Research Protocol

Effect of an Adapted Hospital Elder Life Program on Postoperative Delirium in Older Patients Experiencing Non-cardiac Surgery

Trial site: West China Hospital, Sichuan University

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STUDY ABSTRACT

Design： A single-blind, randomized controlled trial in West China Hospital.

Aims: To evaluate the effectiveness of the modified HELP model by conducting a randomized controlled trial.

Outcome measures: The primary outcome is the incidence of POD within 7 days after surgery. Secondary outcomes are as follows: (1) incidence of severe delirium; (2) cognitive function, using the Short Portable Mental Status Questionnaire (SPMSQ); (3) physical function, using Barthel Index as Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL); (4) length of stay (LOS); (5) adherence to intervention; (6) adverse events; (7) follow-up SPMSQ, ADL, IADL and FRAIL scale at 30 days after discharge.

Population: Old patients (≥70 years of age) from the six surgical floors (gastric surgery, colorectal surgery, pancreatic surgery, biliary surgery, thoracic surgery, and thyroid surgery) will be screened for enrollment.

Eligibility: The inclusion criteria are as follows: age ≥70 years; scheduled for elective surgery, with an anticipated hospital stay longer than 2 days. The exclusion criteria include (1) delirium at baseline, as assessed with the confusion assessment method; (2) a terminal condition with life expectancy <6 months; (3) inability to perform cognitive tests because of legal blindness, severe deafness, or severe dementia; (4) a documented history of schizophrenia or psychosis; and (5) active alcohol abuse.

Treatment: The intervention includes assessments and interdisciplinary intervention daily from the first day after surgery (or from the day of return to the surgical inpatient ward) to the 7th day (or to the day of discharge if the LOS was less than 7 days). The interdisciplinary intervention includes 3 universal protocols and 8 targeted protocols. The universal protocols are orientation, therapeutic activities, and early mobilization. The targeted protocols are implemented according to the presence of delirium-related risk factors, and included pain management, sleep enhancement, nutritional assistance/aspiration prevention, fluid repletion/constipation management, hearing/vision enhancement, hypoxia improvement, catheter-associated urinary tract infections prevention, and multiple medications management. Control patients in a usual care unit receive the usual treatment and care, without individualized assessment or interdisciplinary intervention.

Duration: The trial starts from August 24, 2015, and sustain at least 6 months.

1. BACKGROUND & SIGNIFICANCE

Along with the longer global life expectancy and the rapid development of medical science and technology, more and more elderly patients are undergoing surgery. It is estimated that 50% of patients older than 65 years in the U.S. undergo surgical procedures in the US.[1] Similar trends are seen in Taiwan, with 39% of abdominal surgeries implemented in older patients[2]. Postoperative complications increase with advancing age.[3,4] Usually, surgeons pay more attention to traditional postoperative complications, such as infection, myocardial events, and sepsis, rather than cognitive function. Postoperative delirium (POD) affects 13-50% of patients undergoing non-cardiac surgery,[5] with annual health care costs of more than $182 billion in the US,[6-7] and POD has been included in patient safety indicators.[5] It is associated with a significant increase in functional decline and mortality.[8,9] However, it is often undetected by surgical staff.[10]

Previous studies have demonstrated 30~40% of cases of delirium could be prevented by multi-component non-pharmacologic interventions in medical in-patients.[11] The Hospital Elder Life Program (HELP), the classic interdisciplinary intervention model established by Inouye et al in 1999, [12] includes 6 evidence-based and practical intervention protocols (i.e. reorientation, therapeutic activities, reduced use and doses of psychoactive drugs, early mobilization, promotion of sleep, maintenance of adequate hydration and nutrition, and provision of vision and hearing adaptations) that target multiple risk factors for delirium. The HELP has been proved highly efficient and cost-effective in reducing delirium incidence and preventing functional decline for elderly patients. [13,14] However, modification is necessary depending on available resources and local environments.

In this paper, we present a protocol for a pragmatic,cluster randomized controlled trial with a tailored version of HELP (t-HELP) in West China Hospital. West China Hospital is a teaching hospital and the medical center in the western part of China, with 4300 beds, more than 180,000 admissions, and 106,000 operations per year. We hypothesize Chinese-adapted HELP should be beneficial for elderly patients (≥70 years of age) undergoing elective non-cardiac surgery, in prevention of POD and functional decline.

2. OBJECTIVES

Objective1: To modify and to implement HELP for older patients undergoing elective non-cardiac surgery at West China Hospital.

Objective2: To evaluate the effectiveness of the modified HELP model by conducting a two-armed, parallel group randomized controlled trial in 6 surgical units of West China Hospital.

3. STUDY DESIGN

3.1 Here we adapt the original version of the Hospital Elder Life Program (HELP©) by localizing the content using additional medical resources and translating the modified instrument into Chinese. Finally, the translated instrument will be revised and improved on the basis of experts panel discussions and consultations.

3.2 This is a two-arm, parallel group, single-blind cluster RCT across 6 surgical floors — gastric surgery, colorectal surgery, pancreatic surgery, biliary surgery, thoracic surgery, and thyroid surgery— in West China Hospital.

4. STUDY APPROACH

4.1 Modify and Implement the HELP Model for implementation at a Chinese Hospital

(1) Overview

The program screens older patients before operation for delirium risk factors. The risk factors and corresponding HELP protocols are shown in Table 1. Interventions target these risk factors are implemented by a skilled interdisciplinary team, including Elder Life Specialists (Geriatric Specialists), Elder Life Nurse Specialists (Nurses), and trained volunteers (replaced by family members and family-paid caregivers). Dr. Sharon Inouye – the creator of the HELP model – has provided us with the HELP materials, including manuals and training videos, and will assist with training intervention and assessment staff. We will modify the HELP model with Dr. Sharon Inouye. She is assisting in the adaptation of the HELP model for conditions in the Chinese hospital.

Table 1 Risk Factors and Corresponding HELP Protocols*

Risk Factors	HELP Protocol (interventionists)
Cognitive impairment	Orientation Protocol/Therapeutic Activities Protocol (Nurses, family members, family-paid caregivers)
Sleep deprivation	Sleep Enhancement Protocol (Nurses, family members, family-paid caregivers)
Immobility	Early Mobilization Protocol (Nurses, Physical therapy, family members, family-paid caregivers)
Hearing/Vision impairment	Hearing/Vision Protocol (Nurses, family members, family-paid caregivers)
Dehydration/Constipation	Fluid Repletion/Constipation Protocol (Nurses, Dietitian, family members, family-paid caregivers)
Pain	Pain Management Protocol (Nurses, Anesthetists, family members, , family-paid caregivers)
Hypoxia	Hypoxia Protocol (Nurses)
Infection	Infection Prevention Protocols (Nurses)
Multiple Medications	Psychoactive Medications Protocol (Nurses, clinical pharmacist)
Nutrition	Feeding Assistance (Nurses, family members, family-paid caregivers)

* Full protocols available at HELP website < www.hospitalelderlifeprogram.org>.
ELNS: Elder Life Nurse Specialist, ELS: Elder Life Specialist

(2) Interdisciplinary Team and Responsibilities

The interdisciplinary team comprises 4 levels of team workers. The program director, on the first level, takes charge of the personnel assignment in the surgical units. The geriatric specialists, nurses, and interdisciplinary specialists on the second level, as primary members, are responsible for facilitating the progress of the project. The surgeons, work directly and frequently with the patients, and back up the implementation of the project. Also, they can reject any intervention if it is not applicable. The family members or family-paid caregivers, on the third level, help patients complete some interventions under the guidance and supervision of nurses (Figure 1).

- **Program Directors:** Two directors (Xiuying Hu, Ning Ning) of the nursing department. They are responsible for assigning personnel and coordinating clinical work in general.

- **Geriatric Specialists: The** experienced geriatricians (Jirong Yue, Ning Ge) take charge of recruiting team workers, training for project staff, developing individualized intervention plans, conducting partial protocols, and so on.

- **Nurses (also in control group):** These include advanced geriatric nurses and surgical nurses. They perform daily nursing assessment, making rounds daily with nurses-in-charge, implementing partial protocols, organizing interdisciplinary rounds twice weekly, training and guiding family-paid caregivers or family members, and so on.

- **Interdisciplinary Specialists:** The interdisciplinary team, including an anesthetist, clinical pharmacist, dietician, and physical therapist, provides consultation and support for the program. We add the anesthetist on the team because all patients will experience surgery and the assessment of anesthesia is especially important for elderly patients.

- **Surgeons (also in control group):** They support or reject any intervention if they think it is not necessary or applicable.

- **Family Members or Family-paid caregivers (also in control group):** Because there is no volunteer system in China, we recruit family-paid caregivers or family members to assist completion of some living protocols with the guidance of nurses.

- **Coordinators:** We recruit 3 medical postgraduates to work as coordinators, who play an important role in facilitating effective work of the whole multidisciplinary team. They are responsible for contacting and coordinating team members among different levels whenever necessary, for example reporting to the program director, following the guidance of geriatric specialists, assisting organization of interdisciplinary consultation, and delivering information among different levels of personnel.

All the participants should commit to a minimum of 6 months' work in the program. They are required to receive intensive training, involving 16 hours of didactic and small group training, followed by approximately 16 hours of one-on-one practical training in the hospital units.

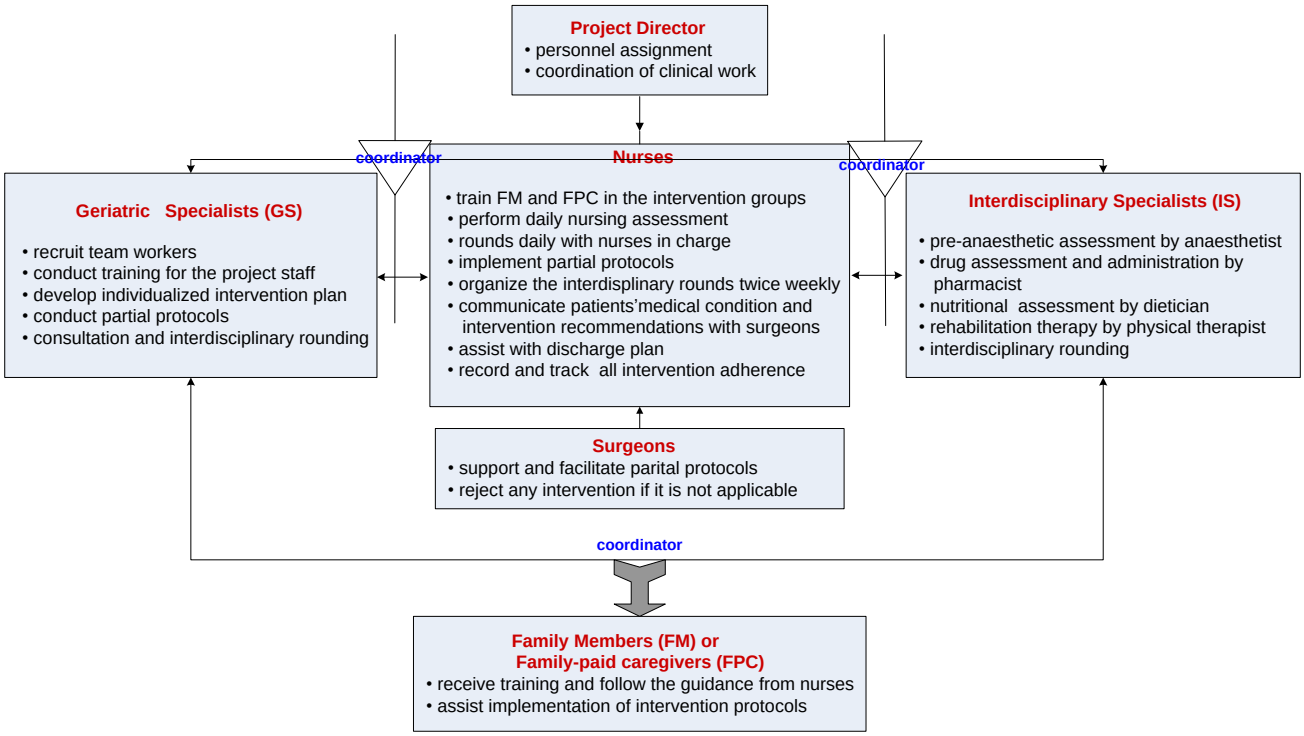

Figure 1 Structure of Interdisciplinary Team and Responsibilities

4.2 Evaluate the Effectiveness of the multidisciplinary intervention - A Cluster Randomized Trial

(1) Setting and Participants

- **Setting:** Patients aged 70 and older undergoing elective surgery and planning admission to the hospital for at least 2 days are recruited from 24 nursing units on 6 surgical floors — gastric surgery, colorectal surgery, pancreatic surgery, biliary surgery, thoracic surgery, and thyroid surgery — in West China Hospital in Sichuan, China. West China Hospital is an academic medical hospital which has 4300 beds with more than 180,000 admissions and 106,000 operations per year.

- **Inclusion criteria:** age ≥70 years; scheduled for elective surgery, with an anticipated hospital stay longer than 2 days.

- **Exclusion criteria:** 1) delirium at baseline, as assessed with the Confusion Assessment Method (CAM); 2) a terminal condition with life expectancy of less than 6 months (e.g., metastatic cancer, pancreatic cancer, or receiving end-of-life care); 3) inability to perform cognitive tests because of severe dementia, legal blindness, severe deafness; 4) a documented history of schizophrenia or psychosis; and (5) a documented history of alcohol abuse or withdrawal within past 6 months and/or reporting more than 5 drinks per day for men (4 for women).

(2) Randomization and Concealment

This is a two-step randomization process. (1) With standard computerized randomization techniques, the nursing units are randomly assigned as either t-HELP (intervention) or Usual Care (control). (2) After admission to the hospital, eligible participants are randomly assigned to t-HELP or Usual Care units according to the randomization codes previously put in sealed, opaque envelopes by a member of the hospital staff (LL G) who is not involved in the research project.

The randomization is performed by a member of the hospital staff who is not involved with the intervention and is not on the research team. The random assignment is concealed from all until the initiation of the intervention. Given the nature of the intervention, it is not feasible to blind participants and t-HELP personnel. However, outcome assessors and statistical analysts are blinded. The hospital wards have similar decoration and facilities in both groups. Blinding is strictly maintained and is monitored by inspectors (DM Xie). Throughout the trial, separation is maintained between (a) the assessors and data management staff and (b) the project staff who deliver the intervention. All investigators, staff, and study participants are masked to outcome measurements during the trial. The patients and family are told to avoid discussing their intervention with assessors. The whole process of the study is monitored by the IRB of West China hospital.

(3) Intervention and control

- **Intervention**

The t-HELP intervention is provided by an interdisciplinary team who are not involved in the outcome assessment. The intervention includes assessments and interdisciplinary intervention daily from the first day after surgery (or from the day of return to the surgical inpatient ward) to the 7th day (or to the day of discharge if the length of stay is less than 7 days). The interdisciplinary intervention includes 3 universal protocols and 8 targeted protocols. The universal protocols are orientation, therapeutic activities, and early mobilization. The targeted protocols are implemented according to the presence of delirium-related risk factors, and include pain management, sleep enhancement, nutritional assistance/aspiration prevention, fluid repletion/constipation management, vision/hearing enhancement, hypoxia improvement, catheter-associated urinary tract infections (CAUTI) prevention, and multiple medications management (Table 2).

Table 2 Differences of t-HELP and Usual Care

t-HELP	Usual Care
Universal protocols for all patients regardless of risk factors	**Usual Care**
Orientation Protocol	
● Orienting communication ● Current events: Patients with normal cognition receive orienting communication 1 time daily, patients with cognitive impairment receive orienting communication 3 times daily.	*None*
Therapeutic Activities Protocol	
Cognitive stimulating activities based on patients' interests and functional status.	*None*
Early Mobilization Protocol	
● Ambulation or active range-of-motion exercises. ● Minimizing use of immobilizing equipment.	Healthy education on early exercise, without specific guideline or supervision
Targeted protocols for patients who had the risk factor	**Usual Care**
Pain Management Protocol	
Complementary therapies：relaxation techniques; backrub or hand massage.	Use analgesic following doctor's prescription
Sleep Enhancement Protocol	
● Environmental modifications ● General sleep hygiene measures ● Relaxation strategy	General sleep hygiene and environmental modifications. Use hypnotics following doctor's advice if severe insomnia
Nutrition Assistance/Aspiration Prevention Protocol	
● Provide regular oral care ● Aspiration precautions ● Encourage assessment of correct placement of feeding tubes	Oral care, die education; Patients with severe malnutrition will be

at regular intervals	consulted with dietitians.
Fluid Repletion/Constipation Protocol ● Early recognition of dehydration, push oral fluids as needed ● Encourage patient mobility and regular toileting; collaborate with dietician	Daily assessment and record of intake and output; encourage oral fluids.
Vision/Hearing Enhancement Protocol ● Visual aids and adaptive equipment ● Portable amplifying devices, and special communication techniques	*None*
Hypoxia Improvement Protocol ● Position patient with the head of the bed elevated to 30~45 degrees ● Oxygen administration strategy	*Similar*
Catheter Associated UTI (CAUTI) Prevention Protocol ● Monitor all patients with indwelling catheters daily, and advocate for removal at the earliest possible time ● Perform meatal care twice daily; Monitor for symptoms of urinary retention	Similar strategies for managing indwelling catheter, but no strict supervision on the time of indwelling catheter.
Multiple Medications Management Protocol ● Performs a past and current medication history review at time of enrollment ● Collaborates with geriatrician and pharmacist	*None*

Note: ©2003, 2018 Hospital Elder Life Program (HELP) as the original source of the intervention protocols.

- **Control: Usual Care**

Usual care consists of standard hospital care provided by surgeons, residents, and nurses. If needed, the interdisciplinary staff consultation (e.g., dieticians, physical therapists) is provided sometimes. The t-HELP staff will not provide services to participants assigned to the control group.

(4) Implementation procedure

- *Screening patients*

Six study nurses from the 6 surgical units screen eligible patients aged 70 and older from Monday to Friday each week, according to the inclusion criteria. After the introduction of aims and significance of the whole program by study nurses, patients decide to accept it or not themselves, and sign the consent form if they agree to participate. Meanwhile, study nurses fill in the registration form for the included patients.

According to the randomization grouping methods described above, if the patients randomly enter the intervention nursing groups, they are provided with the patients' information booklets, which include introduction and significance of the interdisciplinary intervention program (adapted HELP) for POD, especially the details of pain alleviation, sleep improvement, and relaxation skills. Also, study nurses explicate the details of the intervention protocols and some requirements for patients and their family members. Patients in the control group receive these materials by mail, after completion of the whole study, according to ethical principles of fairness and justice.

- *Preoperative assessment*

For both groups: Once the operation schedule is confirmed, nurses start the comprehensive assessments for all patients. Nurses take charge of assessing delirium-related risk factors. Surgery data and some important biomarkers are collected from the Health Information System (HIS). Assessors take charge of assessing sociodemographics, medical history and

comorbidities, physical and cognitive status.

For the intervention group: Geriatric specialists (GS) develop the individualized intervention plan for the patients in the intervention group, if delirium related risk factors are found before and after the surgery.

- *Postoperative intervention*

For both groups: Nurses track and record intraoperative condition, including type of surgery and anesthesia, duration of surgery, blood transfusion, and transfer to ICU once the patients are transferred back to the surgical wards.

For the intervention group: 1) From the 1st day to the 7th day or to the day patients prepare to discharge, nurses develop or correct the intervention plan individually for the patients according to the postoperative assessment every day. 2) Three medical postgraduates, majoring in geriatrics or geriatric nursing, are trained as coordinators. They take charge of delivering the intervention plan to nurses and surgical doctors, as well as other interdisciplinary team staff if needed, in order to make everyone complete their responsibilities. 3) The Family-paid caregivers or family members carry out most of the protocols, such as feeding assistance, sleep enhancement, and relaxation. If there is any problem or controversy during the process of implementation, consulting with GS in time is required. 4) Nurses track and supervise the completion of intervention plan by asking patients directly, or their family members or family-paid caregivers indirectly, about if the patients really complete the planned intervention protocols and how they value it, in order to maintain adherence to the interdisciplinary intervention. 5) Coordinators assist nurses organizing the interdisciplinary consultation twice a week, in order to discuss some special cases in the intervention group and propose individualized solutions. 6) Nurses conduct individualized discharge assessment and plan for each patient.

For the control group: Patients in the control group are assessed the same way as the intervention group from the 1st day to the 7th day or to the day patients prepare to discharge, but following by usual care without individualized interdisciplinary intervention.

(5) Assessment and outcome measures

For the baseline assessment period, all patients undergo preoperative assessment the day before surgery, including an interview and medical record abstraction by the trained research team. Components of the patient interview consist of: 1) Sociodemographic data; 2) Medical history and comorbidities; 3) Cognitive status; 4) Depression status using the Geriatric Depression Scale; 5) Physical function; 6) Data about surgery and anesthesia. The intervention lasts up to 7 days after surgery. Follow-up phone interview is done 1 month after discharge. The implementation procedure is shown in Figure 2.

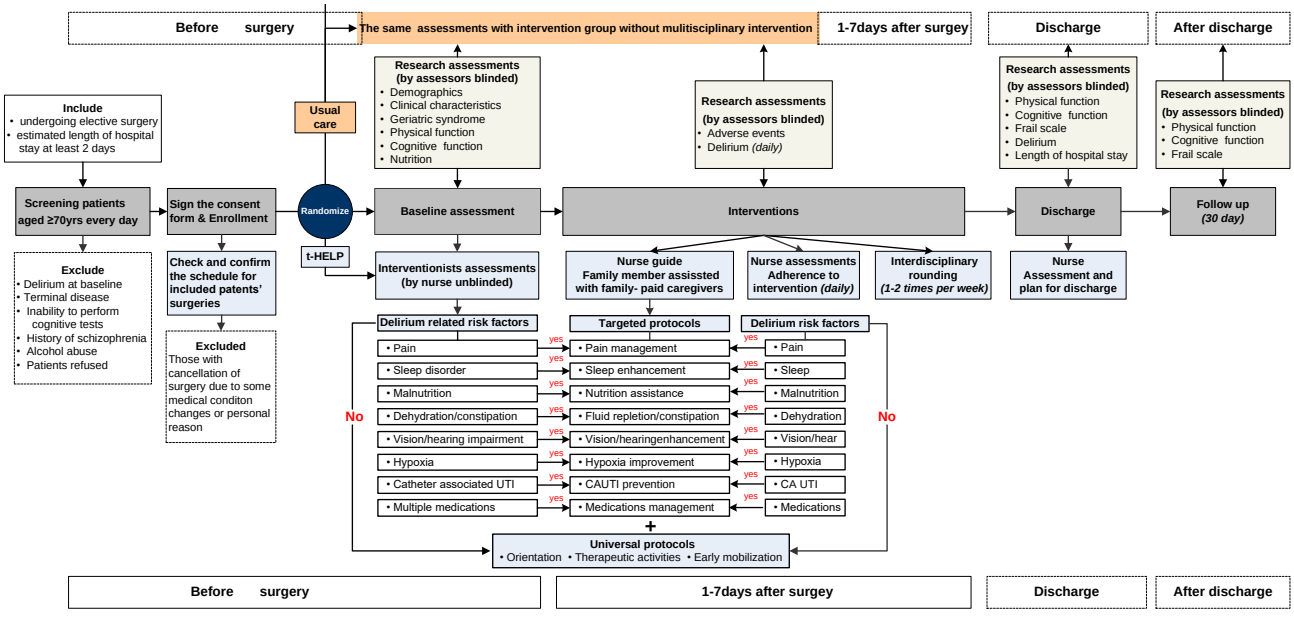

Figure 2. Implementation procedure

(6) Outcomes

- ***Primary Outcome***

The incidence of POD within 7 days after surgery during hospitalization, is assessed with the confusion assessment method (CAM).

- ***Secondary Outcome***

a) Incidence of severe delirium, using the Memorial Delirium Assessment Scale (score≥18), during hospitalization;

b) Changes in cognitive function, using the Short Portable Mental Status Questionnaire (SPMSQ), during hospitalization;

c) Changes in physical function, using Barthel Index as Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL), during hospitalization;

d) Length of Hospital Stay (LOS);

e) Adherence to intervention, during hospitalization;

f) Adverse events, during hospitalization;

g) Follow-up SPMSQ, ADL, IADL and FRAIL scale, at 30 days after discharge.

- ***Outcome Measures***

The characteristic variables and outcomes are collected according to the following time schedule using the related tools (Table 3).

Table 3 Overview of assessment during the study

Domain	Indicators/Tools	Pre- [a]	After- Daily[b]	Discharge	30 days [c]
Demographics	Age, gender, marriage, education	X	-	-	-
Clinical characteristics	Principle diagnosis	X	-	-	-
	Disease severity (APACHE II)	X	-	-	-
	Charlson Comorbidity Index (CCI)	X	-	-	-
Geriatric syndrome	Vision, hearing, self-perceived sleep quality, depression (GDS-15)	X	-	-	-
Physical function	ADL (Barthel), IADL	X	-	X	X
FRAIL scale		X	-	X	X
Nutrition (MNA-SF), BMI		X	-	-	-
Cognitive function	SPMSQ	X	-	X	X
Delirium	CAM	-	X	X	-
	Severity (MDAS)	-	X	X	-
Complications or adverse events	Massive haemorrhage, nosocomial infection, fall, etc.	-	X	X	-
Adherence to intervention		-	X	-	-
Length of hospital stay		-	-	X	-

APACHE II, Acute Physiology, Age and Chronic Health Evaluation II score; GDS, Geriatric Depression Scale; ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; MNA-SF, Mini nutritional assessment short form; BMI, Body Mass Index; SPMSQ,Short Portable Mental Status Questionnaire; CAM, Confusion Assessment Method; MDAS, Memorial Delirium Assessment Scale.
[a] Before surgery; [b] Up to 7 days after surgery; [c] Follow-up with phone interview at 30 days after discharge.

5. STATISTICAL PLAN

5.1 Sample size

PASS 11 software (NCSS Statistical Software, Kaysville, UT) is used to calculate the sample size. Sample sizes of 96 in the intervention group and 96 in the control, are obtained by sampling 12 clusters (2 clusters from each of the 6 surgical floors) with 8 subjects each in both the intervention group and the control group, in order to achieve 80% power to detect

a between-group difference of -0.2 in the proportion of having POD or a relative risk of 0.43. The calculation is based on the assumption that the proportion of having incident POD is assumed to be 0.35 under the null hypothesis for both groups, and 0.15 for the intervention group under the alternative hypothesis[15,16]. The test statistic used is the two-sided Z-Test (Unpooled) with a 0.05 Type I error and a conservative intracluster correlation of 0.05. By allowing for 20% attrition, the total sample size is estimated to be 230.

5.2 Statistical analysis

We used SPSS 19.0 (IBM) for all statistical analyses, with two-tailed tests where appropriate, and *P* values < .05 were considered statistically significant. Participants' baseline characteristics were compared using Student's *t* test, or, if the variables were not normally distributed, the Mann-Whitney *U* test. Chi-square or Fisher's exact test was used for categorical or ranked variables.

To account for the hierarchical structure of the data, i.e., study participants nested within nursing units, the multilevel binomial regression model was used to estimate the effect of treatment on primary outcome (delirium incidence). Generalized estimating equation was built to examine the association between intervention and secondary outcomes (ADL, IADL, the FRAIL scale, and SPMSQ before surgery, at discharge, and 30 days after discharge).The cluster or type of surgery were treated as random-effect factor in the models. Within the multilevel binomial regression analysis, two nested models were fitted. First, an unadjusted model was fit without confounding variables while treating nursing unit/surgical floor as a random effect. Next, a fully adjusted model (cluster or surgery level) was fit by including age and sex to study the independent effect of treatment on delirium incidence.

Intention-to-treat (ITT) analyses (all randomized patients) and per-protocol (PP) analyses (excluding all subjects who withdrew or were lost to follow-up) were used for the primary outcome, delirium incidence. The number needed to treat (NNT) was calculated when *P* < .05. For secondary outcomes, only PP analysis was performed. Adherence to the intervention was quantified as the proportion of days with complete adherence. All adverse events were evaluated by the principal investigator and an expert panel to determine whether they were intervention related.

We conduct sensitivity analysis to verify the robustness of our findings by conservatively recoding missing values due to study withdrawals as "delirium positive" for the intervention group or "delirium negative" for the control group.

6. DATA MANAGEMENT AND MONITORING

We use paper forms for local data collection. Epilnfo software is used for data entry and management. To ensure accuracy, two research assistants input the data independently, for double entry. They independently use Epilnfo to check each item against the original records for verification. We randomly select 10 cases reported in the database, and compare to ensure consistency with the original data.

Internal management of data includes daily collection forms, morning reporting of scheduling information, and development of an interim project database for preliminary analyses. After the data are verified and cleaned, we perform data freezes. No changes are made to the frozen data file. During all preliminary analyses, the analysts and investigators remain blinded to results linked to the main study hypotheses. External management of data is conducted by the Data and Safety Monitoring Board (DSMB) on a quarterly basis, including study-related adverse events, data quality, completeness, and timeliness, adherence to the protocol and dropouts, and so on.

7. ADVERSE EVENTS AND MONITORING

The trial protocol is approved by the Institutional Review Boards at West China Hospital and conducted according to Good Clinical Practice guidelines. Full informed consent is obtained from all trial participants.

Assessors monitor adverse events on a daily basis. The intervention team also monitors the adverse events on rounds and by chart review. Any reported adverse events are categorized as related or not related to the study intervention by the investigators. These events are reported in real time to the principal investigators for confirmation and review of grading. Regardless of causality, all unanticipated serious adverse events, are reported to the IRB for review. Any adverse events that occur are discussed at team meetings with the project leadership team, on an ongoing basis, to make a decision regarding overall safety of the study, whether subject participation should be stopped, and plans for communicating safety concerns to the local healthcare providers. The conclusions and recommendations are summarized in quarterly reports by the project manager. Our study statistician is blinded to subject randomization when analyzing the safety data.

Also, safety data are reviewed by the DSMB every 3 months. Our principal investigators and project manager accept the recommendations from the DSMB, and decide to modify our study protocol if required, according to the recommendations.

8. QUALITY CONTROL

8.1 Bias

Before starting the trial, all participants should receive training as required, including theoretical knowledge and assessment skills for delirium, in order to maintain high consistency of delirium assessment in all included units. To minimize error and maximize reliability, the project director performed the following: (1) providing intensive training to the assessors including a review of the t-HELP procedure outlined in a short booklet and video to ensure high inter-rater reliability (Kappa $\geq$ 0.9); (2) monitoring the assessors' administration of questionnaires with older patients who were not part of the study; (3) meeting with the assessors every week to review procedures and check the quality of the assessment for the primary outcome.

8.2 Blinding

It is impossible to blind interdisciplinary team workers and patients to allocation, because the professional workers know which patients need interdisciplinary intervention, and also patients' cooperation is important for adherence to the intervention. However, outcome assessors and the statistical expert do not have access to the group assignment, nor to the study hypothesis.

8.3 Contamination

Due to different nursing groups taking charge of different rooms, patients from the intervention group or control group stay in different rooms. Besides, research personnel are divided into two groups, one serving the intervention group patients, and another serving the control group patients. Besides, they do not communicate about patients' conditions and intervention protocols between the two groups within the research period. The personnel assignment remains until the end of the program to avoid contamination due to personnel exchange.

8.4 Adherence

As adherence to the interdisciplinary intervention is important for assuring the effectiveness of adapted HELP for the intervention group, nurses supervise adherence and record the actual completion of the intervention by comparing it with the intervention plan, and determine reasons for non-completion.

9. APPROVALS AND HUMAN SUBJECT PROTECTION

The study is carried out in accordance with the Helsinki Declaration. The study is approved by the Institutional Review Boards of West China Hospital. The trial registration number is ChiCTR-POR-15006944 (http://www.chictr.org.cn/). At the beginning of all contacts with patients, the purpose of the study is explained, participants' right to refuse to answer all or some of the questions is described, and written consent is obtained from all trial participants or their next of kin or legal representatives before initiating the trial. All information provided to subjects contains the following elements: title of study, name of investigator and affiliation, purpose of study, description of procedures, duration of participation, as well as expected risks, inconvenience, and benefits. Mechanisms are in place to ensure the safety of patients when implementing t-HELP interventions.

References

1. Beliveau MM, Multach M. Perioperative care for the elderly patient. *The Medical clinics of North America*. Jan 2003; 87(1):273-289. doi: 10.1016/S0025-7125(02)00155-4
2. Chen CC, Lin MT, Tien YW, Yen CJ, Huang GH, Inouye SK. Modified hospital elder life program: effects on abdominal surgery patients. *J Am Coll Surg*. 2011; 213(2):245-252. doi: 10.1016/j.jamcollsurg.2011.05.004
3. Gajdos C, Kile D, Hawn MT, Finlayson E, Henderson WG, Robinson TN. Advancing age and 30-day adverse outcomes after nonemergent general surgeries. *J Am Geriatr Soc*. 2013; 61(9):1608-1614. doi: 10.1111/jgs.12401
4. Polanczyk CA, Marcantonio E, Goldman L, et al. Impact of age on perioperative complications and length of stay in patients undergoing noncardiac surgery. *Ann Intern Med*. 2001;134 (8):637-643. doi: 10.7326/0003-4819-134-8-200104170-00008
5. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet*. 2014; 383(9920):911-922. doi: 10.1016/S0140-6736(13)60688-1
6. Pitkala KH, Laurila JV, Strandberg TE, Tilvis RS. Prognostic significance of delirium in frail older people. *Dement Geriatr Cogn Disord*. 2005;19(2-3):158-163. doi: 10.1159/000082888
7. Gleason LJ, Schmitt EM, Kosar CM, et al. Effect of Delirium and Other Major Complications on Outcomes After Elective Surgery in Older Adults. *JAMA surg*. 2015;150(12):1134-1140. doi: 10.1001/jamasurg.2015.2606
8. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia. *JAMA*. 2010; 304(4): 443-451. doi:

10.1001/jama.2010.1013
9. Inouye, Sharon K., Rudi GJ Westendorp, and Jane S. Saczynski. Delirium in elderly people. *Lancet*. 2013;. 383(9920): 911–922. doi: 10.1016/S0140-6736(13)60688-1
10. Fick DM, Inouye SK, Guess J, et al. Preliminary development of an ultrabrief two-item bedside test for delirium. *J Hosp Med*. 2015;10(10):645-650. doi: 10.1002/jhm.2418
11. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age Ageing*. 2006; 35(4):350-364. doi: 10.1093/ageing/afl005
12. Inouye SK, Bogardus ST, Jr., Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med*. 1999; 340(9):669-676. doi: 10.1056/NEJM199903043400901
13. Inouye SK, Bogardus ST, Jr., Baker DI, Leo-Summers L, Cooney LM, Jr. The Hospital Elder Life Program: a model of care to prevent cognitive and functional decline in older hospitalized patients. Hospital Elder Life Program. *J Am Geriatr Soc*. 2000; 48(12):1697-1706. doi: 10.1111/j.1532-5415.2000.tb03885.x
14. Inouye SK, Baker DI, Fugal P, Bradley EH, HELP Dissemination Project. Dissemination of the hospital elder life program: implementation, adaptation, and successes. *J Am Geriatr Soc*. 2006; 54(10):1492-1499. doi: 10.1111/j.1532-5415.2006.00869.x
15. Yue J, Tabloski P, Dowal SL, Puelle MR, Nandan R, Inouye SK. NICE to HELP: operationalizing National Institute for Health and Clinical Excellence guidelines to improve clinical practice. *J Am Geriatr Soc*. 2014; 62(4): 754–761. doi: 10.1111/jgs.12768
16. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. *J Am Geriatr Soc*. 2001; 49(5): 516–522. Doi:10.1046/j.1532-5415.2001.49108.x