

# BMJ Open New warfarin anticoagulation management model after heart valve surgery: rationale and design of a prospective, multicentre, randomised trial to compare an internet-based warfarin anticoagulation management model with the traditional warfarin management model

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## ABSTRACT

**Introduction** Warfarin is an effective anticoagulant and the only oral anticoagulant available for patients with mechanical heart valves. The prothrombin time and the associated international normalised ratio (INR) are routinely tested to monitor the response to anticoagulation therapy in patients. Patients who undergo mechanical heart valve replacement need lifelong anticoagulation therapy, and their INR is regularly measured to adjust the anticoagulation strength and the dose of anticoagulation drugs. Appropriate warfarin anticoagulation management can reduce patient complications, such as bleeding and thrombosis, and improve the long-term survival rate. We propose modern internet technology as a platform to build a warfarin anticoagulation follow-up system after valve replacement surgery. This system will provide doctors and patients with more standardised and safer follow-up methods as well as a method to further reduce the risk of warfarin anticoagulation-related complications and improve its therapeutic effects.

**Methods and analysis** A prospective, multicentre, randomised, controlled trial will be conducted. A total of 700 patients who require long-term warfarin anticoagulation monitoring after heart valve replacement will be enrolled and randomly divided at a 1:1 ratio into a traditional outpatient anticoagulation management group and a group undergoing a new method of management based on the internet technology with follow-up for 1 year. Differences in the percentage of time in the therapeutic range (TTR), drug dose adjustments, bleeding/thrombosis and other related complications will be observed. The primary endpoint is the difference in the TTR between the two groups. The purpose of this study is to explore a safer and more effective mode of doctor–patient interaction and

## Strengths and limitations of this study

- This is a prospective, multicentre, randomised, controlled trial with tools, including a regular seminar regarding the annual progress reported by sub-centres, monthly reports on the number of enrolled patients, and researcher training sessions and recognition, for improving the quality of the project.
- The scientific committee, which includes experienced clinical trial experts and cardiologists from China, will help to ensure that a scientific and rational study design is used and will oversee randomisation, data collection, quality control and data analysis. Peking University Clinical Research Institute has created a data monitoring committee to evaluate and supervise data quality.
- Experience from this programme will help to increase the number of dose adjustments for patients and reduce the bleeding/thrombosis rates after surgery.
- Only five tertiary hospitals were recruited for participation in the study, and thus, the results may not be representative of anticoagulation treatment in China overall.
- The patient's age, education level and disease severity may affect their compliance, which also affects the occurrence of complications and the quality of anticoagulation after surgery.

communication in the internet era. As of 13 July 2019, 534 patients had been enrolled.

**Ethics and dissemination** This study protocol was approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University. The results will be published in a peer-reviewed medical journal.

## INTRODUCTION

Follow-up is an important part of clinical work.<sup>1-3</sup> In China, medical care tends to focus on acute care activities, that is, inpatient treatment, but patient follow-up is often missed, especially in areas with poor healthcare. However, the efficacy of treatment is highly dependent on recovery after hospital discharge.<sup>4</sup> Compared with the developed eastern region, the central and western regions in this country are underdeveloped. Whereas the eastern region has adequate healthcare resources, the central and western regions lack high-quality healthcare resources.<sup>5-7</sup> This apparent inequality based on the geographical distribution of healthcare resources in China has also influenced the management of patients after discharge.<sup>8,9</sup> Moreover, the implementation of electronic medical record (EMR) systems in China has witnessed rapid growth.<sup>10</sup> Although the vast majority of Chinese hospitals have implemented EMR systems, each hospital chooses its own EMR system provider. Thus, patient information cannot be shared across different centres or different inpatient and outpatient physicians.<sup>11-14</sup>

After mechanical heart valve replacement surgery, patients must undergo warfarin anticoagulation therapy for a long period of time.<sup>15,16</sup> In the traditional anticoagulation management model, patients must visit large tertiary hospitals for blood analysis. After reviewing the laboratory results, the outpatient cardiologist decides whether to adjust the warfarin dosage until the next time the patient visits.<sup>17,18</sup> In Chinese tertiary hospitals, the prothrombin time (PT) blood draw is certified by the National Center for Clinical Laboratories External Quality Assessment Programs in Laboratory Medicine. Therefore, PT test indicators are reliable across different tertiary hospitals. Compared with warfarin, the use of direct oral anticoagulants in patients with mechanical heart valves is associated with increased incidences of thromboembolism and bleeding complications.<sup>19,20</sup> The PT and the associated international normalised ratio (INR) are routinely tested to monitor the response to anticoagulation therapy in patients. Although achieving a stable INR is critical, it can be challenging.<sup>21</sup> Warfarin is characterised by a narrow therapeutic range and large interpatient variability, and close monitoring of the intensity of anticoagulation with warfarin can reduce patient complications, such as bleeding and thrombosis, and improve their long-term survival rate.<sup>22-25</sup> In clinical practice, patients often pay insufficient attention to warfarin anticoagulation and do not undergo laboratory testing at the hospital in a timely manner. Moreover, many local hospitals have insufficient experience in adjusting the warfarin dosage based on the INR test results, and thus, many patients suffer from severe postoperative complications, such as cerebral haemorrhage or thrombosis. Furthermore, irregular drug dosage adjustments and an undesirable anticoagulant detection frequency

worsen the patient's condition.<sup>26-31</sup> In addition, along with increases in the number of patients under anticoagulation therapy, the workload of doctors in large hospitals has also increased dramatically. Therefore, the existing traditional anticoagulation monitoring model is becoming difficult to manage.

Anticoagulation management services are now available as online services, based on short message service, telephone, WeChat (a social software widely used in China) and other communication platforms.<sup>32-37</sup> Foreign studies have shown the efficacy of telemedicine for the management of warfarin use after heart valve surgery.<sup>38-41</sup> Currently, in China, a few hospitals have started to use this method in clinical practice, but it has not become a large-scale practice, as there are still many deficiencies and gaps in anticoagulation management models that rely on the internet technology. In developed countries, most hospitals treat patients from nearby regions, which is convenient for follow-up and management. In contrast, large cardiovascular hospitals in China treat patients from all over the country. Therefore, the demand for telemedicine in developed countries is not as large as that in China, and little research has been reported in this area.

## Study objectives

For patients receiving warfarin anticoagulation treatment after heart valve replacement, we will evaluate the safety and efficacy of a new anticoagulation management model based on the internet technology compared with the traditional outpatient anticoagulation management model.

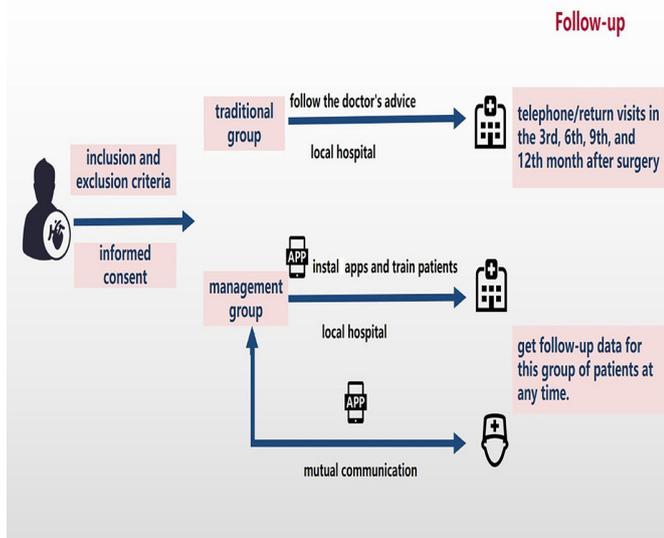
A new warfarin anticoagulation management model based on wired and wireless network communication was established for use after thoracic and cardiovascular valve surgery with modern communication technology. It includes a computer network, data storage technology, e-commerce operation, a management model as vehicle, clinical medical diagnosis and treatment knowledge. This model provides an open, flexible and highly efficient communication platform for attending physicians, scientific researchers and discharged patients. Through standardised follow-up behaviours and styles, we will strengthen postoperative warfarin anticoagulation monitoring and health education, improve the service concept, focus on patients, serve clinical research and provide technical support for the ultimate goal of improving overall medical service and academic research standards.

It is expected that the new warfarin management model will further improve the patient's time in the therapeutic range (TTR), increase the frequency of warfarin anticoagulation monitoring, and reduce both bleeding/thrombosis and mortality.

## METHODS

### Trial design

This is a prospective, multicentre, randomised, open-label, controlled trial. The patient flow chart is shown in [figure 1](#). A total of 700 patients (n=700) requiring long-term warfarin anticoagulation after heart valve



**Figure 1** Study flow chart.

replacement will participate in this study and will be randomly divided into a traditional outpatient anticoagulation monitoring and management group (management via laboratory testing and drug dose adjustment at the closest hospital as instructed by the doctor) and a group assigned to the new anticoagulation management model based on the internet technology (management via a mobile medical network follow-up platform) using a randomised envelope method. Clinical follow-up will be conducted at 3, 6, 9 and 12 months after discharge (figure 1). The investigators will conduct follow-up evaluations via telephone interviews or office visits. The researchers will observe differences in the TTR, drug dose adjustment, bleeding/thrombosis and other related complications in patients using warfarin anticoagulation. At each follow-up time point, the researchers will ask the patients questions and complete a clinical case report form (CRF). The primary endpoint of the study is the TTR, and the secondary endpoint is bleeding/thrombotic complications.

### Organisational framework

The project will be organised and implemented by Beijing Anzhen Hospital affiliated with Capital Medical University. Cardiac centres at five Chinese hospitals (Beijing Anzhen Hospital affiliated with Capital Medical University, Fuwai Hospital of the Chinese Academy of Medical Sciences, General Hospital of the People's Liberation Army, People's Hospital of Peking University and Xuanwu Hospital affiliated with Capital Medical University) will participate in the clinical trial. These centres should meet the following criteria: (1) large/medium cardiac disease centre; (2) more than 100 heart valve surgery cases annually; (3) strong clinical and scientific research programmes and (4) willingness to continuously recruit and randomise patients for the present study. The principal investigator

### Box 1 Inclusion and exclusion criteria

#### Inclusion criteria

- ▶ Patients have full civil capability and are aged 18–65 years.
- ▶ Patients or guardians agree to the study plan and sign the informed consent form.
- ▶ Long-term warfarin anticoagulation is required after mechanical heart valve replacement.
- ▶ Patients and their families can effectively operate smartphone software.

#### Exclusion criteria

- ▶ Emergency surgical patients.
- ▶ Heart valve replacement patients treated with cardiac bypass surgery.
- ▶ Patients with severe chronic diseases, such as malignant tumours, hepatic cirrhosis, diabetes, cerebral haemorrhage (cerebral infarction), convalescence, thyroid dysfunction and respiratory failure.
- ▶ Patients with severe renal insufficiency (endogenous creatinine clearance rate  $\leq 20$  mL/min).
- ▶ Patients with severe hepatic insufficiency (Child-Pugh  $\geq 10$ ).
- ▶ Patients with severe heart failure (cardiac function New York Heart Association grade IV and above).
- ▶ Patients with postoperative infective endocarditis.
- ▶ Patients with severe postoperative complications and poor prognosis.
- ▶ Patients who are unable to comply with this study.

is responsible for all aspects of the project, including the design, implementation and reporting of the research project. The scientific committee, which includes experienced clinical trial experts and cardiologists from China, will help to ensure that a scientific and rational study design is used and oversee randomisation, data collection, quality control and data analysis. The Peking University Clinical Research Institute (PUCRI) has created a data monitoring committee to evaluate and supervise the data quality. As an open-labelled study, an independent event committee will adjudicate the events. Data management and statistical analysis will be conducted by the Beijing Research Institute of Cardiopulmonary and Vascular Diseases. Additionally, the subcentre will have its own independent research team, including a local principal investigator, a research coordinator, investigators, research assistants and a local quality control manager.

### Patient eligibility

Participants who comply with the criteria stated in box 1 will be eligible for participation in the randomised controlled trial.

### Randomisation and blinding

The central stratified randomisation method will be used in this study. Patients who meet the inclusion and exclusion criteria and consent to participate in this study will be randomised at a 1:1 ratio into the traditional outpatient anticoagulation monitoring and management group (management via laboratory testing and drug dose adjustment at the closest hospital as instructed by a doctor) and the group using the new anticoagulation management



based on the internet technology (management via a mobile medical network follow-up platform). Patients will be aware of their grouping, whereas the researchers conducting endpoint evaluations will be blinded to their grouping.

### Participant education and training

Patients in the traditional group will undergo INR measurement and drug adjustment at the surgical hospital or a nearby hospital as directed by their doctor. Patients will be asked to record the results of each examination and to note the physical symptoms related to anticoagulation, such as haemorrhage and embolism, to prepare for follow-up after discharge.

In the internet-based model group, electronic information registration files will be established for all patients discharged normally after surgery, and the patients will complete follow-up network registration. The information file will include their name, sex, date of birth, contact phone number, inpatient number, time of admission and discharge, diagnosis and surgery type. Before the completion of network registration, all patients and their families will attend at least three follow-up training sessions, which will include watching an educational video and installation and simulation of the follow-up software and mobile apps. Patients will be asked to go to the surgical hospital or a nearby hospital for blood analysis and then upload the INR and other laboratory test results to the apps.

All patients in both groups will receive education and training on warfarin anticoagulation before discharge, including diet, drug interactions, and the importance of testing and compliance with dosing.

### Anticoagulation treatment strategies

The INR will be measured every 3–5 days for 1 month after discharge. After the patient's examination results stabilise, the INR will be measured every 10–14 days from 1 to 3 months after discharge, once a month from 3 to 6 months after discharge and once every 2 months from 6 to 12 months after discharge. The target INR window is 1.8–2.5 (1.8–2.2 for aortic valve replacement, 2.0–2.5 for mitral valve replacement and 2.0–2.5 for double valve replacement).

### Introduction of the app software for the internet-based follow-up management system

In the early stages of this study in 2012, the research group developed and constructed an internet-based follow-up system for clinical use.<sup>42</sup> Led by the director of surgery and including surgeons, trained physician assistants, staff nurses and others, a new anticoagulation management model was developed that combined health science promotion and education, portable coagulation indicator monitoring, warfarin-related gene monitoring, warfarin dosage prediction, access to a professional outpatient clinic and a publicity manual.

Mobile apps are specific for doctors and patients. The app for doctors will be distributed to cardiovascular

surgeons from the collaborating units participating in the study by the lead unit of the study; the app for patients will be distributed to patients enrolled in this study by doctors participating in this study.

The app for doctors is mainly composed of a patient management module and a professional learning module and will allow timely patient contact. The patient management module is designed to communicate with enrolled patients, guide treatment, improve patient compliance and serve as a tool for doctors to upload relevant clinical data. The professional learning module provides a platform for peers participating in this study to conduct analysis and discussion. The leading research hospital (Beijing Anzhen Hospital) will release the advanced research data worldwide through this module to allow communication and learning among their peers in cardiac surgery.

The patient app contains the patient's personal information, including hospitalisation information and discharge matters requiring attention. The patient app is mainly divided into a health management module, doctor consultation module and medical science popularisation module. The health management module records the patients' individualised recommended warfarin dose and target INR after discharge. Patients' current INR, rate of change and missed doses will be recorded in the module. The app regularly reminds patients of the time of the INR examination. If patients miss the examination, the software will warn them. The health management module also records daily exercise, pulse, blood pressure and other daily indicators. The doctor consultation module provides an opportunity for patients to contact the doctors that they have consulted online. Meanwhile, relevant examination records will be uploaded, and patient health files will be generated using the health management module. Using the medical science popularisation module, the leading research hospital (Beijing Anzhen Hospital) will regularly distribute popularised medical science knowledge to the patients, such as information related to diet or new drugs that might interact with warfarin.

Preliminary, single-centre study results showed that the total follow-up rate was greater than 90% using this internet-based follow-up management system.<sup>42</sup>

### Endpoints

The primary endpoint of this study is the TTR, that is, the percentage of time a patient's INR is within the desired treatment target window. The following factors will be considered: (1) the time period of the analysis, for example, the TTR from month 1 to month 12 after randomisation; (2) the target INR window of 1.8–2.5 (1.8–2.2 for aortic valve replacement, 2.0–2.5 for mitral valve replacement and 2.0–2.5 for double valve replacement) and (3) a minimum of six INR tests for inclusion in the final analysis. The secondary endpoint is the incidence of anticoagulation-related embolism and bleeding. Embolism includes any embolic event that occurs in the absence of infection after the immediate perioperative period.

Embolism may manifest as a neurologic event or a non-cerebral embolic event. Severe bleeding associated with anticoagulation includes any episode of major internal or external bleeding that causes death, hospitalisation or permanent injury (eg, vision loss), or necessitates transfusion. General bleeding related to anticoagulation refers to bleeding of the nasal cavity and gums, skin ecchymosis, menorrhoea, haematuria, melena and so on.<sup>43</sup> The TTR is measured by Rosendaal linear interpolation.<sup>44</sup>

### Sample size

The sample size was calculated according to the expected difference between the target INR goal attainment rate in the traditional and new anticoagulation management model groups.

Based on previous Chinese research and actual clinical situations in China, it is estimated that the target INR goal attainment rates of the traditional anticoagulation management model group will be set at 50%. We expected an INR attainment rate of 60% in the new anticoagulation management model group based on the internet technology. A total of 610 patients will be needed based on a power of 80% and a two-tailed z-test with  $\alpha=0.05$ . Considering a 10% loss to follow-up, 678 patients will be required. Finally, we decided that 700 patients should be enrolled in the study to provide the power required to identify the expected difference under the aforementioned assumptions.

### Follow-up

All surviving patients will be followed for up to 1 year, even if they reach an endpoint of the study. The researchers plan to follow-up with patients at 3 months ( $\pm 30$  days), 6 months ( $\pm 30$  days), 9 months ( $\pm 30$  days) and 12 months ( $\pm 30$  days) after discharge.

Patients in the traditional group can be followed up by telephone if they cannot return to the hospital at the scheduled follow-up time points. Patients must complete the 12-month follow-up visit at the hospital. At each follow-up point, patients will be asked to bring their original hospitalisation records and all medical examination results after discharge, and the researchers will complete the CRF.

For patients in the new model group, the researchers will check the data results uploaded by the patients in the new follow-up system app and complete the CRF at the follow-up time points.

### Adverse events

In this study, adverse events include complications associated with anticoagulant treatment, including bleeding and thrombosis. Additionally, a CRF table will also be used to record adverse events, such as recurrent valve surgery, readmission, new atrial fibrillation, heart failure, severe infection and death.

### Data collection and monitoring

The medical information of each patient enrolled in the internet-based model group, in this study, will be stored

in a monitoring database. Professionals will ensure the security of patients' personal information and keep these files confidential. The data required for this study will be collected using a network-based CRF table, which will be specifically edited to minimise missing data and entry errors. After the researchers input the patient information, the system will regularly remind the recording personnel to follow-up with the patients and complete the information. PUCRI has created a data monitoring committee to evaluate and supervise the data quality, follow-up with the project progress in real time and regularly check the data quality.

### Statistical analyses

Continuous variables will be expressed as the mean $\pm$ SD or median (IQR), and categorical variables will be expressed as frequencies and percentages. Baseline characteristics will be compared between the two groups by the  $\chi^2$ , t and Mann-Whitney tests, as appropriate. The Mann-Whitney test will be used to determine the difference in the TTR between the traditional anticoagulation management model group and the internet-based anticoagulation management model group. The incidence of adverse events (bleeding or thrombosis) will be compared by the  $\chi^2$  test. A two-sided p value $<0.05$  will be regarded as statistically significant. Statistical analyses will be performed using SAS V.9.2.

### Planned timetable

The first patient in this study was randomised on 13 July 2018. At the time of manuscript submission, 534 patients had been randomised (268 patients in the test arm and 266 patients in the active control arm). Recruitment is expected to be completed by December 2019, and the follow-up of the last enrolled patient will be completed by December 2020. Interim safety analyses are planned after 350 patients have completed at least 6 months of follow-up. An overall safety analysis will be released by December 2020.

### Patient and public involvement

Neither the public nor the patients were engaged in the proposal of the research question, the design or implementation of the study or patient recruitment. The results will be dispersed to the study participants via public reports and academic papers.

## DISCUSSION

Warfarin anticoagulation therapy is required for a long period of time after heart valve surgery, and the warfarin level must be maintained within a target range to achieve a therapeutic effect. Otherwise, excessive or insufficient anticoagulation will result, leading to complications, such as bleeding and thrombosis.<sup>45</sup> In the previous traditional outpatient anticoagulation monitoring and management model, patients often paid insufficient attention to warfarin anticoagulation and did not undergo timely



testing. Additionally, many local hospitals have insufficient experience in adjusting warfarin anticoagulation indicators, leading to irregular long-term drug adjustments and anticoagulation index tests in many patients.

This study was conducted across several representative research centres and uses a mobile medical network follow-up platform technology that has been preliminarily established in a previous study to further improve data collection and to compare the differences between the traditional anticoagulation management model and the new management model based on current internet technology. During the follow-up period, we will observe differences in patient compliance regarding warfarin use for anticoagulation, the percentage of target anticoagulant index attainment, drug dose adjustment and related complications, such as haemorrhage and thrombosis, to explore a safer and more effective follow-up model for doctor–patient interactions in the internet era, thus further reducing the risk of warfarin-related complications and improving its therapeutic effects. In future studies and follow-up research, we will compare the associated medical costs during follow-up and rehabilitation under the two warfarin management models.

This study has the potential for great social and economic benefits in terms of further improving the treatment standards of cardiac surgery as well as the long-term survival and quality of life of patients after surgery.

### Ethics and dissemination

All participants will provide written informed consent. The study will follow the Consolidated Standards of Reporting Trials guidelines. The results will be published in a peer-reviewed medical journal.

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**Contributors** HZ, ZZ and YL conceived the study idea. YQ, JH, YL, XM, JS and KL made substantial contributions to the development of the study protocol. ZZ drafted the manuscript, and all the authors contributed to the critical revisions of the paper. The final manuscript was read and approved by all the authors.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** The study protocol was approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University. The approved study protocol and related materials, such as consent forms and CRFs, have been submitted to the participating centres. Ethics approval was obtained from the ethics committees of all participating centres. All centres received institutional review board approval from their own ethics committees or accepted approval from the central ethics committee.

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