



BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-030041
Article Type:	Protocol
Date Submitted by the Author:	24-Feb-2019
Complete List of Authors:	Dai, Wei; Sichuan Cancer Hospital and Research Institute, Sichuan Cancer Center Zhang, Yuanqiang; Zigong First People's Hospital, Department of Cardiothoracic Surgery Feng, Wenhong ; Jiangyou People's Hospital, Department of Thoracic and Cardiovascular Surgery Liao, Xiaoqing ; Dazhu County People's Hospital, Department of Cardiothoracic Surgical Oncology Mu, Yunfei ; The Third People's Hospital of Chengdu, Department of Thoracic Surgery Zhang, Rui ; The Seventh People's Hospital of Chengdu, Department of Thoracic Surgery Wei, Xing ; Sichuan Cancer Hospital and Research Institute, Department of Thoracic Surgery Wu, Chuanmei ; Sichuan Cancer Hospital and Research Institute, Department of Thoracic Surgery Xie, Shaohua; Sichuan Cancer Hospital and Chengdu Medical College, Department of Thoracic Surgery Li, Qiang; Sichuan Cancer Hospital and Research Institute, Department of Thoracic Surgery Shi, Qiuling; University of Texas MD Anderson Cancer Center
Keywords:	lung cancer, patient reported outcomes, postoperative symptom management, randomised controlled trial

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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,^{1#} Yuanqiang Zhang,^{2#} Wenhong Feng,^{3#} Xiaoqing Liao,^{4#} Yunfei Mu,^{5#} Rui Zhang,⁶ Xing Wei,¹ Chuanmei Wu,¹ Shaohua Xie,^{1,7} Qiang Li,¹ Qiuling Shi⁸

Institutions:

¹Department of Thoracic Surgery, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, Sichuan, China.

²Department of Cardiothoracic Surgery, Zigong First People's Hospital, Zigong, Sichuan, China.

³Department of Thoracic and Cardiovascular Surgery, Jiangyou People's Hospital, Jiangyou, Sichuan, China.

⁴Department of Cardiothoracic Surgical Oncology, Dazhu County People's Hospital, Dazhu County, Dazhou, Sichuan, China.

⁵Department of Thoracic Surgery, The Third People's Hospital of Chengdu, Chengdu, Sichuan, China.

⁶Department of Thoracic Surgery, The Seventh People's Hospital of Chengdu, Chengdu, Sichuan, China.

⁷Graduate School, Chengdu Medical College, Chengdu, Sichuan, China.

⁸Department of Symptom Research, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA.

Correspondence to

Dr Qiuling Shi, Department of Symptom Research, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Unit 1450 Houston, TX 77030, USA. Telephone: 713/745-3504, e-mail: qshi@mdanderson.org.

Dr Qiang Li, Department of Thoracic Surgery, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, No. 55, Section 4, South Renmin Road, Chengdu 610041,

31 Sichuan, China. Telephone: +86-028-85420229, e-mail: liqiang@sichuancancer.org.

32

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

34

35 **Word count:** 2728 words

36

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

65

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

68

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

83

84

INTRODUCTION

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

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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).¹⁰

115 Currently, PROs are mainly used in non-surgical treatment settings,¹⁰⁻¹³ and they are
116 still in the early stage of application in the surgical treatment setting.^{5 7 14-28} 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.^{5 18-28} 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;⁵ (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;⁵ (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

7

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

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)²⁹ 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).³⁰ The results of this trial will be reported according to the guidelines of Consolidated Standards of Reporting Trials (CONSORT).³¹ 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)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

clinically diagnosed as primary lung cancer, (3) clinical stage I-IIIa (8th edition),³² and (4) planning to receive surgery. The exclusion criteria are: (1) history of neoadjuvant therapy, (2) having other malignant tumours, and (3) unable to understand the study requirements.

Sample size calculation

The primary end point of this study will be the mean symptom threshold events within 4 weeks after discharge or before the start of postoperative oncologic treatment. To meet the minimal clinically important difference (0.5 standard deviation)³³ for the mean symptom threshold events, the required sample size is 64 for each group, when rejecting the null hypothesis (the difference between the two groups < 0.5 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, allocation concealment and blinding procedure

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>) of our hospital 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. The blinding of participants and investigators is impossible due to the nature of the interventions.

193

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 (± 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 ≥ 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.

206

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.

217

218 **Withdrawal criteria**

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 ≥ 4 , it is identified as moderate severity.^{34 35} In this study, a score of 4 is set as the threshold value for intervention, and a target symptom score of ≥ 4 is reported as a threshold event.

The primary PRO tool used in this study is the MDASI-LC.²⁹ 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.

245

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,³⁶ 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.

258

259 Data collection, management, and quality control

260 REDCap,^{37 38} 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

317 **Acknowledgements** The authors thank all the patients and patient advisers who are involved in this
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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

324 **Funding** This work was supported by [Bethune charitable foundation], [Sichuan Science and
325 Technology Program] grant number [18PJ436] and [National Natural Science Foundation of China]
326 grant number [81872506].

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.

331

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Supérieur (ABES).

REFERENCES

1. Chen W, Zheng R, Baade PD, *et al.* Cancer statistics in China, 2015. *CA Cancer J Clin* 2016;66:115-32.
2. Bray F, Ferlay J, Soerjomataram I, *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394-424.
3. Lowery AE, Krebs P, Coups EJ, *et al.* Impact of symptom burden in post-surgical non-small cell lung cancer survivors. *Support Care Cancer* 2014;22:173-80.
4. Yang P, Cheville AL, Wampfler JA, *et al.* Quality of life and symptom burden among long-term lung cancer survivors. *J Thorac Oncol* 2012;7:64-70.
5. Fagundes CP, Shi Q, Vaporciyan AA, *et al.* Symptom recovery after thoracic surgery: Measuring patient-reported outcomes with the MD Anderson Symptom Inventory. *J Thorac Cardiovasc Surg* 2015;150:613-9 e2.
6. Basch E. Patient-Reported Outcomes - Harnessing Patients' Voices to Improve Clinical Care. *N Engl J Med* 2017;376:105-8.
7. Khullar OV, Fernandez FG. Patient-Reported Outcomes in Thoracic Surgery. *Thorac Surg Clin* 2017;27:279-90.
8. U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. *Health Qual Life Outcomes* 2006;4:79.
9. Basch E. The missing voice of patients in drug-safety reporting. *N Engl J Med* 2010;362:865-9.
10. Basch E, Deal AM, Dueck AC, *et al.* Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. *JAMA* 2017;318:197-8.
11. Basch E, Deal AM, Kris MG, *et al.* Symptom Monitoring With Patient-Reported Outcomes

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

During Routine Cancer Treatment: A Randomized Controlled Trial. *J Clin Oncol* 2016;34:557-65.

12. Novello S, Kaiser R, Mellemaard A, *et al.* Analysis of patient-reported outcomes from the LUME-Lung 1 trial: a randomised, double-blind, placebo-controlled, Phase III study of second-line nintedanib in patients with advanced non-small cell lung cancer. *Eur J Cancer* 2015;51:317-26.

13. Popat S. Patient reported outcomes from LUX-Lung 3: first-line afatinib is superior to chemotherapy-would patients agree? *Ann Palliat Med* 2014;3:19-21.

14. Rolfson O, Donahue GS, Hallsten M, *et al.* Patient-reported outcomes in cemented and uncemented total hip replacements. *Hip Int* 2016;26:451-7.

15. Day RW, Cleeland CS, Wang XS, *et al.* Patient-Reported Outcomes Accurately Measure the Value of an Enhanced Recovery Program in Liver Surgery. *J Am Coll Surg* 2015;221:1023-30 e1-2.

16. Poghosyan H, Sheldon LK, Leveille SG, *et al.* Health-related quality of life after surgical treatment in patients with non-small cell lung cancer: a systematic review. *Lung Cancer* 2013;81:11-26.

17. Cleeland CS, Wang XS, Shi Q, *et al.* Automated symptom alerts reduce postoperative symptom severity after cancer surgery: a randomized controlled clinical trial. *J Clin Oncol* 2011;29:994-1000.

18. Khullar OV, Rajaei MH, Force SD, *et al.* Pilot Study to Integrate Patient Reported Outcomes After Lung Cancer Operations Into The Society of Thoracic Surgeons Database. *Ann Thorac Surg* 2017;104:245-53.

19. Shi Q, Wang XS, Vaporciyan AA, *et al.* Patient-Reported Symptom Interference as a Measure of Postsurgery Functional Recovery in Lung Cancer. *J Pain Symptom Manage* 2016;52:822-31.

20. Li WW, Lee TW, Lam SS, *et al.* Quality of life following lung cancer resection: video-assisted thoracic surgery vs thoracotomy. *Chest* 2002;122:584-9.

21. Kenny PM, King MT, Viney RC, *et al.* Quality of life and survival in the 2 years after surgery for non small-cell lung cancer. *J Clin Oncol* 2008;26:233-41.

22. Balduyck B, Hendriks J, Lauwers P, *et al.* Quality of life after lung cancer surgery: a prospective pilot study comparing bronchial sleeve lobectomy with pneumonectomy. *J Thorac Oncol* 2008;3:604-8.
23. Ferguson MK, Parma CM, Celauro AD, *et al.* Quality of life and mood in older patients after major lung resection. *Ann Thorac Surg* 2009;87:1007-12; discussion 12-3.
24. Sartipy U. Prospective population-based study comparing quality of life after pneumonectomy and lobectomy. *Eur J Cardiothorac Surg* 2009;36:1069-74.
25. Ostroff JS, Krebs P, Coups EJ, *et al.* Health-related quality of life among early-stage, non-small cell, lung cancer survivors. *Lung Cancer* 2011;71:103-8.
26. Moller A, Sartipy U. Long-term health-related quality of life following surgery for lung cancer. *Eur J Cardiothorac Surg* 2012;41:362-7.
27. Zhao J, Zhao Y, Qiu T, *et al.* Quality of life and survival after II stage nonsmall cell carcinoma surgery: Video-assisted thoracic surgery versus thoracotomy lobectomy. *Indian J Cancer* 2015;52 Suppl 2:e130-3.
28. Yun YH, Kim YA, Sim JA, *et al.* Prognostic value of quality of life score in disease-free survivors of surgically-treated lung cancer. *BMC Cancer* 2016;16:505.
29. Mendoza TR, Wang XS, Lu C, *et al.* Measuring the symptom burden of lung cancer: the validity and utility of the lung cancer module of the M. D. Anderson Symptom Inventory. *Oncologist* 2011;16:217-27.
30. Chan AW, Tetzlaff JM, Altman DG, *et al.* SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200-7.
31. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010;152:726-32.
32. Goldstraw P, Chansky K, Crowley J, *et al.* The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol* 2016;11:39-51.
33. Revicki DA, Cella D, Hays RD, *et al.* Responsiveness and minimal important differences for patient reported outcomes. *Health & Quality of Life Outcomes* 2006;4:70.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

34. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Adult Cancer Pain. Version 1.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf.

35. Wang XS, Zhao F, Fisch MJ, *et al*. Prevalence and characteristics of moderate to severe fatigue: a multicenter study in cancer patients and survivors. *Cancer* 2014;120:425-32.

36. Sloan JA, Loprinzi CL, Kuross SA, *et al*. Randomized comparison of four tools measuring overall quality of life in patients with advanced cancer. *J Clin Oncol* 1998;16:3662-73.

37. Tomko RL, Gray KM, Oppenheimer SR, *et al*. Using REDCap for ambulatory assessment: Implementation in a clinical trial for smoking cessation to augment in-person data collection. *Am J Drug Alcohol Abuse* 2018;1-16.

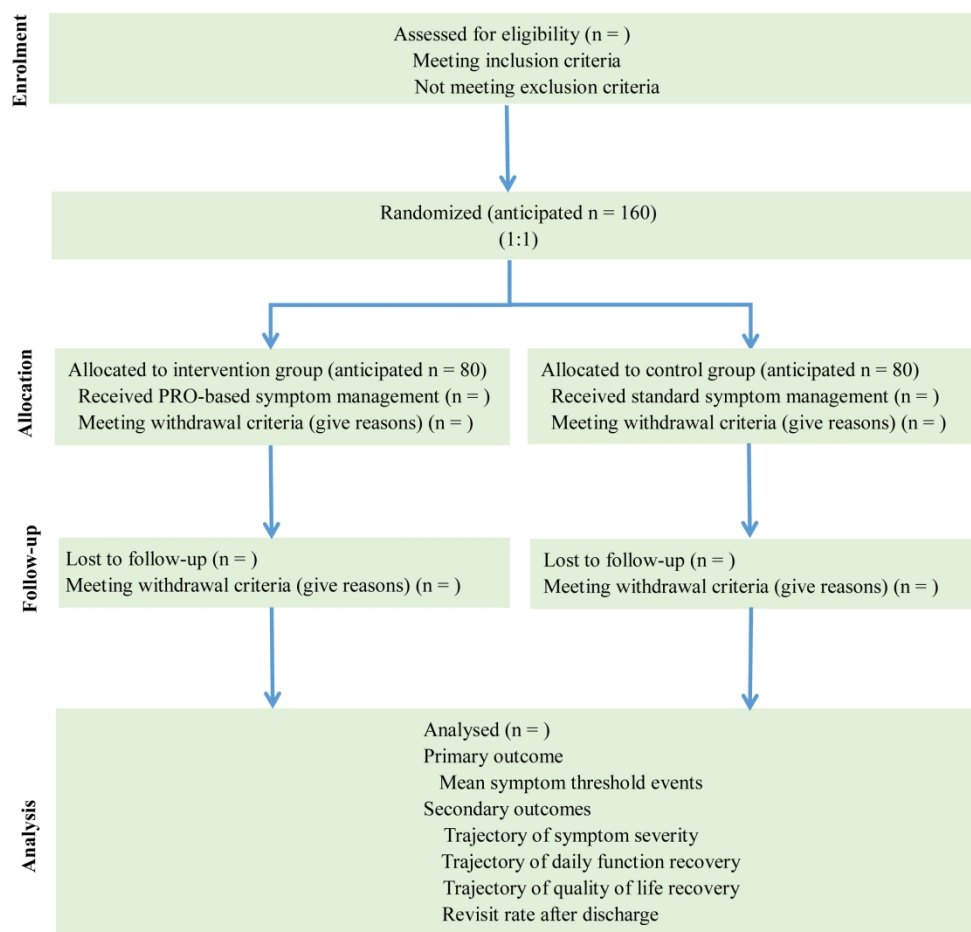
38. Harvey LA. REDCap: web-based software for all types of data storage and collection. *Spinal Cord* 2018;56:625.

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Supérieur (ABES).

429 **Figure legends**

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

For peer review only





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 14-15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1, 14
	5b	Name and contact information for the trial sponsor	Page 1, 14
	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 14
	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 12-13
Introduction			

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

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

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 10
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 9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	None
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 9
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 9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 9
	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 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	Page 10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 14
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)	Page 14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not Applicable
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	Page 12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 15
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	Page 12-13
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	Page 14
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	Page 14

	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.

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-030041.R1
Article Type:	Protocol
Date Submitted by the Author:	15-May-2019
Complete List of Authors:	Dai, Wei; Sichuan Cancer Hospital and Research Institute, Sichuan Cancer Center Zhang, Yuanqiang; Zigong First People's Hospital, Department of Cardiothoracic Surgery Feng, Wenhong ; Jiangyou People's Hospital, Department of Thoracic and Cardiovascular Surgery Liao, Xiaoqing ; Dazhu County People's Hospital, Department of Cardiothoracic Surgical Oncology Mu, Yunfei ; The Third People's Hospital of Chengdu, Department of Thoracic Surgery Zhang, Rui ; The Seventh People's Hospital of Chengdu, Department of Thoracic Surgery Wei, Xing ; Sichuan Cancer Hospital and Research Institute, Department of Thoracic Surgery Wu, Chuanmei ; Sichuan Cancer Hospital and Research Institute, Department of Thoracic Surgery Xie, Shaohua; Sichuan Cancer Hospital and Chengdu Medical College, Department of Thoracic Surgery Li, Qiang; Sichuan Cancer Hospital and Research Institute, Department of Thoracic Surgery Shi, Qiuling; University of Texas MD Anderson Cancer Center
Primary Subject Heading:	Patient-centred medicine
Secondary Subject Heading:	Surgery, Oncology, Nursing
Keywords:	lung cancer, patient reported outcomes, postoperative symptom management, randomised controlled trial

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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,^{1#} Yuanqiang Zhang,^{2#} Wenhong Feng,³ Xiaoqing Liao,⁴ Yunfei Mu,⁵ Rui Zhang,⁶ Xing Wei,¹ Chuanmei Wu,¹ Shaohua Xie,^{1,7} Qiang Li,¹ Qiuling Shi⁸

Institutions:

¹Department of Thoracic Surgery, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, Sichuan, China.

²Department of Cardiothoracic Surgery, Zigong First People's Hospital, Zigong, Sichuan, China.

³Department of Thoracic and Cardiovascular Surgery, Jiangyou People's Hospital, Jiangyou, Sichuan, China.

⁴Department of Cardiothoracic Surgical Oncology, Dazhu County People's Hospital, Dazhu County, Dazhou, Sichuan, China.

⁵Department of Thoracic Surgery, The Third People's Hospital of Chengdu, Chengdu, Sichuan, China.

⁶Department of Thoracic Surgery, The Seventh People's Hospital of Chengdu, Chengdu, Sichuan, China.

⁷Graduate School, Chengdu Medical College, Chengdu, Sichuan, China.

⁸Department of Symptom Research, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA.

Correspondence to

Dr Qiuling Shi, Department of Symptom Research, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Unit 1450 Houston, TX 77030, USA. Telephone: 713/745-3504, e-mail: qshi@mdanderson.org.

Dr Qiang Li, Department of Thoracic Surgery, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, No. 55, Section 4, South Renmin Road, Chengdu 610041,

31 Sichuan, China. Telephone: +86-028-85420229, e-mail: liqiang@sichuancancer.org.

32

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

34

35 **Word count:** 3508 words

36

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

65

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

68

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

83

84

85 INTRODUCTION

86 Lung cancer is the most common cancer and the leading cause of cancer death in China
87 and worldwide.^{1 2} 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.³⁻⁵ 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.³
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.^{3 4} Therefore, effective
98 interventions are needed to alleviate post-surgery symptoms in patients with lung
99 cancer.^{3 4}

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.^{6 7} 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.⁸ 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.⁹ 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.^{6 10-15} 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.^{10 11} When compared to a

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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, $p = 0.03$).¹⁰ 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,¹⁰⁻¹³ and they are
118 still in the early stage of application in the surgical treatment setting.^{5 7 14-28} 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.^{5 18-28} 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;⁵ (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;⁵ (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)²⁹ 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)³⁰ 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).³¹ The results of this trial will be reported according to the guidelines of Consolidated Standards of Reporting Trials (CONSORT).³² 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

171 **Participant recruitment**

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

187 **Sample size calculation**

188 The primary end point of this study will be the mean symptom threshold events, defined
189 as the average number of target symptom threshold events per patient, at each time
190 point. To meet the minimal clinically important difference (0.5 standard deviation)³⁴
191 for the mean symptom threshold events, the required sample size is 64 for each group,
192 when rejecting the null hypothesis (the difference between the two groups < 0.5

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 ≥ 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.

245

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.

265

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 ≥ 4 , it is identified as moderate severity.^{35 36} In this study, a score of 4 is set as the threshold value for intervention, and a target symptom score of ≥ 4 is reported as a threshold event.

The primary PRO tool used in this study is the MDASI-LC.³⁰ 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,³⁷ 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,^{38 39} 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.

322

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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-

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

Acknowledgements The authors thank all the patients and patient advisers who are involved in this study.

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.

Funding This work was supported by [Bethune charitable foundation], [Sichuan Science and Technology Program] grant number [18PJ436] and [National Natural Science Foundation of China] grant number [81872506].

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.

401

For peer review only

REFERENCES

1. Chen W, Zheng R, Baade PD, *et al.* Cancer statistics in China, 2015. *CA Cancer J Clin* 2016;66:115-32.

2. Bray F, Ferlay J, Soerjomataram I, *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394-424.

3. Lowery AE, Krebs P, Coups EJ, *et al.* Impact of symptom burden in post-surgical non-small cell lung cancer survivors. *Support Care Cancer* 2014;22:173-80.

4. Yang P, Cheville AL, Wampfler JA, *et al.* Quality of life and symptom burden among long-term lung cancer survivors. *J Thorac Oncol* 2012;7:64-70.

5. Fagundes CP, Shi Q, Vaporciyan AA, *et al.* Symptom recovery after thoracic surgery: Measuring patient-reported outcomes with the MD Anderson Symptom Inventory. *J Thorac Cardiovasc Surg* 2015;150:613-9 e2.

6. Basch E. Patient-Reported Outcomes - Harnessing Patients' Voices to Improve Clinical Care. *N Engl J Med* 2017;376:105-8.

7. Khullar OV, Fernandez FG. Patient-Reported Outcomes in Thoracic Surgery. *Thorac Surg Clin* 2017;27:279-90.

8. U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. *Health Qual Life Outcomes* 2006;4:79.

9. Basch E. The missing voice of patients in drug-safety reporting. *N Engl J Med* 2010;362:865-9.

10. Basch E, Deal AM, Dueck AC, *et al.* Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. *JAMA* 2017;318:197-8.

11. Basch E, Deal AM, Kris MG, *et al.* Symptom Monitoring With Patient-Reported Outcomes

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Ensignement Supérieur (ABES).

- 430 During Routine Cancer Treatment: A Randomized Controlled Trial. *J Clin Oncol* 2016;34:557-
- 431 65.
- 432 12. Novello S, Kaiser R, Mellemgaard A, *et al.* Analysis of patient-reported outcomes from the
- 433 LUME-Lung 1 trial: a randomised, double-blind, placebo-controlled, Phase III study of second-
- 434 line nintedanib in patients with advanced non-small cell lung cancer. *Eur J Cancer* 2015;51:317-
- 435 26.
- 436 13. Popat S. Patient reported outcomes from LUX-Lung 3: first-line afatinib is superior to
- 437 chemotherapy-would patients agree? *Ann Palliat Med* 2014;3:19-21.
- 438 14. Ng S, Pusic A, Parker E, *et al.* Patient-Reported Outcome Measures for Breast Implant Surgery:
- 439 A Pilot Study. *Aesthet Surg J* 2019;sjz023.doi:10.1093/asj/sjz023.[Epub ahead of print].
- 440 15. Coronini-Cronberg S, Appleby J, Thompson J. Application of patient-reported outcome
- 441 measures (PROMs) data to estimate cost-effectiveness of hernia surgery in England. *J R Soc*
- 442 *Med* 2013;106:278-87.
- 443 16. Poghosyan H, Sheldon LK, Leveille SG, *et al.* Health-related quality of life after surgical
- 444 treatment in patients with non-small cell lung cancer: a systematic review. *Lung Cancer*
- 445 2013;81:11-26.
- 446 17. Cleeland CS, Wang XS, Shi Q, *et al.* Automated symptom alerts reduce postoperative symptom
- 447 severity after cancer surgery: a randomized controlled clinical trial. *J Clin Oncol* 2011;29:994-
- 448 1000.
- 449 18. Khullar OV, Rajaei MH, Force SD, *et al.* Pilot Study to Integrate Patient Reported Outcomes
- 450 After Lung Cancer Operations Into The Society of Thoracic Surgeons Database. *Ann Thorac*
- 451 *Surg* 2017;104:245-53.
- 452 19. Shi Q, Wang XS, Vaporciyan AA, *et al.* Patient-Reported Symptom Interference as a Measure
- 453 of Postsurgery Functional Recovery in Lung Cancer. *J Pain Symptom Manage* 2016;52:822-31.
- 454 20. Li WW, Lee TW, Lam SS, *et al.* Quality of life following lung cancer resection: video-assisted
- 455 thoracic surgery vs thoracotomy. *Chest* 2002;122:584-9.
- 456 21. Kenny PM, King MT, Viney RC, *et al.* Quality of life and survival in the 2 years after surgery
- 457 for non small-cell lung cancer. *J Clin Oncol* 2008;26:233-41.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

22. Balduyck B, Hendriks J, Lauwers P, *et al.* Quality of life after lung cancer surgery: a prospective pilot study comparing bronchial sleeve lobectomy with pneumonectomy. *J Thorac Oncol* 2008;3:604-8.

23. Ferguson MK, Parma CM, Celauro AD, *et al.* Quality of life and mood in older patients after major lung resection. *Ann Thorac Surg* 2009;87:1007-12; discussion 12-3.

24. Sartipy U. Prospective population-based study comparing quality of life after pneumonectomy and lobectomy. *Eur J Cardiothorac Surg* 2009;36:1069-74.

25. Ostroff JS, Krebs P, Coups EJ, *et al.* Health-related quality of life among early-stage, non-small cell, lung cancer survivors. *Lung Cancer* 2011;71:103-8.

26. Moller A, Sartipy U. Long-term health-related quality of life following surgery for lung cancer. *Eur J Cardiothorac Surg* 2012;41:362-7.

27. Zhao J, Zhao Y, Qiu T, *et al.* Quality of life and survival after II stage nonsmall cell carcinoma surgery: Video-assisted thoracic surgery versus thoracotomy lobectomy. *Indian J Cancer* 2015;52 Suppl 2:e130-3.

28. Yun YH, Kim YA, Sim JA, *et al.* Prognostic value of quality of life score in disease-free survivors of surgically-treated lung cancer. *BMC Cancer* 2016;16:505.

29. Montag C, Becker B, Gan C. The Multipurpose Application WeChat: A Review on Recent Research. *Front Psychol* 2018;9:2247.

30. Mendoza TR, Wang XS, Lu C, *et al.* Measuring the symptom burden of lung cancer: the validity and utility of the lung cancer module of the M. D. Anderson Symptom Inventory. *Oncologist* 2011;16:217-27.

31. Chan AW, Tetzlaff JM, Altman DG, *et al.* SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200-7.

32. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010;152:726-32.

33. Goldstraw P, Chansky K, Crowley J, *et al.* The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol* 2016;11:39-51.

34. Revicki DA, Cella D, Hays RD, *et al.* Responsiveness and minimal important differences for patient reported outcomes. *Health & Quality of Life Outcomes* 2006;4:70.
35. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Adult Cancer Pain. Version 1.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf.
36. Wang XS, Zhao F, Fisch MJ, *et al.* Prevalence and characteristics of moderate to severe fatigue: a multicenter study in cancer patients and survivors. *Cancer* 2014;120:425-32.
37. Sloan JA, Loprinzi CL, Kross SA, *et al.* Randomized comparison of four tools measuring overall quality of life in patients with advanced cancer. *J Clin Oncol* 1998;16:3662-73.
38. Tomko RL, Gray KM, Oppenheimer SR, *et al.* Using REDCap for ambulatory assessment: Implementation in a clinical trial for smoking cessation to augment in-person data collection. *Am J Drug Alcohol Abuse* 2018;1-16.
39. Harvey LA. REDCap: web-based software for all types of data storage and collection. *Spinal Cord* 2018;56:625.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

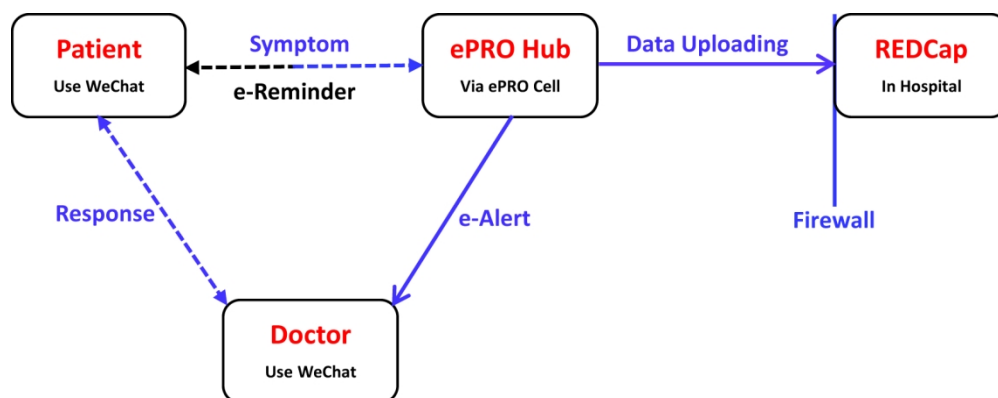
Figure legends

Figure 1 Schematic diagram of the SMARS.

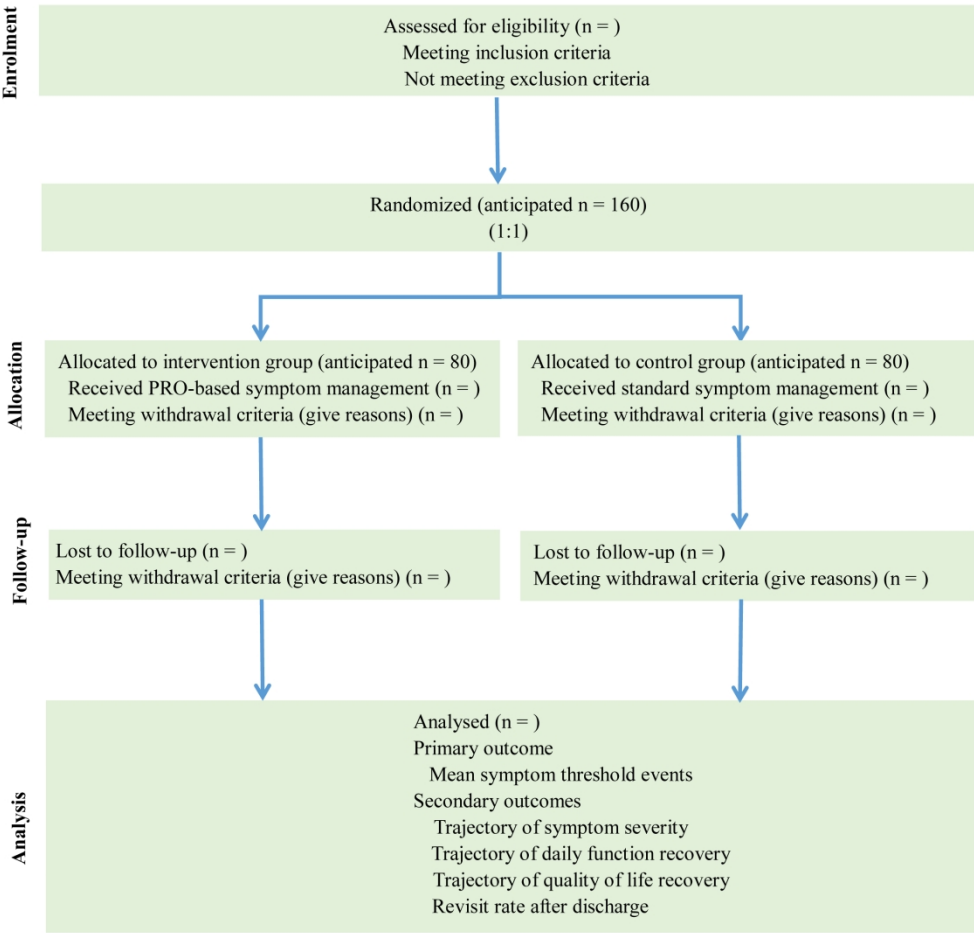
Figure 2 Flow chart of this parallel group randomised trial.

For peer review only

Enseignement Supérieur (ABES).
Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.



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 14-15
Introduction			

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

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

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 8-9
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 9-10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 9
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
	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 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	Page 14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 15
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 16
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)	Page 16
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not Applicable
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	Page 14--15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 18
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	Page 16
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	Page 9
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	Page 16

	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.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-030041.R2
Article Type:	Protocol
Date Submitted by the Author:	18-Jul-2019
Complete List of Authors:	Dai, Wei; Sichuan Cancer Hospital and Research Institute, Sichuan Cancer Center Zhang, Yuanqiang; Zigong First People's Hospital, Department of Cardiothoracic Surgery Feng, Wenhong ; Jiangyou People's Hospital, Department of Thoracic and Cardiovascular Surgery Liao, Xiaoqing ; Dazhu County People's Hospital, Department of Cardiothoracic Surgical Oncology Mu, Yunfei ; The Third People's Hospital of Chengdu, Department of Thoracic Surgery Zhang, Rui ; The Seventh People's Hospital of Chengdu, Department of Thoracic Surgery Wei, Xing ; Sichuan Cancer Hospital and Research Institute, Department of Thoracic Surgery Wu, Chuanmei ; Sichuan Cancer Hospital and Research Institute, Department of Thoracic Surgery Xie, Shaohua; Sichuan Cancer Hospital and Chengdu Medical College, Department of Thoracic Surgery Li, Qiang; Sichuan Cancer Hospital and Research Institute, Department of Thoracic Surgery Shi, Qiuling; University of Texas MD Anderson Cancer Center
Primary Subject Heading:	Patient-centred medicine
Secondary Subject Heading:	Surgery, Oncology, Nursing
Keywords:	lung cancer, patient reported outcomes, postoperative symptom management, randomised controlled trial

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1

Title page

2

Title: Using patient-reported outcomes to manage postoperative symptoms in patients

3

with lung cancer: protocol for a multicentre, randomised controlled trial

4

Authors: Wei Dai,^{1#} Yuanqiang Zhang,^{2#} Wenhong Feng,³ Xiaoqing Liao,⁴ Yunfei

5

Mu,⁵ Rui Zhang,⁶ Xing Wei,¹ Chuanmei Wu,¹ Shaohua Xie,^{1,7} Qiang Li,¹ Qiuling Shi⁸

6

Institutions:

7

¹Department of Thoracic Surgery, Sichuan Cancer Hospital & Institute, Sichuan Cancer

8

Center, School of Medicine, University of Electronic Science and Technology of China,

9

Chengdu, Sichuan, China.

10

²Department of Cardiothoracic Surgery, Zigong First People's Hospital, Zigong,

11

Sichuan, China.

12

³Department of Thoracic and Cardiovascular Surgery, Jiangyou People's Hospital,

13

Jiangyou, Sichuan, China.

14

⁴Department of Cardiothoracic Surgical Oncology, Dazhu County People's Hospital,

15

Dazhu County, Dazhou, Sichuan, China.

16

⁵Department of Thoracic Surgery, The Third People's Hospital of Chengdu, Chengdu,

17

Sichuan, China.

18

⁶Department of Thoracic Surgery, The Seventh People's Hospital of Chengdu, Chengdu,

19

Sichuan, China.

20

⁷Graduate School, Chengdu Medical College, Chengdu, Sichuan, China.

21

⁸Department of Symptom Research, The University of Texas MD Anderson Cancer

22

Center, Houston, Texas, USA.

23

24

Correspondence to

25

Dr Qiuling Shi, Department of Symptom Research, The University of Texas MD

26

Anderson Cancer Center, 1515 Holcombe Blvd., Unit 1450 Houston, TX 77030, USA.

27

Telephone: 713/745-3504, e-mail: qshi@mdanderson.org.

28

Dr Qiang Li, Department of Thoracic Surgery, Sichuan Cancer Hospital & Institute,

29

Sichuan Cancer Center, School of Medicine, University of Electronic Science and

30

Technology of China, No. 55, Section 4, South Renmin Road, Chengdu 610041,

31 Sichuan, China. Telephone: +86-028-85420229, e-mail: liqiang@sichuancancer.org.

32

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

34

35 **Word count:** 3699 words

36

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 PRO-based
50 symptom management from the specialists 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.

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Supérieur (ABES)

64 **Trials registration number** ChiCTR1900020846.

65

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

68

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

83

84

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Supérieur (ABES).

INTRODUCTION

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

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

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, $p = 0.03$).¹⁰ 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,¹⁰⁻¹³ and they are
118 still in the early stage of application in the surgical treatment setting.^{5 7 14-28} 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.^{5 18-28} 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;⁵ (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;⁵ (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)²⁹ 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)³⁰ 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).³¹ The results of this trial will be reported according to the guidelines of Consolidated Standards of Reporting Trials (CONSORT).³² 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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),³³ 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)³⁴ 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.

219

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 ≥ 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.

259

260 Control group

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

269

270 **Withdrawal criteria**

271 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 (\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 ≥ 4 , it is identified as moderate severity.^{35 36} In this study, a score of 4 is set as the threshold value for intervention, and a target symptom score of ≥ 4 is reported as a threshold event.

The primary PRO tool used in this study is the MDASI-LC.³⁰ 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,³⁷ 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.

321

322 Data collection, management, and quality control

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

REDCap,^{38 39} 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

Acknowledgements The authors thank all the patients and patient advisers who are involved in this study.

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.

Funding This work was supported by [Bethune charitable foundation], [Sichuan Science and Technology Program] grant number [18PJ436 and 2019YFH0070] and [National Natural Science Foundation of China] grant number [81872506].

Competing interests None declared.

Patient consent Obtained.

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

428

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Supérieur (ABES).

REFERENCES

1. Chen W, Zheng R, Baade PD, *et al.* Cancer statistics in China, 2015. *CA Cancer J Clin* 2016;66:115-32.
2. Bray F, Ferlay J, Soerjomataram I, *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394-424.
3. Lowery AE, Krebs P, Coups EJ, *et al.* Impact of symptom burden in post-surgical non-small cell lung cancer survivors. *Support Care Cancer* 2014;22:173-80.
4. Yang P, Cheville AL, Wampfler JA, *et al.* Quality of life and symptom burden among long-term lung cancer survivors. *J Thorac Oncol* 2012;7:64-70.
5. Fagundes CP, Shi Q, Vaporciyan AA, *et al.* Symptom recovery after thoracic surgery: Measuring patient-reported outcomes with the MD Anderson Symptom Inventory. *J Thorac Cardiovasc Surg* 2015;150:613-9 e2.
6. Basch E. Patient-Reported Outcomes - Harnessing Patients' Voices to Improve Clinical Care. *N Engl J Med* 2017;376:105-8.
7. Khullar OV, Fernandez FG. Patient-Reported Outcomes in Thoracic Surgery. *Thorac Surg Clin* 2017;27:279-90.
8. U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. *Health Qual Life Outcomes* 2006;4:79.
9. Basch E. The missing voice of patients in drug-safety reporting. *N Engl J Med* 2010;362:865-9.
10. Basch E, Deal AM, Dueck AC, *et al.* Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. *JAMA* 2017;318:197-8.
11. Basch E, Deal AM, Kris MG, *et al.* Symptom Monitoring With Patient-Reported Outcomes

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

457 During Routine Cancer Treatment: A Randomized Controlled Trial. *J Clin Oncol* 2016;34:557-
458 65.

459 12. Novello S, Kaiser R, Mellemgaard A, *et al.* Analysis of patient-reported outcomes from the
460 LUME-Lung 1 trial: a randomised, double-blind, placebo-controlled, Phase III study of second-
461 line nintedanib in patients with advanced non-small cell lung cancer. *Eur J Cancer* 2015;51:317-
462 26.

463 13. Popat S. Patient reported outcomes from LUX-Lung 3: first-line afatinib is superior to
464 chemotherapy-would patients agree? *Ann Palliat Med* 2014;3:19-21.

465 14. Ng S, Pusic A, Parker E, *et al.* Patient-Reported Outcome Measures for Breast Implant Surgery:
466 A Pilot Study. *Aesthet Surg J* 2019;sjz023.doi:10.1093/asj/sjz023.[Epub ahead of print].

467 15. Coronini-Cronberg S, Appleby J, Thompson J. Application of patient-reported outcome
468 measures (PROMs) data to estimate cost-effectiveness of hernia surgery in England. *J R Soc*
469 *Med* 2013;106:278-87.

470 16. Poghosyan H, Sheldon LK, Leveille SG, *et al.* Health-related quality of life after surgical
471 treatment in patients with non-small cell lung cancer: a systematic review. *Lung Cancer*
472 2013;81:11-26.

473 17. Cleeland CS, Wang XS, Shi Q, *et al.* Automated symptom alerts reduce postoperative symptom
474 severity after cancer surgery: a randomized controlled clinical trial. *J Clin Oncol* 2011;29:994-
475 1000.

476 18. Khullar OV, Rajaei MH, Force SD, *et al.* Pilot Study to Integrate Patient Reported Outcomes
477 After Lung Cancer Operations Into The Society of Thoracic Surgeons Database. *Ann Thorac*
478 *Surg* 2017;104:245-53.

479 19. Shi Q, Wang XS, Vaporciyan AA, *et al.* Patient-Reported Symptom Interference as a Measure
480 of Postsurgery Functional Recovery in Lung Cancer. *J Pain Symptom Manage* 2016;52:822-31.

481 20. Li WW, Lee TW, Lam SS, *et al.* Quality of life following lung cancer resection: video-assisted
482 thoracic surgery vs thoracotomy. *Chest* 2002;122:584-9.

483 21. Kenny PM, King MT, Viney RC, *et al.* Quality of life and survival in the 2 years after surgery
484 for non small-cell lung cancer. *J Clin Oncol* 2008;26:233-41.

22. Balduyck B, Hendriks J, Lauwers P, *et al.* Quality of life after lung cancer surgery: a prospective pilot study comparing bronchial sleeve lobectomy with pneumonectomy. *J Thorac Oncol* 2008;3:604-8.
23. Ferguson MK, Parma CM, Celauro AD, *et al.* Quality of life and mood in older patients after major lung resection. *Ann Thorac Surg* 2009;87:1007-12; discussion 12-3.
24. Sartipy U. Prospective population-based study comparing quality of life after pneumonectomy and lobectomy. *Eur J Cardiothorac Surg* 2009;36:1069-74.
25. Ostroff JS, Krebs P, Coups EJ, *et al.* Health-related quality of life among early-stage, non-small cell, lung cancer survivors. *Lung Cancer* 2011;71:103-8.
26. Moller A, Sartipy U. Long-term health-related quality of life following surgery for lung cancer. *Eur J Cardiothorac Surg* 2012;41:362-7.
27. Zhao J, Zhao Y, Qiu T, *et al.* Quality of life and survival after II stage nonsmall cell carcinoma surgery: Video-assisted thoracic surgery versus thoracotomy lobectomy. *Indian J Cancer* 2015;52 Suppl 2:e130-3.
28. Yun YH, Kim YA, Sim JA, *et al.* Prognostic value of quality of life score in disease-free survivors of surgically-treated lung cancer. *BMC Cancer* 2016;16:505.
29. Montag C, Becker B, Gan C. The Multipurpose Application WeChat: A Review on Recent Research. *Front Psychol* 2018;9:2247.
30. Mendoza TR, Wang XS, Lu C, *et al.* Measuring the symptom burden of lung cancer: the validity and utility of the lung cancer module of the M. D. Anderson Symptom Inventory. *Oncologist* 2011;16:217-27.
31. Chan AW, Tetzlaff JM, Altman DG, *et al.* SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200-7.
32. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010;152:726-32.
33. Goldstraw P, Chansky K, Crowley J, *et al.* The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol* 2016;11:39-51.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

34. Revicki DA, Cella D, Hays RD, *et al.* Responsiveness and minimal important differences for patient reported outcomes. *Health & Quality of Life Outcomes* 2006;4:70.

35. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Adult Cancer Pain. Version 1.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf.

36. Wang XS, Zhao F, Fisch MJ, *et al.* Prevalence and characteristics of moderate to severe fatigue: a multicenter study in cancer patients and survivors. *Cancer* 2014;120:425-32.

37. Sloan JA, Loprinzi CL, Kross SA, *et al.* Randomized comparison of four tools measuring overall quality of life in patients with advanced cancer. *J Clin Oncol* 1998;16:3662-73.

38. Tomko RL, Gray KM, Oppenheimer SR, *et al.* Using REDCap for ambulatory assessment: Implementation in a clinical trial for smoking cessation to augment in-person data collection. *Am J Drug Alcohol Abuse* 2018;1-16.

39. Harvey LA. REDCap: web-based software for all types of data storage and collection. *Spinal Cord* 2018;56:625.

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Supérieur (ABES)

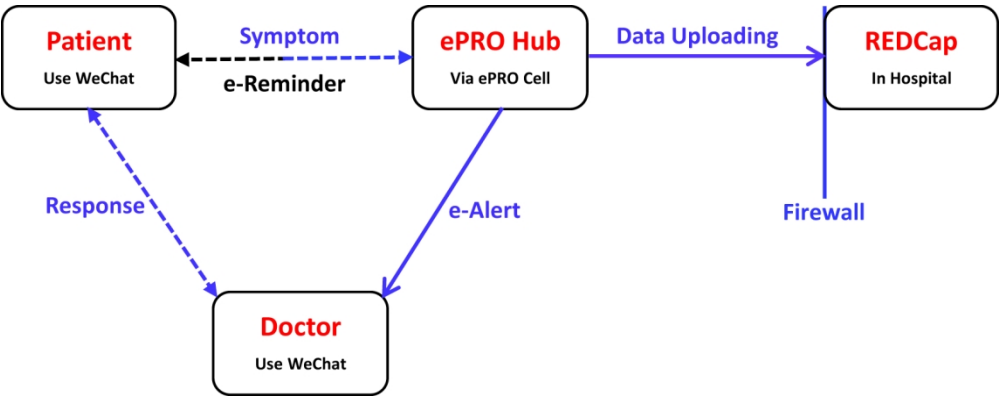
529 **Figure legends**

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

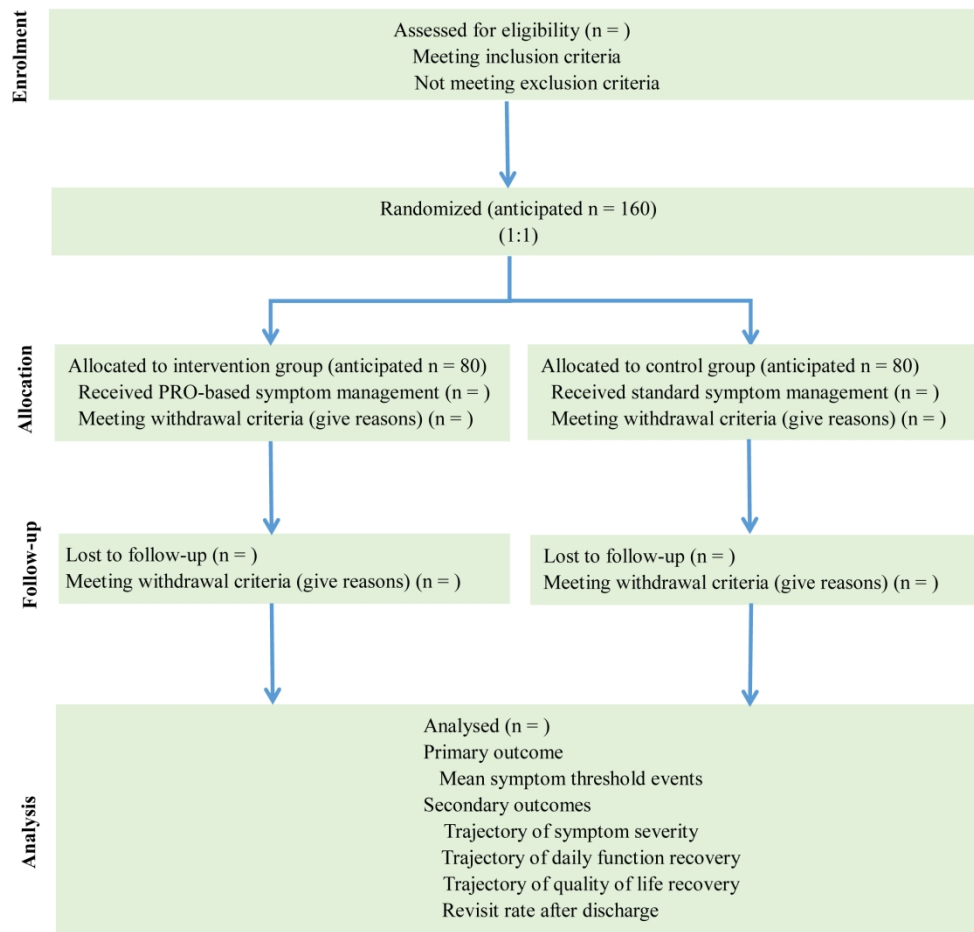
531 **Figure 2** Flow chart of this parallel group randomised trial.

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			

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 11-12
	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 12-13
	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 12-13
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

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
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 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	Page 14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 16
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)	Page 16
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not Applicable
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	Page 14--15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 18
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	Page 16
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	Page 9
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	Page 16

	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.