Clinical study protocol

Title: A randomized controlled trial of mobile technology-assisted outpatient maintenance therapy in children with acute lymphoblastic leukaemia (ALL)

Portocol number: mM-002

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Declaration of Secrecy

1. Abstract

Title	A randomized controlled trial of mobile technology-assisted outpatient maintenance therapy in children with acute lymphoblastic leukaemia (ALL).
Study objective	To assess the efficacy of using mobile technology to improve the percentage of time wherein drug dosing is within the target range.
Study design	Single-center, randomized controlled trial.
Study population	Children with ALL receiving outpatient maintenance therapy.
Inclusion criteria	1) < 16 years old at diagnosis; 2) having demonstrated ≥ 3 months of > 90% compliance with using a mobile app to log in records of daily medication and weekly blood test results; 3) patient or legal guardian provides informed consent.
Exclusion criteria	None.
Sample size	≥ 200 subjects
Dosage regimen	A mobile application classifies each subject's maintenance therapy dosing status as 'On Track', 'Orange Alert', or 'Red Alert' based on analysis of his/her electronic diary of medication and blood tests. Subjects classified as 'Orange Alert' receive mobile-phone alert messages that instruct them to self-adjust dose of oral medication. Subjects classified as 'Red Alert' are directed to a mobile-phone portal for scheduling a telemedicine clinic visit and receive periodic model-phone messages instructing follow-up blood testing and dose adjustment.
Study endpoints	Primary endpoint: · Percentage of time wherein white blood cell concentration is within the target range 2.0 – 3.0 × 10^9/L after randomization. Secondary endpoints: · Percentage of time wherein white blood cell concentration is < 1.0 or > 5.0 × 10^9/L;

Statistical analysis	Wilcoxon test will be used to test the significance of change(s) in clinical endpoints.

2. Research background

Modern treatment for acute lymphoblastic leukaemia (ALL) in children lasts ≈ 2.5 years, consisting of inpatient chemotherapy lasting 1 year and ensuing outpatient maintenance therapy lasting 1.5 years. During the outpatient maintenance therapy phase, subjects live at home, which are often ≥ hundreds of miles away from the 'principal medical center' (that is, the hospital where they receive inpatient chemotherapy), and they are to take oral 6-mercaptopurine daily and methotrexate weekly at home. Also, subjects are to monitor their blood cell counts weekly at their local healthcare facilities. Subjects and their guardians are instructed to self-adjust dosage of maintenance therapy with the goal to maintain white blood cell concentration within the target range $2.0 – 3.0 \times 10^9$/L. When white blood cell concentration is too low, drug dosage should be decreased. On the other hand, when the white blood cell concentration is too high, dosage should be increased. Only once every ≈3 months, subjects travel to the principal medical center for outpatient periodic check-up. The principal medical center needs a method to better monitor subjects' compliance of drug in-take and their adherence to the target range of white blood cell concentration.

3. Study objective

To assess whether the use of mobile technology can improve the percentage of time wherein outpatient drug dosing is 'on target'.

4. Study design

Enrolled subjects enter electronic diaries of oral medication and outpatient blood test results in a mobile application. The mobile application classifies each subject's maintenance therapy dosing status as 'On Track', 'Orange Alert', or 'Red Alert' based on his/her electronic diary.

Subjects whose white blood cell concentration is $2.0 – 2.3 \times 10^9$/L in the most recent test or $3.5 – 5.0 \times 10^9$/L for < 3 most-recent weeks will be classified as 'Orange Alert'. Subjects whose white blood cell concentration is $3.5 – 5.0 \times 10^9$/L for ≥ 3 most-recent weeks or whose white blood cell concentration is < 2.0 or > 5.0×10^9/L in the most recent blood

test are classified as ‘Red Alert’. The other subjects are classified as ‘On Track’.

Subjects classified as ‘Orange Alert’ receive mobile-phone alert messages that are tailored to their situations to help them self-adjust dose of oral medication. Subjects classified as ‘Red Alert’ are directed to a mobile-phone portal for scheduling an online doctor visit.

5. Study population

Children with ALL receiving outpatient maintenance therapy.

6. Inclusion criteria

1) < 16 years old at diagnosis;
2) having demonstrated ≥ 3 months of > 90% compliance with using a mobile app to log in records of daily medication and weekly blood test results;
3) patient or legal guardian provides informed consent.

7. Exclusion criteria

None.

8. Drop-out and withdrawal criteria

1) Drop-out criteria: Relapse or death.

2) Withdrawal criteria: Any subject wishing to discontinue participating can withdraw from the study, and the date and reason for withdrawal shall be recorded.

9. Follow-up

⩾ 3 months after randomization.

10. Primary endpoint

Percentage of time wherein white blood cell concentration is within the range $2.0 – 3.0 \times 10^9$/L.

11. Secondary endpoints

Percentage of time wherein white blood cell concentration is < 1.0 or $> 5.0 \times 10^9$/L;

12. Sample size calculation

To attain a 0.05 significance level and a 0.9 power at a presumed 5% dropout rate, we estimated ≥ 200 subjects will need to be enrolled.

13. Statistical analysis

Wilcoxon test will be used to test the significance of change(s) in clinical endpoints.

14. Ethical review

The Institute of Hematology, Chinese Academy of Medical Sciences (IHCAMS) has approved this study and its associated informed consent form. The study will be conducted in accordance with the Declaration of Helsinki, regulations issued by the government of the People's Republic of China, and additional precautions required by the Ethics Committee at the IHCAMS. During the study, if there is any amendment to the study protocol, renewed approval shall be obtained from the IHCAMS Ethics Committee before continuation of the study.

15. Preservation of research data

All data of this study will be stored at the IHCAMS. Data sharing among the researchers will abide by the regulations of the People's Republic of China regarding subject privacy protection.