Hantangping-a traditional Chinese medicine compound versus metformin for treating early type 2 diabetes mellitus:study protocol for a non-inferiority randomized controlled trial

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Study protocol

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Abstract

Background: Hantangping is a traditional Chinese medicine compound, founded by Professor Saimei Li of the First Affiliated Hospital of Guangzhou University of Chinese Medicine, and has been used to treat type 2 diabetes mellitus for more than 10 years. Clinical practice has shown that for early stage type 2 diabetes patients with acceptable islet secretion function, Hantangping can reduce blood glucose and improve islet function while correcting lipid metabolism disorders, preventing diabetes complications, and reducing adverse reactions..However, there is currently a lack of randomized controlled clinical trials that can confirm the efficacy of Hantangping in the treatment of early type 2 diabetes. We designed this study to objectively evaluate the effectiveness and safety of Hantangping in the treatment of early type 2 diabetes.

Methods/Design: A randomized, open, parallel controlled and non-inferiority clinical trial was designed. Participants were randomly divided into Hantangping group(experimental group) and metformin group(positive control group) at a ratio of 1:1, and were intervened with Chinese medicine Hantangping and Western medicine metformin respectively.The participants will receive 12 weeks of drug intervention and 8 weeks of follow-up.The primary outcome measure is glycosylated hemoglobin a1c. The secondary outcome measures are fasting blood glucose index of β-cell function in Homeostasis Model Assessment,and index of Insulin resistance in Homeostasis Model Assessment, etc.

Discussion: This study can provide scientific and rigorous evidence-based medical evidence for the effectiveness and safety of Hantangping in the treatment of early type 2 diabetes, and may also provide new ideas and methods for the treatment of type 2 diabetes.

Trial registration : Chinese Clinical Trial Registry, ChiCTR1900023378. Registered on 25 May 2019, http://www.chictr.org.cn/listbycreater.aspx .

Background

With the development of economy and society, the prevalence rate of pre-diabetes and diabetes is rising all over the world. Epidemiological survey showed that the prevalence of diabetes in Chinese adults in 2013 was as high as 10.9%[1], and most of them were type 2 diabetes (T2DM), with a prevalence of 10.4% [2]. Although there are many treatment options for diabetes, the current control of T2DM is still not optimistic. A recent study showed that only half of the patients undergoing treatment had their blood glucose level adequately controlled[3].

T2DM is a metabolic disease characterized by hyperglycemia. Insulin resistance and insufficient insulin secretion caused by β-cell dysfunction are the two core pathogenesis of T2DM. In traditional Chinese medicine (TCM), T2DM usually presents different TCM syndromes at different stages, and its treatment varies accordingly. Professor Saimei Li, who works at the First Affiliated Hospital of Guangzhou University of Chinese Medicine, advocated that in TCM T2DM should be treated by stages and syndromes. She believes that in the early stages of T2DM, most patients have adequate pancreatic islet

secretion function, and the hyperglycemia is clinically manifested as Yang syndrome and heat syndrome of TCM. She founded the Chinese medicine compound Han Tang Ping to treat T2DM (patients' islet secretion function is acceptable).Clinical reports show that Hantangping has a significant effect on the treatment of early T2DM. With independent treatment of Hantangping, the patient's hyperglycemia and dyslipidemia may return to normal, and the islet function is significantly improved [4]. At present, both international and Chinese diagnosis and treatment guidelines of diabetes recommend metformin as the first-line medication for the treatment of T2DM and the basic medication in the drug combination. Metformin, recognized as the first choice and basic antidiabetic drug for T2DM, has reliable short-term and long-term hypoglycemic efficacy. Since some original trials, follow-up and short-term studies (usually 3–6 months) using metformin have demonstrated mean glycosylated hemoglobin a1c (HbA1c) reductions on the order of 1% (10.9 mmol/mol) to 1.5% (16.4 mmol/mol). [5, 6, 7]. Therefore, in this study, metformin is used as a positive control drug to carry out a randomized controlled clinical trial to objectively evaluate the clinical efficacy of Chinese herbal compound Hantangping.

Methods/design

Study design

This study adopts a randomized, open, parallel controlled trial design. The participants are randomly divided into Hantangping group and metformin group at a ratio of 1:1. Well-trained researchers must introduce the trial to the participants, give them information sheets and consent forms. All participants must sign a written informed consent form before enrolment. The study's flow chart is shown in Fig. 1.

Figure 1. Study flow chart. The flow chart of enrolment, allocation, intervention, and analysis.

Participant screening and selection

70 patients with T2DM who meet the screening criteria will be recruited through recruitment advertisements and introductions from outpatient doctors of endocrinology department from the First Affiliated Hospital of Guangzhou University of Chinese Medicine, China.

TCM syndrome differentiation criteria

In accordance with the Diabetes Professional Committee of China Association of Chinese Medicine, "Diabete Diagnosis and Syndrome Differentiation Reference criteria" of"Diabetes Traditional Chinese Medicine Staging and Efficacy Evaluation criteria(1992)", the Diagnostic criteria for the of excess-heat syndrome in middle burner in diabetes were formulated.

Symptoms:Polyphagia or easy to hunger, Dry mouth or drink more or bitter taste or ozostomia, Dry throat or pharyngalgia, Oral ulcer or acne or swelling and aching of gum, Insomnia or irritability, Flushed face or erubescence, Yellow urine, Dry stool or sticky stool;

Conditions of tongue and pulse: Red or dull-red tongue, Yellow coating on tongue, Rapid or full or slippery pulse;

It can be diagnosed with two symptoms or one symptom plus one tongue pulse.

Inclusion criteria

1. Participant is between 18 and 60 years of age;
2. Participant met the diagnostic criteria for diabetes issued by the World Health Organization in 1999 and the classification criteria for T2DM in the classification criteria for the etiology of diabetes issued by the American Diabetes Association in 1997;
3. Participant meets the criteria of TCM syndrome diagnosis of excess-heat syndrome in middle burner;
4. Participant had not received any hypoglycemic treatment and had poor blood glucose control after 3 months of diet and exercise treatment, or had short-term hypoglycemic treatment (< 1 month) and stopped more than 3 Months;
5. Participant's pancreatic islet secretion function is acceptable, and the insulin releasing test shows that the peak insulin/ original insulin ≥ 3 (Ip/ Io ≥ 3), or the insulin release time is normal or delayed;
6. Participant's body mass index(BMI)range: 18 kg/m^2 ≤ BMI ≤ 35 kg/m^2r;
7. Participant voluntarily participates in this study and signs informed consent forms.

Exclusion criteria

1. Participant reduced his/her blood glucose levels below the diagnostic criteria value by controlling their diet and strengthening exercise;
2. Participant has hemoglobin abnormalities;
3. Participant was a pregnant or lactating woman;
4. Participant met the contraindications for metformin;
5. Participant was allergic to Chinese medicine;
6. Participant had serious complications of heart, liver, kidney, brain, or other serious primary diseases;
7. Participant had acute metabolic disorders such as diabetic ketoacidosis or concurrent infection in the past month;
8. Participant is unwilling to cooperate or suffered from mental illness;
9. Participant had diabetes complications as the main symptoms.

Termination criteria

1. Participant is medically deemed necessary by the researcher to discontinue participation in the trial;
2. Participant ask to stop participating in the trial.

Interventions

All participants must receive basic diabetes treatment, including diet therapy and exercise therapy, while undergoing experimental intervention. The participants will be asked to record their daily diet and exercise in the form (Additional file 2). Every week after the intervention, the researchers will contact the participants by phone and ask about the implementation of diet and exercise therapy, medication consumption, blood glucose self-test level, adverse events, which will be recorded in the case report form (CRF).

(1) Hantangping group(exprimental group)

Participants in the Hantangping group will be treated with Chinese medicine compound Hantangping granules (in its composition, red yeast rice and stevia rebaudiana granules have not been produced yet, so the dosage form will still be Chinese herbal decoction pieces). The participants will take Hantangping granules orally, one dose each time, twice a day, half an hour after breakfast and dinner. The Chinese medicine decoction, boiled from 500 ml water decocting red yeast rice and stevia rebaudiana decoction pieces to 250 ml, flushes other Chinese medicine formula granule. A course of treatment requires 12 weeks, and the observation window is a course of treatment. The drug manufacturers are Guangdong Yifang Pharmaceutical Co., Ltd. (Chinese medicine granules) and Guangzhou Zhixin Pharmaceutical Co., Ltd. (Chinese medicine decoction pieces).

The composition of Hantangping includes kudzuvine root, zingiber, zingiber, golden thread, rhubarb root and rhizome, unprocessed rehmannia root, ginseng, red yeast rice, stevia rebaudiana, etc. (Because the TCM compound Hantangping has been patented, its composition and dosage cannot be published temporarily due to confidentiality) .

(2) Metformin group(positive control group)

Participants in the metformin group will receive western medicine metformin hydrochloride tablets (trade name: Glucophage). Participants will orally take metformin hydrochloride tablets after meals, 1 tablet each time, 3 times a day. The observation window is the same as that of the Hantangping Group. The drug manufacturer is Sino-US Shanghai Squibb Pharmaceutical Co., Ltd.

Randomization and allocation

Use SAS 9.4 software for randomization to generate a random number table, and formulate a corresponding drug and case allocation plan (enclosed with an opaque envelope). After informed consent, the participants will be randomly divided into Hantangping group (experimental group) and metformin group (positive control group). The trial doctor will dispense the medications in the order originally arranged. An independent staff (Xiaoli He) who is not involved in observing or evaluating participants has a computer-generated random sequence.

Blinding

Open design is adopted in this study. Due to the large differences in the appearance and dosage of the drugs between the two groups, the participants could not be kept blind. But in order to control bias as

much as possible, some measures have been taken:

1. Conduct unified training for the staff involved in the research. Two staff members measure or record data at the same time to reduce measurement and record deviation;
2. Concomitant medication should be minimized during the intervention process, and the researchers should be informed if it must be used.
3. The concealment of the random allocation plan adopts the envelope random method to select participants;
4. Researchers and supervisors involved in recording results, efficacy evaluation, data management, and statistical analysis remain blind during the trial.

Outcome measures

The schedule for all outcome measures is shown in Fig. 2. All demographic data will be determined prior to treatment, including the date of birth, gender, past medical history, medication history, smoking and drinking history.

The primary outcome is the change in HbA1c from baseline after 12 weeks of treatment.HbA1C is the product of the combination of hemoglobin in red blood cells and glucide in serum, which is formed through a slow, continuous and irreversible glycation reaction. It is an important evaluation indicator for overall blood glucose control, and it can effectively reflect the blood glucose control of diabetic patients in the past 2 to 3 months.

The secondary outcomes included changes of the following indexes from the baseline to the end: fasting blood glucose (FBG), 2-hour post-meal blood glucose (2hPG), index of β-cell function in homeostasis model assessment (HOMA-β), index of insulin resistance in homeostasis model assessment (HOMA-IR), area under the curve of insulin (AUCI), total cholesterol (TC), triglyceride, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), body weight, BMI.

Safety assessments

During the trial, all researchers must comply with Good Clinical Practice (GCP) and the protocol of the clinical trial. Specialized medical examiners will be dispatched to perform physical examinations on participants. At each visit of the participant, examiners will observe the patient's systemic response and evaluate the participant's safety indicators, including blood pressure, heart rate, electrocardiogram, blood routine, urine routine, liver function and renal function.

Researchers will record all adverse events during the study, including toxicity and side effects, such as gastrointestinal reactions, medicamentous liver impairment and renal damage, and grade them in detail. When a serious adverse event occurs, should immediately terminate the ongoing trial intervention and provide all necessary treatments. Then researchers will report the adverse event to the Ethics Committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine. Patients who experience adverse reactions during the trial will receive free medical care.

Sample size calculation

The number of participants in this study is calculated based on relevant literature data and statistical principles. According to the unilateral test level α, the allowable probability of the second type of error does not exceed β. Under the condition of T = S, a non-inferiority test The sample size required for each group is: $n = 2[(\mu_{1-\alpha} + \mu_{1-\beta})(s/\delta)]^2$

n is the sample size of each group, α is the inspection level, β is the second type of error, 1-β is the power, μ is the standard normal deviation boundary value ($\mu_{1-\alpha}$ and $\mu_{1-\beta}$ represent 1-α and 1-β respectively corresponding one-sided boundary value), s is the standard deviation, and δ is the non-inferiority boundary value.

After estimation, the final sample size was determined to be 35 cases in the Hantangping group and 35 cases in the metformin group, with a total of 70 patients..

Data collection and management

A comprehensive data and safety monitoring committee will be established to ensure that the quality of each step in the testing process is as high as possible. As an independent party, the Data Monitoring Committee is responsible for the quality control and safety supervision of this study.

After completing the observation of each participant, the researchers should immediately submit the study record to the designated CRF input personnel. CRF importers are responsible for recording the clinical examination, treatment effect evaluation and follow-up information in the CRF of each patient. And they are responsible for form's completeness and authenticity. The research record is the original document of the clinical research object and should be kept in the hospital. CRF will be counted and analyzed by the data statisticians of this institution. When the statistician has any questions about the original data, the researchers should answer the questions in time.

Confidentiality

All study-related information will be stored at the study site securely. All participants' information will be stored in a locked file cabinet in a restricted-access area. All reports, data and forms will be identified by a coded identification (ID) number. All records containing the participant' s name or other personal identifiers will be stored separately from the study records identified by the code number. All local databases will be protected with a password-protected access system. The information will not be released outside of the study without the participant' s written permission.

Dissemination

We plan to report the results of the trials in appropriate journals and exchange them at academic conferences. Our final report will follow the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Statistical analysis

The statistical analysis of this study will be carried out by statisticians from Guangzhou University of Chinese Medicine. They will use statistical analysis software packages SPSS 23.0 and SAS 9.1. $P < .05$ is considered statistically signifificant. Full analysis set (FAS) will analyze with intention-to-treat (ITT), and per-protocol set (PPS) will be statistically analyzed by per-protocol(PP). Demographic and other baseline characteristics will be analyzed using FAS. The efficacy and safety analysis will use PPS. Normally distributed data is represented by the mean ± standard deviation, and non-normally distributed data is represented by the median and interquartile range. Comparisons between measurements from the two groups will be performed using the independent sample T-test, and intra-group differences will be tested with paired T-test. Differences between the count data sets will be assessed with chi-square test. Multiple imputation will be adopted to handle missing data statistically. An exploratory subgroup analysis will be conducted to explore clues for further research when necessary.

Discussion

Currently, there are many clinical trials evaluating the efficacy of TCM in the treatment of T2DM. Compared with modern medicine, TCM has many advantages in the treatment of T2DM, such as overall regulation, co-regulation of blood glucose and blood lipids, and improvement of patients' quality of life. Tu et al. conducted an RCT on the efficacy of Fructus Mume Formula in the treatment of T2DM. The results showed that Fructus Mume Formula can reduce the blood glucose level and HbA1c value of patients with T2DM, and there is no statistically significant difference compared with metformin[8]. You et al. designed a non-inferiority trial to evaluate the efficacy of Jiangtangxiaozhi capsule in the treatment of T2DM with qi-yin deficiency phlegm-stasis inter-obstruction syndrome. The results showed that the HbA1c, 2hPG and BMI of the Jiangtang Xiaozhi capsule group were significantly reduced. Compared with the pioglitazone tablet group, the difference was not statistically significant[9].However, there are few studies evaluating the efficacy of TCM in enhancing pancreas islet function in the published randomized controlled trials.

A number of studies have shown that a variety of TCMs can significantly reduce blood glucose levels independently. Such as golden thread, prepared rehmannia root, ginseng, kudzuvine root, rhubarb root and rhizome, etc. can lower blood glucose level and improve clinical outcomes, and may also lower HbA1c levels[10].The composition of Hantangping contains these Chinese medicines. In terms of TCM theory, the TCM compound Hantangping was established on the basis of the therapeutic idea of "lowering blood glucose not far from cold, strengthening body depending on nourishing spleen and kidney, and qi and blood preferring smooth circulation". It is based on the principle of "both lowering blood glucose and strengthening the body", taking into account the therapies of clearing internal heat, opening stagnation, tonifying deficiency,invigorating pulse-beat, and dissipating dampness, so as to achieve the effects of strengthening the body, lowering blood glucose and regulating blood lipids, reducing insulin resistance and preventing diabetes complications.

This study has limitations. The sample size of this study is small, so the credibility of the results is limited. In order to provide more stable and consistent results, our later clinical trials will expand the

sample size on this basis for further verification.

TCM has accumulated rich experience in diagnosis and treatment In long-term clinical practice. But it is a subjective assessment and is considered to be low-quality evidence-based medical evidence. Therefore, it is important to conduct well-designed clinical studies to provide high-quality evidence-based medicine. Therefore, it is important to conduct well-designed clinical studies to provide high-quality evidence-based medicine.Based on the sound theory of TCM and rigorous trial design, the completion of this study will provide the necessary foundation for future large-scale multi-center clinical trials. Furthermore, Hantangping, as a kind of TCM for treating type 2 diabetes in stages, may open up new ideas for the treatment of type 2 diabetes.

Trial status
The protocol version was V3.0 and the date was May 20,2019.

Recruitment of participants for this trial has started in June 2019 and is scheduled to be completed by the end of January 2021. Data collection is planned to continue until the end of June 2021.

Abbreviations

T2DM: Type 2 diabetes mellitus; TCM: Traditional Chinese medicine; BMI: Body mass index; FBG: Fasting blood glucose; 2hPG: 2-hour post-meal blood glucose; HOMA-β: Index of β-cell function in homeostasis model assessment; HOMA-IR: Index of insulin resistance in homeostasis model assessment; AUCI: area under the curve of insulin; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; GCP: Good Clinical Practice; CRF: Case Report Form; ID: identification; CONSORT: Consolidated Standards of Reporting Trials; FAS: Full analysis set; ITT: intention-to-treat; PPS: per-protocol set;PP: per-protocol.

Declarations

Acknowledgements

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Authors’ contributions

XJ initiated the study protocal. BHW contributed to the improvement of the protocal. XLC and XJ formulated plans for data management and statistical analysis. SML provided key suggestions for the conception, design and program revision of this research, and made substantial contributions. XJ, BHW, ZBC, KXL, JYL, XLH and SML participated in the project development. XJ drafted the manuscript. All authors read and approve the final manuscript.

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Availability of data and materials

Not applicable.

Ethics approval and Informed consent

Ethical approval

This study must follow the Declaration of Helsinki and relevant Chinese clinical trial research norms and regulations. Before the start of the trial, it has passed the review of the ethics committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine (No. ZYYECK[2018]142).

Informed consent

Before each participant is enrolled in this study, it is the researchers' responsibility to provide, in writing, to the participant or his/her designated representative, a complete and comprehensive description of the purpose, procedures and possible risks of this study. Participants should be informed that they have the right to withdraw from the study at any time.The informed consent form should be in duplicate, one will be kept by the participants, and the other will be kept in the study archives.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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Figures

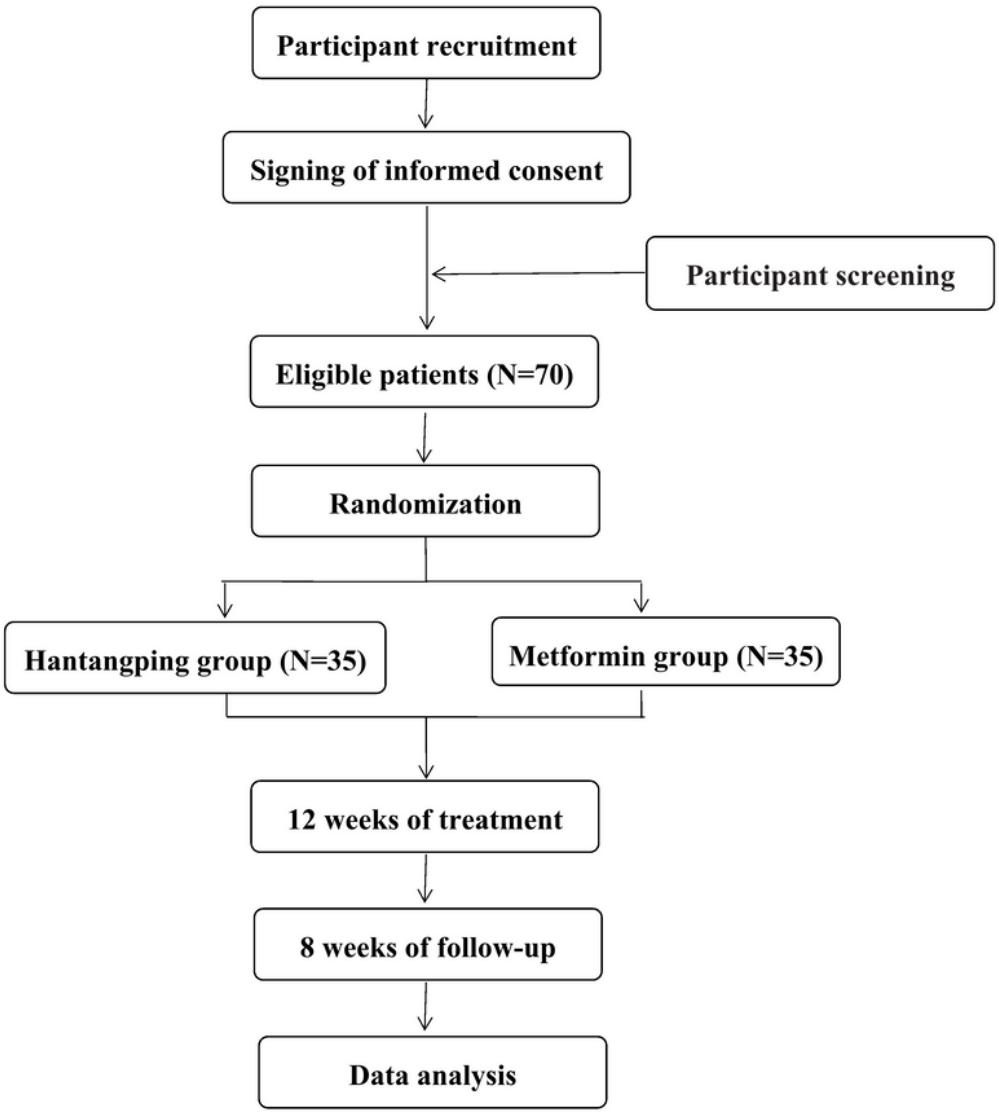

Figure 1

Study flow chart. The flow chart of enrolment, allocation, intervention, and analysis.

		STUDY PERIOD						
		Enrollment	Allocation	Intervention			Fellow-up	
TIMEPIONT		-1Week	Week 0	Week 4	Week 8	Week 12	Week 16	Week 20
ENROLMENT	Eligibility screen	X						
	Informed consent	X						
	Randomization	X						
	Allocation		X					
INTERVEN-TIONS	Diet and exercise therapy			X	X	X	X	X
	Hantangping granules/metformin hydrochloride tablets			X	X	X		
ASSESSMENT	HbA1c	X				X		X
	FBG	X		X	X	X	X	X
	2hPG	X				X		X
	HOMA-β	X				X		X
	HOMA-IR	X				X		X
	AUCI	X				X		X
	TC	X		X	X	X	X	X
	Triglyceride	X		X	X	X	X	X
	HDL-C	X		X	X	X	X	X
	LDL-C	X		X	X	X	X	X
	Body weight	X		X	X	X	X	X
	BMI	X		X	X	X	X	X
SAFETY ASSESSMENT	Blood pressure	X		X	X	X	X	X
	Heart rate	X		X	X	X	X	X
	Electrocardiogram	X		X	X	X	X	X
	Blood routine	X		X	X	X	X	X
	Urine routine	X		X	X	X	X	X
	Liver function	X		X	X	X	X	X
	Renal function	X		X	X	X	X	X

Figure 2

Schedule of enrollment and assessments.

Supplementary Files

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- spiritchecklist.doc