of stroke and OT, which will be pre-determined by our experts.

We expect that the whole procedure will take about 2 to 3 weeks (i.e., two to three times of education). The time that the patient/caregiver devotes to learning the related materials will be recorded. We will also document the difficulties/questions raised by the participants. Such information will be useful for further improving the efficiency the system.

The participants in the control group will not be given the results of testing. However, oral explanations will be given by the research assistant if they have questions about the testing. These participants in the control group will be offered additional rehabilitation programs to serve as placebo. The time of the additional rehabilitation program will be similar to the time that the participants spend taking part in the experimental group, which we expect to be about 2 hours per week for 3 consecutive weeks.

Data analysis:

Baseline characteristics will be reported by descriptive statistics (e.g., mean and SD for continuous variables, or frequency tabulations for categorical variables) for each group. Homogeneity of both groups at the baseline (time 1) will be examined using a Student's t test or Mann-Whitney U test where appropriate. If there are between significant differences between both groups, statistical control (e.g., analysis of covariance, ANCOVA) will be applied for further analysis of effectiveness.

The primary analysis of effectiveness (full-analysis set) will consist of a comparison of the change scores between time 2 to time 1 and time 3 to time 2 in primary and secondary outcome measures. Analysis of variance (ANOVA) will be used to compare the change scores between groups. The analyses will be adjusted using ANCOVA for any significant differences at baseline. Intention-to-treat analysis will be applied. Alpha level will be set at 0.05. The statistical analyses will be done by use of SPSS (version 16.0).

Incremental cost-effectiveness ratios will be calculated as cost per QALY to assess the cost-effectiveness of the different programs.

(F) Anticipated Results

We expect that the patients and caregivers' original knowledge of stroke and OT would be limited or modest. Our adaptive knowledge and education system will efficiently improve their knowledge of stroke and OT. We anticipate that the CATs for stroke and OT knowledge can reach an overall reliability above 0.95 (i.e., excellent reliability) and require less than 10 minutes to administer or test fewer than 20 items to ensure its efficiency.

Furthermore, the patient-centered OT program using the adaptive knowledge and education system will improve ADL independence in stroke patients. The patient-centered OT program will be cost-effective in increasing ADL function and quality-adjusted life years.

Significance:

1. The adaptive knowledge and education system will be useful for clinicians to promote stroke and OT knowledge for stroke patients and their families.
2. There is no computerized adaptive stroke and OT knowledge and education system yet. Our system could be the first one in the world.
3. The adaptive knowledge and education system may be so efficient that it can facilitate the administration of the patient-centered OT approach in busy clinical settings. Thus, the patient-centered OT approach will be feasible and effective.
4. We will develop clinical guidelines on the basis of the patient-centered OT program to disseminate this program to daily clinical practice.
5. We hope that our project will allow us to combine patient-centered care and evidence-based medicine while addressing the imperatives of cost effectiveness and utility.

Anticipated challenges:

We may face one challenge to collecting the cost of rehabilitation (including both direct and indirect costs). To address this issue, we will consult with an expert in health economy (Dr. Ming-Chin Yang[75, 76]) before the inception of our study.

In addition, we will consult Dr. Jung-Der Wang, who has supervised our team for more than 10 years, for calculation of quality-adjusted life year.

(G) Human Subjects

We will obtain the approval of the Institution Review Boards of the National Taiwan University Hospital. We propose to recruit about 700 eligible stroke patients and 450 caregivers during the study period. Clinical information about the patients will be obtained from medical records. Assessments of functional outcomes and related health status will be conducted using personal interview or performance rating scales. All the assessments will be administered by experienced occupational therapists or physical therapists. In some neurobehavioral assessments, some movements difficult for the patients will, unavoidably, have to be performed. In addition, some patients might feel that there are too many questions. An invitation letter will be sent out to obtain written informed consent from each participant. The letter will explain, plainly and in simple terms, the purposes of the study, the procedures, and the risks and benefits in this project, as well as the process of informed consent.

The potential risk in this research is minimal. In Phases 4 and 6, some patients will need to have their motor function examined and might feel insecure when asked to execute certain movements (e.g., climbing stairs). Procedures to minimize the risk will include careful training and safety education for the therapists.

All the data collected for this project will remain confidential. The participants' data will be kept in locked file cabinets located in the PI's office, accessible only to the study personnel.

The benefits for the participants/caregivers and/or their clinical therapists will be the results of this study. These results will help both clinicians and researchers to promote patient-centered care and evidence-based medicine.

(H) Gene Recombination

NA

(I) Animal Investigations

NA

(J) Potential Hazards

The whole project requires interviews with patients and caregivers. We will also examine the neurobehavioral performance of the patients. There will be no potential risks for patients and caregivers. However, the patients might feel tired sometimes. We will allow the patients to rest if necessary. Some stroke patients might lose their balance and thus suffer injury. To avoid this, all personnel, as mentioned in section G above, will receive extensive training on how to anticipate and avoid such occurrences.

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