

# BMJ Open Early intervention with tiotropium in Chinese patients with GOLD stages I–II chronic obstructive pulmonary disease (Tie-COPD): study protocol for a multicentre, double-blinded, randomised, controlled trial

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## ABSTRACT

**Introduction:** Owing to the high and increasing morbidity and mortality, chronic obstructive pulmonary disease (COPD) has become a major public health problem worldwide. Although the majority of patients with COPD are in the early stages, little attention has been paid to them, in particular regarding to early intervention. Tiotropium bromide can significantly relieve symptoms and reduce the incidence of acute exacerbations of COPD. Therefore, we hypothesise that therapy with tiotropium bromide will benefit patients with COPD with early-stage disease.

**Method/analysis:** A randomised, double-blinded, placebo-controlled, parallel-group, multicentre clinical trial (Tiotropium In Early COPD study, Tie-COPD study) is being conducted to evaluate the efficacy and safety of long-term intervention with tiotropium in patients with COPD with early-stage disease. A total of 839 patients with COPD who satisfied the eligibility criteria were randomly assigned (1:1) to receive a once daily inhaled capsule of either tiotropium bromide (18 µg) or matching placebo for 2 years. Measurements will include forced expiratory volume in 1 s, health-related quality of life, grade degree of breathlessness related to activities, COPD exacerbations and pharmaco-economic analysis.

**Ethics/dissemination:** This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University. Recruitment started in November 2011 and ended in October 2013, with 839 patients randomised. The treatment follow-up of participants with Tie-COPD is currently ongoing and is due to finish in November 2015. The authors will disseminate the findings in peer-reviewed publications, conferences and seminar presentations.

**Trial registration:** ClinicalTrials.gov (NCT01455129).

## Strengths and limitations of this study

- A large sample of patients in early stages of the disease who are asymptomatic have been included in the randomised, double-blinded, placebo-controlled, parallel-group, multicentre clinical trial.
- Compliance of participants may challenge the success of the project.
- The results of the trial may shed new light on the long-term intervention of long-acting bronchodilators in patients with early-stage COPD.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the most common respiratory diseases. Using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) standard, the prevalence of COPD may be as high as 4–10% worldwide in adults 40 years and older.<sup>1</sup> Worldwide, there has been increasing morbidity and mortality associated with COPD over the past few decades, and COPD is predicted to rise from the sixth leading cause of death in 1990 to the third in 2020 and to rank as the fifth largest economic burden among diseases in 2020.<sup>2</sup>

Better medications and more aggressive intervention strategies have been used to manage COPD, but patients at later stages of the disease have shown poor responses to such treatments, associated with high mortality, incidence of rehospitalisation and disability, which causes a burden both for the families of patients and society.<sup>3 4</sup> Currently, data show that the annual rate of decline in forced expiratory volume in 1 s (FEV<sub>1</sub>) in patients with COPD with GOLD stages I–II is more

rapid than those with GOLD stages III–IV.<sup>5–7</sup> The DIMCA study showed that early intervention with fluticasone in participants with objective signs of obstructive airway disease resulted in significant health gains at relatively low financial cost.<sup>8</sup> Therefore, we hypothesise that there may be more beneficial effects if the patients receive routine treatment at an earlier stage of the disease.

Tiotropium bromide is the first once daily long-acting anticholinergic bronchodilator with selective action against M<sub>3</sub> receptors on bronchial smooth muscle cells.<sup>9</sup> It has a good safety profile and most of its undesirable effects can be assigned to its anticholinergic properties.<sup>10</sup> Previous studies indicate that tiotropium significantly relieves air flow restrictions in patients with COPD and results in improvements in spirometry, dyspnoea, exercise tolerance and health-related quality of life.<sup>6–7</sup> Subgroup analyses of UPLIFT indicate that tiotropium was able to reduce the annual decline in FEV<sub>1</sub> among patients with GOLD stage II and patients who had not received any maintenance medication for COPD before enrolling in UPLIFT.<sup>7–11</sup>

Therefore, it would be of great significance for COPD treatment if we could demonstrate that tiotropium improves lung function, decreases lung function decline and reverses disease progression in patients with early-stage COPD after long-term intervention with maintenance treatment. However, there is no large-scale clinical trial on long-term intervention with tiotropium bromide in patients with early-stage COPD (ie, GOLD stages I–II COPD).

On this basis, we designed a trial entitled ‘Tiotropium in Early Chronic Obstructive Pulmonary Disease Patients in China (Tie-COPD)’. It is a 2-year randomised, double-blinded, placebo controlled, parallel, multicentre clinical trial in China to study early intervention with tiotropium.

## METHODS AND ANALYSIS

### Study design

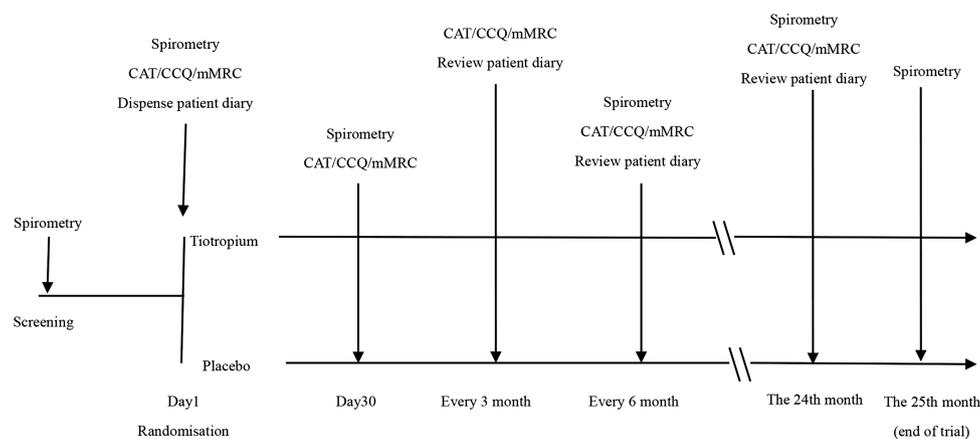
This is a 2-year, multicentre, double-blinded, randomised controlled trial of maintenance treatment with once daily tiotropium for patients with early-stage COPD. Screening

(visit 0) was undertaken within 7 days before randomisation (visit 1) to assess eligibility and collect baseline data. Patients who satisfied the eligibility criteria were randomly assigned (1:1) to receive tiotropium bromide (18 µg once daily inhaled) or placebo. Patients have an appointment 1 month after randomisation (visit 2), at 3 months (visit 3) and then every 3 months until study drug termination (2 years). After that, a 1-month follow-up period is scheduled. The data collected at each visit will include a patient diary, a symptom score assessment (modified British Medical Research Council (mMRC)), an assessment of quality of life (COPD assessment test (CAT) and COPD clinical questionnaire (CCQ)), results of a physical examination, documentation of adverse events, a record of medication administration, exacerbation, smoking status, documentation of medical expenses and so on. Self-reported smoking status is recorded at each visit too. Pulmonary function tests will be conducted at the first monthly visit and then every 6 months thereafter. [Figure 1](#) is a trial procedures flow chart.

The primary objective of this trial was to determine the efficacy of treatment using a once daily tiotropium inhalation capsule via a HandiHaler device on trough FEV<sub>1</sub> after 2 years of maintenance treatment. Hence, the primary endpoint will be difference of trough FEV<sub>1</sub> at 24 months from baseline. Secondary endpoints will include differences in peak FEV<sub>1</sub> at 24 months; trough and peak FEV<sub>1</sub> at 1, 6, 12 and 18 months; yearly rate of decline in FEV<sub>1</sub>, forced vital capacity (FVC) and FEV<sub>1</sub>/FVC (including trough and peak) from 1 month until completion of the double-blinded treatment; quality of life; symptom scores; frequency, interval, duration and severity of COPD exacerbations; time to first COPD exacerbation; administration of rescue medication and a cost-effectiveness analysis.

### Recruitment

A total of 839 patients with COPD at GOLD stages I and II have been enrolled. The majority of them are



**Figure 1** Clinical trial design. CAT, COPD assessment test; CCQ, COPD clinical questionnaire; COPD, chronic obstructive pulmonary disease; mMRC, modified British Medical Research Council, Patient diary covers daily used investigational drugs, medication prescribed for COPD exacerbations, contacting health care providers, duration of illness and lost working days.

symptom-free or have very slight symptoms. Most of them were recruited from the community through a population survey for COPD. Before recruitment, active smokers were advised to discontinue smoking and were offered a smoking cessation programme as counselling sessions, patient education and supportive literature in the survey. After the survey, usually 2–3 months, patients with COPD at GOLD stages I and II were recruited, informed about the study and the benefit of smoking cessation again. After obtaining written informed consent, screening (visit 0) was undertaken.

The inclusion criteria include a clinical diagnosis of COPD, presence or absence of respiratory symptoms, age between 40 and 85 years, with or without smoking history, a maximal postbronchodilator  $FEV_1/FVC < 70\%$  and  $FEV_1 \geq 50\%$  predicted and the ability to participate in study-related auxiliary examinations.

Patients will be excluded if they have had a respiratory infection or an exacerbation in the 4 weeks prior to screening, frequent use of glucocorticosteroids orally or intravenously (prednisone  $> 10$  mg/day). Patients with a history of asthma, allergic rhinitis, active pulmonary tuberculosis and pneumonectomy or those who have a blood eosinophil count  $\geq 600/mm^3$  will also be excluded. The presence or absence of reversibility to a bronchodilator will not be an exclusion criterion.

### Randomisation and blinding

The investigational drug tiotropium bromide capsule (Spiriva) is manufactured and packaged by Boehringer Ingelheim. The department of labelling and packaging will execute the allocation concealment according to a blind code provided by the statistical participants while the investigators enter the patients and allocate the number in increasing order. The block randomisation method will be applied in this trial and the blind code will be generated by a statistician from Rundo International Pharmaceuticals Research & Development Co, Ltd. with SAS V.9.2.2. According to the blind code provided by the statistician, the allocation concealment will be completed at the labelling place. Emergency envelopes for accidents will be prepared for emergency unblinding and will be retained by investigational sites.

### Concomitant medication and treatment

Because the majority of participants enrolled are symptom-free or have very slight symptoms, in principle, the long-term concomitant application of bronchodilators and other COPD medications with the exception of the drugs under investigation should be avoided during the screening phase and the treatment phase of the study. Long-term concomitant medication except for the investigational drugs could be allowed as prescribed if it is clinically necessary or if it has been initiated before the recruitment of the patient in question. For COPD exacerbations, an ipratropium bromide metered-dose inhaler could be applied if needed, or medical intervention could be applied according to the GOLD guideline

for no longer than 2 weeks (see online supplementary table S1; concomitant medication and treatment).

### Measures

Regular follow-ups with physical examination and symptom score documentation will be conducted after the first month and then once every 3 months thereafter. Any abnormal observation will be recorded in the case report form. Self-reported smoking status is also recorded at each visit. A patient diary will be dispensed at every visit and retrieved at the next visit. The diary should be reviewed by the investigator together with the patient. In case any adverse event or exacerbation is defined by the investigator, relevant documentation should be made in the case report form. The patient diary should cover daily used investigational drugs, medication prescribed for COPD exacerbation (rescue drugs, antitussives, expectorants, inhaled corticosteroids (ICS) and antibiotics), contacting healthcare providers, duration of illness and lost working days (see online supplementary table S2; flow chart).

### Spirometry

Pulmonary function testing will be conducted at the flow-up visit in the first month and then every 6 months. It will be started at approximately the same time ( $\pm 2$  h) on all testing days and will be performed using standardised spirometers, equipment and techniques that conform to the American Thoracic Society (ATS) and European Respiratory Society (ERS) criteria.<sup>12</sup> Pulmonary function testing will not be conducted within 6 h after the use of any short-acting bronchodilators. Spirometry is performed prebronchodilator and post-bronchodilator. Salbutamol 400  $\mu$ g will be inhaled 20 min prior to conducting reversibility testing. Pulmonary function parameters will include  $FEV_1$ , FVC and  $FEV_1/FVC$ . Manoeuvres are performed in triplicate, although up to five forced expiratory manoeuvres are obtained in an effort to achieve three acceptable efforts. The highest acceptable  $FEV_1$  and the highest FVC each obtained on any of three blows meeting the ATS/ERS criteria constitute the data for that test set.<sup>12</sup>

### Exacerbations of COPD

Information on exacerbations of COPD will be recorded in the patient diary and collected at all visits. A COPD exacerbation is defined as the onset or worsening of at least two of the following symptoms: cough, sputum production, purulent sputum, wheezing and dyspnoea lasting for at least 48 h.<sup>13</sup> The duration of a COPD exacerbation is defined as the number of days from the emergence of the exacerbation event to the termination of treatment for that event. The duration of hospitalisation is defined as the days from admission to discharge from the hospital. The interval between COPD exacerbations is defined as the days between the previous exacerbation event and the next event.

Severity of COPD exacerbations are categorised as mild, moderate and severe according to the following definitions: mild: adding other commonly used COPD medications at home without making outpatient hospital visits or being hospitalised; moderate: resulting in outpatient visits or emergency room visits and modification of a regimen which may include the use of antibiotics and/or systemic glucocorticosteroids; and severe: resulting in hospitalisation.<sup>14</sup>

### Quality of life

Quality of life will be assessed at all visits by patients at outpatient visits with designated patient record questionnaires, the CAT and the CCQ. The mMRC will be observed and recorded at every visit to evaluate the symptom of dyspnoea.

### Quality control

The principal investigator at each site is responsible for the inspection of the compliance to the protocol in terms of study conduction and accurate and timely data documentation in the CRF by investigators. The investigator/institution will permit trial-related monitoring, auditing, IRB/IEC review and regulatory inspection and will be providing relevant inspectors with direct access to all related source data/documents. The principal investigator should ensure that adequate training and updated information or notifications have been delivered to study-relevant personnel, including physicians and nurses. Data from the study will be documented in CRFs at the termination of the study and then entered into the database with blinded design for data checking and reviewing. All of the documents relevant to patient information should be kept in the database and kept confidential according to the relevant laws and regulations. The quantity of the retrieved investigational drug (capsules) should be recorded in the case report form. Administration of 80–120% of the predicted use of the investigational drug will be considered to be good compliance.

### Statistical methods

The sample size has been calculated with regard to the primary endpoint. Patients with mild-to-moderate COPD (GOLD stages I–II) will form the relevant patient group for this study. From the UPLIFT mega trial, it is known that patients with COPD with GOLD stage II had an estimated difference of 100 mL in trough FEV<sub>1</sub> after 2 years (SD 350 mL) between the tiotropium and control group.<sup>6</sup> Assuming a significance level of 5% and a power of 90% to detect a difference in trough FEV<sub>1</sub>, approximately 260 patients per treatment group will be required. Assuming a 35% patient dropout rate of patients, then 400 patients will need to be randomised to each group.<sup>15</sup> Therefore, the overall sample size required for the study is 800 patients.

Only the primary endpoint will be tested in a confirmatory way. All secondary endpoint analyses will be exploratory and the results will have to be interpreted in a

descriptive manner. The difference between the two treatment groups in trough FEV<sub>1</sub> and peak FEV<sub>1</sub> at 1, 6, 12 and 18 months will be compared using an analysis of variance with repeated measurements. The comparison of annual decline rates in FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC between groups will be analysed using a random coefficient regression model based on the presumption that efficacy changes linearly with time. The annual rate of decline will be expressed using the regression coefficient of the model. The mMRC data will be described and compared by transfer form both before and after treatment. Repeated measures analysis of variance will be used in the CCQ and CAT data assessment. The time to first COPD exacerbation will be assessed by comparison of curves from different treatment groups via Log rank test. Group description will be applied in the assessment of interval, duration and severity of COPD exacerbations. The application of rescue medication will be analysed with Fisher's exact test, while further describing the relief-related information such as frequency of drug use. The number of acute exacerbations and severe acute exacerbations will be compared between the two groups with the use of Poisson regression with correction for treatment exposure and overdispersion. Time and cost of hospitalisation due to COPD will be described by grouping, and the Wilcoxon rank-sum test will be applied for intergroup comparison when necessary. The analysis plan will be specified in detail in a separately prepared Statistical Analysis Plan (SAP) prior to database lock.

### Ethics and dissemination

Recruitment into the Tie-COPD trial started in November 2011 and ended in October 2013, with 839 patients (104% of target enrolment) randomised, one-third of whom are patients with GOLD stage I. The treatment follow-up of tiotropium is currently ongoing and the last trial visit of the last participants is due to take place in November 2015. The study findings will be presented at conferences and will be reported in peer-reviewed journals.

### DISCUSSION

Until now, there is little available evidence on the impact of medication intervention on the prognosis and relief of lung function decline. This study will be the first large-scale long-term intervention in patients with early COPD, in particular the symptom-free patients with COPD, aimed at exploring an efficient and safe approach to attenuate or even reverse the progression of COPD.

Currently, there is no precise definition of early-stage COPD. Previous studies have included patients with stage 0 COPD, categorising them as those who need earlier medical intervention. However, this strategy has not as yet been supported by concrete evidence. It has been recognised that GOLD stage 0 is not equivalent to early-stage COPD.<sup>16 17</sup> Based on currently available clinical evidence, we define the early-stage COPD as GOLD stages I–II.

As reported in China, the proportion of patients with GOLD stages I and II (mild and moderate) COPD is

70.7% of the patient population and most of them are undertreated.<sup>4</sup> Although most of these patients, especially those with stage I, have few symptoms and nearly normal spirometry (ie, a relatively preserved FEV<sub>1</sub>), it has been found that active small-airway inflammation and significant V<sub>A</sub>/Q abnormalities existed in these patients.<sup>18–20</sup> It has also been confirmed that patients with COPD with GOLD stage I have a remarkable loss of small conducting airways when compared with healthy controls, which may increase peripheral airways resistance.<sup>21</sup> Furthermore, the rate of decline in FEV<sub>1</sub> is more greatly accelerated in the early stages (stages I–II) of COPD than the more severe stages (stages III–IV), which has been validated in the TORCH and the UPLIFT studies.<sup>6 22</sup> That is to say that patients with the lowest FEV<sub>1</sub> had the lowest rate of decline, and vice versa. The research of Scanlon showed a similar result.<sup>23</sup> Therefore, if the decline in FEV<sub>1</sub> is faster in the early-stage disease, then early intervention may be necessary and reasonable in the prevention of progressive pulmonary function decline.

Traditionally, smoking cessation was thought to be the only therapy that could influence mortality and the progression of the disease by reducing the rate of decline of FEV<sub>1</sub>.<sup>24 25</sup> As pharmacotherapy for COPD has developed in the last decade, outcomes of patients with COPD have improved substantially with the availability of long-acting agonists (LABAs), fixed-dose combinations of ICS and LABAs, and long-acting muscarinic antagonists. The traditional concept on the basis of ICS research that pharmacotherapy does not affect the progression of COPD<sup>5 26–28</sup> had been challenged by observations from some large clinical trials. As exacerbations are considered to influence the decline in FEV<sub>1</sub>,<sup>29 30</sup> some large-scale studies such as TORCH and UPLIFT strongly supported the contention that these pharmaceuticals could affect the progression of COPD by reducing the exacerbation rate. Reduction of the annual rate of decline in FEV<sub>1</sub> was discovered in a post hoc analysis of the TORCH study.<sup>30</sup> The annual rate of decline of FEV<sub>1</sub> in the three groups, LABAs, ICS and the fixed combination of these drugs, decreased by 13, 13 and 16 mL, respectively, when compared with controls.<sup>30</sup> In the UPLIFT study, treatment with tiotropium also hinted at how to slow the decline rate of FEV<sub>1</sub> in patients who did not take concomitant medication.<sup>6 11</sup>

Although the TORCH and UPLIFT studies focused on more severe patients with COPD, because of the relatively large numbers of patients with GOLD stage II, they had sufficient power to allow subgroup analysis that supported the efficacy of early intervention. In the TORCH study, it was discovered that the improvement in postbronchodilator FEV<sub>1</sub>, reduction in the annual rate of decline of FEV<sub>1</sub> and exacerbation rate of patients with GOLD stage II treated with the fixed combination product were slightly but significantly higher than in the case of patients in severe stages of disease.<sup>31</sup> Some subgroup analyses from the UPLIFT study also support these concepts. One analysis by Decramer *et al*<sup>7</sup> showed that in patients with

GOLD stage II, tiotropium not only increased prebronchodilator (100–118 mL) and postbronchodilator FEV<sub>1</sub> (52–81 mL), but also reduced the rate of decline in FEV<sub>1</sub> compared with controls. Another analysis of the UPLIFT study also suggested that in patients who had not taken any maintenance medication before, treatment with tiotropium not only increased prebronchodilator and postbronchodilator FEV<sub>1</sub> and improved the health-related quality of life, but also reduced the rate of decline of FEV<sub>1</sub> and that approximately 60% of the patients in that subgroup analysis were patients with GOLD stage II disease.<sup>11</sup> A prospective study showing that treatment with 18 µg of tiotropium once daily for 12 weeks improved FEV<sub>1</sub> and FVC in patients with mild-to-moderate COPD, when compared with placebo, also supported the concept.<sup>32</sup> This evidence implies that treatment with tiotropium may slow the progression of COPD in its early stages. Tiotropium is most likely beneficial to patients with COPD in early stages, as well as to those with disease in the more severe stages.

However, most of these encouraging data have come from subgroup analyses of large long-term studies, and the outcomes of the subgroup analysis were not the primary outcomes in these studies. Furthermore, most of the patients in the aforementioned studies were symptomatic patients. As many patients with COPD in early stages are asymptomatic, they could not be representative of the average patients with early-stage disease encountered in general practice. And for long-term treatment of early-stage COPD, the cost effectiveness of treatment is also an important issue, which was not addressed in these studies. Therefore, further longitudinal studies are required to confirm the clinical relevance of these discoveries.

The Tie-COPD study has been designed for this reason. In long-term clinical trials, the most critical methodological challenge is to determine the primary outcome variable. Although there are many disadvantages to using FEV<sub>1</sub>, as it is non-invasive, repeatable and accessible, it has been chosen as the primary outcome variable in the Tie-COPD trial. Premature patient withdrawals must also be considered in trial design and analysis. The discontinuation rate generally increases with the study duration in long-term trials. Discontinuations are usually higher in the placebo group. The placebo group discontinuation rate in ISOLDE, EUROSCOP and UPLIFT ranged from 30% to 53%.<sup>6 26 27</sup> As with the protocol of UPLIFT, we have estimated a 35% discontinuation rate in our study to ensure that it will be adequately powered to enable evaluation of the primary outcome.<sup>15</sup> In order to reduce the dropout rate, we will conduct scheduled health education for patients, including smoking cessation, benefit of early intervention and health consultation, etc. Meanwhile, we will establish a good relationship with the participants, and supervise them through unscheduled telephone follow-up.

The majority of participants enrolled are symptom-free or have very slight symptoms, and the mere

presence of respiratory symptoms or a gradually reduced lung function is insufficient reason for patients to seek medical help.<sup>33</sup> So most of the patients came from population screening for COPD in the community. In the population survey, we had suggested to active smokers to discontinue smoking and offered them a smoking cessation programme. After the survey, patients who satisfied the eligibility criteria were recruited. They will be advised to quit smoking at each visit. However, in order to avoid the confounding effects of smoking cessation, we will not provide special smoking cessation intervention. According to Hurst *et al*,<sup>34</sup> up to 22% of patients in GOLD stage II can be considered frequent exacerbations. So there were still some moderate patients with COPD with a history of exacerbations from hospital enrolled in the study. They may not at present be identified for interventions to reduce exacerbations and may get more benefit from the intervention.

In summary, the Tie-COPD trial will provide an opportunity to explore the effect of once daily inhaled tiotropium in patients with COPD in early-stage disease. The data gathered may not only shed new light on the long-term intervention with long-acting bronchodilators such as tiotropium in early-stage patients with COPD, but may also provide a basis for early detection of patients with COPD. At present, recruitment of patients has been completed. Results are anticipated in 2016.

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**Contributors** NZ, PR and YZ conceived the original idea for the study. JZ, XL and SC participated in the design and supervision of the study. XL wrote the first draft of the manuscript and the final content was developed in collaboration with all authors. All authors saw and approved the final version of the manuscript.

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**Competing interests** None.

**Ethics approval** The study was approved by the medical ethical committee of Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University.

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