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## Assessing the safety and feasibility of neoadjuvant hormone and radiation therapy followed by robot-assisted radical prostatectomy for treating locally advanced prostate cancer: protocol for an open-label, dose-escalation, singlecentre, phase I clinical trial

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5	label, dose-escalation, single-centre, phase I clinic trial
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## 23 Abstract

## 24 Introduction

Patients with locally advanced prostate cancer are at high risk of recurrence after definitive treatment. There are emerging data that radical prostatectomy can delay the progression of castration resistance and potentially prolong survival. Neoadjuvant radiation therapy improves local control and has shown survival benefit with favorable toxicity profile in several other malignancies. We have designed this trial to investigate whether this combination, which theoretically maximizes local control, is a safe and feasible approach for treating locally advanced prostate cancer.

## 33 Methods and analysis

This study is a phase I, open-label study to investigate the safety and feasibility of neoadjuvant hormone and radiation therapy followed by robot-assisted radical prostatectomy by a traditional 3+3 dose-escalation design with 4 planned radiation dose levels (39.6 Gy/22F, 45 Gy/25F, 50.4 Gy/28F, and 54 Gy/30F). Locally advanced prostate cancer patients with positive pelvic and/or retroperitoneal lymph nodes will be recruited. The primary objective is to determine the adverse events and maximal tolerable dose neoadjuvant of radiotherapy. Toxicity will be assessed using the National Cancer Institute Common Toxicity Criteria V5.0. 

## 43 Ethics and dissemination

This protocol was approved by the institutional review board of Shanghai
Changhai Hospital (ref. CHEC2019-070 & CHEC2019-082). The study will be
performed in compliance with applicable local legislation and in accordance

47	with the ethical principles developed by the World Medical Association in the
48	Declaration of Helsinki 2013. Study results will be disseminated through
49	conferences and peer-reviewed scientific journals.
50	Trial registration number
51	ChiCTR1900022716 & ChiCTR1900022754; Pre-results.
52	
53	
54	
55	Strengths and Limitations of this study
56	This protocol describes a phase I study with a traditional 3+3 dose-
57	escalation design.
58	> This study is expected to provide safety and feasibility profile to inform
59	future prospective trials on preoperative radiotherapy in locally advanced
60	prostate cancer.
61	This study is monocentric, with relatively small sample size.
62	

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Page 5 of 25

# 63 Introduction

Prostate cancer is a major health problem worldwide, accounting for one fifth of newly-diagnosed malignancies in men. The number of prostate cancer patients in China have been continuously mounting and shows no sign at present of ceasing to rise, with approximately 99, 322 new diagnoses in the year 2018.<sup>1</sup> Radical prostatectomy, commonly performed in a laparoscopic or robot-assisted fashion, is the first-line active treatment for localized prostate cancer.<sup>2</sup> Patients with locally advanced prostate cancer are at higher risk of recurrence, and the optimal treatment approach is still controversial. Current National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) guidelines all recommend radiation therapy plus long-term androgen deprivation therapy (ADT) as a primary treatment option.<sup>34</sup> Increasingly, surgery-based multimodality treatment (MDT) has become a feasible approach for treating high-risk localized and locally advanced prostate cancer.<sup>5</sup> Whether individual patient may benefit from surgery remains to be elucidated, and a prospective phase III randomized controlled trial (RCT) comparing radical prostatectomy against radiation therapy and ADT for locally advanced prostate cancer patients is currently recruiting<sup>6</sup>. However, there is evidence that patients might benefit from maximizing local control with a combination of radiation therapy and surgery. Results from three phase III RCTs suggest improved biochemical progression-free survival and metastasis-free survival from immediate post-operative radiation therapy.<sup>7-9</sup> We argue that similar survival benefits could be achieved through radiation therapy plus ADT in a neoadjuvant setting. Theoretically, the 

87 additional advantages of neoadjuvant radiation therapy include: 1) potential

88 down-staging of the tumors, decreased rate of positive surgical margins, and

lower incidence of positive lymph nodes, 2) decreased hypoxia-induced radio-resistance because of unaltered prostatic blood supply, and 3) potential decrease in dosage and radiation-related toxicity. Indeed, the superiority of preoperative over postoperative chemoradiotherapy in terms of improved local control and reduced toxicity has been demonstrated by the phase III CAO/ARO/AIO-94 study in locally advanced rectal cancer.<sup>10</sup> In addition, given the considerable overlap of the radiation target volume, dose, and schedule, the safety profile of preoperative radiotherapy for locally advanced prostate cancer and rectal cancer is roughly comparable. Therefore, we hypothesize that neoadjuvant radiation therapy is a safe and feasible approach for treating locally advanced prostate cancer.

# 101 Methods and analysis

## 102 Study design

This is a phase I, single-arm, single-centre observational study in Shanghai Changhai Hospital. The participants enrolled will be assigned to one of the four groups receiving 39.6 Gy/22F, 45 Gy/25F, 50.4 Gy/28F, and 54 Gy/30F of preoperative radiation therapy plus ADT. A traditional 3+3 dose escalation design will be utilized to determine the maximal tolerable dose (MTD) of radiation therapy. Participants will then undergo robot-assisted radical prostatectomy (RARP) and extended pelvic lymph node dissection (ePLND), followed by post-operative ADT for at least 2 years. The trial schedule is illustrated in Figure 1. The trial is approved by the institutional review board of Shanghai Changhai Hospital (ref. CHEC2019-070 & CHEC2019-082) and is prospectively registered at the Chinese Clinical Trial Registry 

2		
3 4	114	(ChiCTR1900022716 & ChiCTR1900022754). This trial protocol is structured
5 6 7	115	and reported in accordance with the SPIRIT 2013 statement. $^{1112}$
7 8 9	116	
10 11 12	117	Recruitment
13 14	118	Patients who refer to the outpatient department of the trial site and meet the
15 16	119	inclusion criteria will be recommended to participate in this trial by the
17 18	120	physicians in charge of the study.
19 20 21	121	
22 23 24	122	Study participants
25 26 27	123	Inclusion Criteria
28 29 30	124	<ul> <li>Men between 18 and 75 years of age.</li> </ul>
31 32 33	125	• A diagnosis of prostate cancer confirmed by biopsy pathology.
34 35	126	<ul> <li>Locally advanced disease with positive pelvic lymph node(stage N1M0,</li> </ul>
36 37	127	ChiCTR1900022716) or positive retroperitoneal lymph node(stage M1a,
38 39	128	ChiCTR1900022754), as determined by contrast-enhanced CT, bone scan,
40 41	129	and/or MRI.
42 43 44	130	• Eastern Cooperative Oncology Group (ECOG) performance status 0-1.
45 46	131	• An expected life expectancy of at least 5 years.
47 48	132	<ul> <li>Patients who are well-informed of the current treatment options and</li> </ul>
49 50 51	133	willing to participate in the trial.
52 53 54	134	• Signed, written informed consent.
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2 3 4	135	Exclusion Criteria				
5 6 7	136	A patient may not enter the study if ANY of the following applies:				
7 8 9 10	137	• Lymph node metastases spreading beyond pelvic and retroperitoneal				
10 11 12	138	nodes.				
13 14	139	• Presence of bone metastasis or distant organ metastasis.				
15 16	140	Prior exposure to any treatment for prostate cancer, including surgery,				
17 18 19	141	radiotherapy, chemotherapy, hormone therapy, focal therapy, etc.				
20 21	142	Prior transurethral enucleation or resection of the prostate.				
22 23 24	143	• Any abdominal surgery performed within 3 months prior to enrollment.				
25 26	144	A transrectal prostate biopsy performed within 2 weeks prior to				
27 28 29	145	enrollment.				
30 31	146	Sustained use of anticoagulation and antiplatelet drugs.				
32 33 34	147	Any other previous or concurrent malignancies.				
35 36	148	Disease complicated by other severe systemic diseases which, in the				
37 38	149	judgment of the investigators, are likely to interfere with the treatment,				
39 40 41	150	assessment or compliance associated with this trial.				
41 42 43	151	Participation in any other trial which is ongoing or has been completed				
44 45	152	within 3 months.				
46 47 48	153	• Any contraindication for radiation therapy or surgery.				
49 50	154	Dropout or suspension of the trial				
51 52 53	155	Occurrence of Grade III/IV adverse events according to Common				
53 54 55 56 57 58	156	Terminology Criteria for Adverse Events (CTCAE) V.5.0.				

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1 2		
2 3 4	157	• Requests from patients to withdraw from the trial.
5 6 7	158	<ul> <li>Lost to follow-up.</li> </ul>
8 9	159	Disease progression.
10 11 12 13	160	• Other potential situations that necessitate the termination of the trial.
14 15	161	
16 17 18 19	162	Interventions
20 21	163	Baseline evaluation
22 23	164	Patients with histologically confirmed locally advanced prostate cancer who
24 25	165	are eligible for this study will be evaluated for baseline characteristics. The
26 27	166	evaluation will include demographics, medical history, concomitant diseases
28 29	167	and medications, physical exam, vital signs, digital rectal exam, routine blood
30	168	tests, high-resolution MRI of the pelvis, and bone scan in selected patients.
31 32	169	Baseline characteristics of the included participants will be collected within
33 34 35	170	two weeks prior to the initiation of ADT.
36 37 38	171	Neoadjuvant radiation therapy plus ADT
39 40	172	The ADT regimen for this trial includes bicalutamide 50mg PO once daily and
41 42	173	goserelin acetate, a gonadotropin-releasing hormone agonist. The latter will
43 44	174	be administered subcutaneously either at a dose of 3.6mg every 4 weeks, or
45 46	175	at a dose of 10.8mg every 12 weeks.
47 48 49	176	Intensity modulated radiation therapy (IMRT) will be administered 4 months
50	177	after the initiation of preoperative ADT. All patients shall undergo a
51 52	178	contrasted CT simulation of the pelvis or abdomen of 5-mm-slice thickness in
53 54	179	a supine position. The CT images will then be transferred to the treatment
55 56 57	180	planning system for contouring the target volume and organs at risk (OARs)
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and planning. Critical normal structures include the small bowel, bladder,
femoral head, rectum, spinal cord, prostatic urethra (if visualised), bulbous
urethra, kidney, etc. OARs shall be contoured according to the pelvic normal
tissue contouring guidelines of Radiation Therapy Oncology Group (RTOG).<sup>13</sup>
This protocol offers dose guidelines to OARs based upon prior published
RTOG trials.<sup>14-16</sup>

The gross tumor volume (GTV) is contoured based on MRI. GTV includes prostate and seminal vesicle glands. GTV of the pelvic or retroperitoneal metastatic lymph node (GTVnd) is further confirmed by imaging. The clinical tumor volume (CTV) includes GTV, GTVnd, pelvic/ retroperitoneal lymphatic drainage area. The superior border of the whole pelvis field extends to the L5-S1 interspace for N1 subgroup. The pelvic lymphatic drainage area includes bilateral total iliac lymph nodes, extra-iliac lymph nodes, intra-iliac lymph nodes, S1-S3 levels presacral lymph nodes and obturator lymph nodes. The superior border of the retroperitoneal field is 2-3 cm above the positive lymph nodes not exceeding renal artery level. The primary gross tumor volume (pGTV) is 5-10mm outwards for GTV in any direction, but only 5 mm in the posterior to reduce rectal irradiation. pGTVnd for GTVnd shall be delineated with an additional 5mm margin and pCTV for CTV shall be delineated with an additional 5mm margin separately.

Four radiation dose levels were planned: 39.6 Gy, 45 Gy, 50.4 Gy, and 54 Gy.
Radiation therapy will be delivered in 5 1.8-Gy fractions per week. The initial
two dose levels target whole pelvis/ retroperitoneum, whereas in the latter
two dose levels a subsequent boost to the prostate, seminal vesicles and
pelvic/ retroperitoneal metastatic lymph nodes were added after reaching 45
Gy.

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## 207 Dose escalation

	208	Dose escalation will be conducted in a 3+3 design with dose levels of 39.6, 45,
	209	50.4, and 54 Gy in 22, 25, 28 and 30 fractions respectively. A traditional 3+3
1	210	dose-escalation design will be adopted <mark>(Figure 2)</mark> . Briefly, three participants
	211	will initially be allocated into the starting dose cohort. If no dose-limiting
	212	toxicity (DLT) is observed in any of the three participants, the dose will be
	213	escalated and three new patients will be enrolled to receive the next level of
	214	radiation dose. If one participant develops any DLT, an additional three
1	215	participants will be allocated into the same dose cohort. If there are multiple
	216	observations of DLT at any given dose level, the dose escalation will be
	217	stopped and the previous dose level will be identified as the MTD. In this trial,
	218	DLTs are defined as any Grade III/IV toxicities.
	219	Robot-assisted radical prostatectomy
1	220	Surgery will be scheduled 8 weeks after the completion of radiation therapy,
	221	via a robot-assisted laparoscopic approach. Extended pelvic lymph node
	222	dissection (ePLND) will be performed. All surgical procedures will be
1	223	performed by a single highly experienced robotic surgeon (R.S.).
	224	Post-operative treatment
	225	Participants will receive long-term post-operative ADT for at least 2 years.
	226	The regimen will remain the came. Participants will be monthly evaluated for

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The regimen will remain the same. Participants will be monthly evaluated for
serum PSA level at their local primary healthcare facilities. They will be
followed up every 3 months for the first year and every 6 months for the
following year. Upon tumor progression, salvage treatment including but not
limited to abiraterone acetate/prednisone treatment, chemotherapy, and
surgery, will be administered to the trial participants upon documented
progression in accordance with standard clinical practice.

#### **Outcomes and Measurements**

The primary objective of this trial is to determine the adverse events and MTD of radiotherapy. Adverse events throughout the study will be assessed via CTCAE v5.0 by research physicians or nurses. Secondary endpoints include perioperative safety profile, efficacy of neoadjuvant treatment, rates of positive surgical margins, biochemical recurrence-free survival, overall survival, and functional outcomes.

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#### **Determination of sample size**

The study is a dose-escalation study which implements a traditional 3+3 design with 4 dose levels. Three to six participants will be allocated to each dose level cohort. Therefore, the maximum per protocol sample size for this Liey trial is 24.

#### **Data Management and Monitoring**

The institutional review board of Shanghai Changhai Hospital will monitor the reporting of adverse events and the quality of collected data on a semiannual basis. A planned interim analysis will be performed by the

- principle investigator when median post-operative follow-up reached 1 year.
- **Statistical analysis**
- All characteristics will be described by the frequency for classified variables, mean  $\pm$  SD and 95% confidence intervals for normally distributed continuous data, and the median and range for non-normal distributional continuous data. Should any statistical hypothesis testing be used, a two-tailed test is

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2 3 4	257	preferred and the significance level threshold( $\alpha$ ) is set as 0.05. Statistical
5 6	258	analyses will be performed using the R software v3.6.0 or higher. <sup>17</sup>
7 8 9	259	
10 11	260	Biological specimens
12 13	261	Biological specimens acquired throughout the trial, including blood and tissue
14 15	262	samples, will be stored for subsequent exploratory biomarker research.
16 17	263	Informed consent of participants will be obtained prior to the acquisition of
18 19	264	biological specimens.
20 21 22 23	265	
24 25 26	266	Patient and public involvement
27 28 29	267	Patients or public have not been involved in the design of the present study.
30 31	268	
32 33 34 35 36	269	Ethics and dissemination
37 38	270	Eligible patients will be well informed of the purpose and schedule of this
39 40	271	study. Written informed consent will be obtained by research physicians or
41	272	nurses if patients decide to participate. All clinical data will be confidentially
42 43	273	collected by research members. Findings of the study will be disseminated
44 45	274	through publication in peer-reviewed scientific journals as well as relevant
46 47	275	medical conferences.
48 49 50 51 52	276	Discussion
53 54	277	The idea for maximizing cancer local control originates from the "seed and
55 56 57 58	278	soil" hypothesis, which postulates that the growth of disseminating tumor
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cells is driven by factors secreted by the primary tumor.<sup>18</sup> It has been demonstrated in metastatic prostate cancer that aggressive subclones persist in primary tumor site and can seed to metastatic lesions, leading to a vicious cycle of metastatic disease.<sup>19 20</sup> Furthermore, overall survival benefits can be observed in metastatic prostate cancer patients who have been treated with radiotherapy plus ADT compared to ADT alone.<sup>21</sup> These data collectively suggest a role of maximizing local control in the management of locally advanced and metastatic prostate cancer.

Currently, clinical trials on preoperative radiation therapy for prostate cancer have focused primarily on men with high-risk localized disease. To the best of our knowledge, there are two published modern-era trials that evaluated preoperative radiation therapy in localized prostate cancer. Koontz et al. conducted a phase I clinical trial in 13 men with high-risk localized prostate cancer evaluating long-course preoperative radiation therapy followed by radical prostatectomy.<sup>22</sup> The reported two-year biochemical recurrence-free survival was 67%. Glicksman et al. recently reported the long-term results of their phase I pilot study of 15 patients.<sup>23</sup> At a median follow-up of 12.2 years, 7 patients were free from biochemical relapse and 6 patients were metastasis-free. These have motivated us to assess this treatment combination in locally advanced disease. Despite the limitations, the impact of this study has the potential to drive a paradigm shift in the management of locally advanced prostate cancer.

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development.

manuscript.

Changhai Hospital (2019YXK058).

Patient consent for publication

**Competing interests** 

None declared.

Not required.

**Ethics approval** 

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**Author Contributions** 

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YTX, XZ, YC, HZ, and SR were involved in literature search, study conception,

protocol development, conduct of the study, and manuscript writing. XL was

coordinators. All authors contributed to and approved the final version of the

involved in the conduct of the study. YW was involved in writing the

manuscript. SR is the principle investigator. YTX, XZ, and YC are the trial

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#### **Provenance and peer review**

Not commissioned; externally peer reviewed.

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## **References**

1. Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer, 2018. 2. Chang SL, Kibel AS, Brooks JD, Chung BI. The impact of robotic surgery on the surgical management of prostate cancer in the USA. BJU Int 2015;115(6):929-36. 3. Mottet N, van den Bergh RCN, Briers E, et al. EAU - ESTRO - ESUR - SIOG Guidelines on Prostate Cancer 2018. Arnhem, The Netherlands: European Association of Urology Guidelines Office, 2018. 4. Mohler JL, Antonarakis ES, Armstrong AJ, et al. Prostate Cancer, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2019;17(5):479-505. 5. Costello AJ. Considering the role of radical prostatectomy in 21st century prostate cancer care. Nat Rev Urol 2020;17(3):177-188.

Page 17 of 25

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6. Stranne J, Brasso K, Brennhovd B, et al. SPCG-15: a prospective randomized study comparing primary radical prostatectomy and primary radiotherapy plus and rogen deprivation therapy for locally advanced prostate cancer. Scand J Urol 2018;52(5-6):313-320.

7. Bolla M, van Poppel H, Tombal B, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet 2012;380(9858):2018-27. 

8. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol 2009;181(3):956-62. 

9. Wiegel T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. J Clin Oncol 2009;27(18):2924-30. 

10. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351(17):1731-40. 

- 11. Chan AW, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
- 12. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158(3):200-7.
- 13. Gay HA, Barthold HJ, O'Meara E, et al. Pelvic normal tissue contouring guidelines for radiation therapy: a Radiation Therapy Oncology Group consensus panel atlas. Int J Radiat Oncol Biol Phys 2012;83(3):e353-62.
- 14. Michalski JM, Purdy JA, Winter K, et al. Preliminary report of toxicity following 3D radiation therapy for prostate cancer on 3DOG/RTOG 9406. Int J Radiat Oncol Biol Phys 2000;46(2):391-402.
- 15. Michalski JM, Bae K, Roach M, et al. Long-term toxicity following 3D conformal radiation therapy for prostate cancer from the RTOG 9406 phase I/II dose escalation study. Int J Radiat Oncol Biol Phys 2010;76(1):14-22.
- 16. Roach M, Winter K, Michalski JM, et al. Penile bulb dose and impotence after three-dimensional conformal radiotherapy for prostate cancer on RTOG 9406: findings from a prospective, multi-institutional, phase I/II dose-escalation study. Int J Radiat Oncol Biol Phys 2004;60(5):1351-6.
- 17. R Core Team. R: A language and environment for statistical computing. [program]. Vienna, Austria. R Foundation for Statistical Computing, 2019.

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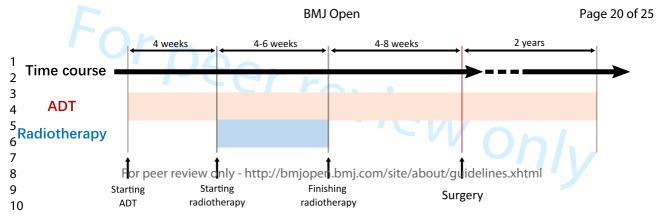
18. Psaila B, Lyden D. The metastatic niche: adapting the foreign soil. Nat Rev Cancer 2009;9(4):285-93.

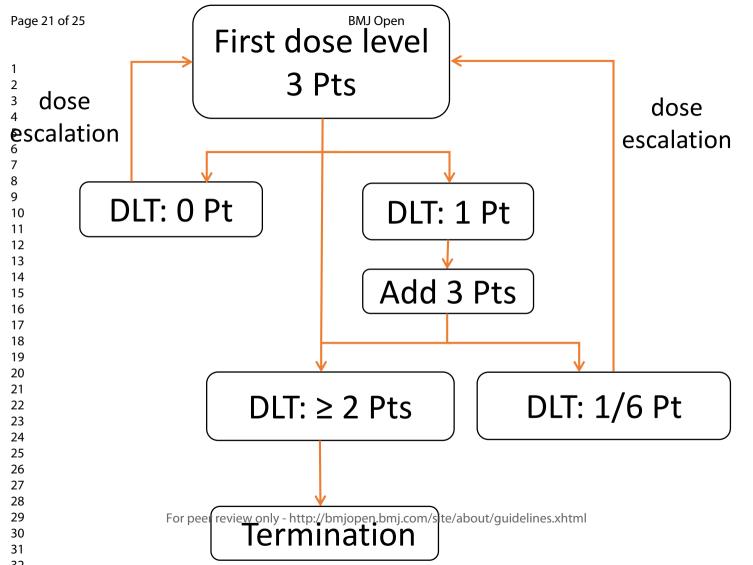
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- 19. Gundem G, Van Loo P, Kremeyer B, et al. The evolutionary history of lethal metastatic prostate cancer. Nature 2015;520(7547):353-357.
- 20. Tzelepi V, Efstathiou E, Wen S, et al. Persistent, biologically meaningful prostate cancer after
- 1 year of androgen ablation and docetaxel treatment. J Clin Oncol 2011;29(18):2574-81.
- 21. Rusthoven CG, Jones BL, Flaig TW, et al. Improved Survival With Prostate Radiation in
- Addition to Androgen Deprivation Therapy for Men With Newly Diagnosed Metastatic Prostate Cancer. J Clin Oncol 2016;34(24):2835-42.
- 22. Koontz BF, Quaranta BP, Pura JA, et al. Phase 1 trial of neoadjuvant radiation therapy before
  - prostatectomy for high-risk prostate cancer. Int J Radiat Oncol Biol Phys 2013;87(1):88-93.
- 23. Glicksman R, Sanmamed N, Thoms J, et al. A Phase 1 Pilot Study of Preoperative Radiation
- Therapy for Prostate Cancer: Long-Term Toxicity and Oncologic Outcomes. Int J Radiat Oncol
  - Biol Phys 2019;104(1):61-66.

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1		
2 3 4 5 6	402	Figure Legends
7 8	403	
9 10	404	Figure 1. Schedule of the study. ADT, androgen deprivation therapy.
11 12	405	
13 14 15	406 407	Figure 2. Graphical depiction of the 3+3 dose-escalation study design. DLT, dose-limiting toxicity. Pt, participant.
$\begin{array}{c} 16\\ 17\\ 18\\ 19\\ 20\\ 21\\ 22\\ 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 546\\ 47\\ 48\\ 49\\ 50\\ 51\\ 52\\ 53\\ 54\\ 55\\ 56\\ 57\\ 58\\ 59\end{array}$	408	to beet teriew only
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			BMJ Open Correction	Page 22 of 25
1 2 3 4			STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS	
5 6 7 8 9	SPIRIT 2013 Check	dist: Reco	ommended items to address in a clinical trial protocol and related documents*	
10 11 12	Section/item	ltem No	Description	Addressed on page number
13 14 15	Administrative inf	ormation	t Superior text and	
16	Title	1	Descriptive title identifying the study design, population, interventions, and, if apple by trial acronym	Page 1
17 18	Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 6-7
19 20		2b	All items from the World Health Organization Trial Registration Data Set	Not included in the manuscript. Av <u>ailable on the registration</u> website.
21 22	Protocol version	3	All items from the World Health Organization Trial Registration Data Set	Not included in the manuscript.
23 24	Funding	4	Sources and types of financial, material, and other support	Page 15
25 26	Roles and	5a	Names, affiliations, and roles of protocol contributors	<u>Page 1, Page 15.</u>
27 28	responsibilities	5b	Name and contact information for the trial sponsor	Not applicable
29 30 31 32		5c	Role of study sponsor and funders, if any, in study design; collection, managemers, 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	<u>Page I, Page 15.</u> <u>Not applicable</u> <u>Not applicable</u>
33 34 35 36 37 38 39 40 41		5d	Composition, roles, and responsibilities of the coordinating centre, steering committee endpoint adjudication committee, data management team, and other individuals or groups over eeing the trial, if applicable (see Item 21a for data monitoring committee)	<u>Page 12</u>
42 43 44 45 46			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	1

Page	23 of 25		BMJ Open BMJ Open BMJ Open BMJ Open BMJ Open BMJ Open	
1 2	Introduction		ig ht, -038	
3 4 5	Background and rationale	6a	Description of research question and justification for undertaking the trial, including sugnmary of relevant <u>lage S-6</u> studies (published and unpublished) examining benefits and harms for each intergented	
6 7		6b	Explanation for choice of comparators	.)
8 9	Objectives	7	Explanation for choice of comparators       Not applicable (single-arrested)         Specific objectives or hypotheses       Image 12         Description of trial design including type of trial (eg, parallel group, crossover, factor group),       Single group),	
10 11 12 13	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factor signade group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploration of trial group)	
14 15	Methods: Participa	nts, inte	erventions, and outcomes	
16 17 18	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of community study sites can be obtained	
19 20 21	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and <u>Page 7-9; Page 11</u> individuals who will perform the interventions (eg, surgeons, psychotherapists)	
22 23 24 25	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including hogy and when they will be <u>Page 9-12</u> administered	
26 27 28		11b	Criteria for discontinuing or modifying allocated interventions for a given trial partigpaget (eg, drug dose <u>Page 8-11</u> change in response to harms, participant request, or improving/worsening disease g	
29 30 31		11c	Strategies to improve adherence to intervention protocols, and any procedures for manipulation adherence <u>Page II</u> (eg, drug tablet return, laboratory tests)	
32 33		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial <u>Page 7-9</u>	
34 35 36 37 38 39	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, <u>lage 11.</u> median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
40 41 42	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for <u>Page 6-11; Figure 1-2</u> . participants. A schematic diagram is highly recommended (see Figure)	
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Page 24 of 25

			BMJ Open BMJ Open Page 2	4 of 2
1 2 3 4 5	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was getermined, including Page 12 clinical and statistical assumptions supporting any sample size calculations	
	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size g	
6 7	Methods: Assignme	ent of i	nterventions (for controlled trials)	
8 9	Allocation:		ses reig	
10 11 12 13 14 15	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random not be been been been been been been been	
16 17 18 19	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequery ally numbered,	
20 21 22	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who was a sign participants to	
23 24 25 26	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome	
26 27 28 29 30		17b	If blinded, circumstances under which unblinding is permissible, and procedure for gealing a participant's allocated intervention during the trial	
31 32	Methods: Data colle	ection,	management, and analysis	
33 34 35 36 37 38 39 40 41	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related <u>frage 11-12.</u> 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 ballidity, if known. Reference to where data collection forms can be found, if not in the protocol	
		18b	Plans to promote participant retention and complete follow-up, including list of any outgome data to be Not included in the manuscription collected for participants who discontinue or deviate from intervention protocols	:p+.
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Page 25 of 25			BMJ Open cop
1 2 3 4	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 the management procedures can be found, if not in the protocol
5 6 7	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the <u>Page 12-13</u> . statistical analysis plan can be found, if not in the protocol
8 9 10 11 12 13		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
		20c	Definition of analysis population relating to protocol non-adherence (eg, as randor is analysis), and any statistical methods to handle missing data (eg, multiple imputation)
14 15	Methods: Monitorin	ıg	and c
16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and report reference statement of <u>lave 13.</u> whether it is independent from the sponsor and competing interests; and reference whether further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
		21b	Description of any interim analyses and stopping guidelines, including who will have be been stored interim from the second stopping guidelines, including who will have be been stored interim from the second stopping guidelines, including who will have be been stored interim from the second stopping guidelines, including who will have be been stored interimed as the second stopping guidelines including who will have be been stopping guidelines.
	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse <u>Page 12</u> .
	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process $\frac{2}{5}$ from investigators and the sponsor
32 33	Ethics and dissemination		ogies.
34 35 36 37 38 39 40 41 42	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval <u>Page 12</u> . Plans for communicating important protocol modifications (eg, changes to eligibility creeria, outcomes, <u>Not included in the manuscript</u> .
	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility creeria, outcomes, Not included in the manuscript analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
43 44 45 46			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

			BMJ Open BMJ Open Page 26 of 25
1 2 3 4 5 6 7 8 9	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or autherised surrogates, and <u>امود اع</u> how (see Item 32)
		26b	Additional consent provisions for collection and use of participant data and biologinal gradient in ancillary $\underline{P_{age} 13}$ . studies, if applicable
	Confidentiality	27	How personal information about potential and enrolled participants will be collected and maintained <u>face 13</u>
10 11 12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall tree by deach study site <u>fage IS</u> .
13 14 15	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contract al agreements that Not included in the manuscript.
16 17 18 19	Ancillary and post- trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those with suffer harm from trial Not included in the manuscript.
20 21 22 23	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healtheare professionals, <u>Page 13</u> the public, and other relevant groups (eg, via publication, reporting in results data bases, or other data sharing arrangements), including any publication restrictions
24 25		31b	Authorship eligibility guidelines and any intended use of professional writers
26 27 28		31c	Authorship eligibility guidelines and any intended use of professional writers Plans, if any, for granting public access to the full protocol, participant-level datas at and statistical code Not included in the manuscript.
29 30	Appendices		lec hr
31 32 33	Informed consent materials	32	Model consent form and other related documentation given to participants and autorities Not included in the manuscript.
34 35 36	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for generative trial and for future use in ancillary studies, if applicable
37 38 39 40	Amendments to the p	rotocol	that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaborati to for important clarification on the items. should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons -NoDerivs 3.0 Unported" license.
41 42 43 44 45			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml <b>6</b> 5

## Assessing the safety and feasibility of neoadjuvant hormone and radiation therapy followed by robot-assisted radical prostatectomy for treating locally advanced prostate cancer: protocol for an open-label, dose-escalation, singlecentre, phase I clinical trial

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<b>Primary Subject Heading</b> :	Urology
Secondary Subject Heading:	Oncology, Surgery
Keywords:	Urological tumours < UROLOGY, Radiation oncology < RADIOTHERAPY, Urological tumours < ONCOLOGY, SURGERY

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5 6	1	Assessing the safety and feasibility of neoadjuvant
7 8	2	hormone and radiation therapy followed by robot-
9 10	3	assisted radical prostatectomy for treating locally
11 12		
13 14	4	advanced prostate cancer: protocol for an open-
15 16	5	label, dose-escalation, single-centre, phase I clinical
17 18	6	trial
19 20 21	7	
22 23	8	Yu-Tian Xiao <sup>1,#</sup> , Xianzhi Zhao <sup>2,#</sup> , Yifan Chang <sup>1</sup> , Xiaojun Lu <sup>1</sup> , Ye Wang <sup>1</sup> , Huojun
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## 23 Abstract

## 24 Introduction

Patients with locally advanced prostate cancer are at high risk of recurrence after definitive treatment. There are emerging data that radical prostatectomy can delay the progression of castration resistance and potentially prolong survival. Neoadjuvant radiation therapy improves local control and has shown survival benefit with favorable toxicity profiles in several other malignancies. We have designed this trial to investigate whether this combination, which theoretically maximizes local control, is a safe and feasible approach for treating locally advanced prostate cancer.

## 33 Methods and analysis

This study is a phase I, open-label study to investigate the safety and feasibility of neoadjuvant hormone and radiation therapy followed by robot-assisted radical prostatectomy by a traditional 3+3 dose-escalation design with 4 planned radiation dose levels (39.6 Gy/22F, 45 Gy/25F, 50.4 Gy/28F, and 54 Gy/30F). Locally advanced prostate cancer patients with positive pelvic and/or retroperitoneal lymph nodes will be recruited. The primary objective is to determine the adverse events and maximal tolerable dose neoadjuvant of radiotherapy. Toxicity will be assessed using the National Cancer Institute Common Toxicity Criteria V5.0. 

## 43 Ethics and dissemination

This protocol was approved by the institutional review board of Shanghai
Changhai Hospital (ref. CHEC2019-070 & CHEC2019-082). The study will be
performed in compliance with applicable local legislation and in accordance

47	with the ethical principles developed by the World Medical Association in the
48	Declaration of Helsinki 2013. Study results will be disseminated through
49	conferences and peer-reviewed scientific journals.
50	Trial registration number
51	ChiCTR1900022716 & ChiCTR1900022754; Pre-results.
52	
53	
54	
55	Strengths and Limitations of this study
56	This protocol describes a phase I study with a traditional 3+3 dose-
57	escalation design.
58	> This study is expected to provide safety and feasibility profile to inform
59	future prospective trials on preoperative radiotherapy in locally advanced
60	prostate cancer.
61	This study is monocentric, with relatively small sample size.
62	

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Page 5 of 26

# 63 Introduction

Prostate cancer is a major health problem worldwide, accounting for one fifth of newly-diagnosed malignancies in men. The number of prostate cancer patients in China have been continuously mounting and shows no sign at present of ceasing to rise, with approximately 99, 322 new diagnoses in the year 2018.<sup>1</sup> Radical prostatectomy, commonly performed in a laparoscopic or robot-assisted approach, is a first-line curative treatment option for localized prostate cancer.<sup>2</sup> Patients with locally advanced prostate cancer are at higher risk of recurrence, and the optimal treatment is still controversial. Current National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) guidelines all recommend radiation therapy plus long-term androgen deprivation therapy (ADT) as a primary treatment option.<sup>34</sup> Increasingly, surgery-based multimodality treatment (MDT) has become a feasible approach for treating high-risk localized and locally advanced prostate cancer.<sup>5</sup> Whether individual patients may benefit from surgery remains to be elucidated, and a prospective phase III randomized controlled trial (RCT) comparing radical prostatectomy against radiation therapy and ADT for locally advanced prostate cancer patients is currently recruiting<sup>6</sup>. However, there is evidence that patients might benefit from maximizing local control with a combination of radiation therapy and surgery. Results from three phase III RCTs suggest improved biochemical progression-free survival and metastasis-free survival from immediate post-operative radiation therapy.<sup>7-9</sup> We argue that similar survival benefits could be achieved through the use of radiation therapy and ADT in a neoadjuvant setting. Theoretically, 

- 87 the additional advantages of neoadjuvant radiation therapy include: 1)
- 88 potential down-staging of the tumors, decreased rate of positive surgical

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margins, and lower incidence of positive lymph nodes, 2) decreased hypoxia-induced radio-resistance because of unaltered prostatic blood supply, and 3) potential decrease in dosage and radiation-related toxicity. Indeed, the superiority of preoperative over postoperative chemoradiotherapy in terms of improved local control and reduced toxicity has been demonstrated by the phase III CAO/ARO/AIO-94 study in locally advanced rectal cancer.<sup>10</sup> In addition, given the considerable overlap of the radiation target volume, dose, and schedule, the safety profile of preoperative radiotherapy for locally advanced prostate cancer and rectal cancer is roughly comparable. Therefore, we hypothesize that neoadjuvant radiation therapy is a safe and feasible approach for treating locally advanced prostate cancer.

# 101 Methods and analysis

## 102 Study design

This is a phase I, single-arm, single-centre observational study in Shanghai Changhai Hospital. The participants enrolled will be assigned to one of the four groups receiving 39.6 Gy/22F, 45 Gy/25F, 50.4 Gy/28F, and 54 Gy/30F of preoperative radiation therapy plus ADT. A traditional 3+3 dose escalation design will be utilized to determine the maximal tolerable dose (MTD) of radiation therapy. Participants will then undergo robot-assisted radical prostatectomy (RARP) and extended pelvic lymph node dissection (ePLND), followed by post-operative ADT for at least 2 years. The trial schedule is illustrated in Figure 1. The trial is approved by the institutional review board of Shanghai Changhai Hospital (ref. CHEC2019-070 & CHEC2019-082) and is prospectively registered at the Chinese Clinical Trial Registry 

1 2					
3 4	114	(ChiCTR1900022716 & ChiCTR1900022754). This trial protocol is structured			
5	115	and reported in accordance with the SPIRIT 2013 statement. $^{1112}$			
7 8 9	116				
10 11 12	117	Recruitment			
13 14	118	Patients who refer to the outpatient department of the trial site and meet the			
15 16	119	inclusion criteria will be recommended to participate in this trial by the			
17 18	120	physicians in charge of the study.			
19 20	121				
21 22	121				
23 24	122	Study participants			
25 26	123	Inclusion Criteria			
27 28	120				
29 30	124	<ul> <li>Men between 18 and 75 years of age.</li> </ul>			
31 32	125	Biopsy confirmed prostate adenocarcinoma without neuroendocrine			
33 34	126	differentiation, signet cell, or small cell features.			
35 36	127	<ul> <li>Locally advanced disease with positive pelvic lymph node(stage N1M0,</li> </ul>			
37 38	128	ChiCTR1900022716) or positive retroperitoneal lymph node(stage M1a,			
39 40	129	ChiCTR1900022754), as determined by contrast-enhanced CT, bone scan,			
41 42	130	and/or-MRI, and/or 68Ga-PSMA PET/CT.			
43 44 45	 131	• Eastern Cooperative Oncology Group (ECOG) performance status 0-1.			
46 47 48	132	• An expected life expectancy of at least 5 years.			
49 50	133	Patients who are well-informed of the current treatment options and			
51 52	134	willing to participate in the trial.			
53 54 55 56 57	135	<ul> <li>Signed, written informed consent.</li> </ul>			
58 59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml			

2 3		
4 5	136	Exclusion Criteria
6 7	137	A patient may not enter the study if ANY of the following applies:
8 9 10	138	Lymph node metastases spreading beyond pelvic and retroperitoneal
10 11 12	139	nodes.
13 14	140	• Presence of bone metastasis or distant organ metastasis.
15 16	141	Prior exposure to any treatment for prostate cancer, including
17 18 19	142	radiotherapy, chemotherapy, hormone therapy, focal therapy, etc.
20 21 22	143	Prior transurethral enucleation or resection of the prostate.
23 24	144	• Any abdominal surgery performed within 3 months prior to enrollment.
25 26 27	145	Sustained use of anticoagulation and antiplatelet drugs.
28 29 30	146	<ul> <li>Any other previous or concurrent malignancies.</li> </ul>
31 32	147	• Disease complicated by other severe systemic diseases which, in the
33 34	148	judgment of the investigators, are likely to interfere with the treatment,
35 36	149	assessment or compliance associated with this trial.
37 38	150	Participation in any other trial which is ongoing or has been completed
39 40 41	151	within 3 months.
42 43	152	Any contraindication for radiation therapy or surgery.
44 45 46	153	Dropout or suspension of the trial
47 48	154	Occurrence of Grade III/IV adverse events according to Common
49 50 51	155	Terminology Criteria for Adverse Events (CTCAE) V.5.0.
52 53	156	• Requests from patients to withdraw from the trial.
54 55 56	157	<ul> <li>Lost to follow-up.</li> </ul>
57 58		

59 60

1 2		
3 4	158	Disease progression.
5 6 7	159	• Other potential situations that necessitate the termination of the trial.
, 8 9 10	160	
11 12 13	161	Interventions
14 15 16	162	Baseline evaluation
17 18	163	Patients with histologically confirmed locally advanced prostate cancer who
19 20	164	are eligible for this study will be evaluated for baseline characteristics. The
20 21 22	165	evaluation will include demographics, medical history, concomitant diseases
23	166	and medications, physical exam, vital signs, digital rectal exam, routine blood
24 25	167	tests, high-resolution MRI of the pelvis, <del>and</del> bone scan <u>, and 68Ga-PSMA</u>
26 27	168	<u>PET/CT</u> . Baseline characteristics of the included participants will be collected
28 29	169	within two weeks prior to the initiation of ADT.
30 31 32 33	170	Neoadjuvant radiation therapy plus ADT
34 35	171	The ADT regimen for this trial includes bicalutamide 50mg PO once daily and
36 37	172	goserelin acetate, a gonadotropin-releasing hormone agonist. The latter will
38	173	be administered subcutaneously either at a dose of 3.6mg every 4 weeks, or
39 40 41	174	at a dose of 10.8mg every 12 weeks.
42 43	175	Intensity modulated radiation therapy (IMRT) will be administered 4 weeks
44 45	176	after the initiation of preoperative ADT. All patients shall undergo a
46 47	177	contrasted CT simulation of the pelvis or abdomen of 5-mm-slice thickness in
48 49	178	a supine position. The CT images will then be transferred to the treatment
50 51	179	planning system for contouring the target volume and organs at risk (OARs)
52 53	180	and planning. Critical normal structures include the small bowel, bladder,
54	181	femoral head, rectum, spinal cord, prostatic urethra (if visualised), bulbous
55 56 57 58	182	urethra, kidney, etc. OARs shall be contoured according to the pelvic normal

tissue contouring guidelines of Radiation Therapy Oncology Group (RTOG).<sup>13</sup>
This protocol offers dose guidelines to OARs based upon prior published
RTOG trials.<sup>14-16</sup>

The gross tumor volume (GTV) is contoured based on MRI. GTV includes prostate and seminal vesicle glands. GTV of the pelvic or retroperitoneal metastatic lymph node (GTVnd) is further confirmed by imaging. The clinical tumor volume (CTV) includes GTV, GTVnd, pelvic/retroperitoneal lymphatic drainage area. The superior border of the whole pelvis field extends to the L5-S1 interspace for N1 subgroup. The pelvic lymphatic drainage area includes bilateral total iliac lymph nodes, extra-iliac lymph nodes, intra-iliac lymph nodes, S1-S3 levels presacral lymph nodes and obturator lymph nodes. The superior border of the retroperitoneal field is 2-3 cm above the positive lymph nodes not exceeding renal artery level. The primary gross tumor volume (pGTV) is 5-10mm outwards for GTV in any direction, but only 5 mm in the posterior to reduce rectal irradiation. pGTVnd for GTVnd shall be delineated with an additional 5mm margin and pCTV for CTV shall be delineated with an additional 5mm margin separately.

Four radiation dose levels were planned: 39.6, 45, 50.4, and 54 Gy. Radiation
therapy will be delivered in 5 1.8-Gy fractions per week. The initial two dose
levels target whole pelvis/ retroperitoneum, whereas in the latter two dose
levels a subsequent boost to the prostate, seminal vesicles and pelvic/
retroperitoneal metastatic lymph nodes were added after reaching 45 Gy.

**Dose escalation** 

Dose escalation will be conducted in a 3+3 design with dose levels of 39.6, 45,
50.4, and 54 Gy in 22, 25, 28 and 30 fractions respectively. A traditional 3+3
dose-escalation design will be adopted (Figure 2). Briefly, three participants
will initially be allocated into the starting dose cohort. If no dose-limiting

1 2		
- 3 4	210	toxicity (DLT) is observed in any of the three participants, the dose will be
5 6 7 8	211	escalated and three new patients will be enrolled to receive the next level of
	212	radiation dose. If one participant develops any DLT, an additional three
9	213	participants will be allocated into the same dose cohort. If there are multiple
10 11	214	observations of DLT at any given dose level, the dose escalation will be
12 13	215	stopped, and the previous dose level will be identified as the MTD. In this trial,
14 15 16 17 18 19	216	DLT is defined as (1) any grade 4+ toxicity, (2) any grade 3 toxicity except
	217	urinary incontinence, erectile dysfunction, and responsive diarrhea, (3) grade
	218	2+ fistula, (4) any grade colonic or rectal perforation, or (5) any grade
20 21	219	intraoperative rectal injury.
21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36	220	Robot-assisted radical prostatectomy
	221	Surgery will be scheduled within 4–8 weeks after the completion of radiation
	222	therapy, via a robot-assisted laparoscopic approach. Extended pelvic lymph
	223	node dissection (ePLND) will be performed. All surgical procedures will be
	224	performed by one single highly experienced robotic surgeon (R.S.).
	225	Post-operative treatment
37 38	226	Participants will receive long-term post-operative ADT for at least 2 years.
39	227	The regimen will remain the same. Participants will be monthly evaluated for
40 41	228	serum PSA and testosterone level at their local primary healthcare facilities.
42 43	229	They will be followed up every 3 months for the first year and every 6 months
44 45	230	for the following year. Upon tumor progression, salvage treatment including
46 47	231	but not limited to abiraterone acetate/prednisone treatment, chemotherapy,
48 49	232	and surgery, will be administered to the trial participants upon documented
50 51	233	progression in accordance with standard clinical practice.
52 53		
54		

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#### **Outcomes and Measurements**

The primary objective of this trial is to determine the adverse events and MTD of radiotherapy. Adverse events throughout the study will be assessed via CTCAE v5.0 by research physicians or nurses.

Secondary endpoints include perioperative safety profile, efficacy of 

neoadjuvant treatment, rates of positive surgical margins, biochemical

recurrence-free survival, overall survival, and functional outcomes.

Perioperative complications will be measured by Clavien-Dindo classification 

within 30 postoperative days. Continence will be measured by patient-

reported pads used per day. Quality of life will be measured using Karnofsky 

Performance Status Scale,<sup>17</sup> the Functional Assessment of Cancer Therapy-

Prostate (FACT-P, version 4) instrument,<sup>18</sup> and the 5-level EQ-5D (EQ-5D-5L) 

instrument.<sup>19</sup>

# elieu **Determination of sample size**

The study is a dose-escalation study which implements a traditional 3+3 design with 4 dose levels. Three to six participants will be allocated to each dose level cohort. Therefore, the maximum per protocol sample size for this trial is 24. 

#### **Data Management and Monitoring**

The institutional review board of Shanghai Changhai Hospital will monitor the reporting of adverse events and the quality of collected data on a

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1 2		
2 3 4	257	semiannual basis. A planned interim analysis will be performed by the
5 6	258	principal investigator when median post-operative follow-up reached 1 year.
7 8	259	
9 10	260	Statistical analysis
11 12	200	Statistical allarysis
13 14	261	All characteristics will be described by the frequency for classified variables,
15 16	262	mean $\pm$ SD and 95% confidence intervals for normally distributed continuous
17 18	263	data, and the median and range for non-normal distributional continuous
19 20	264	data. Should any statistical hypothesis testing be used, a two-tailed test is
21 22	265	preferred and the significance level threshold ( $\alpha$ ) is set as 0.05. Statistical
23 24	266	analyses will be performed using the R software v <u>4.0.</u> 0 or higher. <sup>20</sup>
25 26	267	
27 28		Distantial encointeres
29 30	268	Biological specimens
31 32	269	Biological specimens acquired throughout the trial, including blood and tissue
33 34	270	samples, will be stored for subsequent exploratory biomarker research.
35	271	Informed consent of participants will be obtained prior to the acquisition of
36 37	272	biological specimens.
38 39	273	
40 41	270	
42 43	274	Patient and public involvement
44 45	275	Patients or public have not been involved in the design of the present study.
46 47		r dienes of public have not been involved in the design of the present study.
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## **Ethics and dissemination**

This study was approved by the institutional review board of Shanghai Changhai Hospital (ref. CHEC2019-070 & CHEC2019-082). The study will be performed in compliance with applicable local legislation and in accordance with the ethical principles in the Declaration of Helsinki 2013. Eligible patients will be well informed of the purpose and schedule of this study. Written informed consent will be obtained by research physicians or nurses if patients decide to participate. All clinical data will be confidentially collected by research members. Findings of the study will be disseminated through publication in peer-reviewed scientific journals as well as relevant medical conferences. 

#### **Discussion**

The idea for maximizing cancer local control originates from the "seed and soil" hypothesis, which postulates that the growth of disseminating tumor cells is driven by factors secreted by the primary tumor.<sup>21</sup> It has been demonstrated in metastatic prostate cancer that aggressive subclones persist in primary tumor site and can seed to metastatic lesions, leading to a vicious cycle of metastatic disease.<sup>22 23</sup> Furthermore, overall survival benefits can be observed in metastatic prostate cancer patients who have been treated with radiotherapy plus ADT compared to ADT alone.<sup>24</sup> These data collectively suggest a role of maximizing local control in the management of locally advanced and metastatic prostate cancer.

Page 15 of 26

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Currently, clinical trials on preoperative radiation therapy for prostate cancer have focused primarily on men with high-risk localized disease. To the best of our knowledge, there are two published modern-era trials that evaluated preoperative radiation therapy in localized prostate cancer. Koontz et al. reported a phase I clinical trial in 12 men with high-risk localized prostate cancer who had completed long-course preoperative radiation therapy followed by radical prostatectomy.<sup>25</sup> Radiation therapy was dose-escalated with dose levels of 39.6, 45, 50.4, and 54 Gy in 5 1.8-Gy fractions per week. The pelvic lymph nodes were treated up to 45 Gy with any additional dose given to the prostate and seminal vesicles. The superior border of the whole pelvis field extended to the L5-S1 interspace. Two patients developed urethral strictures requiring dilation. The reported two-year biochemical recurrence-free survival was 67%. Glicksman et al. recently reported the long-term results of their phase I pilot study of 15 patients.<sup>26</sup> Patients received 25 Gy in 5 consecutive daily fractions to the prostate only. At a median follow-up of 12.2 years, 7 patients were free from biochemical relapse and 6 patients were metastasis-free. These results have motivated us to assess this treatment combination in locally advanced disease. Despite the limitations, the impact of our study has the potential to drive a paradigm shift in the management of locally advanced prostate cancer. 

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31 32	357	
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36 37 38	359	References
39 40	360	1. Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. Lyon, France:
41 42	361	International Agency for Research on Cancer, 2018.
43	362	2. Chang SL, Kibel AS, Brooks JD, Chung BI. The impact of robotic surgery on the surgical
44 45	363	management of prostate cancer in the USA. BJU Int 2015;115(6):929-36.
46	364	3. Mottet N, van den Bergh RCN, Briers E, et al. EAU - ESTRO - ESUR - SIOG Guidelines on
47 48	365	Prostate Cancer 2018. Arnhem, The Netherlands: European Association of Urology
49 50	366	Guidelines Office, 2018.
51	367	4. Mohler JL, Antonarakis ES, Armstrong AJ, et al. Prostate Cancer, Version 2.2019, NCCN
52 53	368	Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2019;17(5):479-505.
54 55	369	5. Costello AJ. Considering the role of radical prostatectomy in 21st century prostate cancer care.
56 57 58	370	<i>Nat Rev Urol</i> 2020;17(3):177-188.
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
50 51 52 53 54 55 56 57 58 59	367 368 369	<ol> <li>Mohler JL, Antonarakis ES, Armstrong AJ, et al. Prostate Cancer, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. <i>J Natl Compr Canc Netw</i> 2019;17(5):479-505.</li> <li>Costello AJ. Considering the role of radical prostatectomy in 21st century prostate cancer care. <i>Nat Rev Urol</i> 2020;17(3):177-188.</li> </ol>

6. Stranne J, Brasso K, Brennhovd B, et al. SPCG-15: a prospective randomized study comparing primary radical prostatectomy and primary radiotherapy plus androgen deprivation therapy for locally advanced prostate cancer. Scand J Urol 2018;52(5-6):313-320. 7. Bolla M, van Poppel H, Tombal B, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet 2012;380(9858):2018-27. 8. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol 2009;181(3):956-62. 9. Wiegel T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. J Clin Oncol 2009;27(18):2924-30. 10. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351(17):1731-40. 11. Chan AW, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 2013;346:e7586. 12. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158(3):200-7. 13. Gay HA, Barthold HJ, O'Meara E, et al. Pelvic normal tissue contouring guidelines for radiation therapy: a Radiation Therapy Oncology Group consensus panel atlas. Int J Radiat Oncol Biol Phys 2012;83(3):e353-62. 14. Michalski JM, Purdy JA, Winter K, et al. Preliminary report of toxicity following 3D radiation therapy for prostate cancer on 3DOG/RTOG 9406. Int J Radiat Oncol Biol Phys 2000;46(2):391-402. 15. Michalski JM, Bae K, Roach M, et al. Long-term toxicity following 3D conformal radiation therapy for prostate cancer from the RTOG 9406 phase I/II dose escalation study. Int J Radiat Oncol Biol Phys 2010;76(1):14-22. 16. Roach M, Winter K, Michalski JM, et al. Penile bulb dose and impotence after three-dimensional conformal radiotherapy for prostate cancer on RTOG 9406: findings from a prospective, multi-institutional, phase I/II dose-escalation study. Int J Radiat Oncol Biol Phys 2004;60(5):1351-6. 17. Péus D, Newcomb N, Hofer S. Appraisal of the Karnofsky Performance Status and proposal of a simple algorithmic system for its evaluation. BMC Med Inform Decis Mak 2013;13:72. 

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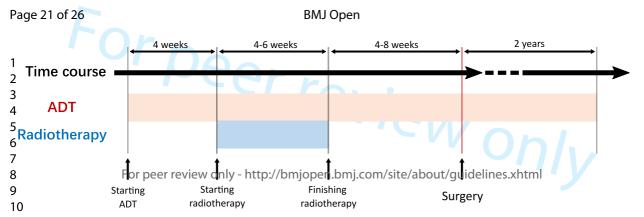
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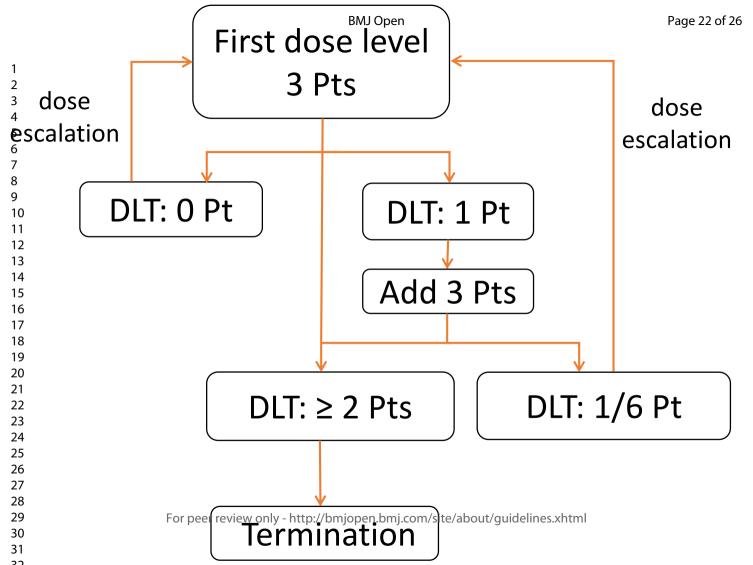
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## **Figure Legends**

Figure 1. Schedule of the study. ADT, androgen deprivation therapy.

ical u., oxicity. Pt, ps. Figure 2. Graphical depiction of the 3+3 dose-escalation study design. DLT, dose-limiting toxicity. Pt, participant. 





Page	23 of 26		BMJ Open Correction	
1 2 3 4 5			STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS	
6 7 8 9	SPIRIT 2013 Check	klist: Reco	ommended items to address in a clinical trial protocol and related documents*	
10 11 12	Section/item	ltem No	Description	Addressed on page number
13 14	Administrative inf	ormation	t Super text and a super	
15 16	Title	1	Descriptive title identifying the study design, population, interventions, and, if apple by, trial acronym	Page 1
17 18	Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 6-7
19 20		2b	All items from the World Health Organization Trial Registration Data Set	Not included in the manuscript. Av <u>ailable on the registration</u> website.
21 22	Protocol version	3	Date and version identifier	Not included in the manuscript.
23 24	Funding	4	Sources and types of financial, material, and other support	<u>Page 15</u>
25 26	Roles and	5a	Names, affiliations, and roles of protocol contributors	<u>Page 1, Page 15.</u>
27 28	responsibilities	5b	Name and contact information for the trial sponsor	Not applicable
29 30 31 32		5c	Role of study sponsor and funders, if any, in study design; collection, managemers, abalysis, 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	<u>Page I , Page 15.</u> <u>Not applicable</u> <u>Not applicable</u>
33 34 35 36 37 38 39 40 41		5d	Composition, roles, and responsibilities of the coordinating centre, steering committee endpoint adjudication committee, data management team, and other individuals or groups over eeing the trial, if applicable (see Item 21a for data monitoring committee)	<u>Page 12</u>
42 43 44 45 46			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	1

			BMJ Open BMJ Open BMJ Open	Page 24 of 26
1 2	Introduction		ight, =:	
3 4 5	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 inter with the studies (published and unpublished) examining benefits and harms for each interview of the studies (published and unpublished) examining benefits and harms for each interview of the studies (published and unpublished) examining benefits and harms for each interview of the studies (published and unpublished) examining benefits and harms for each interview of the studies (published and unpublished) examining benefits and harms for each interview of the studies (published and unpublished) examining benefits and harms for each interview of the studies (published and unpublished) examining benefits and harms for each interview of the studies (published and unpublished) examining benefits and harms for each interview of the studies (published and unpublished) examining benefits and harms for each interview of the studies (published and unpublished and	<u>Page 5-6</u>
6 7		6b	Explanation for choice of comparators	Not applicable (single-arm)
8 9	Objectives	7	Specific objectives or hypotheses	<u>Not applicable (single-arm)</u> <u>Page 12</u>
10 11 12 13	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, facອີ້ເອີ້ຊີຊີ່ single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, explorate ry) ອີ້ຂອງຊີ	Page 11
14 15	Methods: Participa	nts, inte	erventions, and outcomes	
16 17 18	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of community stes can be obtained	<u>Page 5-6</u>
19 20 21	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)	<u>Page 7-9 ; Page 11</u>
22 23 24 25	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	<u>Page 9-12:</u>
26 27 28		11b	Criteria for discontinuing or modifying allocated interventions for a given trial partigpaget (eg, drug dose change in response to harms, participant request, or improving/worsening diseas	<u>Page 8-11.</u>
29 30 31		11c	Strategies to improve adherence to intervention protocols, and any procedures for to intervence (eg, drug tablet return, laboratory tests)	<u>Page 11</u>
32 33		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	<u>Page 7-9.</u>
34 35 36 37 38 39	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	<u>_Page 11.</u>
40 41 42	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), ass sments, and visits for participants. A schematic diagram is highly recommended (see Figure)	<u>Page 6-11 ; Figure 1</u> -2.
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Page	25 of 26		BMJ Open cop	
1 2 3	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was betermined, including clinical and statistical assumptions supporting any sample size calculations	Page 12
4 5 6 7	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size g	<i>NA</i>
	Methods: Assignm	ent of ir	nterventions (for controlled trials)	
8 9	Allocation:		ses rei rei	
10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random not be been been been been been been been	
	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequertially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until in the method are assigned	
	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who was sign participants to interventions	
	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care provigers, outcome assessors, data analysts), and how	
		17b	If blinded, circumstances under which unblinding is permissible, and procedure for gealing a participant's allocated intervention during the trial	
30 31 32	Methods: Data collection, management, and analysis			
32 33 34 35 36 37	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	<u>Page 11-12.</u>
38 39 40 41 42		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	o <u>t included in the man</u> uscript.
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1 2 3 4	Data management	19	Plans for data entry, coding, security, and storage, including any related process toporomote data quality <u>المعود الك</u> (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	
5 6 7	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the <u>page 12-13</u> statistical analysis plan can be found, if not in the protocol	<u>,                                    </u>
8 9		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	[
10 11 12 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)	
14 15	Methods: Monitorin	ıg	and d d d	ļ
16 17 18 19 20 21	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and report	
22 22 23 24		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim <u>lage 12</u> . results and make the final decision to terminate the trial	
25 26 27	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse Page 12.	—
28 29 30 31	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent $Page_{12}$ from investigators and the sponsor	
32 33	Ethics and dissemination		gies.	
34 35 36	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval <u>Page 12</u> .	
37 38 39 40 41 42	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility creeria, outcomes, No <u>t included in H</u> analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial regiseries, journals, regulators)	<u>le m</u> anuscript.
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Page	Page 27 of 26		BMJ Open Sop P-2
1 2 3 4 5 6 7 8 9	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or autherised surrogates, and <u>lage 13</u> . how (see Item 32)
		26b	Additional consent provisions for collection and use of participant data and biolog and gradient data
	Confidentiality	27	How personal information about potential and enrolled participants will be collected and maintained <u>face 13</u> .
10 11 12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall transformed and each study site <u>fage_IS</u> .
13 14 15 16	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contracted a greements that Not included in the manuscript limit such access for investigators
17 18 19	Ancillary and post- trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those with suffer harm from trial Not included in the manuscript.
20 21 22 23 24 25 26 27 28 29	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healtheare professionals, the public, and other relevant groups (eg, via publication, reporting in results data tasks, or other data sharing arrangements), including any publication restrictions
		31b	Authorship eligibility guidelines and any intended use of professional writers
	Appendices	31c	Authorship eligibility guidelines and any intended use of professional writers Plans, if any, for granting public access to the full protocol, participant-level datas in the manuscript.
0 1 2 3	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates Not included in the manuscript.
34 35 36	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for generative contraction of the current trial and for future use in ancillary studies, if applicable
37 38 39 40 41	Amendments to the p	rotocol	that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboratien for important clarification on the items. should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons NoDerivs 3.0 Unported" license.
42 43 44 45 46			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml