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Long-term prognosis and quality of life in early rheumatoid arthritis patients treated by the 2015 ACR Guideline (LELAND): Protocol for a multicentre prospective observational study in southern China

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Long-term prognosis and quality of life in early rheumatoid arthritis patients treated by the 2015 ACR Guideline (LELAND): Protocol for a multicentre prospective observational study in southern China

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ABSTRACT

Introduction: Rheumatoid arthritis (RA) is a chronic systemic disease and one of the most disabling diseases in clinical practice. Recent research has shown that rapid progression of cartilage and bone damage can occur in the early stage of RA, and clinicians must develop strategies to prevent further deterioration, such as early diagnosis, early treatment and treat-to-target therapy. While only half of RA patients worldwide achieve low disease activity, only approximately 10% of RA patients exhibit low disease activity in China according to data released two years ago.

In 2015, the American College of Rheumatology (ACR) issued a new guideline for the treatment of RA to achieve better outcomes. Most published research has primarily focused on the medications used for RA treatment, and many investigations did not follow the 2015 ACR Guideline strictly and had few observational targets. Consequently, these studies do not reflect the real-world treat-to-target rate of RA.

This study will focus on the real-world treat-to-target rate of early RA patients, who will be treated according to the 2015 ACR Guideline. Additionally, the factors influencing the treat-to-target outcomes will be analysed, and long-term prognosis and quality of life will be assessed.

Method and analysis: 200 early RA patients will be enrolled, treated and followed up for 48 months. The patients should fulfil the 1987 ACR classification criteria for RA or the 2010 Rheumatoid arthritis classification criteria of the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR), with a disease course of no more than 6 months, and meet other conditions. They will be evaluated to determine their illness state and instructed to complete several questionnaires every 3 months.

Ethics and dissemination: This research was approved by the Nanfang Hospital Ethics

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Committee (NFEC-2017-192). The results of the study will be published in international peer-reviewed journals.

Keywords: Rheumatoid Arthritis (RA), treat-to-target, real-world, 2015 ACR Guideline.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Early diagnosis and treatment of RA can improve patients' prognosis and quality of life. Therefore, treat-to-target therapy at an early stage is very important.¹ There are many problems in current clinical practice, such as failure to follow the 2015 ACR Guideline for the Treatment of RA. Consequently, only approximately 10% of RA patients in China achieve treat-to-target goals, which is significantly lower than the corresponding proportion of patients worldwide. Observing real-world data on early RA patients in China is very important. Most published research mainly focuses on the medications used for RA treatment, and many studies did not follow the 2015 ACR Guideline strictly and included few observational targets. Consequently, they could not reflect the real-world treat-to-target rate of RA or disease development and prognosis.

Two hundred early RA patients will be enrolled, treated and followed up for 48 months. The study will determine their long-term prognosis and evaluate their quality of life, without adding an economic burden. At the same time, the research will explore the reasons why Chinese early RA patients have a much lower treat-to-target rate and may provide some feasible solutions to improve it.

We do not deny that there are some limitations of the research, such as the number of enrolled patients, which will only be 200, and the inclusion of research centres mainly located in

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown cause. In genetically susceptible individuals, an external stimulus, such as cigarette smoking or infection, is theorized to trigger an autoimmune reaction, leading to synovial hypertrophy and chronic joint inflammation along with the potential for extra-articular manifestations.² In China, the disease incidence is 0.3-0.4%, and females are 2 times more likely to develop RA than males. With the emergence of an ageing population in China, the number of RA patients is increasing rapidly. If they cannot be treated properly, half of these patients may become disabled, and their life span may decrease 3-5 years, which will impose a heavy burden on the social medical system.³⁻⁵ Fortunately, in recent years, due to tight control of treat-to-target therapy, increasingly more biological agents are becoming available, and rheumatologists can treat RA patients more appropriately and expect better outcomes, with 50% of RA patients maintaining low disease activity and approximately 15% of RA patients achieving complete remission and even stopping treatment.⁶⁻¹⁰ Tight control of treat-to-target therapy can effectively stop bone destruction, lower the RA-induced disability rate and help RA patients achieve a better quality of life.⁸ Recent research has shown that rapid progression of cartilage and bone damage can occur at the early stage of RA,^{11, 12} and evidence indicates that early, tightly controlled treatment results in

greater improvement than therapy initiated at a later stage.¹³ Therefore, clinicians should develop strategies to prevent further deterioration, such as early diagnosis, early treatment and treat-to-target therapy. In 2015, the ACR published a guideline for the treatment of RA.¹⁴ We searched for clinical trials on RA at <u>http://www.chictr.org.cn/</u> and <u>http://apps.who.int/trialsearch</u> from 2010 to 2017 and found that most published studies did not follow the 2015 ACR Guideline

for the Treatment of RA, mainly focused on medications, and had few observational targets; therefore, they did not reflect the real-world treat-to-target rate or disease progression and prognosis. Unfortunately, insufficient training of rheumatologists on RA and inadequate care for RA patients have resulted in $\leq 10\%$ of RA patients achieving treatment targets in China.¹⁵ The remission rate in early RA patients treated according to the 2015 ACR Guideline in China, the factor or factors that influence the treat-to-target rate, and the long-term prognosis and quality of

life among RA patients remain unclear. This study seeks to address these topics.

Rationale and hypothesis

In 2015, the American College of Rheumatology provided a guideline for the treatment of RA, and patients were classified into early RA patients and established RA patients and were treated accordingly. Early RA patients are treated as shown in Figure 1.14 RA patients who achieve treat-to-target goals have a DAS28≤3. 2, a simplified disease activity index (SDAI)≤11, clinical disease activity index (CDAI)≤10 and routine assessment of patient index data (RAPID-3)≤2.14,16 The formulas for the measurement tools are as follows.^{16, 17}

DAS28-CRP=0.56*sqrt(28TJC) +0.28*sqrt(28SJC) +0.36*Ln(CRP+1) +0.014*PGA+0.96,

DAS28-ESR=0.56*sqrt(28TJC) +0.28*sqrt(28SJC) +0.70*Ln(ESR) +0.014*PGA,

CDAI=28TJC+28SJC+PGA+EGA (TJC: tender joint count; SJC: swollen joint count; PGA: patient's global assessment of disease activity; EGA: evaluator's global assessment of disease activity).

SDAI=28TJC+28SJC+PGA+EGA+CRP (mg/dl),

RAPID-3=(FN+PN+PTGL)/3 (only patients' reported outcomes. FN: functional score, 0-10; PN:

pain score on the VAS, 0-10; PTGL: patient's global assessment of disease activity).¹⁸

Early RA patients who achieve the indicated targets will have a good long-term prognosis and good quality life compared with patients who do not achieve these targets. However, these targets are not easy to achieve, and some factors may influence the target rate, such as disease activity (mild, moderate, and severe), treatment medications (traditional DMARDs and biological agents), blood parameters (anti-cyclic citrullinated peptide antibody (CCP) and rheumatoid factor (RF)), and ultrasonic and radiographic progression.

Objectives

To investigate the real-world treat-to-target rate of early RA patients treated following the 2015 n progno. ACR Guideline for the Treatment of RA, the long-term prognosis and quality of life, and the factors influencing the target rate.

METHODS

Study design

This multicentre prospective observational study will be conducted in Nanfang Hospital and Zhujiang Hospital of Southern Medical University and will recruit 200 early RA patients. The follow-up will be 48 months. The real-world treat-to-target rate and the factors that influence this rate will be explored, as well as the long-term prognosis, quality of life and personal medical costs. The participants will be followed up once every 3 months to survey their work efficiency and health-related quality of life. All doctors who collect data will be trained to follow specific

standards, and a specialized expert will be assigned to assemble and analyse the data.

Participants

Participants will be recruited from two centres: Nanfang Hospital and Zhujiang Hospital of Southern Medical University. The participants must meet the following criteria:

(A) ≥ 18 years of age,

(B) fulfilment of the 1987 ACR classification criteria for rheumatoid arthritis¹⁹ or the ACR/EULAR 2010 Rheumatoid arthritis classification criteria,²⁰

(C) disease course of less than 6 months,

(D) ability to complete questionnaires independently, and

(E) complete comprehension of the survey and willingness to participate in the study, sign the consent form, and allow the researchers to use personal health information.

Exclusion criteria: Patients who meet one of the following conditions at baseline will be excluded:

(F) pregnant or lactating women or women who plan to become pregnant in the next 2 years,

(G) enrolment in another RA clinical study in the last 24 weeks, or

(H) confirmed inability to report quality of life or medical resources.

Drop-out criteria: Participants can drop out of the study at any time. Participants will be removed

from the study if they meet one of the following conditions:

(I) the researchers believe that study removal will benefit the patient, or

(J) failure to follow the study protocol.

Variables and outcome measures

The participants will follow the procedure shown in Table 1. The primary outcome variables are the real-world treat-to-target rate and changes in the DAS28 and Health Assessment Questionnaire Disability Index (HAQ-DI).

The secondary outcome variables are the results of the SDAI, CDAI, and RAPID-3; imaging data, including musculoskeletal ultrasound and modified total Sharp score (mTSS); HAQ-DI; The Work Productivity and Activity Impairment Questionnaire (WPAI); European Quality of Life-5 Dimensions (EQ-5D); Short Form 36 Health Survey Questionnaire (SF-36); self-rating anxiety scale (SAS); self-rating depression scale (SDS); health care resource utilization (HCRU); and the patient global impression change (PGIC), which will be completed by the participants at each follow-up.

Additional secondary outcome variables are as follows: changes in patient-reported outcomes (PROs) pre- and post-treatment, such as those related to the SF-36, EQ-5D and WPAI, and correlations between disease severity and PROs, correlations between changes in disease severity and changes in PROs, and correlations between changes in disease severity and imaging data, including musculoskeletal ultrasound and mTSS.

The exploratory outcome variables are changes in subjects' satisfaction with the primary treatment throughout the follow-up and the factors influencing the target rate, such as the disease activity index at baseline, treatment medications (e.g., traditional DMARDs or biological agents), haematology indexes (e.g., CCP and RF), and radiographic progression.

Clinical examinations and blood samples

TJC and SJC joints assessed include the proximal interphalangeal (PIP) joint and

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metacarpophalangeal joints of the hands, wrists, elbows, shoulders and knees on both sides. Rest pain and morning stiffness will be scored by the patients according to the visual analogue scale. Blood samples will be collected every 3 months by a trained laboratory technician. Routine tests, including hepatic and renal function, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), immune globulin and complement, anti-cyclic citrullinated peptide antibody (CCP) and anti-Keratin antibody (AKA), will be tested once a year.

Sample size considerations and statistical analyses

This survey will be conducted at Nanfang Hospital and Zhujiang Hospital of Southern Medical University and will recruit 200 early RA patients whose disease courses are no more than 6 months. Considering a mean \triangle HAQ-DI of -0.21, a standard deviation of 0.5, a significance level of 0.05 in two-sided tests, and a drop-out rate of 20%, the indicated sample size will result in 99% statistical power, suggesting that \triangle HAQ-DI<0 reflects a statistically significant improvement. Considering a mean \triangle HAQ-DI of -0.5, a standard deviation of 0.7, a significance level of 0.05 in two-sided tests, and a drop-out rate of 20%, the indicated sample size will result in 99% statistical power, suggesting that \triangle HAQ-DI<0 reflects a statistically significance level of 0.05 in two-sided tests, and a drop-out rate of 20%, the indicated sample size will result in 99% statistical power, suggesting that \triangle HAQ-DI<-0.22 reflects clinically significant improvement. For WPAI, the secondary end point analysis indicator, considering a significance level of 0.05 in two-sided tests, a drop-out rate of 20%, a mean score of 10 for loss of working time, a standard deviation of 30, and a population unemployment rate of 50%, the indicated sample size will result in 83% statistical power, suggesting that loss of working time is clinically significant.

All statistical tests will be two-sided. A P-value ≤ 0.05 will indicate a statistically significant outcome that will be included in the descriptive statistical analysis. Key parameters will also be

included in the descriptive statistical analysis. Continuous variables will be described by the mean, standard deviation, minimum, maximum and median. Categorical variables will be described by numbers and percentages. Significant changes in parameters will be estimated by T tests or variance analysis, and significant changes in nonparametric data will be assessed using the Wilcoxon symbol rank test. The data analysis will also include severity levels, such as moderate and severe, and the quartiles of the disease course will be compared over time in a maximum of two other subgroups. The Cochran-Armitage trend test or other similar tests can also be used to compare different categories of subjects. Multiple regression analysis will be used to obtain mixed-effects models to statistically analyse the factors influencing the target rate, such as the initial disease activity index, the choice of therapy drugs (e.g., traditional DMARDs or biological agents), haematology indexes (e.g., CCP and RF), and radiographic progression.

Patient and Public Involvement

Neither patients nor public were involved in the development of the research question, study design, outcome measures, recruitment to and conduct of the study or assessment of the burden of the intervention. Thanking for the patients' support, we will allowance the study participant 200 RMB at each follow-up as transportation costs. The research result will be disseminated to study participants on subsequent visit.

Lip

DISCUSSION

This study aims to explore the real-world treat-to-target rate of early RA patients treated following

the 2015 ACR Guideline for the Treatment of RA in southern China. The RA patients who achieve treat-to-target goals will have a DAS28≤3.2, SDAI≤11, CDAI≤10 and RAPID-3≤2. The study classifies RA patients into three groups according to outcome. The first outcome category is sustained remission, which includes patients who achieve 4 targets every year. The second category is intermittent remission, which includes patients who achieve 2-3 targets, and the third category is active disease, which includes patients who achieve 0-1 targets. The trend of the HAQ-DI from baseline to the end of the study may reflect treatment effects and provide guidance for treating RA patients.

In the research, the factors influencing the treat-to-target rate, long-term prognosis, and quality of life among patients will be observed. Multiple regression analysis will be adopted to obtain mixed-effects models to analyse these factors, including the initial disease activity index, the choice of traditional DMARDs or biological agents, haematology indexes such as CCP and RF, and radiographic progression. Changes in the HAQ-DI and PROs related to the SF-36, EQ-5D and WPAI will be analysed at every follow-up point to determine the trend of patients' disease changes. At the same time, correlations between disease severity and PROs and their changes will be explored, as well as the SDS and SAS.

China's ageing population is increasing rapidly, and increasingly more people have been diagnosed with RA. An estimated 5 million RA patients, but no more than 8000 rheumatologists, are present in China. Most RA patients are inclined to explore traditional Chinese medicine as their first choice of treatment due to the myth that traditional Chinese medicine can cure the disease, while DMARDs only relieve symptoms. Therefore, this research will benefit RA patients in China in terms of the provision of appropriate and timely treatment and medication selection.

ETHICS AND DISSEMINATION

This study mainly aims to determine the real-world treat-to-target rate, long-term prognosis and quality of life among early RA patients treated following the development of the 2015 American College of Rheumatology Guideline for the Treatment of RA. It is an observational study with no patient interaction. All data will be processed under the rules of government and law. All researchers will guarantee the anonymity of the patients and will not reveal patient names on forms or reports or in articles unless legally required. Only authorized individuals can access the patients' health information. All researchers handling data must follow specific training for addressing adverse events. The study has been approved by the Nanfang Hospital Ethics Committee (identification number NFEC-2017-192). The results will be published in international peer-reviewed journals.

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CONTRIBUTORS

Min Yang, Jinjun Zhao responsible for all phases from setup to the end of this study, including

data collection, analysis and interpret the manuscript. Min Yang, Jinjun Zhao and Taihe Zhan participated in the drafting of the protocol and applied for ethics committee approval. Min Yang, Jinjun Zhao, Taihe Zhan, Qin Huang, Hao Ren, Qinghong Yu, Jing Wu, Jingli Lin, Shengli An and Junqing Zhu all participated in the design of the study. All authors have checked and approved the protocol to be published.

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COMPETING INTERESTS

None.

ETHICS APPROVAL

The study has been approved by the Nanfang Hospital ethics committee.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

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5.8). DA, et al. unatoid arthritis. ACREULAR 201. Juis-9

FIGURE LEGENDS

Figure 1. 2015 American College of Rheumatology recommendations for the treatment of early RA,¹⁴ defined as a disease duration <6 months. ~: consider adding low-dose glucocorticoids (\leq 10 mg/day of prednisone or equivalent) in patients with moderate or high disease activity when starting disease-modifying antirheumatic drugs (DMARDs) and in patients with DMARD failure or biologic failure. †: consider using short-term glucocorticoids (defined as <3 months of treatment) for RA disease flares. Glucocorticoids should be used at the lowest possible dose and for the shortest possible duration to provide the best benefit-risk ratio for patients. #: treatment target should ideally be low disease activity or remission. For the level of evidence supporting each recommendation, see the related section in the results. MTX: methotrexate. TNF: tumour necrosis factor.

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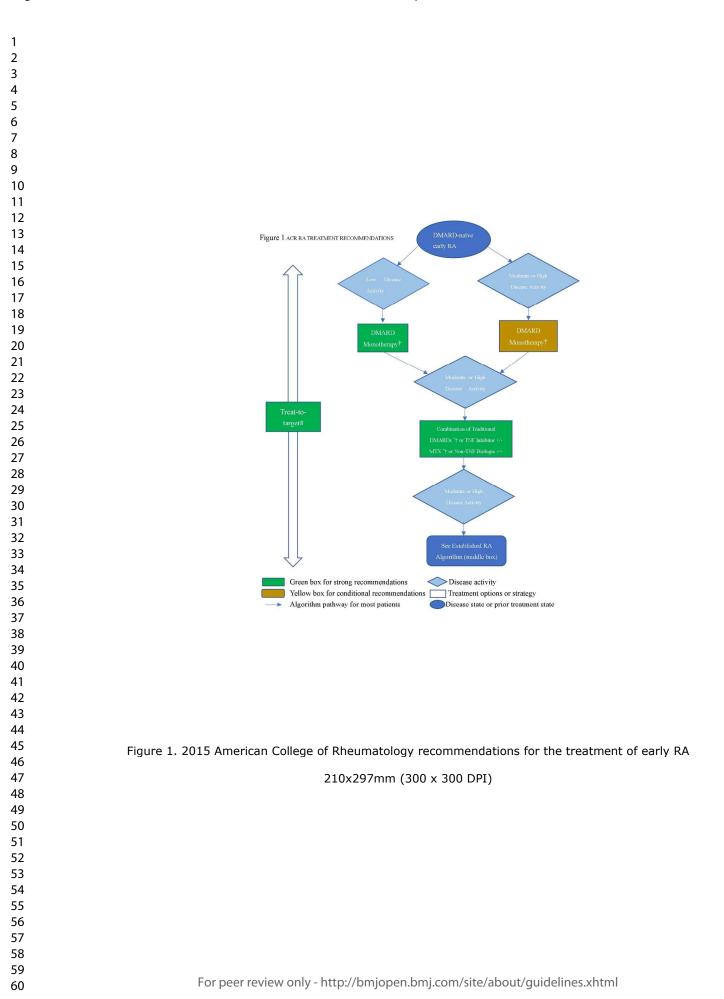
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	Sign informed notice	\checkmark				1	
Fill by clinicians	Patients' case history and demographics data	\checkmark					
linician	Intercurrent disease	\checkmark					
S	DAS28(ESR) or DAS28(CRP)	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark
	Adverse event		\checkmark	\checkmark	\checkmark	\checkmark	\checkmark
	Pregnancy report	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark
	Clinical routine	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark

Table1	Summary	of measures	to be collected:
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	inspection						
	EQ-5D	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark
	SF-36	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark
	HAQ-DI	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark
Ē	WPAI	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark
lled	HCRU	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark
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Filled by subjects	SAS	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark
ects	SDS	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark
	Satisfaction questionnaires post-treatment	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark

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ABSTRACT

21	Introduction: Rheumatoid arthritis (RA) is a chronic systemic disease and one of the most
22	disabling diseases for patients. The American College of Rheumatology (ACR) issued a new
23	guideline in 2015 for the treatment of RA based on the treat-to-target strategy to achieve better
24	outcomes. This study will focus on the real-world treat-to-target rate of early RA patients in China,
25	who will be treated according to the 2015 ACR Guideline. Additionally, factors influencing
26	treat-to-target outcomes will be analysed, and long-term prognosis and quality of life will be
27	assessed.
28	Method and analysis: Two hundred early RA patients will be enrolled, treated and followed up
29	once every 3 months for 48 months. These patients should fulfil the 2010 rheumatoid arthritis
30	classification criteria of the American College of Rheumatology/European League Against
31	Rheumatism (ACR/EULAR) with a disease course of no more than 6 months and should also
32	fulfil other eligibility criteria. The patients will be treated following the 2015 ACR Guideline.
33	Their disease activity will be assessed, and they will be instructed to complete several
34	questionnaires once every 3 months. The primary outcomes are DAS28 and Health Assessment
35	Questionnaire Disability Index (HAQ-DI). The secondary outcome variables are SDAI, CDAI and
36	RAPID-3 results, imaging data and personal medical costs. The data will be analysed using
37	appropriate statistical analyses.
38	Ethics and dissemination: This research was approved by the Nanfang Hospital Ethics
39	Committee (NFEC-2017-192). The results of the study will be published in international
40	peer-reviewed journals.

Keywords: rheumatoid arthritis (RA), treat-to-target, real-world, 2015 ACR Guideline.

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3 4	42	STRENGTHS AND LIMITATIONS OF THIS STUDY
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6	43	1) This study will last for 4 years and will reflect the real-world treat-to-target rate of RA patients
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8	44	in China.
9	44	in China.
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11	45	2) In addition to the primary outcome variables, this study will collect many secondary outcome
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13 14	46	variables, such as economic analysis, and intends to identify relevant factors affecting disease
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16	47	activity and prognosis in a real-world setting.
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18	48	3) The follow-up protocol and medication changes will be performed according to the 2015 ACR
19	10	s) The follow up protocol and incurcation changes will be performed according to the 2015 Hore
20	40	Cridalina
21	49	Guideline.
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23	50	4) This study is an investigation of real-world early RA patients, and some confounders may
24 25		
26	51	induce a certain degree of bias.
27		
28	52	5) Two research centres located in Guangdong Province of China are participating in this study,
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30	53	and more samples and research centres may be added in the future based on the study results.
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INTRODUCTION

5	5	Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown cause. In
5	6	genetically susceptible individuals, an external stimulus, such as cigarette smoking or infection, is
5	7	theorized to trigger an autoimmune reaction, leading to synovial hypertrophy and chronic joint
5	8	inflammation along with the potential for extra-articular manifestations. ¹ In China, the disease
5	9	incidence is 0.19-0.41%, and females are 4 times more likely to develop RA than are males. ^{2, 3}
6	0	With the emergence of an ageing population in China, the number of RA patients is increasing
6	1	rapidly. ^{2 3} If these patients cannot be treated properly, half of them may become disabled, and their
6	2	life spans may decrease 3-5 years, which will impose a heavy burden on the social medical
6	3	system. ⁴⁻⁶
6	4	Fortunately, the treat-to-target concept was put forward in 2010. A RA patient with a DSA28≤3.2
6	5	indicates that he/she has achieved the treat-to-target goal. The real-world treat-to-target rate is the
6	6	proportion of patients who achieve the treat-to-target goal out of the total number of RA patients.
6	7	Recently, due to tight control of treat-to-target therapy and the availability of several biological
6	8	agents, rheumatologists have been able to treat RA patients more appropriately and obtain better
6	9	disease outcomes, with 50% of RA patients maintaining low disease activity and approximately 15%
7	0	achieving complete remission. ⁷⁻¹¹ Tight control of treat-to-target therapy can effectively halt bone
7	1	destruction, decrease the RA-induced disability rate and help RA patients achieve a better quality
7	2	of life. ⁹
7	3	Recent research has shown that rapid progression of cartilage and bone damage occur during the
7	4	early stage of RA ^{12, 13} and thus tightly controlled treatment at the early stage has a better outcome
7	5	than does treatment initiated at a later stage. ¹⁴ Therefore, clinicians should develop strategies to
		4

76	obtain better outcome, such as early diagnosis, early treatment and treat-to-target therapy. We
77	searched for clinical trials of RA at http://www.chictr.org.cn/ and http://apps.who.int/trialsearch
78	from 2010 to 2017 and found that those studies mainly focused on medications and had few
79	observation indexes. Thus, they did not reflect the current state of real-world treat-to-target
80	research.
81	Unfortunately, insufficient training of rheumatologists on RA and inadequate care of RA patients
82	have resulted in $\leq 10\%$ of RA patients in China achieving treat-to-target goals. ¹⁵ The treat-to-target
83	rate in early RA patients treated following the 2015 ACR Guideline, the factor or factors that
84	influence the treat-to-target rate and the long-term prognosis and quality of life among RA patients
85	in China remain unclear. This study seeks to address these topics.
86	Rationale
87	In 2015, the American College of Rheumatology provided a guideline for RA treatment. Patients
88	were classified into early RA patients and established RA patients and treated accordingly. Early
89	RA patients are treated as shown in Figure 1. ¹⁶
90	Early RA patients who meet the treat-to-target targets will have a good long-term prognosis and
91	quality of life compared with those who do not achieve these targets. However, these targets are
92	not easy to achieve, and some factors may influence the target rate, such as disease activity (mild,
93	moderate and severe), medications (traditional DMARDs and biological agents), blood parameters
94	(anti-cyclic citrullinated peptide antibody (CCP) and rheumatoid factor (RF)), ultrasonic and
95	radiographic progression and economic factors.
96	Aims
97	To investigate the real-world treat-to-target rate of early RA patients treated following the 2015
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98	ACR Guideline for the Treatment of RA, the long-term prognosis and quality of life and the
99	factors influencing the treat-to-target rate.
100	METHODS
101	Study design
102	This multicentre prospective observational study will be conducted in Nanfang Hospital and
103	Zhujiang Hospital of Southern Medical University and will recruit 200 early RA patients. The
104	participants will be followed up once every 3 months for 48 months to assess their disease activity
105	and to survey their health-related quality of life and their work efficiency. The study will be
106	conducted in full compliance with the articles of the Declaration of Helsinki. All analyses will be
107	conducted by a statistician according to the prespecified statistical analysis plan.
108	Participants
109	The participants must meet the following criteria:
110	$1. \geq 18$ years of age,
111	2. fulfil the ACR/EULAR 2010 Rheumatoid arthritis classification criteria, ¹⁷
112	3. disease course of less than 6 months,
113	4. demonstrate complete understanding of the survey and have the ability to complete the
114	questionnaires independently and
115	5. willingness to enrol in the study and sign the consent form allowing the researchers to use their
116	personal health information.
117	Exclusion criteria: Patients who meet one of the following conditions at baseline will be excluded:
118	1. pregnant or lactating women or women who plan to become pregnant within the next 2 years,
119	2. enrolment in another RA clinical study in the last 24 weeks and
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120	3. inability to report quality of life or medical resources.
121	Drop-out criteria: Participants can drop out of the study at any time. Participants will be removed
122	from the study if they meet one of the following conditions:
123	1. the researchers believe that study removal will benefit the patient and
124	2. the participants refuse to answer the questionnaires or do not follow the follow-up time
125	schedule included in the research protocol.
126	Sample size calculation
127	This study will recruit 200 early RA patients whose disease courses are no more than 6 months.
128	Considering a mean \triangle Health Assessment Questionnaire Disability Index (HAQ-DI) of -0.21, a
129	standard deviation of 0.5, a significance level of 0.05 in two-sided tests and a drop-out rate of 20%,
130	the indicated sample size will result in 99% statistical power, suggesting that a Δ HAQ-DI<0
131	reflects a statistically significant improvement. Considering a mean △HAQ-DI of -0.5, a standard
132	deviation of 0.7, a significance level of 0.05 in two-sided tests and a drop-out rate of 20%, the
133	indicated sample size will result in 99% statistical power, suggesting that a Δ HAQ-DI<-0.22
134	reflects clinically significant improvement. For the WPAI, which is the secondary end point
135	analysis indicator, considering a significance level of 0.05 in two-sided tests, a drop-out rate of
136	20%, a mean score of 10 for loss of working time, a standard deviation of 30 and a population
137	unemployment rate of 50%, the indicated sample size will result in 83% statistical power,
138	suggesting that loss of working time is clinically significant.
139	Clinical examinations and blood samples
140	At baseline (pre-treatment), the participants will be asked to register data for their case history,

141 demographics and intercurrent diseases. The participants will follow the procedure shown in Table

142	1.
143	The tender joint count (TJC) and swollen joint count (SJC) assessments include the proximal
144	interphalangeal (PIP) joint and metacarpophalangeal joints of the hands, wrists, elbows, shoulders
145	and knees on both sides. Rest pain and morning stiffness will be scored by the patients according
146	to the visual analogue scale. The above clinical examinations will be assessed once every 3
147	months. Blood samples will be collected once every 3 months by a trained laboratory technician.
148	Routine tests, including a routine blood test, hepatic and renal function, erythrocyte sedimentation
149	rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), immunoglobulin and complement
150	will be tested once every 3 months. The anti-cyclic citrullinated peptide antibody (CCP) and
151	anti-keratin antibody (AKA) will be tested once a year.
152	Outcomes
153	The primary outcome variables are DAS28 and HAQ-DI. The formulas for measurement of
154	DSA28 refer to the relevant literature. ¹⁸
155	The secondary outcome variables are SDAI, CDAI and RAPID-3 results, imaging data, including
156	musculoskeletal ultrasound and modified total Sharp score (mTSS), European Quality of Life-5
157	Dimensions (EQ-5D), Short Form 36 Health Survey Questionnaire (SF-36), The Work
158	Productivity and Activity Impairment Questionnaire (WPAI), self-rating anxiety scale (SAS),
159	self-rating depression scale (SDS), health care resource utilization (HCRU), the patient global
160	impression change (PGIC) and personal medical costs, including the costs of medicine and
160 161	impression change (PGIC) and personal medical costs, including the costs of medicine and examinations. The above variables will be recorded at each follow-up. Other secondary outcome

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164	between changes in disease severity and changes in PROs and between changes in disease severity
165	and imaging data, including musculoskeletal ultrasound and mTSS.
166	The exploratory outcome variables are changes in the subjects' satisfaction with the primary
167	treatment throughout the follow-up and the factors influencing the treat-to-target rate, such as the
168	disease activity index at baseline, treatment medications (e.g., traditional DMARDs or biological
169	agents), haematology indexes (e.g., CCP and RF) and radiographic progression.
170	Statistical analyses
171	All statistics will be calculated independently with SPSS (V.20, SPSS Inc., Chicago, IL, USA).
172	Continuous variables will be described by the mean, standard deviation, minimum, maximum and
173	median. Categorical variables will be described by numbers and percentages. Significant changes
174	in parameters will be estimated by T tests or variance analysis, and significant changes in
175	nonparametric data will be assessed using the Wilcoxon symbol rank test. The data analysis will
176	also include the severity levels, such as moderate and severe, and the quartiles of the disease
177	course will be compared over time with a maximum of two other subgroups. The
178	Cochran-Armitage trend test or other similar tests can also be used to compare different categories
179	of subjects. Multiple regression analysis will be used to obtain mixed-effects models to
180	statistically analyse the factors influencing the target rate, such as the initial disease activity index,
181	the choice of therapeutic drugs (e.g., traditional DMARDs or biological agents), haematology
182	indexes (e.g., CCP and RF) and radiographic progression. The study will classify RA patients into
183	three groups according to their outcomes. The first outcome category is sustained remission,
184	which includes patients who achieve 4 targets every year. The second category is intermittent
185	remission, which includes patients who achieve 2-3 targets, and the third category is active disease,
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which includes patients who achieve 0-1 targets. The HAQ-DI of these three groups from baseline to post-treatment will be analysed. Bivariate analysis will be performed between the clinical categories and the HAQ-DI. The odds ratios (ORs) and their 95% CIs will be reported. In addition, the regression model will be used to identify the effect of each potential risk factor adjusted for other factors. Variables with p < 0.05 in the bivariate analysis will be included in the regression models. The adjusted odds ratios (AORs) and 95% CIs will be reported. All p values are two-tailed. A p < 0.05 is considered statistically significant. Patient and public involvement Neither patients nor the public were involved in the development of the research question, study design, outcome measures, recruitment and conduct of the study or the assessment of the burden of the intervention. We will make an allowance of 200 RMB at each follow-up for transportation costs. The research results will be disseminated to the study participants on the subsequent visit. DISCUSSION This study aims to explore the real-world treat-to-target rate of early RA patients treated following the 2015 ACR Guideline for the Treatment of RA in southern China. The trend of DSA28 and HAQ-DI from baseline to the end of the study may reflect the treatment effects and provide guidance for the treatment of RA patients. In this study, factors influencing the treat-to-target rate, long-term prognosis and quality of life among patients will be observed. Multiple regression analysis will be adopted to obtain mixed-effects models to analyse these factors, including the initial disease activity index, the medicine selection of traditional DMARDs or biological agents, haematology indexes, such as CCP and RF, and radiographic progression, such as mTSS. HAQ-DI and PROs related to SF-36,

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208	EQ-5D and WPAI will be analysed at every follow-up time point to determine trends in patients'
209	disease changes. At the same time, correlations between disease severity and PROs and their
210	changes will be explored, as well as the SDS and SAS.
211	China's society is experiencing rapid aging. Approximately 5 million RA patients have been
212	diagnosed, although China has no more than 8000 rheumatologists. Influenced by traditional
213	culture, most RA patients are inclined to adopt traditional Chinese medicine as their first choice,
214	and these patients have been lulled into thinking that traditional Chinese medicine can cure the
215	disease with few side effects but that DMARDs only relieve symptoms with many side effects.
216	Therefore, this research will benefit RA patients in China by educating them on how to obtain
217	appropriate and timely treatment and how to achieve a good prognosis.
218	This study has some limitations. Both research centres in this study are located in Guangdong
219	Province, China, which may induce poor representativeness of the samples. The non-randomised
220	study design inherits the risks of confounding; therefore, thorough statistical analysis and
221	confounder adjustment are important.
222	ETHICS AND DISSEMINATION
223	This study mainly focuses on the real-world treat-to-target rate, long-term prognosis and quality of
224	life of early RA patients treated following the 2015 American College of Rheumatology Guideline
225	for the Treatment of RA. The study is an observational study with no patient interaction. All data
226	will be processed under the rules of the government and law. All researchers will guarantee the
227	anonymity of the patients and will not reveal patient names on forms or reports or in articles
228	unless legally required. Only authorized individuals can access the patients' health information.
229	All researchers handling data must follow specific training to address adverse events. The study

230	has been approved by the Nanfang Hospital Ethics Committee (identification number
231	NFEC-2017-192). The results will be published in international peer-reviewed journals.
232	ACKNOWLEDGEMENTS
233	All authors acknowledge all of the contributors to this study, especially the nurses in the
234	Departments of Rheumatology of Nanfang Hospital and Zhujiang Hospital. We are also grateful
235	for the patients' support and the patients' advisers.
236	CONTRIBUTORS
237	Min Yang and Jinjun Zhao are responsible for all phases from setup to the end of this study,
238	including data collection, analysis and interpretation of the manuscript. Min Yang, Jinjun Zhao
239	and Taihe Zhan participated in the drafting of the protocol and applied for ethics committee
240	approval. Min Yang, Jinjun Zhao, Taihe Zhan and Junqing Zhu participated in revising the
241	manuscript. Min Yang, Jinjun Zhao, Taihe Zhan, Junqing Zhu, Meida Fan, Qin Huang, Hao Ren,
242	Qinghong Yu, Jing Wu, Jingli Lin, Qingqing Ouyang and Shengli An all participated in the study
243	design. All authors have checked and approved the protocol to be published.
244	FUNDING
245	This study was supported by Southern Medical University (grant number [LC2016PY020]).
246	COMPETING INTERESTS
247	None.
248	ETHICS APPROVAL
249	The study has been approved by the Nanfang Hospital ethics committee.
250	PROVENANCE AND PEER REVIEW
251	Not commissioned; externally peer reviewed.
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298 FIGURE LEGENDS

299 Figure 1. 2015 ACR RA Treatment Recommendations

- 300 The 2015 American College of Rheumatology recommendations for the treatment of
- 301 early RA,¹⁶ which is defined as a disease duration <6 months. ~: consider adding
- low-dose glucocorticoids ($\leq 10 \text{ mg/day of prednisone or equivalent}$) in patients with
- 303 moderate or high disease activity when starting disease-modifying antirheumatic
- 304 drugs (DMARDs) and in patients with DMARD failure or biologic failure. †: consider
- 305 using short-term glucocorticoids (defined as <3 months of treatment) for RA disease
- 306 flares. Glucocorticoids should be used at the lowest possible dose and for the shortest
- 307 possible duration to provide the best benefit-risk ratio for patients. #: the treatment
- 308 target should ideally be low disease activity or remission. For the level of evidence

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- 309 supporting each recommendation, see the related section in the results. MTX:
- 310 methotrexate. TNF: tumour necrosis factor.

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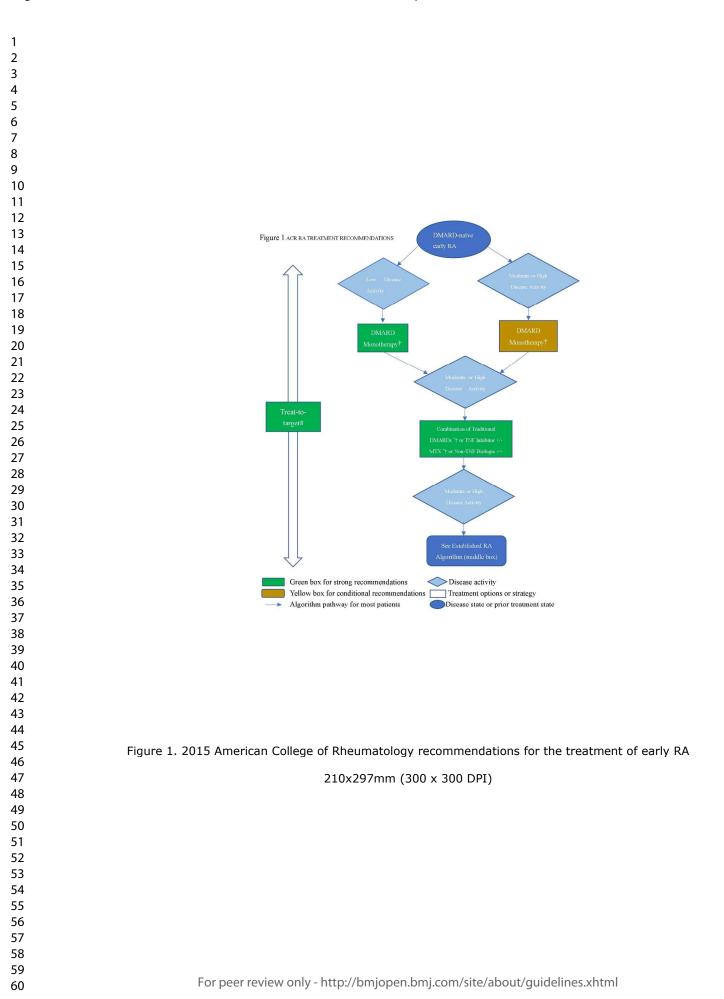
Note: DAS, disease activity score; ESR, erythrocyte sedimentation rate; CRP, C-reactive

protein; HAQ-DI, Health Assessment Questionnaire Disability Index; SF-36, Short Form 36

Health Survey Questionnaire; EQ-5D, European Quality of Life-5 Dimensions; WPAI, Activity

Impairment Questionnaire; HCRU, Health Care Resource Utilization; PGIC, Patient Global

Impression Change; SAS, self-rating anxiety scale; SDS, self-rating depression scale.



STROBE Statement-checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
itle and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1	Title: a multicentre prospective observational study
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	observational studyThis study will focus on the real-worldtreat-to-target rate of early RA patients,treated according to the 2015 ACRGuideline. Additionally, factorsinfluencing the treat-to-target outcomeswill be analysed, and long-term prognosicand quality of life will be assessed.Two hundred early RA patients will beenrolled, treated and followed up onceevery 3 months for 48 months. Thosepatients should fulfil the 2010 Rheumatoarthritis classification criteria of theAmerican College ofRheumatology/European League AgainstRheumatism (ACR/EULAR), with adisease course of no more than 6 monthsand fulfil other eligibility criteria. Thepatients will be treated following the 201ACR Guideline. Their disease activity widebe assessed, and they will be instructed tocomplete several questionnaires onceevery 3 months. The primary outcomes aDAS28 and Health Assessment
				Questionnaire Disability Index (HAQ-D The secondary outcome variables are

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				imaging data and personal medical costs. The data will be analysed using appropriate statistical analyses.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5	lines 55-95 of the manuscript.
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6	To investigate the real-world treat-to-targe rate of early RA patients treated following the 2015 ACR Guideline for the Treatmer of RA, the long-term prognosis and qualit of life, and the factors influencing the target rate.
Methods				
Study design	4	Present key elements of study design early in the paper	6	lines 102-107 of the manuscript.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8	This multicentre prospective observationa study will be conducted in full compliance with the articles of the Declaration of Helsinki. It will be conducted in Nanfang Hospital and Zhujiang Hospital of Southern Medical University and will recruit 200 early RA patients treated according to the 2015 ACR Guideline. Th participants will be followed up once ever 3 months for 48 months to assess their disease activity and to survey their health related quality of life and their work efficiency.
Participants	6	 (a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of 	6-7	 The participants must meet the following criteria: 1. ≥18 years of age, 2. fulfil the ACR/EULAR 2010 Rheumatoid arthritis classification
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participants	criteria, ¹⁷
	3. disease course of less than 6 months,
	4. demonstrate complete understanding of
	the survey and have the ability to complete
	the questionnaires independently and
	5. willingness to enrol in the study and
	sign the consent form allowing the
	researchers to use their personal health
	information.
	Exclusion criteria: Patients who meet one
	of the following conditions at baseline will
	be excluded:
	1. pregnant or lactating women or women
	who plan to become pregnant within the
	next 2 years,
	2. enrolment in another RA clinical study
	in the last 24 weeks and
	3. inability to report quality of life or
	medical resources.
	Drop-out criteria: Participants can drop ou
	of the study at any time. Participants will
	be removed from the study if they meet
	one of the following conditions:
	1. the researchers believe that study
	removal will benefit the patient and
	2. the participants refuse to answer the
	questionnaires or do not follow the follow- up time schedule included in the research
	protocol.
(b) Cohort study—For matched studies, give matching criteria and number of exposed and N/A	
unexposed	
<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per	
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Variables	7	case Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers.	8,9	Demonstrate under spection handing
variables	1	Give diagnostic criteria, if applicable	8,9	Paragraph under section heading, Outcomes .
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9	Paragraph under section heading, Clinica examinations and blood samples and Outcomes.
Bias	9	Describe any efforts to address potential sources of bias	6,11	All analyses will be conducted by a statistician, according to the prespecified statistical analysis plan. statistical analys and confounder adjustment are taken. Al researchers handling data must follow specific training to address adverse event
Study size	10	Explain how the study size was arrived at	7	Paragraph under section heading, Sample size calculation
		Explain how the study size was arrived at		
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Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,9,10	Paragraphs in the Sample size calculation and statistical analyse
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9,10	Paragraphs in the Statistical analyses
		(b) Describe any methods used to examine subgroups and interactions	9,10	Paragraphs in the Statistical analyses
		(c) Explain how missing data were addressed	None	The patients missing data will not be included in the analysis
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed	None	The patients missing data will not
		Case-control study—If applicable, explain how matching of cases and controls was addressed		be included in the analysis
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy		
		(<u>e</u>) Describe any sensitivity analyses	9,10	Paragraphs in the Statistical analyses
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A	N/A
		(b) Give reasons for non-participation at each stage	N/A	N/A
		(c) Consider use of a flow diagram	N/A	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A	N/A
		(b) Indicate number of participants with missing data for each variable of interest	N/A	N/A
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	N/A	N/A
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	N/A	N/A
		Case-control study-Report numbers in each exposure category, or summary measures of exposure	N/A	N/A
		Cross-sectional study-Report numbers of outcome events or summary measures	N/A	N/A
Main results	16	(<i>a</i>) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A	N/A
		(b) Report category boundaries when continuous variables were categorized	N/A	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time	N/A	N/A
		5		

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Continued on next page		
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Discussion		Report other analyses done-eg analyses of subgroups and interactions, and sensitivity analyses	N/A	N/A
Key results	18	Summarise key results with reference to study objectives	10	the real-world treat-to-target rate of
				early RA patients
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss	11	This study has some limitations.
		both direction and magnitude of any potential bias		Both research centres in this study
				are located in Guangdong Province,
				China, which may induce poor
				representativeness of the samples.
				The non-randomised study design
				inherits the risks of confounding;
				therefore, thorough statistical
				analysis and confounder adjustment
				are important
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of	10,11	DISCUSSION (paragraphs 1,2,4).
		analyses, results from similar studies, and other relevant evidence		
Generalisability	21	Discuss the generalisability (external validity) of the study results	11	DISCUSSION (paragraph 3).
Other informati	ion			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the	12	Provided. Southern Medical
		original study on which the present article is based		University
*Give informatio	n con	arataly for cases and controls in case, control studies and if applicable, for exposed and unexposed group	s in cohort and	cross sectional studies
Note: An Explan checklist is best u	nation used i	arately for cases and controls in case-control studies and, if applicable, for exposed and unexposed group and Elaboration article discusses each checklist item and gives methodological background and publishen n conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosme /, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at v	ed examples of the dicine.org/, An	ransparent reporting. The STROBE nals of Internal Medicine at
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BMJ Open

Long-term prognosis and quality of life in early rheumatoid arthritis patients treated according to the 2015 ACR Guideline (LELAND): Protocol for a multicentre prospective observational study in southern China

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1 2 3	Long-term prognosis and quality of life in early rheumatoid arthritis patients treated according to the 2015 ACR Guideline (LELAND): Protocol for a multicentre prospective observational study in southern China
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5	Jinjun Zhao ^{1†} , Taihe Zhan ^{1†} , Junqing Zhu ¹ , Meida Fan ¹ , Qin Huang ¹ , Hao Ren ¹ , Jing Wu ² ,
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18	
19	[†] These authors contributed equally in this study.

20 ABSTRACT

Introduction: Rheumatoid arthritis (RA) is a chronic systemic disease and one of the most disabling diseases for patients. The American College of Rheumatology (ACR) issued a new guideline in 2015 for the treatment of RA based on the treat-to-target strategy to achieve better outcomes. This study will focus on the real-world rates of remission and low disease activity (LDA) of early RA patients in China, who will be treated according to the 2015 ACR Guideline. Additionally, factors influencing treat-to-target outcomes will be analysed, and long-term prognosis and quality of life will be assessed.

Method and analysis: Two hundred early RA patients will be enrolled, treated and followed up once every 3 months for 48 months. These patients should fulfil the 2010 RA classification criteria of the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) with a disease course of no more than 6 months and should also fulfil other eligibility criteria. The patients will be treated following the 2015 ACR Guideline. Their disease activity will be assessed, and they will be instructed to complete several questionnaires once every 3 months. The primary outcomes are the Disease Activity Score on 28 joints (DAS28) and Health Assessment Questionnaire Disability Index (HAQ-DI). The secondary outcome variables are the Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) and Routine Assessment of Patient Index Data (RAPID-3) results, imaging data and personal medical costs. The data will be analysed using appropriate statistical analyses. Ethics and dissemination: This research was approved by the Nanfang Hospital Ethics

40 Committee (NFEC-2017-192). The results of the study will be published in international
41 peer-reviewed journals.

42 Keywords: rheumatoid arthritis (RA), treat-to-target, real-world, 2015 ACR Guideline.

43 STRENGTHS AND LIMITATIONS OF THIS STUDY

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44	1) This study will last for 4 years and will reflect the real-world rates of remission and LDA of RA
45	patients in China.
46	2) In addition to the primary outcome variables, this study will collect many secondary outcome
47	variables, such as economic analysis, and intends to identify relevant factors affecting disease
48	activity and prognosis in a real-world setting.
49	3) The follow-up protocol and medication changes will be performed according to the 2015 ACR
50	Guideline.
51	4) This study is an investigation of real-world early RA patients, and some confounders may
52	induce a certain degree of bias.
53	5) Two research centres located in Guangdong Province of China are participating in this study,
54	and more samples and research centres may be added in the future based on the study results.

INTRODUCTION

56	Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown cause. In
57	genetically susceptible individuals, an external stimulus, such as cigarette smoking or infection, is
58	theorized to trigger an autoimmune reaction, leading to synovial hypertrophy and chronic joint
59	inflammation along with the potential for extra-articular manifestations. ¹ In China, the disease
60	incidence is 0.19-0.41%, and females are 4 times more likely to develop RA than are males. ^{2, 3}
61	With the emergence of an ageing population in China, the number of RA patients is increasing
62	rapidly. ^{2, 3} If these patients cannot be treated properly, half of them may become disabled, and
63	their life spans may decrease 3-5 years, which will impose a heavy burden on the social medical
64	system. ⁴⁻⁶
65	Fortunately, the treat-to-target concept was put forward in 2010. According to the 2015 American
66	College of Rheumatology (ACR) Guideline, patients are in remission if their Disease Activity
67	Score on 28 joints (DAS28) < 2.6, whereas patients with a DAS28 \geq 2.6 and < 3.2 are in low
68	disease activity (LDA), and the treatment target should ideally be remission or LDA, that is a
69	DAS28 < 3.2 . ^{7, 8} Recently, due to tight control of treat-to-target therapy and the availability of
70	several biological agents, rheumatologists have been able to treat RA patients more appropriately
71	and obtain better disease outcomes, with 50% of RA patients maintaining LDA and approximately
72	15% achieving complete remission.9-13 Tight control of treat-to-target therapy can effectively halt
73	bone destruction, decrease the RA-induced disability rate and help RA patients achieve a better
74	quality of life. ¹¹
75	Recent research has shown that rapid progression of cartilage and bone damage occur during the
76	early stage of RA ^{14, 15} and thus tightly controlled treatment at the early stage has a better outcome

77	than does treatment initiated at a later stage. ¹⁶ Therefore, clinicians should develop strategies to
78	obtain better outcome, such as early diagnosis, early treatment and treat-to-target therapy. We
79	searched for clinical trials of RA at http://www.chictr.org.cn/ and http://apps.who.int/trialsearch
80	from 2010 to 2017 and found that those studies mainly focused on medications and had few
81	observation indexes. Thus, they did not reflect the current state of real-world treat-to-target
82	research.
83	Unfortunately, insufficient training of rheumatologists on RA and inadequate care of RA patients
84	have resulted in $\leq 10\%$ of RA patients in China achieving treat-to-target goals. ¹⁷ The rates of
85	remission and LDA in early RA patients treated following the 2015 ACR Guideline, the factor or
86	factors that influence the rates of remission and LDA, and the long-term prognosis and quality of
87	life among RA patients in China remain unclear. This study seeks to address these topics.
88	Rationale
88	Rationale
88 89	Rationale In 2015, the ACR provided a guideline for RA treatment. Patients were classified into early RA
88 89 90	Rationale In 2015, the ACR provided a guideline for RA treatment. Patients were classified into early RA patients and established RA patients and treated accordingly. Early RA patients are treated as
88 89 90 91	Rationale In 2015, the ACR provided a guideline for RA treatment. Patients were classified into early RA patients and established RA patients and treated accordingly. Early RA patients are treated as shown in Figure 1. ⁷
88 89 90 91 92	Rationale In 2015, the ACR provided a guideline for RA treatment. Patients were classified into early RA patients and established RA patients and treated accordingly. Early RA patients are treated as shown in Figure 1. ⁷ Early RA patients who meet the treat-to-target targets will have a good long-term prognosis and
 88 89 90 91 92 93 	Rationale In 2015, the ACR provided a guideline for RA treatment. Patients were classified into early RA patients and established RA patients and treated accordingly. Early RA patients are treated as shown in Figure 1. ⁷ Early RA patients who meet the treat-to-target targets will have a good long-term prognosis and quality of life compared with those who do not achieve these targets. However, these targets are
 88 89 90 91 92 93 94 	Rationale In 2015, the ACR provided a guideline for RA treatment. Patients were classified into early RA patients and established RA patients and treated accordingly. Early RA patients are treated as shown in Figure 1. ⁷ Early RA patients who meet the treat-to-target targets will have a good long-term prognosis and quality of life compared with those who do not achieve these targets. However, these targets are not easy to achieve, and some factors may influence the rates of remission and LDA, such as
 88 89 90 91 92 93 94 95 	Rationale In 2015, the ACR provided a guideline for RA treatment. Patients were classified into early RA patients and established RA patients and treated accordingly. Early RA patients are treated as shown in Figure 1. ⁷ Early RA patients who meet the treat-to-target targets will have a good long-term prognosis and quality of life compared with those who do not achieve these targets. However, these targets are not easy to achieve, and some factors may influence the rates of remission and LDA, such as disease activity (mild, moderate and severe), medications (traditional disease-modifying
 88 89 90 91 92 93 94 95 96 	Rationale In 2015, the ACR provided a guideline for RA treatment, Patients were classified into early RA patients and established RA patients and treated accordingly. Early RA patients are treated as shown in Figure 1. ⁷ Early RA patients who meet the treat-to-target targets will have a good long-term prognosis and quality of life compared with those who do not achieve these targets. However, these targets are not easy to achieve, and some factors may influence the rates of remission and LDA, such as disease activity (mild, moderate and severe), medications (traditional disease-modifying anti-rheumatic drugs (DMARDs) and biological agents), blood parameters (anti-cyclic

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99	Aims
100	To investigate the real-world rates of remission and LDA of early RA patients treated following
101	the 2015 ACR Guideline for the Treatment of RA, the long-term prognosis and quality of life and
102	the factors influencing the rates of remission and LDA.
103	METHODS
104	Study design
105	This multicentre prospective observational study will be conducted in Nanfang Hospital and
106	Zhujiang Hospital of Southern Medical University and will recruit 200 early RA patients. The
107	participants will be followed up once every 3 months for 48 months to assess their disease activity
108	and to survey their health-related quality of life and their work efficiency. The study will be
109	conducted in full compliance with the articles of the Declaration of Helsinki. All analyses will be
110	conducted by a statistician according to the prespecified statistical analysis plan.
111	Participants
112	The participants must meet the following criteria:
113	$1. \geq 18$ years of age,
114	2. fulfil the ACR/European League Against Rheumatism (ACR/EULAR) 2010 RA classification
115	criteria, ¹⁸
116	3. disease course of less than 6 months,
117	4. demonstrate complete understanding of the survey and have the ability to complete the
118	questionnaires independently and
119	5. willingness to enrol in the study and sign the consent form allowing the researchers to use their
120	personal health information.
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	121	Exclusion criteria: Patients who meet one of the following conditions at baseline will be excluded:	
	122	1. pregnant or lactating women or women who plan to become pregnant within the next 2 years,	
	123	2. enrolment in another RA clinical study in the last 24 weeks and	
	124	3. inability to report quality of life or medical resources.	
	125	Drop-out criteria: Participants can drop out of the study at any time. Participants will be removed	
	126	from the study if they meet one of the following conditions:	
	127	1. the researchers believe that study removal will benefit the patient and	
	128	2. the participants refuse to answer the questionnaires or do not follow the follow-up time	
	129	schedule included in the research protocol.	
	130	Sample size calculation	
	131	This study will recruit 200 early RA patients whose disease courses are no more than 6 months.	
	132	Considering a mean △ Health Assessment Questionnaire Disability Index (HAQ-DI) of -0.21, a	
	133	standard deviation of 0.5, a significance level of 0.05 in two-sided tests and a drop-out rate of 20%,	
	134	the indicated sample size will result in 99% statistical power, suggesting that a Δ HAQ-DI<0	
	135	reflects a statistically significant improvement. Considering a mean △HAQ-DI of -0.5, a standard	
	136	deviation of 0.7, a significance level of 0.05 in two-sided tests and a drop-out rate of 20%, the	
	137	indicated sample size will result in 99% statistical power, suggesting that a Δ HAQ-DI<-0.22	
	138	reflects clinically significant improvement. For the Work Productivity and Activity Impairment	

Questionnaire (WPAI), which is the secondary end point analysis indicator, considering a significance level of 0.05 in two-sided tests, a drop-out rate of 20%, a mean score of 10 for loss of working time, a standard deviation of 30 and a population unemployment rate of 50%, the indicated sample size will result in 83% statistical power, suggesting that loss of working time is

143	clinically significant.	

- 144 Clinical examinations and blood samples
- At baseline (pre-treatment), the participants will be asked to register data for their case history,
 demographics and intercurrent diseases. The participants will follow the procedure shown in Table

147 1.

148	The tender joint count (TJC) and swollen joint count (SJC) assessments include the proximal
149	interphalangeal (PIP) joint and metacarpophalangeal joints of the hands, wrists, elbows, shoulders
150	and knees on both sides. Rest pain and morning stiffness will be scored by the patients according
151	to the visual analogue scale. The above clinical examinations will be assessed once every 3
152	months. Blood samples will be collected once every 3 months by a trained laboratory technician.
153	Routine tests, including a routine blood test, hepatic and renal function, erythrocyte sedimentation
154	rate (ESR), C-reactive protein (CRP), RF, immunoglobulin and complement will be tested once
155	every 3 months. The CCP and anti-keratin antibody (AKA) will be tested once a year.
156	Outcomes
157	The primary outcome variables are DAS28 and HAQ-DI. The formulas for measurement of
158	DSA28 refer to the relevant literature. ⁸
159	The secondary outcome variables are the Simplified Disease Activity Index (SDAI), Clinical
160	Disease Activity Index (CDAI) and Routine Assessment of Patient Index Data (RAPID-3) results,
161	imaging data, including musculoskeletal ultrasound and modified total Sharp score (mTSS),
162	European Quality of Life-5 Dimensions (EQ-5D), Short Form 36 Health Survey Questionnaire
163	(SF-36), WPAI, self-rating anxiety scale (SAS), self-rating depression scale (SDS), health care
164	resource utilization (HCRU), the patient global impression change (PGIC) and personal medical
	8

costs, including the costs of medicine and examinations. The above variables will be recorded at each follow-up. Other secondary outcome variables include changes in patient-reported outcomes (PROs) pre- and post-treatment, such as those related to the SF-36, EQ-5D and WPAI, and correlations between disease severity and PROs, between changes in disease severity and changes in PROs and between changes in disease severity and imaging data, including musculoskeletal ultrasound and mTSS. The exploratory outcome variables are changes in the subjects' satisfaction with the primary treatment throughout the follow-up and the factors influencing the rates of remission and LDA, such as the disease activity index at baseline, treatment medications (e.g., traditional DMARDs or biological agents), haematology indexes (e.g., CCP and RF) and radiographic progression. Statistical analyses All statistics will be calculated independently with Statistical Product and Service Solutions (SPSS) (V.20, SPSS Inc., Chicago, IL, USA). Continuous variables will be described by the mean, standard deviation, minimum, maximum and median. Categorical variables will be described by numbers and percentages. Significant changes in parameters will be estimated by T tests or variance analysis, and significant changes in nonparametric data will be assessed using the Wilcoxon symbol rank test. The data analysis will also include the severity levels, such as moderate and severe, and the quartiles of the disease course will be compared over time with a maximum of two other subgroups. The Cochran-Armitage trend test or other similar tests can also be used to compare different categories of subjects. Multiple regression analysis will be used to obtain mixed-effects models to statistically analyse the factors influencing the rates of remission and LDA, such as the initial disease activity index, the choice of therapeutic drugs (e.g., traditional

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187	DMARDs or biological agents), haematology indexes (e.g., CCP and RF) and radiographic
188	progression. To investigate the effect of duration of treatment target on RA patients, the study will
189	classify RA patients into three groups according to their outcomes. The first outcome category is
190	sustained remission, which includes patients who achieve 4 targets every year. The second
191	category is intermittent remission, which includes patients who achieve 2-3 targets, and the third
192	category is active disease, which includes patients who achieve 0-1 targets. The HAQ-DI of these
193	three groups from baseline to post-treatment will be analysed. Bivariate analysis will be performed
194	between the clinical categories and the HAQ-DI. The odds ratios (ORs) and their 95% confidence
195	intervals (CIs) will be reported. In addition, the regression model will be used to identify the effect
196	of each potential risk factor adjusted for other factors. Variables with $p < 0.05$ in the bivariate
197	analysis will be included in the regression models. The adjusted odds ratios (AORs) and 95% CIs
198	will be reported. All p values are two-tailed. A $p < 0.05$ is considered statistically significant.
198 199	will be reported. All p values are two-tailed. A p <0.05 is considered statistically significant. Patient and public involvement
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199 200 201	Patient and public involvement Neither patients nor the public were involved in the development of the research question, study design, outcome measures, recruitment and conduct of the study or the assessment of the burden
199 200 201 202	Patient and public involvement Neither patients nor the public were involved in the development of the research question, study design, outcome measures, recruitment and conduct of the study or the assessment of the burden of the intervention. We will make an allowance of 200 Chinese Yuan (CNY) at each follow-up for
 199 200 201 202 203 	Patient and public involvement Neither patients nor the public were involved in the development of the research question, study design, outcome measures, recruitment and conduct of the study or the assessment of the burden of the intervention. We will make an allowance of 200 Chinese Yuan (CNY) at each follow-up for transportation costs. The research results will be disseminated to the study participants on the
 199 200 201 202 203 204 	Patient and public involvement Neither patients nor the public were involved in the development of the research question, study design, outcome measures, recruitment and conduct of the study or the assessment of the burden of the intervention. We will make an allowance of 200 Chinese Yuan (CNY) at each follow-up for transportation costs. The research results will be disseminated to the study participants on the subsequent visit.
 199 200 201 202 203 204 205 	Patient and public involvement Neither patients nor the public were involved in the development of the research question, study design, outcome measures, recruitment and conduct of the study or the assessment of the burden of the intervention. We will make an allowance of 200 Chinese Yuan (CNY) at each follow-up for transportation costs. The research results will be disseminated to the study participants on the subsequent visit. DISCUSSION
 199 200 201 202 203 204 205 206 	Patient and public involvement Neither patients nor the public were involved in the development of the research question, study design, outcome measures, recruitment and conduct of the study or the assessment of the burden of the intervention. We will make an allowance of 200 Chinese Yuan (CNY) at each follow-up for transportation costs. The research results will be disseminated to the study participants on the subsequent visit. DISCUSSION This study aims to explore the real-world rates of remission and LDA of early RA patients treated

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209	provide guidance for the treatment of RA patients.
210	In this study, factors influencing the rates of remission and LDA, long-term prognosis and quality
211	of life among patients will be observed. Multiple regression analysis will be adopted to obtain
212	mixed-effects models to analyse these factors, including the initial disease activity index, the
213	medicine selection of traditional DMARDs or biological agents, haematology indexes, such as
214	CCP and RF, and radiographic progression, such as mTSS. HAQ-DI and PROs related to SF-36,
215	EQ-5D and WPAI will be analysed at every follow-up time point to determine trends in patients'
216	disease changes. At the same time, correlations between disease severity and PROs and their
217	changes will be explored, as well as the SDS and SAS.
218	China's society is experiencing rapid aging. Approximately 5 million RA patients have been
219	diagnosed, although China has no more than 8000 rheumatologists. Influenced by traditional
220	culture, most RA patients are inclined to adopt traditional Chinese medicine as their first choice,
221	and these patients have been lulled into thinking that traditional Chinese medicine can cure the
222	disease with few side effects but that DMARDs only relieve symptoms with many side effects.
223	Therefore, this research will benefit RA patients in China by educating them on how to obtain
224	appropriate and timely treatment and how to achieve a good prognosis.
225	This study has some limitations. Both research centres in this study are located in Guangdong
226	Province, China, which may induce poor representativeness of the samples. The non-randomised
227	study design inherits the risks of confounding; therefore, thorough statistical analysis and
228	confounder adjustment are important.
229	ETHICS AND DISSEMINATION
230	This study mainly focuses on the real-world rates of remission and LDA, long-term prognosis and

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231	quality of life of early RA patients treated following the 2015 ACR Guideline for the Treatment of
232	RA. The study is an observational study with no patient interaction. All data will be processed
233	under the rules of the government and law. All researchers will guarantee the anonymity of the
234	patients and will not reveal patient names on forms or reports or in articles unless legally required.
235	Only authorized individuals can access the patients' health information. All researchers handling
236	data must follow specific training to address adverse events. The study has been approved by the
237	Nanfang Hospital Ethics Committee (identification number NFEC-2017-192). The results will be
238	published in international peer-reviewed journals.
239	ACKNOWLEDGEMENTS
240	All authors acknowledge all of the contributors to this study, especially the nurses in the
241	Departments of Rheumatology of Nanfang Hospital and Zhujiang Hospital. We are also grateful
242	for the patients' support and the patients' advisers.
243	CONTRIBUTORS
244	Min Yang and Jinjun Zhao are responsible for all phases from setup to the end of this study,
245	including data collection, analysis and interpretation of the manuscript. Min Yang, Jinjun Zhao
246	and Taihe Zhan participated in the drafting of the protocol and applied for ethics committee
247	approval. Min Yang, Jinjun Zhao, Taihe Zhan and Junqing Zhu participated in revising the
248	manuscript. Min Yang, Jinjun Zhao, Taihe Zhan, Junqing Zhu, Meida Fan, Qin Huang, Hao Ren,
249	Qinghong Yu, Jing Wu, Jingli Lin, Qingqing Ouyang and Shengli An all participated in the study

- design. All authors have checked and approved the protocol to be published.
- FUNDING
- This study was supported by Southern Medical University (grant number [LC2016PY020]).

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4 253	COMPETING INTERESTS
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6 254 7	None.
8 255	ETHICS APPROVAL
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11 256	The study has been approved by the Na
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13 257 14	PROVENANCE AND PEER REVIE
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307	FIGURE LEGENDS
308	Figure 1. 2015 ACR RA Treatment Recommendations
309	The 2015 ACR recommendations for the treatment of early RA, ⁷ which is defined as a disease
310	duration <6 months. $$: consider adding low-dose glucocorticoids ($\leq 10 \text{ mg/day of prednisone or}$
311	equivalent) in patients with moderate or high disease activity when starting disease-modifying
312	anti-rheumatic drugs (DMARDs) and in patients with DMARD failure or biologic failure. †:
313	consider using short-term glucocorticoids (defined as <3 months of treatment) for RA disease
314	flares. Glucocorticoids should be used at the lowest possible dose and for the shortest possible
315	duration to provide the best benefit-risk ratio for patients. #: the treatment target should ideally be
316	low disease activity or remission. For the level of evidence supporting each recommendation, see
317	the related section in the results. ACR: American College of Rheumatology. RA: rheumatoid
318	arthritis. MTX: methotrexate. TNF: tumour necrosis factor.
	arthritis. M1X: methotrexate. 1NF: tumour necrosis factor.

Fable	1 Summary of measure	s to be colle	ected				
	Protocol	Baseline	Month 3	Month 6	Month 9	Every 3 months	Early termination or drop out
	Inclusion or exclusion standard table	\checkmark					
Fill	Sign informed notice	\checkmark					
Fill out by clinicians	Patients' case history and demographic data	\checkmark					
cliniciar	Intercurrent diseases	\checkmark					
SI	DAS28-ESR or DAS28-CRP		\checkmark			\checkmark	\checkmark
	Adverse events					\checkmark	\checkmark
	Pregnancy report	V	\checkmark	\checkmark	\checkmark	\checkmark	
	Clinical routine inspection	V	V	\checkmark	\checkmark	\checkmark	\checkmark
	HAQ-DI	\checkmark	V	\checkmark	\checkmark	\checkmark	\checkmark
	SF-36	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark
	EQ-5D	\checkmark		\checkmark	\checkmark	\checkmark	\checkmark
Filled out by subjects	WPAI	\checkmark	\checkmark	V	\checkmark	\checkmark	\checkmark
	HCRU	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark
	PGIC		\checkmark	V	V	\checkmark	\checkmark
	SAS		\checkmark	\checkmark	\checkmark	\checkmark	\checkmark
	SDS	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark
S	Satisfaction questionnaires	\checkmark	\checkmark	\checkmark	\checkmark	V	\checkmark
	post-treatment						

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Note: DAS, disease activity score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein;

HAQ-DI, Health Assessment Questionnaire Disability Index; SF-36, Short Form 36 Health Survey

Questionnaire; EQ-5D, European Quality of Life-5 Dimensions; WPAI, Work Productivity and

Activity Impairment Questionnaire; HCRU, Health Care Resource Utilization; PGIC, Patient

Global Impression Change; SAS, self-rating anxiety scale; SDS, self-rating depression scale. Figure 1 ACR RA TREATMENT RECOMMENDATIONS

Green box for strong recommendations

Algorithm pathway for most patients

Yellow box for conditional recommendations

Figure 1. 2015 ACR RA Treatment Recommendations

The 2015 ACR recommendations for the treatment of early RA,7 which is defined as a disease duration <6

months. ~: consider adding low-dose glucocorticoids (<10 mg/day of prednisone or equivalent) in patients with moderate or high disease activity when starting disease-modifying anti-rheumatic drugs (DMARDs) and

in patients with DMARD failure or biologic failure. +: consider using short-term glucocorticoids (defined as

<3 months of treatment) for RA disease flares. Glucocorticoids should be used at the lowest possible dose

and for the shortest possible duration to provide the best benefit-risk ratio for patients. #: the treatment

target should ideally be low disease activity or remission. For the level of evidence supporting each

recommendation, see the related section in the results. ACR: American College of Rheumatology. RA:

rheumatoid arthritis. MTX: methotrexate. TNF: tumour necrosis factor.

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Disease activity

Treatment options or strategy

Disease state or prior treatment state

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STROBE Statement-checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1	Title: a multicentre prospective
				observational study
		(b) Provide in the abstract an informative and balanced summary of what was done and what was	2	This study will focus on the real-world
		found		rates of remission and low disease activit
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found		(LDA) of early RA patients in China, wh
				will be treated according to the 2015 AC
				Guideline. Additionally, factors
				influencing treat-to-target outcomes will
				be analysed, and long-term prognosis and
				quality of life will be assessed. Two
				hundred early RA patients will be enrolle
				treated and followed up once every 3
				months for 48 months. Those patients
				should fulfil the 2010 RA classification
				criteria of the American College of
				Rheumatology/European League Agains
				Rheumatism (ACR/EULAR), with a
				disease course of no more than 6 months
				and fulfil other eligibility criteria. The
				patients will be treated following the 201
				ACR Guideline. Their disease activity w
				be assessed, and they will be instructed t
				complete several questionnaires once
				every 3 months. The primary outcomes a

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				DAS28 and HAQ-DI. The secondary outcome variables are SDAI, CDAI and RAPID-3 results, imaging data and personal medical costs. The data will be analysed using appropriate statistical analyses.
Introduction Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5	lines 56-98 of the manuscript.
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6	To investigate the real-world rates of remission and LDA of early RA patients treated following the 2015 ACR Guideline for the Treatment of RA, the long-term prognosis and quality of life and the factors influencing the rates of remission and LDA.
Methods				
Study design	4	Present key elements of study design early in the paper	6	lines 105-110 of the manuscript.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8	This multicentre prospective observational study will be conducted in full compliance with the articles of the Declaration of Helsinki. It will be conducted in Nanfang Hospital and Zhujiang Hospital of Southern Medical University and will recruit 200 early RA patients treated according to the 2015 ACR Guideline. The participants will be followed up once every 3 months for 48 months to assess their disease activity and to survey their health- related quality of life and their work efficiency.
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gence Bibliographidu		8789 on 15 November 2018. Downloaded from http://bmjopen.bmj.com/ on June 13, 2029 Enseignement Superieur (BBES) מַפּוּוְמָּוְסָמַרָּאַרָאַפּאַבּאַבּאַבּאַלאַרָאַרָאָנאַג פּאַדָאַרָאָשָרָאָשָ אָדָאָזאָאַזאַ אַדאָאָדאָראָדאָ		

Participants	6	(<i>a</i>) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7	The participants must meet the following criteria:
		Case-control study—Give the eligibility criteria, and the sources and methods of case		$1. \geq 18$ years of age,
		ascertainment and control selection. Give the rationale for the choice of cases and controls		2. fulfil the ACR/EULAR 2010
		participants		3. disease course of less than 6 months,
				4. demonstrate complete understanding o
				the survey and have the ability to complet
				the questionnaires independently and
				5. willingness to enrol in the study and
				sign the consent form allowing the
				researchers to use their personal health
				information.
		Cross-sectional study—Crove the englishinty criteria, and the sources and methods of selection of participants		Exclusion criteria: Patients who meet one
				of the following conditions at baseline will
				be excluded:
				1. pregnant or lactating women or women
				who plan to become pregnant within the
				next 2 years,
				2. enrolment in another RA clinical study
				in the last 24 weeks and
				3. inability to report quality of life or
				medical resources.
				Drop-out criteria: Participants can drop ou
				of the study at any time. Participants will
				be removed from the study if they meet
				one of the following conditions:
				1. the researchers believe that study
				removal will benefit the patient and
				2. the participants refuse to answer the
				questionnaires or do not follow the follow
				up time schedule included in the research
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				protocol.
		 (b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case 	N/A	N/A
/ariables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8,9	Paragraph under section heading, Outcomes .
Data sources/ neasurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9	Paragraph under section heading, Clinical examinations and blood samples and Outcomes.
Bias	9	Describe any efforts to address potential sources of bias	6,11	All analyses will be conducted by a statistician, according to the prespecified statistical analysis plan. statistical analysis and confounder adjustment are taken. All researchers handling data must follow specific training to address adverse events
Study size	10	Explain how the study size was arrived at	7,8	Paragraph under section heading, Sample size calculation
Continued on next page				
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Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8,9,10	Paragraphs in the Sample size calculation and statistical analyse
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9,10	Paragraphs in the Statistical analyses
		(b) Describe any methods used to examine subgroups and interactions	9,10	Paragraphs in the Statistical analyses
		(c) Explain how missing data were addressed	None	The patients missing data will not be included in the analysis
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed	None	The patients missing data will not
		Case-control study-If applicable, explain how matching of cases and controls was addressed		be included in the analysis
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy		
		(<u>e</u>) Describe any sensitivity analyses	9,10	Paragraphs in the Statistical analyses
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined	N/A	N/A
		for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed		
		(b) Give reasons for non-participation at each stage	N/A	N/A
		(c) Consider use of a flow diagram	N/A	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A	N/A
		(b) Indicate number of participants with missing data for each variable of interest	N/A	N/A
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	N/A	N/A
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	N/A	N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A	N/A
		Cross-sectional study-Report numbers of outcome events or summary measures	N/A	N/A
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision	N/A	N/A
		(eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were		
		included		
		(b) Report category boundaries when continuous variables were categorized	N/A	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time	N/A	N/A
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period			
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Discussion Key results				
Key results				
	18	Summarise key results with reference to study objectives	10	the real-world rates of remission and LDA of early RA patients
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11	This study has some limitations. Both research centres in this study
		both direction and magnitude of any potential blas		are located in Guangdong Province
				China, which may induce poor
				representativeness of the samples.
				The non-randomised study design
				inherits the risks of confounding; therefore, thorough statistical
				analysis and confounder adjustmer
				are important
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of	10,11	DISCUSSION (paragraphs 1,2,4).
		analyses, results from similar studies, and other relevant evidence		
Generalisability	21	Discuss the generalisability (external validity) of the study results	11	DISCUSSION (paragraph 3).
Other informat	ion			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the	12	Provided. Southern Medical
		original study on which the present article is based		University
		0		· · · ·
Note: An Explan checklist is best	nation used i	arately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups and Elaboration article discusses each checklist item and gives methodological background and published n conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmed /, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at w	l examples of t licine.org/, An	cross-sectional studies. ransparent reporting. The STROBE nals of Internal Medicine at
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