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# BMJ Open

## Using patient-reported outcomes to manage postoperative symptoms in patients with lung cancer: protocol for a multicentre, randomised controlled trial

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Keywords:	lung cancer, patient reported outcomes, postoperative symptom management, randomised controlled trial

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Title page

**Title:** Using patient-reported outcomes to manage postoperative symptoms in patients with lung cancer: protocol for a multicentre, randomised controlled trial

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33 **#These authors contributed equally to this work.**

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35 **Word count:** 2728 words

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37     **ABSTRACT**

38     **Introduction** Surgery is the primary treatment for lung cancer. The postoperative  
39     symptom burden experienced by patients with lung cancer is substantial, seriously  
40     delaying their recovery from surgery and impairing their quality of life significantly.  
41     Patient-reported outcome (PRO)-based symptom management is increasingly regarded  
42     as an optimal model for patient-centred care. Currently, clinical trial-based evidence  
43     involving early-phase (immediately after surgery for up to one month) symptom  
44     management of lung cancer is lacking. We propose a randomised trial to evaluate the  
45     effect of a PRO-based symptom-monitoring program with over-threshold alerts and  
46     responses for postoperative recovery in patients with lung cancer.

47     **Methods and analysis** The study will recruit 160 patients with lung cancer from six  
48     hospitals. The patients will be randomly allocated to the intervention group or control  
49     group in a ratio of 1:1. Patients in the intervention group will receive consultation from  
50     clinicians to follow-up on symptoms when their reported target symptom (pain,  
51     coughing, fatigue, disturbed sleep, and shortness of breath) scores reach the pre-set  
52     threshold (score  $\geq$  4). Patients in the control group will not generate alerts and will  
53     follow the standard procedure for symptom management. All patients will receive  
54     symptom assessments via the MD Anderson Symptom Inventory – lung cancer module  
55     on the day before surgery, daily after surgery, and twice a week after discharge for up  
56     to 4 weeks or until the start of postoperative oncologic treatment. The primary  
57     outcome—mean symptom threshold events—will be compared between the  
58     intervention and standard groups via independent sample Student’s t-test.

59     **Ethics and dissemination** The study was approved by the Ethics Committee of  
60     Sichuan Cancer Hospital on November 22, 2018 (No. SCCHEC-02-2018-045). This  
61     manuscript is based on Version 1.0, September 9, 2018 of the protocol. The study  
62     results will be disseminated in publications in peer-reviewed journals and presentations  
63     at academic conferences.

64 **Trials registration number** ChiCTR1900020846.

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66 **Keywords:** lung cancer, patient reported outcomes, postoperative symptom  
67 management, randomised controlled trial.

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69     **ARTICLE SUMMARY**

70     **Strengths and limitations of this study**

- 71     1. This is an interventional study, comparing PRO-based postoperative symptom  
72     management with standard postoperative symptom management in patients with lung  
73     cancer.
- 74     2. It is a multicentre, randomised controlled trial, conducted in six tertiary hospitals in  
75     China.
- 76     3. It focuses on the early postoperative period with a high frequency of data collection,  
77     including daily in-hospital after surgery, and twice a week after discharge for up to 4  
78     weeks or until the start of postoperative oncologic treatment.
- 79     4. We use a lung cancer-specific scale and the recall period is 24 hours, which is more  
80     suitable to measure rapidly changing symptoms during the early recovery phase.
- 81     **5.** The lack of blinding for the participants and investigators delivering the intervention  
82     may be a limitation.

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## 85 INTRODUCTION

86 Lung cancer is the most common cancer and the leading cause of cancer death in China  
87 and worldwide.<sup>1 2</sup> With the application of low-dose computed tomography in screening,  
88 more and more patients with early stage lung cancer are being diagnosed and treated  
89 with surgery. However, the postoperative symptom burden of lung cancer patients is  
90 very severe, and this detrimentally affects their quality of life (QOL). Patients have  
91 various symptoms, such as pain, coughing, fatigue, and shortness of breath, in the early  
92 stages after surgery or even a long time after surgery.<sup>3-5</sup> Lowery *et al* followed 183 lung  
93 cancer patients for 1-6 years and found that 79.8% of them had a variety of symptoms.<sup>3</sup>  
94 Among these patients, 30.6% had one symptom, 27.9% had two symptoms, and 21.3%  
95 had three or more symptoms. The most frequent symptoms were pain and shortness of  
96 breath. If these symptoms are not effectively controlled, the postoperative recovery of  
97 patients will be severely affected, resulting in a poor QOL.<sup>3 4</sup> Therefore, effective  
98 interventions are needed to alleviate post-surgery symptoms in patients with lung  
99 cancer.<sup>3 4</sup>

100 Symptom management is the foundation of clinical care, particularly for patients  
101 with cancer. Patient-reported outcome (PRO)-based symptom management is  
102 increasingly regarded as an optimal model for patient-centred care.<sup>6 7</sup> A PRO is a  
103 measurement of a patient's health status that comes directly from the patient's subjective  
104 evaluation, with no interpretation by medical providers or anyone else.<sup>8</sup> Studies have  
105 shown that it may be more accurate for patients to evaluate their own health status  
106 themselves than evaluation by medical providers.<sup>9</sup> The application of PRO-based  
107 symptom monitoring and alerting followed by real-time symptom management from  
108 health care professionals can improve the QOL of patients, prolong survival, increase  
109 patient satisfaction, and allow evaluation of the treatment method.<sup>6 10-15</sup> Basch *et al*  
110 reported a randomised controlled trial (RCT) result, suggesting that PRO-based  
111 proactive symptom monitoring could improve symptom management and thus bring  
112 survival benefits in patients undergoing chemotherapy.<sup>10 11</sup> When compared to a

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113 traditional reactive monitoring group, median survival was 5.2 months longer among  
114 patients in the proactive monitoring group (31.2 vs. 26.0 months,  $p = 0.03$ ).<sup>10</sup>  
  
115 Currently, PROs are mainly used in non-surgical treatment settings,<sup>10-13</sup> and they are  
116 still in the early stage of application in the surgical treatment setting.<sup>5 7 14-28</sup> Studies on  
117 postoperative symptom management of lung cancer, especially in the early  
118 postoperative period are lacking. In addition, most of the published literature has a low  
119 level of evidence, due to its design.<sup>5 18-28</sup> The limitations of these studies include: (1)  
120 most were observational studies; (2) they had small sample sizes ranging from 30 to  
121 200 subjects with few exceptions; (3) they did not focus on the early postoperative  
122 period, typically including the in-hospital period immediately after surgery and 4 weeks  
123 after discharge when patients frequently report multiple severe symptoms, leading to  
124 later negative recovery events, i.e. higher symptom burden, delayed return to intended  
125 oncologic therapy, and poorer QOL; (4) they used a variety of survey instruments and  
126 some were not on a lung cancer-specific scale; (5) most of the scales used such as the  
127 European Organization for Research and Treatment of Cancer Quality of Life  
128 Questionnaire–Lung Cancer Module (EORTC QLQ-LC13), had a recall period of 1  
129 week, which may not be able to identify the rapidly changing symptoms during early  
130 postoperative phase;<sup>5</sup> (6) only one study assessed in-hospital patients immediately after  
131 surgery, but the MD Anderson Symptom Inventory (MDASI) scale used did not include  
132 lung cancer-specific symptoms, i.e. coughing;<sup>5</sup> (7) the symptom assessments were  
133 inadequate, mostly at just two or three time points post-surgery; (8) most of the surgical  
134 approaches were thoracotomies, not representing the current mainstream minimally  
135 invasive thoracoscopic surgery for lung cancer; (9) there were very few studies on the  
136 Chinese population.  
  
137 We have already conducted an observational study of perioperative symptom  
138 management in patients with lung cancer based on PRO (registration number  
139 NCT03341377). Now, we propose an RCT, aiming to evaluate the efficacy of a PRO-  
140 based symptom monitoring, alerting, and response system (SMARS) to improve

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postoperative recovery of lung cancer patients. This study will provide evidence for early postoperative phase symptom management for patients with lung cancer. We will use the MDASI lung cancer-specific scale (MDASI-LC)<sup>29</sup> to frequently monitor symptoms and their impact on the functioning of lung cancer patients from pre-operation to 4 weeks after discharge or until the beginning of postoperative oncologic treatment. The recall period of MDASI-LC is 24 hours, which is more suitable to measure rapidly changing, early postoperative period symptoms compared with other QOL scales for 1 week or longer. Our research hypothesis is that patients with lung cancer undergoing PRO-based symptom management have a lower postoperative symptom burden than patients undergoing standard symptom management.

## METHODS AND ANALYSIS

### Study design

The trial is a multicentre, open, randomised, parallel group controlled, and superiority design. This protocol will be consistent with the Standard Protocol Items: Recommendations For Interventional Trials (SPIRIT).<sup>30</sup> The results of this trial will be reported according to the guidelines of Consolidated Standards of Reporting Trials (CONSORT).<sup>31</sup> A flow chart of this trial is shown in figure 1.

### Participants

Participants will be recruited from six tertiary hospitals in different cities in China. The six hospitals are Sichuan Cancer Hospital, Zigong First People's Hospital, Jiangyou People's Hospital, Dazhu County People's Hospital, The Third People's Hospital of Chengdu, and The Seventh People's Hospital of Chengdu. The anticipated dates of the study are from December 1, 2018 to December 31, 2020. We haven't started recruiting patients yet. The inclusion criteria for the participants are: (1) aged 18 to 75 years, (2)

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4167 clinically diagnosed as primary lung cancer, (3) clinical stage I-III A (8th edition),<sup>32</sup> and

5168 (4) planning to receive surgery. The exclusion criteria are: (1) history of neoadjuvant

6169 therapy, (2) having other malignant tumours, and (3) unable to understand the study

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9170 requirements.

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15172 **Sample size calculation**

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17173 The primary end point of this study will be the mean symptom threshold events within

18174 4 weeks after discharge or before the start of postoperative oncologic treatment. To

19175 meet the minimal clinically important difference (0.5 standard deviation)<sup>33</sup> for the mean

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21176 symptom threshold events, the required sample size is 64 for each group, when rejecting

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23177 the null hypothesis (the difference between the two groups < 0.5 standard deviation). A

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25178 total of 128 cases with valid data are needed. Considering a 20% attrition rate, we will

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27179 need 80 patients for each group (64/0.8). The sample size calculation is based on the

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29180 independent sample Student's t-test, using a two-tailed alpha level of 0.05 and a beta

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31181 error probability of 0.02 (80% power).

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38183 **Randomisation, allocation concealment and blinding procedure**

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41184 The process of randomisation will be carried out online using the central randomisation

42185 module on the REDCap platform (<http://125.71.214.100:888/redcap>) of our hospital

43186 after a participant has been recruited to the study and has signed an informed consent

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45187 form. The data analyst will upload the randomisation allocation table to the REDCap

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47188 platform and then save the randomisation allocation table independently. The

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49189 investigator will conduct randomisation by clicking on a randomisation button on the

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51190 REDCap platform. It will then be allocated to the intervention group or control group

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53191 with a 1:1 ratio. Each group will have 80 cases. The blinding of participants and

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55192 investigators is impossible due to the nature of the interventions.

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**194 Intervention procedure****195 Intervention group**

196 The SMARS will be applied for the intervention group. Patients are required to fill out  
197 the MDASI-LC (0-10 points) before surgery (baseline, typically 1 to 3 days before the  
198 operation), daily after surgery (in-hospital, typically 1 to 7 days after the operation),  
199 and twice a week after discharge for up to 4 weeks ( $\pm 3$  days) or until the start of  
200 postoperative oncologic treatment (typically collecting PRO data six to eight times after  
201 discharge). When there are one or more target symptoms (pain, coughing, fatigue,  
202 disturbed sleep, and shortness of breath) and scores reach the pre-set intervention  
203 threshold (score  $\geq 4$ ), a specialist will receive an alert and will contact the patient within  
204 24 hours to implement symptom relief measures, e.g. consultation, education,  
205 medication guidance, and clinic or hospital visit suggestions.

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**207 Control group**

208 The control group will follow the standard symptom management procedure. Patients  
209 will fill out the MDASI-LC at the same schedule as those in the intervention group.  
210 Investigators will inform the patients that the MDASI-LC data collected are only for  
211 scientific research. And the patients' symptom management will follow the current  
212 standard postoperative management model, that is, when the patients report discomfort,  
213 the specialists will take clinical intervention measures according to their own  
214 experience rather than based on the score of the MDASI-LC. Patients will be  
215 encouraged to discuss their symptoms during clinical visits or to seek emergency help  
216 if severe symptoms are reported.

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**218 Withdrawal criteria**

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Participants will be withdrawn from the study and no further data will be collected if they meet the following criteria: (1) unexpected cancellation of surgery, (2) severe postoperative complications affecting symptom data collection, (3) postoperative length of stay > 14 days, (4) postoperative pathology showed non-primary lung cancer, (5) non-R0 resection, (6) pathological stage IV, (7) participant seriously violates the study protocol, or (8) participant asks to withdraw from the study.

**Outcomes and measurement**

**Primary outcomes**

The primary end point of this study is the mean symptom threshold events, defined as the average number of target symptom threshold events per patient, at each time point. According to our pilot study, the five most common postoperative symptoms of lung cancer patients are: pain, coughing, fatigue, disturbed sleep and shortness of breath. In this study, these five symptoms assessed by the MDASI-LC are defined as target symptoms. According to the recommendation of National Comprehensive Cancer Network and published literature, when a patient's symptom score is  $\geq 4$ , it is identified as moderate severity.<sup>34 35</sup> In this study, a score of 4 is set as the threshold value for intervention, and a target symptom score of  $\geq 4$  is reported as a threshold event.

The primary PRO tool used in this study is the MDASI-LC.<sup>29</sup> It is a measure that contains sixteen items of lung cancer-related and treatment-related symptoms, and six items of interference to normal daily life caused by symptoms. All items are rated on 0-10 numerical scales, with 0 representing “symptom not present” or “symptom not interfered with life” and 10 representing “symptom as bad as one can imagine” or “symptom completely interfered with life”. The recall period of the MDASI-LC is 24 hours and it can usually be conducted in 5 minutes. It has been translated and validated for application in a Chinese context.

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## 246 Secondary outcomes

247 The secondary end points of this study include trajectories of PROs (symptom severity,  
248 daily functioning, and QOL) and revisit rate after discharge. Trajectories of PROs are  
249 defined as the longitudinal changing pattern of the mean score of the five target  
250 symptoms for symptom severity, the mean score of the six MDASI-LC interference  
251 items for daily functioning, and the mean score of the single-item QOL scale  
252 (UNISCALE) for QOL,<sup>36</sup> from the baseline to 4 weeks or until the start of postoperative  
253 oncologic treatment. UNISCALE only has one question using a 0-10 scale, with 0  
254 representing “worst QOL” and 10 representing “best QOL”. The revisit rate after  
255 discharge is defined as the ratio of the number of patients who see the doctor again after  
256 discharge including outpatient visits, emergency visits and hospitalisation divided by  
257 the total number of patients.

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## 259 Data collection, management, and quality control

260 REDCap,<sup>37 38</sup> a worldwide popular research data collection and management platform  
261 established in our hospital, will be used for data collection and management in this  
262 study. PRO data will be collected using an e-questionnaire or a paper questionnaire and  
263 recorded in REDCap. Participants should fill out the questionnaires by themselves. If  
264 participants have difficulties in completing the questionnaires, investigators will help  
265 them by reading each item aloud and recording the participant’s responses. All data  
266 including demographics, clinicopathological characteristics, follow-up information and  
267 PRO data will be entered into the REDCap database. Data will be checked regularly by  
268 the quality controller. Participant privacy information will not be recorded in REDCap.  
269 A study number will be allocated to each participant and will be used on all study  
270 documentation, which will only be available to the investigators. Before patients’  
271 enrolment, investigators from each research centre will receive standard operating

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procedure training. Each centre will receive on-site monitoring visits, telephone monitoring, and online guidance during the course of the trial.

**Data analysis**

Data analyses will be performed on an intention-to-treat basis using the SAS 9.4 (SAS Institute, Inc, Cary, NC). Per-protocol analyses may be conducted. To be included in the analysis, a participant must provide MDASI-LC data from the baseline and at least two additional time points. If a participant meets the withdrawal criteria, no data will be included in the analysis. Two-sided P values of  $< 0.05$  are considered to be statistically significant. Continuous variables will be presented as mean  $\pm$  standard deviation or median and interquartile range. Comparisons between groups will be conducted using the Student's t-test or the Wilcoxon rank sum test. Categorical variables will be presented as frequencies or proportions and compared between groups using the chi-square test. Trajectories of PROs will be compared between the intervention group and control group using generalised mixed effects models. Missing data will be processed by the multiple imputation method. Results obtained from data without missed observations will be compared with that from imputed data for sensitive analysis.

**Data monitoring and interim analysis**

A data monitoring committee (DSM) consisting of one clinician, one statistician, and the secretary of the Ethics Committee of Sichuan Cancer Hospital will be set up. Study monitoring will be carried out regularly by DSM members and the process will be independent from investigators. Due to the low-risk of the study content and short-term study duration, interim analysis will not be performed.

## 298 **Data availability statement**

299 Deidentified data generated by this clinical trial to support future research articles will  
300 be available from the corresponding author on reasonable request.

## 302 **Patient and public involvement statement**

303 Patients and the public will not be involved in the design, recruitment to, or conduct of  
304 this study. We will provide all the participants with free long-term medical consultation  
305 after this study. The burden of the intervention in this RCT will not be performed. We  
306 will inform the applicants of the results. There are no plans to disseminate the results  
307 to study participants.

## 309 **ETHICS AND DISSEMINATION**

310 This study was approved by the Ethics Committee of Sichuan Cancer Hospital on  
311 November 22, 2018 (No. SCCHEC-02-2018-045). All recruited patients will be  
312 required to give written informed consent. Any subsequent amendments to the protocol  
313 will be submitted for further review and approval. Sub-centres will gain approval from  
314 their hospital-specific ethics committees. The results of this study will be disseminated  
315 through peer-reviewed publications and academic conferences.

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318 study.

319 **Author contributions** WD and QLS conceived and designed the study. WD and QLS obtained the  
320 funding. WD is the chief investigator of this study. YQZ, WHF, XQL, YFM, and RZ are sub-centre  
321 principal investigators who contributed to the trial feasibility stage. WD, YQZ, WHF, XQL, YFM,  
322 RZ, XW, CMW and SHX drafted the protocol. QLS participated in the statistical plan. QL and QLS

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323 revised the manuscript. All authors have read and approved the manuscript.

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327 **Competing interests** None declared.

328 **Patient consent** Obtained.

329 **Ethics approval** Ethics Committee of Sichuan Cancer Hospital (No. SCCHEC-02-2018-045).

330 **Provenance and peer review** Not commissioned; externally peer reviewed.

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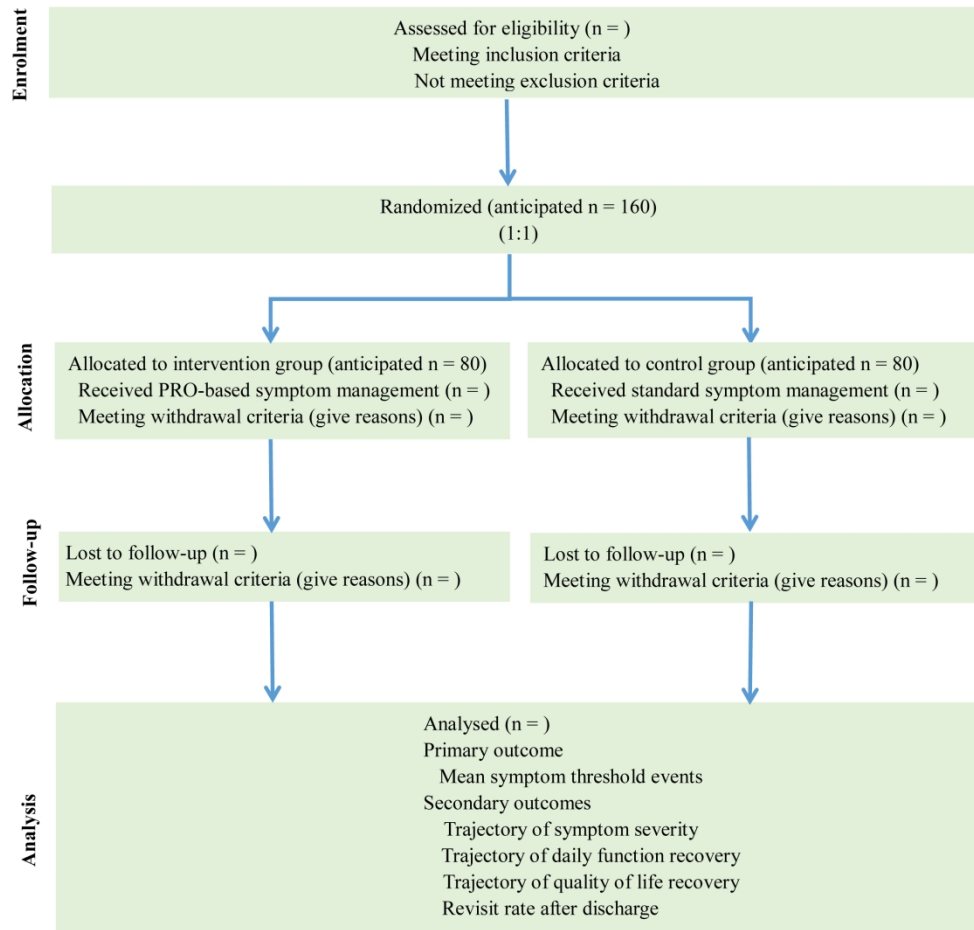
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429 **Figure legends**

430 **Figure 1** Flow chart of this parallel group randomised trial.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Page Number on which item is reported
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	<b>Page 1</b>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<b>Page 4</b>
	2b	All items from the World Health Organization Trial Registration Data Set	<b>Page 4</b>
Protocol version	3	Date and version identifier	<b>Page 3</b>
Funding	4	Sources and types of financial, material, and other support	<b>Page 14-15</b>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<b>Page 1, 14</b>
	5b	Name and contact information for the trial sponsor	<b>Page 1, 14</b>
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	<b>Page 14</b>
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	<b>Page 12-13</b>
<b>Introduction</b>			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 6-7
	6b	Explanation for choice of comparators	Page 8
Objectives	7	Specific objectives or hypotheses	Page 3, 8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 10-11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 11

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Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	<b>Page 10</b>
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	<b>Page 9</b>
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	<b>None</b>
<b>Methods: Assignment of interventions (for controlled trials)</b>			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	<b>Page 9</b>
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	<b>Page 9</b>
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	<b>Page 9</b>
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	<b>Page 9</b>
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	<b>Not Applicable</b>
<b>Methods: Data collection, management, and analysis</b>			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 11
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 13

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	<b>Page 10</b>
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	<b>Page 13</b>
<b>Ethics and dissemination</b>			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<b>Page 14</b>
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	<b>Page 14</b>
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<b>Page 14</b>
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	<b>Not Applicable</b>
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	<b>Page 12</b>
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	<b>Page 15</b>
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	<b>Page 12-13</b>
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	<b>Page 14</b>
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	<b>Page 14</b>

	31b	Authorship eligibility guidelines and any intended use of professional writers	None
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 14
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	None
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not Applicable

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons [“Attribution-NonCommercial-NoDerivs 3.0 Unported”](#) license.

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# BMJ Open

## Using patient-reported outcomes to manage postoperative symptoms in patients with lung cancer: protocol for a multicentre, randomised controlled trial

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<b>Primary Subject Heading</b>:	Patient-centred medicine
Secondary Subject Heading:	Surgery, Oncology, Nursing
Keywords:	lung cancer, patient reported outcomes, postoperative symptom management, randomised controlled trial

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Title page

**Title:** Using patient-reported outcomes to manage postoperative symptoms in patients with lung cancer: protocol for a multicentre, randomised controlled trial

**Authors:** Wei Dai,<sup>1#</sup> Yuanqiang Zhang,<sup>2#</sup> Wenhong Feng,<sup>3</sup> Xiaoqing Liao,<sup>4</sup> Yunfei Mu,<sup>5</sup> Rui Zhang,<sup>6</sup> Xing Wei,<sup>1</sup> Chuanmei Wu,<sup>1</sup> Shaohua Xie,<sup>1,7</sup> Qiang Li,<sup>1</sup> Qiuling Shi<sup>8</sup>

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33 **#These authors contributed equally to this work.**

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35 **Word count:** 3508 words

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37     **ABSTRACT**

38     **Introduction** Surgery is one of the primary treatments for lung cancer. The  
39     postoperative symptom burden experienced by patients with lung cancer is substantial,  
40     seriously delaying their recovery from surgery and impairing their quality of life.  
41     Patient-reported outcome (PRO)-based symptom management is increasingly regarded  
42     as an optimal model for patient-centred care. Currently, clinical trial-based evidence  
43     involving early-phase (immediately after surgery for up to one month) symptom  
44     management of lung cancer is lacking. We propose a randomised trial to evaluate the  
45     effect of a PRO-based symptom-monitoring program with over-threshold alerts and  
46     responses for postoperative recovery in patients with lung cancer.

47     **Methods and analysis** The study will recruit 160 patients with lung cancer from six  
48     hospitals. The patients will be randomly allocated to the intervention group or control  
49     group in a ratio of 1:1. Patients in the intervention group will receive consultation from  
50     clinicians to follow-up on symptoms when their reported target symptom (pain,  
51     coughing, fatigue, disturbed sleep, and shortness of breath) scores reach the pre-set  
52     threshold (score  $\geq$  4). Patients in the control group will not generate alerts and will  
53     follow the standard procedures for symptom management. All patients will receive  
54     symptom assessments via the MD Anderson Symptom Inventory – lung cancer module  
55     on the day before surgery, daily after surgery, and twice a week after discharge until 4  
56     weeks or the start of postoperative oncologic treatment. The primary outcome—mean  
57     symptom threshold events—will be compared between the intervention and control  
58     group via independent sample Student’s t-test.

59     **Ethics and dissemination** The study was approved by the Ethics Committee of  
60     Sichuan Cancer Hospital on November 22, 2018 (No. SCCHEC-02-2018-045). This  
61     manuscript is based on Version 2.0, May 9, 2019 of the protocol. The study results will  
62     be disseminated in publications in peer-reviewed journals and presentations at  
63     academic conferences.

64 **Trials registration number** ChiCTR1900020846.

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66 **Keywords:** lung cancer, patient reported outcomes, postoperative symptom  
67 management, randomised controlled trial.

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69     **ARTICLE SUMMARY**

70     **Strengths and limitations of this study**

- 71     1. This is an interventional study, comparing PRO-based postoperative symptom  
72     management with standard postoperative symptom management in patients with lung  
73     cancer.
- 74     2. It is a multicentre, randomised controlled trial, conducted in six tertiary hospitals in  
75     China.
- 76     3. It focuses on the early postoperative period with a high frequency of data collection,  
77     including baseline before surgery, daily in-hospital after surgery, and twice a week after  
78     discharge until 4 weeks or the start of postoperative oncologic treatment.
- 79     4. We use a lung cancer-specific scale and the recall period is 24 hours, which is more  
80     suitable to measure rapidly changing symptoms during the early recovery phase.
- 81     5. The lack of blinding for the participants and specialists delivering the intervention  
82     may be a limitation.

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## 85 INTRODUCTION

86 Lung cancer is the most common cancer and the leading cause of cancer death in China  
87 and worldwide.<sup>1 2</sup> With the application of low-dose computed tomography in screening,  
88 more and more patients with early stage lung cancer are being diagnosed and treated  
89 with surgery. However, the postoperative symptom burden of lung cancer patients is  
90 very severe, and this detrimentally affects their quality of life (QOL). Patients have  
91 various symptoms, such as pain, coughing, fatigue, and shortness of breath, in the early  
92 stages after surgery or even a long time after surgery.<sup>3-5</sup> Lowery *et al* followed 183 lung  
93 cancer patients for 1-6 years and found that 79.8% of them had a variety of symptoms.<sup>3</sup>  
94 Among these patients, 30.6% had one symptom, 27.9% had two symptoms, and 21.3%  
95 had three or more symptoms. The most frequent symptoms were pain and shortness of  
96 breath. If these symptoms are not effectively controlled, the postoperative recovery of  
97 patients will be severely affected, resulting in a poor QOL.<sup>3 4</sup> Therefore, effective  
98 interventions are needed to alleviate post-surgery symptoms in patients with lung  
99 cancer.<sup>3 4</sup>

100 Symptom management is the foundation of clinical care, particularly for patients  
101 with cancer. Patient-reported outcome (PRO)-based symptom management is  
102 increasingly regarded as an optimal model for patient-centred care.<sup>6 7</sup> A PRO is a  
103 measurement of a patient's health status that comes directly from the patient's subjective  
104 evaluation, with no interpretation by medical providers or anyone else.<sup>8</sup> Studies have  
105 shown that it may be more accurate for patients to evaluate their own health status  
106 themselves than evaluation by medical providers.<sup>9</sup> The application of PRO-based  
107 symptom monitoring and alerting followed by real-time symptom management from  
108 health care professionals can improve the QOL of patients, prolong survival, increase  
109 patient satisfaction, and allow evaluation of the treatment method.<sup>6 10-15</sup> Basch *et al*  
110 reported a randomised controlled trial (RCT) result, suggesting that PRO-based  
111 proactive symptom monitoring could improve symptom management and thus bring  
112 survival benefits in patients undergoing chemotherapy.<sup>10 11</sup> When compared to a

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113 traditional reactive monitoring group, median survival was 5.2 months longer among  
114 patients in the proactive monitoring group (31.2 vs. 26.0 months,  $p = 0.03$ ).<sup>10</sup> However,  
115 it is still not clear if adequate symptom control and improved QOL in the surgical  
116 population can ensure a potential better survival.

117 Currently, PROs are mainly used in non-surgical treatment settings,<sup>10-13</sup> and they are  
118 still in the early stage of application in the surgical treatment setting.<sup>5 7 14-28</sup> Studies on  
119 postoperative symptom management of lung cancer, especially in the early  
120 postoperative period are lacking. In addition, most of the published literature has a low  
121 level of evidence, due to its design.<sup>5 18-28</sup> The limitations of these studies include: (1)  
122 most were observational studies; (2) they had small sample sizes ranging from 30 to  
123 200 subjects with few exceptions; (3) they did not focus on the early postoperative  
124 period, typically including the in-hospital period immediately after surgery and 4 weeks  
125 after discharge when patients frequently report multiple severe symptoms, leading to  
126 later negative recovery events, i.e. higher symptom burden, delayed return to intended  
127 oncologic therapy, and poorer QOL; (4) they used a variety of survey instruments and  
128 some were not a lung cancer-specific scale; (5) most of the scales used such as the  
129 European Organization for Research and Treatment of Cancer Quality of Life  
130 Questionnaire–Lung Cancer Module (EORTC QLQ-LC13), had a recall period of 1  
131 week, which may not be able to identify the rapidly changing symptoms during early  
132 postoperative phase;<sup>5</sup> (6) only one study assessed in-hospital patients immediately after  
133 surgery, but the MD Anderson Symptom Inventory (MDASI) scale used did not include  
134 lung cancer-specific symptoms, i.e. coughing;<sup>5</sup> (7) the symptom assessments were  
135 inadequate, mostly at just two or three time points post-surgery; (8) most of the surgical  
136 approaches were thoracotomies, not representing the current mainstream minimally  
137 invasive thoracoscopic surgery for lung cancer; (9) there were very few studies on the  
138 Chinese population.

139 We have been conducting an observational study of perioperative symptom in  
140 patients with lung cancer based on PRO (registration number NCT03341377). Now,

we propose an RCT, aiming to evaluate the efficacy of a PRO-based symptom monitoring, alerting, and response system (SMARS) to improve postoperative recovery of lung cancer patients. The SMARS (figure 1) includes a research electronic data capture (REDCap) platform, an electronic PRO system (ePRO Hub), and a most popular social software (WeChat)<sup>29</sup> in China. This study will provide evidence for early postoperative phase symptom management for patients with lung cancer. We will use the MDASI lung cancer-specific scale (MDASI-LC)<sup>30</sup> to frequently monitor symptoms and their impact on the functioning of lung cancer patients from pre-operation to 4 weeks after discharge or until the beginning of postoperative oncologic treatment. The recall period of MDASI-LC is 24 hours, which is more suitable to measure rapidly changing, early postoperative period symptoms compared with other QOL scales for 1 week or longer. Our research hypothesis is that patients with lung cancer undergoing PRO-based symptom management have a lower postoperative symptom burden than patients undergoing standard symptom management.

## METHODS AND ANALYSIS

### Study design

The trial is a multicentre, randomised, parallel group controlled, and superiority design. This protocol will be consistent with the Standard Protocol Items: Recommendations For Interventional Trials (SPIRIT).<sup>31</sup> The results of this trial will be reported according to the guidelines of Consolidated Standards of Reporting Trials (CONSORT).<sup>32</sup> A flow chart of this trial is shown in figure 2.

### Setting

Participants will be recruited from six tertiary hospitals in different cities in China. The six hospitals are Sichuan Cancer Hospital, Zigong First People's Hospital, Jiangyou

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4 167 People's Hospital, Dazhu County People's Hospital, The Third People's Hospital of  
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6 168 Chengdu, and The Seventh People's Hospital of Chengdu. The total number of lung  
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8 169 cancer operations in six hospitals is approximately 2,000 per year.  
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13 171 **Participant recruitment**

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15 172 Participant recruitment will be carried out before the surgery by participating clinicians.  
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17 173 Eligible patients should meet all the inclusion criteria and not meet any of the exclusion  
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19 174 criteria. The inclusion criteria for the participants are: (1) aged 18 to 75 years, (2)  
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21 175 clinically diagnosed as primary lung cancer, (3) clinical stage I-III A (8th edition),<sup>33</sup> and  
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23 176 (4) planning to receive surgery, and (5) able and willing to respond to a repeated  
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25 177 electronic questionnaire (e-questionnaire) on a smartphone or a tablet. The exclusion  
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27 178 criteria are: (1) history of neoadjuvant therapy, (2) having other malignant tumours, and  
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29 179 (3) unable to understand the study requirements. Strategies for achieving adequate  
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31 180 participant enrolment to reach a target sample size include inviting more doctors in each  
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33 181 centre to participate in the study and adding more research centres. Plans to promote  
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35 182 participant retention and complete follow-up include education, refill reminders, and  
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37 183 commitments to provide all the patients with free long-term medical consultations after  
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39 184 the trial via WeChat. The anticipated dates of the study are from December 1, 2018 to  
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41 185 December 31, 2020. We haven't started recruiting patients yet.  
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46 187 **Sample size calculation**

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48 188 The primary end point of this study will be the mean symptom threshold events, defined  
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50 189 as the average number of target symptom threshold events per patient, at each time  
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52 190 point. To meet the minimal clinically important difference (0.5 standard deviation)<sup>34</sup>  
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54 191 for the mean symptom threshold events, the required sample size is 64 for each group,  
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56 192 when rejecting the null hypothesis (the difference between the two groups < 0.5  
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standard deviation). A total of 128 cases with valid data are needed. Considering a 20% attrition rate, we will need 80 patients for each group (64/0.8). The sample size calculation is based on the independent sample Student's t-test, using a two-tailed alpha level of 0.05 and a beta error probability of 0.02 (80% power).

### **Randomisation and allocation concealment**

The process of randomisation will be carried out online using the central randomisation module on the REDCap platform (<http://125.71.214.100:888/redcap>) after a participant has been recruited to the study and has signed an informed consent form. The data analyst will upload the randomisation allocation table to the REDCap platform and then save the randomisation allocation table independently. The investigator will conduct randomisation by clicking on a randomisation button on the REDCap platform. It will then be allocated to the intervention group or control group with a 1:1 ratio. Each group will have 80 cases.

### **Blinding**

The blinding of participants and specialists delivering the intervention is impossible due to the nature of the interventions. But the data collectors who help administer PRO collection will be blinded to group allocation to minimise measurement bias. The statisticians analysing the results will also be blinded to group allocation.

### **Intervention**

After enrolment, all the patients will use their WeChat app to connect with the participating specialists' WeChat app via a mini program (ePRO Cell). Then, they will be taught how to use the program. The ePRO questionnaires will be set to send to the

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patients' WeChat app automatically after randomisation. Patients are required to complete the ePRO questionnaires on their smartphone or tablet before surgery (baseline, typically 1 to 3 days before the operation), daily after surgery (in-hospital, typically 1 to 7 days after the operation), and twice a week after discharge until 4 weeks or the start of postoperative oncologic treatment (typically collecting PRO data six to eight times after discharge). In a hospital setting, if the patients do not complete the ePRO questionnaires within the scheduled time, an electronic reminder (e-reminder) and up to two bedside reminders will be delivered at the same day. After discharge, if the patients fail to complete the ePRO questionnaires within the scheduled time, an e-reminder and up to two phone reminders will be delivered with 24 hours.

**Comparison**

Intervention group

Patients will not be informed about the threshold levels. When there are one or more target symptoms (pain, coughing, fatigue, disturbed sleep, and shortness of breath) and scores reach the pre-set intervention threshold (score  $\geq 4$ ), the participating specialist (thoracic surgeon) will simultaneously receive an alert message on his or her WeChat. Then the specialist will mainly use the WeChat or sometimes a telephone to contact the patient within 24 hours to implement symptom relief measures, e.g. consultation, education, medication guidance, and clinic or hospital visit suggestions. The symptom relief measures of the intervention group patients will comply with the latest guidelines and be standardised across all centres, in the form of a standard operating procedure (SOP) handbook. Patients' adherence to the interventions will be asked at each time point. Those who do not follow the specialist's advice will be monitored, and the number of violations will be recorded. Those who refuse to follow the specialist's advice more than three times will be considered as seriously violating the study protocol and will be withdrawn.

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246 Control group

247 The control group patients will be informed that the ePRO data collected are only for  
248 scientific research. They will not generate any alerts or get responses relating to their  
249 symptoms. The patients' symptom management will follow the current standard  
250 postoperative management model. During hospitalization, the doctors manage the  
251 control group patients' symptoms based on their own judgement rather than the score  
252 of the PRO. After discharge, the patients will go home and the first clinic visit is  
253 approximately 4 weeks later. Patients will be encouraged to seek medical help if severe  
254 symptoms are reported.

255

## 256 **Withdrawal criteria**

257 Participants will be withdrawn from the study and no further data will be collected if  
258 they meet the following criteria: (1) unexpected cancellation of surgery, (2) severe  
259 postoperative complications affecting symptom data collection, (3) postoperative  
260 length of stay > 14 days, (4) postoperative pathology shows non-primary lung cancer,  
261 (5) non-R0 resection, (6) pathological stage IV, (7) participant seriously violates the  
262 study protocol (continually not complying with the specialist's advice, intentionally  
263 letting a proxy to complete the PRO surveys, and deliberately providing false PROs),  
264 or (8) participant asks to withdraw from the study.

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## 266 **Outcomes and measurement**

267 Primary outcome

268 The primary end point of this study is the mean symptom threshold events. According  
269 to our pilot study, the five most common postoperative symptoms of lung cancer

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patients are: pain, coughing, fatigue, disturbed sleep and shortness of breath. In this study, these five symptoms assessed by the MDASI-LC are defined as target symptoms. According to the recommendation of National Comprehensive Cancer Network and published literature, when a patient's symptom score is  $\geq 4$ , it is identified as moderate severity.<sup>35 36</sup> In this study, a score of 4 is set as the threshold value for intervention, and a target symptom score of  $\geq 4$  is reported as a threshold event.

The primary PRO tool used in this study is the MDASI-LC.<sup>30</sup> It is a measure that contains sixteen items of lung cancer-related and treatment-related symptoms, and six items of interference to normal daily life caused by symptoms. All items are rated on 0-10 numerical scales, with 0 representing “symptom not present” or “symptom not interfered with life” and 10 representing “symptom as bad as one can imagine” or “symptom completely interfered with life”. The recall period of the MDASI-LC is 24 hours and it can usually be conducted in 5 minutes. It has been translated and validated for application in a Chinese context.

Secondary outcomes

The secondary end points of this study include trajectories of PROs (symptom severity, daily functioning, and QOL) and revisit rate after discharge. Trajectories of PROs are defined as the longitudinal changing pattern of the mean score of the five target symptoms for symptom severity, the mean score of the six MDASI-LC interference items for daily functioning, and the mean score of the single-item QOL scale (UNISCALE) for QOL,<sup>37</sup> from the baseline to 4 weeks after discharge or until the start of postoperative oncologic treatment. UNISCALE only has one question using a 0-10 scale, with 0 representing “worst QOL” and 10 representing “best QOL”. The revisit rate after discharge is defined as the ratio of the number of patients who see the doctor again after discharge including outpatient visits, emergency visits and hospitalisation divided by the total number of patients.

297

298 Other data

299 The clinician workload, clinician system acceptability, and patient satisfaction of the  
300 interventions will be assessed through surveys and interviews. Demographics,  
301 clinicopathological characteristics, follow-up information, and adverse events of the  
302 interventions will also be collected. All the adverse events will be assessed and  
303 managed by a thoracic surgeon.

304

### 305 **Data collection, management, and quality control**

306 REDCap,<sup>38 39</sup> a worldwide popular research data collection and management platform  
307 established in Sichuan Cancer Hospital, will be used for data collection and  
308 management in this study. PRO data will be collected using e-questionnaires and  
309 recorded in REDCap. Participants should fill out the e-questionnaires by themselves. If  
310 participants have difficulties in completing the e-questionnaires, data collectors or their  
311 family members will help them by just reading each item aloud and recording the  
312 participant's responses. The control group patients' PRO data will not be accessed by  
313 the specialists. Specialists can only access the PRO data of the intervention group  
314 patients. Other data including demographics, clinicopathological characteristics, and  
315 follow-up information will also be entered into the REDCap database.

316 Data will be checked regularly by the quality controller. Participant privacy  
317 information will not be recorded in REDCap. A study number will be allocated to each  
318 participant and will be used on all study documentation, which will only be available  
319 to the investigators. Before patients' enrolment, investigators from each research centre  
320 will receive SOP training. Each centre will receive on-site monitoring visits, telephone  
321 monitoring, and online guidance during the course of the trial.

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**Data analysis**

Per-protocol analyses will be conducted. To be included in the analysis, a participant must provide MDASI-LC data from the baseline and at least two additional time points. If a participant meets the withdrawal criteria, no data will be included in the analysis. Two-sided P values of  $< 0.05$  are considered to be statistically significant. Continuous variables will be presented as mean  $\pm$  standard deviation or median and interquartile range. Comparisons between groups will be conducted using the Student's t-test or the Wilcoxon rank sum test. Categorical variables will be presented as frequencies or proportions and compared between groups using the chi-square test. Trajectories of PROs will be compared between the intervention group and control group using generalised mixed effects models. Missing data will be processed by the multiple imputation method. Results obtained from data without missed observations will be compared with that from imputed data for sensitive analysis.

**Data monitoring and interim analysis**

A data monitoring committee (DSM) consisting of one clinician, one statistician, and the secretary of the Ethics Committee of Sichuan Cancer Hospital will be set up. Study monitoring will be carried out regularly by DSM members and the process will be independent from investigators. Due to the low-risk of the study content and short-term study duration, interim analysis will not be performed.

**Data availability statement**

Deidentified data generated by this clinical trial to support future research articles will be available from the corresponding author on reasonable request.

## 348 Patient and public involvement statement

349 Patients and the public will not be involved in the design, recruitment to, or conduct of  
350 this study. The burden of the intervention in this RCT will not be performed. We will  
351 inform the applicants of the results. There are no plans to disseminate the results to  
352 study participants. Participants will be informed that they can obtain the final results of  
353 this study through our future published articles.

354

## 355 ETHICS AND DISSEMINATION

356 This study was approved by the Ethics Committee of Sichuan Cancer Hospital on  
357 November 22, 2018 (No. SCCHEC-02-2018-045). All recruited patients will be  
358 required to give written informed consent. Any subsequent amendments to the protocol  
359 will be submitted for further review and approval. Sub-centres will gain approval from  
360 their hospital-specific ethics committees. The results of this study will be disseminated  
361 through peer-reviewed publications and academic conferences.

362

## 363 DISCUSSION

364 This trial focuses on the early-phase postoperative symptom management after lung  
365 cancer surgery. The potential implications of the findings include: (1) identifying if  
366 PRO-based symptom management is better than usual symptom management, (2)  
367 identifying if proactive symptom management can reduce symptom burden and  
368 improve QOL in the surgical population, (3) laying a foundation for future research on  
369 whether postoperative symptom management improves survival, (4) investigating  
370 whether SMARS is feasible and acceptable in real-world clinical practice in China, and  
371 (5) identifying barriers which will be used to facilitate further revisions of the SMARS  
372 and help extend its implementation in non-surgical settings.

373 There are many limitations in this trial. First, the trial will be carried out in well-

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resourced tertiary hospitals in China. This will limit the generalizability of this study. Second, the inclusion criteria and exclusion criteria are strict. For example, the program is unsuitable for patients without internet access or with poor literacy. This will greatly limit the population for which this study is applicable. Third, the lack of blinding for the participants and specialists delivering the intervention will also be a limitation, because it may increase the measurement bias. Fourth, the follow-up period is very short. The results need confirmation in a study with a longer follow-up period.

In summary, as a RCT, this study will not only test the efficacy of SMARS in postoperative care, but also it will provide data of feasibility for further unblinded pragmatic study when implementing the SMARS in the real world, with the involvement of community hospitals and patients with poor socioeconomic status, while a wider internet access is available for the whole Chinese population.

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**Author contributions** WD and QLS conceived and designed the study. WD and QLS obtained the funding. WD is the chief investigator of this study. YQZ, WHF, XQL, YFM, and RZ are sub-centre principal investigators who contributed to the trial feasibility stage. WD, YQZ, WHF, XQL, YFM, RZ, XW, CMW and SHX drafted the protocol. QLS participated in the statistical plan. QL and QLS revised the manuscript. All authors have read and approved the manuscript.

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**Competing interests** None declared.

**Patient consent** Obtained.

**Ethics approval** Ethics Committee of Sichuan Cancer Hospital (No. SCCHEC-02-2018-045).

400 **Provenance and peer review** Not commissioned; externally peer reviewed.

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For peer review only

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502 **Figure legends**

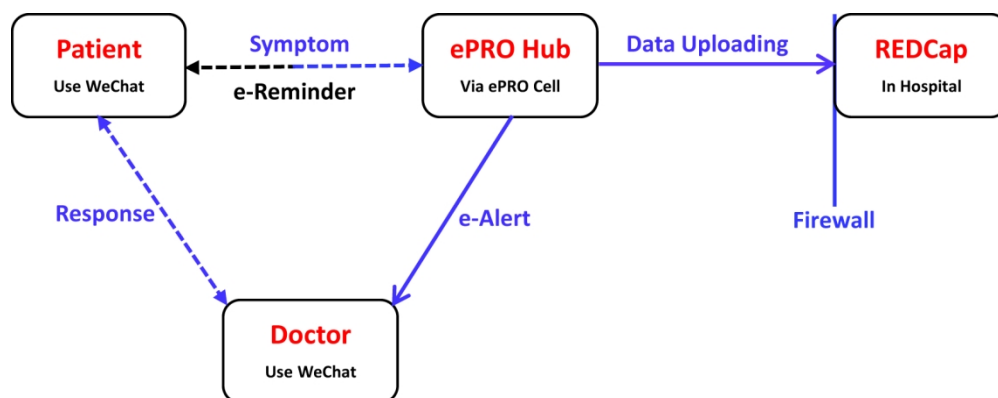
503 **Figure 1** Schematic diagram of the SMARS.

504 **Figure 2** Flow chart of this parallel group randomised trial.

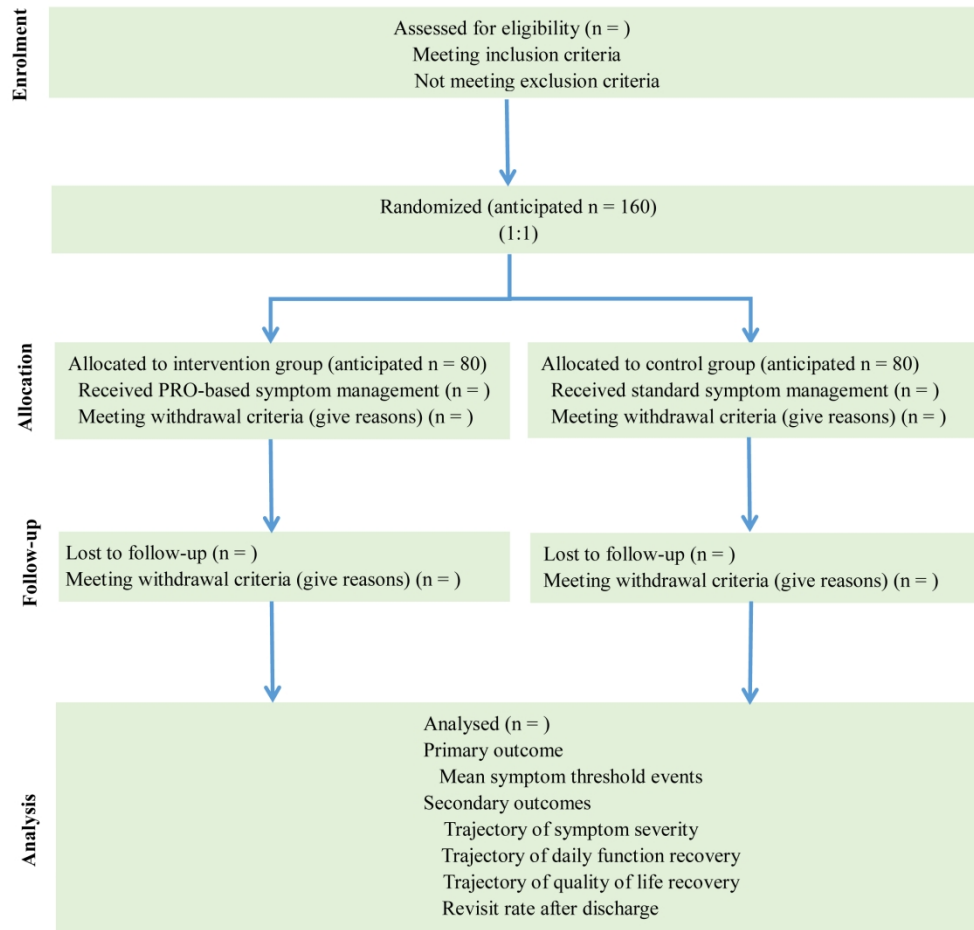
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Schematic diagram of the SMARS.



Flow chart of this parallel group randomised trial.



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Page Number on which item is reported
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	<b>Page 1</b>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<b>Page 4</b>
	2b	All items from the World Health Organization Trial Registration Data Set	<b>Page 4</b>
Protocol version	3	Date and version identifier	<b>Page 3</b>
Funding	4	Sources and types of financial, material, and other support	<b>Page 17-18</b>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<b>Page 1, 17</b>
	5b	Name and contact information for the trial sponsor	<b>Page 1, 17</b>
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	<b>Page 17-18</b>
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	<b>Page 14-15</b>
<b>Introduction</b>			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 6-7
	6b	Explanation for choice of comparators	Page 11-12
Objectives	7	Specific objectives or hypotheses	Page 8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 8-9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 11-12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 13-14

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Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	<b>Page 8-9</b>
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	<b>Page 9-10</b>
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	<b>Page 9</b>
<b>Methods: Assignment of interventions (for controlled trials)</b>			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	<b>Page 10</b>
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	<b>Page 10</b>
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	<b>Page 10</b>
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	<b>Page 10</b>
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	<b>Not Applicable</b>
<b>Methods: Data collection, management, and analysis</b>			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 14-15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 14-15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 15

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	<b>Page 14</b>
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	<b>Page 15</b>
<b>Ethics and dissemination</b>			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<b>Page 16</b>
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	<b>Page 16</b>
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<b>Page 16</b>
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	<b>Not Applicable</b>
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	<b>Page 14--15</b>
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	<b>Page 18</b>
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	<b>Page 16</b>
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	<b>Page 9</b>
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	<b>Page 16</b>

	31b	Authorship eligibility guidelines and any intended use of professional writers	None
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	None
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not Applicable

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.

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# BMJ Open

## Using patient-reported outcomes to manage postoperative symptoms in patients with lung cancer: protocol for a multicentre, randomised controlled trial

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<b>Primary Subject Heading</b>:	Patient-centred medicine
Secondary Subject Heading:	Surgery, Oncology, Nursing
Keywords:	lung cancer, patient reported outcomes, postoperative symptom management, randomised controlled trial

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Title page

**Title:** Using patient-reported outcomes to manage postoperative symptoms in patients with lung cancer: protocol for a multicentre, randomised controlled trial

**Authors:** Wei Dai,<sup>1#</sup> Yuanqiang Zhang,<sup>2#</sup> Wenhong Feng,<sup>3</sup> Xiaoqing Liao,<sup>4</sup> Yunfei Mu,<sup>5</sup> Rui Zhang,<sup>6</sup> Xing Wei,<sup>1</sup> Chuanmei Wu,<sup>1</sup> Shaohua Xie,<sup>1,7</sup> Qiang Li,<sup>1</sup> Qiuling Shi<sup>8</sup>

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33 **#These authors contributed equally to this work.**

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35 **Word count:** 3699 words

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**ABSTRACT**

**Introduction** Surgery is one of the primary treatments for lung cancer. The postoperative symptom burden experienced by patients with lung cancer is substantial, seriously delaying their recovery from surgery and impairing their quality of life. Patient-reported outcome (PRO)-based symptom management is increasingly regarded as an optimal model for patient-centred care. Currently, clinical trial-based evidence involving early-phase (immediately after surgery for up to one month) symptom management of lung cancer is lacking. We propose a randomised trial to evaluate the effect of a PRO-based symptom-monitoring program with over-threshold alerts and responses for postoperative recovery in patients with lung cancer.

**Methods and analysis** The study will recruit 160 patients with lung cancer from six hospitals. The patients will be randomly allocated to the intervention group or control group in a ratio of 1:1. Patients in the intervention group will receive PRO-based symptom management from the specialists when their reported target symptom (pain, coughing, fatigue, disturbed sleep, and shortness of breath) scores reach the pre-set threshold (score  $\geq 4$ ). Patients in the control group will not generate alerts and will follow the standard procedures for symptom management. All patients will receive symptom assessments via the MD Anderson Symptom Inventory – lung cancer module on the day before surgery, daily after surgery, and twice a week after discharge until 4 weeks or the start of postoperative oncologic treatment. The primary outcome—mean symptom threshold events—will be compared between the intervention and control group via independent sample Student’s t-test.

**Ethics and dissemination** The study was approved by the Ethics Committee of Sichuan Cancer Hospital on November 22, 2018 (No. SCCHEC-02-2018-045). This manuscript is based on Version 2.0, May 9, 2019 of the protocol. The study results will be disseminated in publications in peer-reviewed journals and presentations at academic conferences.

64 **Trials registration number** ChiCTR1900020846.

65

66 **Keywords:** lung cancer, patient reported outcomes, postoperative symptom  
67 management, randomised controlled trial.

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69     **ARTICLE SUMMARY**

70     **Strengths and limitations of this study**

- 71     1. This is an interventional study, comparing PRO-based postoperative symptom  
72     management with standard postoperative symptom management in patients with lung  
73     cancer.
- 74     2. It is a multicentre, randomised controlled trial, conducted in six tertiary hospitals in  
75     China.
- 76     3. It focuses on the early postoperative period with a high frequency of data collection,  
77     including baseline before surgery, daily in-hospital after surgery, and twice a week after  
78     discharge until 4 weeks or the start of postoperative oncologic treatment.
- 79     4. We use a lung cancer-specific scale and the recall period is 24 hours, which is more  
80     suitable to measure rapidly changing symptoms during the early recovery phase.
- 81     5. The lack of blinding for the participants and specialists delivering the intervention  
82     may be a limitation.

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## 85 INTRODUCTION

86 Lung cancer is the most common cancer and the leading cause of cancer death in China  
87 and worldwide.<sup>1 2</sup> With the application of low-dose computed tomography in screening,  
88 more and more patients with early stage lung cancer are being diagnosed and treated  
89 with surgery. However, the postoperative symptom burden of lung cancer patients is  
90 very severe, and this detrimentally affects their quality of life (QOL). Patients have  
91 various symptoms, such as pain, coughing, fatigue, and shortness of breath, in the early  
92 stages after surgery or even a long time after surgery.<sup>3-5</sup> Lowery *et al* followed 183 lung  
93 cancer patients for 1-6 years and found that 79.8% of them had a variety of symptoms.<sup>3</sup>  
94 Among these patients, 30.6% had one symptom, 27.9% had two symptoms, and 21.3%  
95 had three or more symptoms. The most frequent symptoms were pain and shortness of  
96 breath. If these symptoms are not effectively controlled, the postoperative recovery of  
97 patients will be severely affected, resulting in a poor QOL.<sup>3 4</sup> Therefore, effective  
98 interventions are needed to alleviate post-surgery symptoms in patients with lung  
99 cancer.<sup>3 4</sup>

100 Symptom management is the foundation of clinical care, particularly for patients  
101 with cancer. Patient-reported outcome (PRO)-based symptom management is  
102 increasingly regarded as an optimal model for patient-centred care.<sup>6 7</sup> A PRO is a  
103 measurement of a patient's health status that comes directly from the patient's subjective  
104 evaluation, with no interpretation by medical providers or anyone else.<sup>8</sup> Studies have  
105 shown that it may be more accurate for patients to evaluate their own health status  
106 themselves than evaluation by medical providers.<sup>9</sup> The application of PRO-based  
107 symptom monitoring and alerting followed by real-time symptom management from  
108 health care professionals can improve the QOL of patients, prolong survival, increase  
109 patient satisfaction, and allow evaluation of the treatment method.<sup>6 10-15</sup> Basch *et al*  
110 reported a randomised controlled trial (RCT) result, suggesting that PRO-based  
111 proactive symptom monitoring could improve symptom management and thus bring  
112 survival benefits in patients undergoing chemotherapy.<sup>10 11</sup> When compared to a

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113 traditional reactive monitoring group, median survival was 5.2 months longer among  
114 patients in the proactive monitoring group (31.2 vs. 26.0 months,  $p = 0.03$ ).<sup>10</sup> However,  
115 it is still not clear if adequate symptom control and improved QOL in the surgical  
116 population can ensure a potential better survival.

117 Currently, PROs are mainly used in non-surgical treatment settings,<sup>10-13</sup> and they are  
118 still in the early stage of application in the surgical treatment setting.<sup>5 7 14-28</sup> Studies on  
119 postoperative symptom management of lung cancer, especially in the early  
120 postoperative period are lacking. In addition, most of the published literature has a low  
121 level of evidence, due to its design.<sup>5 18-28</sup> The limitations of these studies include: (1)  
122 most were observational studies; (2) they had small sample sizes ranging from 30 to  
123 200 subjects with few exceptions; (3) they did not focus on the early postoperative  
124 period, typically including the in-hospital period immediately after surgery and 4 weeks  
125 after discharge when patients frequently report multiple severe symptoms, leading to  
126 later negative recovery events, i.e. higher symptom burden, delayed return to intended  
127 oncologic therapy, and poorer QOL; (4) they used a variety of survey instruments and  
128 some were not a lung cancer-specific scale; (5) most of the scales used such as the  
129 European Organization for Research and Treatment of Cancer Quality of Life  
130 Questionnaire–Lung Cancer Module (EORTC QLQ-LC13), had a recall period of 1  
131 week, which may not be able to identify the rapidly changing symptoms during early  
132 postoperative phase;<sup>5</sup> (6) only one study assessed in-hospital patients immediately after  
133 surgery, but the MD Anderson Symptom Inventory (MDASI) scale used did not include  
134 lung cancer-specific symptoms, i.e. coughing;<sup>5</sup> (7) the symptom assessments were  
135 inadequate, mostly at just two or three time points post-surgery; (8) most of the surgical  
136 approaches were thoracotomies, not representing the current mainstream minimally  
137 invasive thoracoscopic surgery for lung cancer; (9) there were very few studies on the  
138 Chinese population.

139 We have been conducting an observational study of perioperative symptom in  
140 patients with lung cancer based on PRO (registration number NCT03341377). Now,

we propose an RCT, aiming to evaluate the efficacy of a PRO-based symptom monitoring, alerting, and response system (SMARS) to improve postoperative recovery of lung cancer patients. The SMARS (figure 1) includes a research electronic data capture (REDCap) platform, an electronic PRO system (ePRO Hub), and a most popular social software (WeChat)<sup>29</sup> in China. This study will provide evidence for early postoperative phase symptom management for patients with lung cancer. We will use the MDASI lung cancer-specific scale (MDASI-LC)<sup>30</sup> to frequently monitor symptoms and their impact on the functioning of lung cancer patients from pre-operation to 4 weeks after discharge or until the beginning of postoperative oncologic treatment. The recall period of MDASI-LC is 24 hours, which is more suitable to measure rapidly changing, early postoperative period symptoms compared with other QOL scales for 1 week or longer. Our research hypothesis is that patients with lung cancer undergoing PRO-based symptom management have a lower postoperative symptom burden than patients undergoing standard symptom management.

## METHODS AND ANALYSIS

### Study design

The trial is a multicentre, randomised, parallel group controlled, and superiority design. This protocol will be consistent with the Standard Protocol Items: Recommendations For Interventional Trials (SPIRIT).<sup>31</sup> The results of this trial will be reported according to the guidelines of Consolidated Standards of Reporting Trials (CONSORT).<sup>32</sup> A flow chart of this trial is shown in figure 2.

### Setting

Participants will be recruited from six tertiary hospitals in different cities in China. The six hospitals are Sichuan Cancer Hospital, Zigong First People's Hospital, Jiangyou

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People’s Hospital, Dazhu County People’s Hospital, The Third People’s Hospital of Chengdu, and The Seventh People’s Hospital of Chengdu. The total number of lung cancer operations in six hospitals is approximately 2,000 per year.

**Participant recruitment**

Participant recruitment will be carried out before the surgery by participating clinicians. Eligible patients should meet all the inclusion criteria and not meet any of the exclusion criteria. The inclusion criteria for the participants are: (1) aged 18 to 75 years, (2) clinically diagnosed as primary lung cancer, (3) clinical stage I-III A (8th edition),<sup>33</sup> and (4) planning to receive surgery, and (5) able and willing to respond to a repeated electronic questionnaire (e-questionnaire) on a smartphone or a tablet. The exclusion criteria are: (1) history of neoadjuvant therapy, (2) having other malignant tumours, and (3) unable to understand the study requirements.

Strategies for achieving adequate participant enrolment to reach a target sample size include inviting more doctors in each centre to participate in the study and adding more research centres. Plans to promote participant retention and complete follow-up include education, refill reminders, and commitments to provide all the patients with free long-term medical consultations after the trial via WeChat. In China, the first follow-up clinic visit of surgical lung cancer patient is approximately 4 weeks after discharge. There is no usual follow-up within these 4 weeks. In addition, usual care does not include free medical consultations after discharge. Patients usually have to pay for follow-up care. Free long-term medical consultation is an incentive for patients who participate in the study, which may improve compliance. This incentive will do more good than harm to the patients, so it is approved and recommended by the Ethics Committee of Sichuan Cancer Hospital. The anticipated dates of the study are from December 1, 2018 to December 31, 2020. We haven't started recruiting patients yet.

## 194 Sample size calculation

195 The primary end point of this study is the mean symptom threshold events, defined as  
196 the average number of target symptom threshold events per patient, at each time point.  
197 To meet the minimal clinically important difference (0.5 standard deviation)<sup>34</sup> for the  
198 mean symptom threshold events, the required sample size is 64 for each group, when  
199 rejecting the null hypothesis (the difference between the two groups < 0.5 standard  
200 deviation). A total of 128 cases with valid data are needed. Considering a 20% attrition  
201 rate, we will need 80 patients for each group (64/0.8). The 20% attrition rate is based  
202 on our ongoing observational research (NCT03341377). The current withdrawal rate is  
203 about 17% in the observational research. The rate of loss to follow-up in this trial is  
204 estimated to be less than 3%, because this trial is an interventional study and the follow-  
205 up time is very short (less than 4 weeks). In this trial, the 20% attrition include both  
206 withdrawal and loss to follow-up. The sample size calculation is based on the  
207 independent sample Student's t-test, using a two-tailed alpha level of 0.05 and a beta  
208 error probability of 0.02 (80% power).

209

## 210 Randomisation and allocation concealment

211 The process of randomisation will be carried out online using the central randomisation  
212 module on the REDCap platform (<http://125.71.214.100:888/redcap>) after a participant  
213 has been recruited to the study and has signed an informed consent form. The data  
214 manager will upload the randomisation allocation table to the REDCap platform and  
215 then save the randomisation allocation table independently. The investigator will  
216 conduct randomisation by clicking on a randomisation button on the REDCap platform.  
217 It will then be allocated to the intervention group or control group with a 1:1 ratio. Each  
218 group will have 80 cases.

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**Blinding**

The blinding of participants and specialists delivering the intervention is impossible due to the nature of the interventions. But the data collectors who help administer PRO collection will be blinded to group allocation to minimise measurement bias. The statisticians analysing the results will also be blinded to group allocation.

**Intervention**

After enrolment, all the patients will use their WeChat app to connect with the participating specialists' WeChat app via a mini program (ePRO Cell). Then, they will be taught how to use the program. The ePRO questionnaires will be set to send to the patients' WeChat app automatically after randomisation. Patients are required to complete the ePRO questionnaires on their smartphones or tablets before surgery (baseline, typically 1 to 3 days before the operation), daily after surgery (in-hospital, typically 1 to 7 days after the operation), and twice a week after discharge until 4 weeks or the start of postoperative oncologic treatment (typically collecting PRO data six to eight times after discharge). In a hospital setting, if the patients do not complete the ePRO questionnaires within the scheduled time, an electronic reminder (e-reminder) and up to two bedside reminders will be delivered at the same day. After discharge, if the patients fail to complete the ePRO questionnaires within the scheduled time, an e-reminder and up to two phone reminders will be delivered with 24 hours.

**Comparison**

Intervention group

Patients will not be informed about the threshold levels. When there are one or more target symptoms (pain, coughing, fatigue, disturbed sleep, and shortness of breath) and scores reach the pre-set intervention threshold (score  $\geq 4$ ), the participating specialist

(thoracic surgeon) will simultaneously receive an alert message on his or her WeChat. The specialist will manage the patients' symptoms based on the scores of the PRO. After discharge, the specialist will mainly use the WeChat or sometimes a telephone to contact the patient within 24 hours to implement symptom relief measures, e.g. consultation, education, medication guidance, and clinic or hospital visit suggestions. The symptom relief measures of the intervention group patients will comply with the latest guidelines and be standardised across all centres, in the form of a standard operating procedure (SOP) handbook. Patients' adherence to the interventions will be asked at each time point. Those who do not follow the specialist's advice will be monitored, and the number of violations will be recorded. Those who refuse to follow the specialist's advice more than three times will be considered as seriously violating the study protocol and will be withdrawn. Patients will be educated and allowed to seek medical help through usual channels for severe symptoms.

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#### 260 Control group

The control group patients will be informed that the ePRO data collected are only for scientific research. They will not generate any alerts or get responses relating to their symptoms. The patients' symptom management will follow the current standard postoperative management model. During hospitalization, the doctors manage the control group patients' symptoms based on their own judgement rather than the scores of the PRO. After discharge, the patients will go home and the first clinic visit is approximately 4 weeks later. Patients will be encouraged to seek medical help if severe symptoms are reported.

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#### 270 **Withdrawal criteria**

271 Participants will be withdrawn from the study and no further data will be collected if

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they meet the following criteria: (1) unexpected cancellation of surgery, (2) severe postoperative complications ( $\geq$  grade IIIb according to the Clavien-Dindo classification of surgical complications) affecting symptom data collection, (3) postoperative length of stay  $> 14$  days (because patient with a postoperative hospital stay  $> 14$  days usually has a severe complication, and the patient compliance will gradually decrease, affecting the accuracy of PRO data), (4) postoperative pathology shows non-primary lung cancer, (5) non-R0 resection, (6) pathological stage IV, (7) participant seriously violates the study protocol (continually not complying with the specialist's advice, intentionally letting a proxy to complete the PRO surveys, and deliberately providing false PROs), or (8) participant asks to withdraw from the study.

**Outcomes and measurement**

**Primary outcome**

The primary end point of this study is the mean symptom threshold events. According to our pilot study, the five most common postoperative symptoms of lung cancer patients are: pain, coughing, fatigue, disturbed sleep and shortness of breath. In this study, these five symptoms assessed by the MDASI-LC are defined as target symptoms. According to the recommendation of National Comprehensive Cancer Network and published literature, when a patient's symptom score is  $\geq 4$ , it is identified as moderate severity.<sup>35 36</sup> In this study, a score of 4 is set as the threshold value for intervention, and a target symptom score of  $\geq 4$  is reported as a threshold event.

The primary PRO tool used in this study is the MDASI-LC.<sup>30</sup> It is a measure that contains sixteen items of lung cancer-related and treatment-related symptoms, and six items of interference to normal daily life caused by symptoms. All items are rated on 0-10 numerical scales, with 0 representing "symptom not present" or "symptom not interfered with life" and 10 representing "symptom as bad as one can imagine" or

298 “symptom completely interfered with life”. The recall period of the MDASI-LC is 24  
299 hours and it can usually be conducted in 5 minutes. It has been translated and validated  
300 for application in a Chinese context.

301

## 302 Secondary outcomes

303 The secondary end points of this study include trajectories of PROs (symptom severity,  
304 daily functioning, and QOL) and revisit rate after discharge. Trajectories of PROs are  
305 defined as the longitudinal changing pattern of the mean score of the five target  
306 symptoms for symptom severity, the mean score of the six MDASI-LC interference  
307 items for daily functioning, and the mean score of the single-item QOL scale  
308 (UNISCALE) for QOL,<sup>37</sup> from the baseline to 4 weeks after discharge or until the start  
309 of postoperative oncologic treatment. UNISCALE has only one question using a 0-10  
310 scale, with 0 representing “worst QOL” and 10 representing “best QOL”. The revisit  
311 rate after discharge is defined as the ratio of the number of patients who see the doctor  
312 again after discharge including outpatient visits, emergency visits and hospitalisation  
313 divided by the total number of patients.

314

## 315 Other data

316 The clinician workload, clinician system acceptability, and patient satisfaction of the  
317 interventions will be assessed through surveys and interviews. Demographics,  
318 clinicopathological characteristics, follow-up information, and adverse events of the  
319 interventions will also be collected. All the adverse events will be assessed and  
320 managed by a thoracic surgeon.

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## 322 Data collection, management, and quality control

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REDCap,<sup>38 39</sup> a worldwide popular research data collection and management platform established in Sichuan Cancer Hospital, will be used for data collection and management in this study. PRO data will be collected using e-questionnaires and recorded in REDCap. Participants should fill out the e-questionnaires by themselves. If participants have difficulties in completing the e-questionnaires, data collectors or their family members will help them by just reading each item aloud and recording the participant's responses. The control group patients' PRO data will not be accessed by the specialists. Specialists can only access the PRO data of the intervention group patients. Other data including demographics, clinicopathological characteristics, and follow-up information will also be entered into the REDCap database.

Data will be checked regularly by the quality controller. Participant privacy information will not be recorded in REDCap. A study number will be allocated to each participant and will be used on all study documentation, which will only be available to the investigators. Before patients' enrolment, investigators from each research centre will receive SOP training. Each centre will receive on-site monitoring visits, telephone monitoring, and online guidance during the course of the trial.

**Data analysis**

Per-protocol analyses will be conducted. To be included in the analysis, a participant must provide MDASI-LC data from the baseline and at least two additional time points. If a participant meets the withdrawal criteria, no data will be included in the analysis. Two-sided P values of  $< 0.05$  are considered to be statistically significant. Continuous variables will be presented as mean  $\pm$  standard deviation or median and interquartile range. Comparisons between groups will be conducted using the Student's t-test or the Wilcoxon rank sum test. Categorical variables will be presented as frequencies or proportions and compared between groups using the chi-square test. Trajectories of PROs will be compared between the intervention group and control

group using generalised mixed effects models. Missing data will be processed by the multiple imputation method. Results obtained from data without missed observations will be compared with that from imputed data for sensitive analysis.

### **Data monitoring and interim analysis**

A data monitoring committee (DSM) consisting of one clinician, one statistician, and the secretary of the Ethics Committee of Sichuan Cancer Hospital will be set up. Study monitoring will be carried out regularly by DSM members and the process will be independent from investigators. Due to the low-risk of the study content and short-term study duration, interim analysis will not be performed.

### **Data availability statement**

Deidentified data generated by this clinical trial to support future research articles will be available from the corresponding author on reasonable request.

### **Patient and public involvement statement**

Patients and the public will not be involved in the design, recruitment to, or conduct of this study. We will inform the applicants of the results. There are no plans to disseminate the results to study participants, because it is not a routine practice to feed back research results to participants in China. Participants will be informed that they can obtain the final results of this study through our future published articles.

## **ETHICS AND DISSEMINATION**

This study was approved by the Ethics Committee of Sichuan Cancer Hospital on

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November 22, 2018 (No. SCCHEC-02-2018-045). All recruited patients will be required to give written informed consent. Any subsequent amendments to the protocol will be submitted for further review and approval. Sub-centres will gain approval from their hospital-specific ethics committees. The results of this study will be disseminated through peer-reviewed publications and academic conferences.

**DISCUSSION**

This trial focuses on the early-phase postoperative symptom management after lung cancer surgery. The potential implications of the findings include: (1) identifying if PRO-based symptom management is better than usual symptom management, (2) identifying if proactive symptom management can reduce symptom burden and improve QOL in the surgical population, (3) laying a foundation for future research on whether postoperative symptom management improves survival, (4) investigating whether SMARS is feasible and acceptable in real-world clinical practice in China, and (5) identifying barriers which will be used to facilitate further revisions of the SMARS and help extend its implementation in non-surgical settings.

There are many limitations in this trial. First, the trial will be carried out in well-resourced tertiary hospitals in China. This will limit the generalisability to non-tertiary hospitals. Second, the inclusion criteria and exclusion criteria are strict. For example, the program is unsuitable for patients without internet access or with poor literacy. This will greatly limit the population for which this study is applicable. Third, the withdrawal criteria will create selection bias and limit the external validity, although the strict criteria will ensure the compliance of this study. In the future, we will conduct pragmatic clinical trials (PCT) to evaluate the effectiveness of the monitoring system in a more heterogeneous population, to improve the generalisability. Fourth, the lack of blinding for the participants and specialists delivering the intervention will also be a limitation, because it may increase the measurement bias. Fifth, it may affect the

establishment of feasibility if patients are not involved in the design and development of this trial, although previous studies and our ongoing observational study have provided pilot data for the design and development of this trial in terms of feasibility and acceptability. This RCT is designed to test the efficacy of the PRO monitoring system. We will evaluate the effectiveness in a future PCT, with patients' involvement in study design, conduct and interpretation. Sixth, the follow-up period is very short. The results need confirmation in a study with a longer follow-up period.

In summary, as a RCT, this study will not only test the efficacy of SMARS in postoperative care, but also it will provide data of feasibility for further unblinded pragmatic study when implementing the SMARS in the real world, with the involvement of community hospitals and patients with poor socioeconomic status, while a wider internet access is available for the whole Chinese population.

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**Author contributions** WD and QLS conceived and designed the study. WD and QLS obtained the funding. WD is the chief investigator of this study. YQZ, WHF, XQL, YFM, and RZ are sub-centre principal investigators who contributed to the trial feasibility stage. WD, YQZ, WHF, XQL, YFM, RZ, XW, CMW and SHX drafted the protocol. QLS participated in the statistical plan. QL and QLS revised the manuscript. All authors have read and approved the manuscript.

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**Competing interests** None declared.

**Patient consent** Obtained.

**Ethics approval** Ethics Committee of Sichuan Cancer Hospital (No. SCCHEC-02-2018-045).

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427     **Provenance and peer review** Not commissioned; externally peer reviewed.

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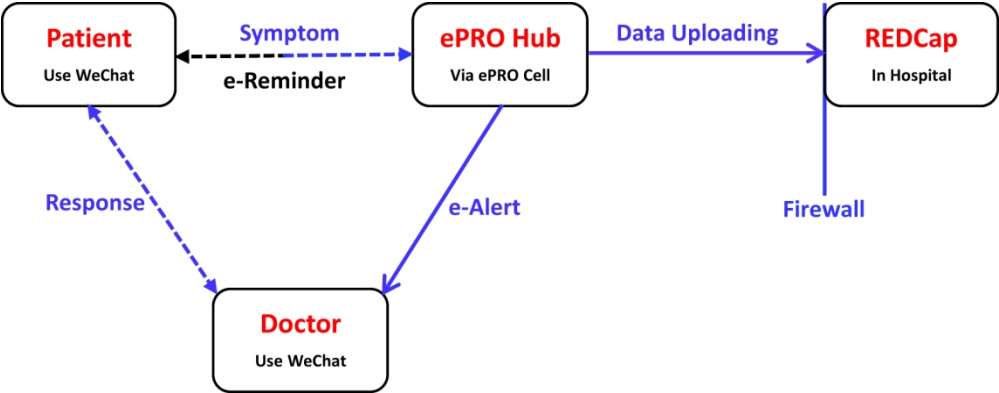
529 **Figure legends**

530 **Figure 1** Schematic diagram of the SMARS.

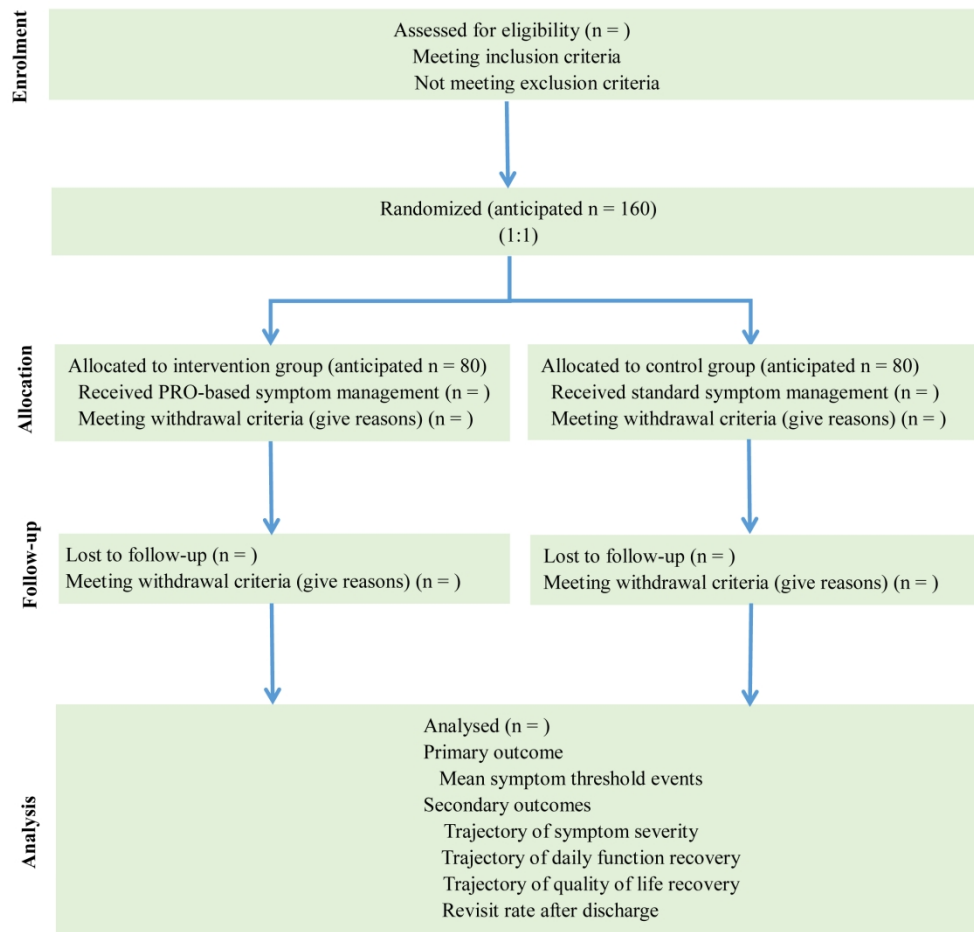
531 **Figure 2** Flow chart of this parallel group randomised trial.

532

For peer review only



Schematic diagram of the SMARS.



Flow chart of this parallel group randomised trial.



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 4
	2b	All items from the World Health Organization Trial Registration Data Set	Page 4
Protocol version	3	Date and version identifier	Page 3
Funding	4	Sources and types of financial, material, and other support	Page 17-18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1, 17
	5b	Name and contact information for the trial sponsor	Page 1, 17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 17-18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page 15-16
Introduction			

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Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	<b>Page 6-7</b>
	6b	Explanation for choice of comparators	<b>Page 11-12</b>
Objectives	7	Specific objectives or hypotheses	<b>Page 8</b>
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	<b>Page 8</b>
<b>Methods: Participants, interventions, and outcomes</b>			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	<b>Page 8-9</b>
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	<b>Page 9</b>
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	<b>Page 11-12</b>
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	<b>Page 12-13</b>
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	<b>Page 9</b>
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	<b>Page 12-13</b>
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	<b>Page 13-14</b>

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 9-11
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 10-11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not Applicable
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 14-15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 15-16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 15
<b>Methods: Monitoring</b>			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 16

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	<b>Page 14</b>
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	<b>Page 16</b>
<b>Ethics and dissemination</b>			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<b>Page 16</b>
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	<b>Page 16</b>
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<b>Page 16</b>
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	<b>Not Applicable</b>
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	<b>Page 14--15</b>
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	<b>Page 18</b>
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	<b>Page 16</b>
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	<b>Page 9</b>
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	<b>Page 16</b>

	31b	Authorship eligibility guidelines and any intended use of professional writers	<b>None</b>
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	<b>Page 16</b>
<b>Appendices</b>			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	<b>None</b>
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	<b>Not Applicable</b>

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.