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—国際調和と独自性、経験知と先端科学

The Latest Development of Traditional Medicine: Harmonization and Specificity, Traditional Knowledge and New Technology

講　演　集

Proceedings of the Symposium

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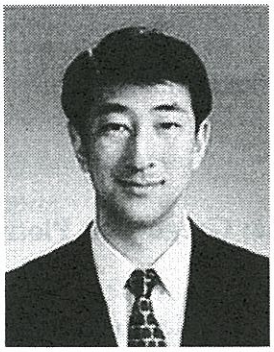
INVITED LECTURE 6

Curriculum Vitae



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INVITED LECTURE 6

Curriculum Vitae

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Dr. Plotnikoff is a United States Food and Drug Administration Investigational New Drug Sponsor and Principle Investigator for a Phase II Clinical Trial (180 subjects) of TU-025, *Keishi Bukuryo Gan*, at the University of Minnesota General Clinical Research Center. At the University of Minnesota, he co-founded and served as the first medical director for the Center for Spirituality and Healing. He is a Faculty Associate at the University of Minnesota's Center for Bioethics, Center for Dietary Supplement Safety and the Center for Plants and Human Health. He is the recipient of the 2004 University of Minnesota Medical School Early Career Distinguished Achievement Award.

KAMPO CLINICAL TRIALS: CHALLENGES AND LESSONS

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Abstract

The internationalization of Kampo will only be possible via rigorous clinical trial data. In the US, all clinical trials must be approved by an institutional review board (IRB). The importance of this approval cannot be overemphasized: it is the foundation for all other requirements including the brand new requirement for clinical trial registration. Such approval requires meeting 1) all of the ethical concerns associated with experimentation on human subjects, and 2) all of the scientific and statistical concerns associated with highly credible data. In the United States, even NIH-funded clinical research at a major research university on a well-known single Western herbal medicine (*Cimicifugua racemosa* (L.) Nutt.) has been delayed as long as 18 months by the absence of IRB approval. To help prevent such problems with not-well-known, multi-herb, Asian medicines, this presentation will provide insights and recommendations based on the experience of one investigator-initiated phase II clinical trial of TJ-25 Kesihi Bukuryo Gan in the United States. FDA and NIH guidelines and other resources for further information will also be provided.

Introduction

Although the dietary supplement market in the United States is quite large and growing rapidly, in recent years, sales and use of herbal medicines have actually declined significantly. Coincidentally, this reversal has occurred following highly publicized problems with herbal medicine safety, reliability and efficacy. Many of these reports are on multi-herb Asian formulas. To reverse negative perceptions requires more than English-language reports on historical use, case reports and underpowered or uncontrolled clinical studies. Both medical professionals and medical journalists in the US consider such information nothing more than hypotheses. Thus, the internationalization of Kampo will only be possible via rigorous clinical trial data.

All clinical trials must be approved by an Institutional Review Board (IRBs). These are Federally-mandated committees that review the ethical and scientific validity of all research on

both human and animal subjects. All IRBs are work with the NIH Office for Human Research Protections (OHRP) in accordance with 45 CFR 46 on the protection of human subjects. These regulations are based upon the Belmont Report.(http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm) and the World Medical Association's Declaration of Helsinki. (http://www.wma.net/e/policy/b3.htm) Requirements for federal recognition and approval of international IRBs are found at http://www.hhs.gov/ohrp/humansubjects/assurance/filasurt.htm#sectionb.

Instruction in protecting human subjects is required by the Department of Health and Human Services for all investigators and research personnel regardless of the source of funding. Thus, the first step for any clinical investigator in the United States is documenting completion of training in the protection of human subjects.
This may be met in one of several ways:

1 Review the online materials available through the Collaborative IRB Training Initiative (CITI) hosted by University of Miami Medical School server. (https://www.citiprogram.org/default.asp)

2. Review the University of Minnesota Office of Human Research Protections' CD-ROM entitled **"Investigator 101"**. (http://www.research.umn.edu/irb/)

3. Review the online " Human Participant Protection Education for Research Teams" from the National Institutes of Health (NIH). This instruction is directed to Biomedical researchers. (http://www.cancer.gov/clinicaltrials/learning/page3)

Ethical concerns with human experimentation are well described in these resources and are thus beyond the scope of this presentation.

I will thus focus on the scientific and statistical concerns of IRBs. As IRB members may not be familiar with botanical medicines, all herbal medicine research may be subject to excessively strict review. It is best to be overly prepared.

Key to over-preparation is a focus on the following issues:

Investigators must provide enough evidence to convince the IRB that:

1) the proposed trial is of sufficient scientific interest and necessity. This includes rationale for the study drug, its form, dose/concentration, dosing schedule for the disease/condition being studied.

2) the study drug and the placebo are of sufficient quality. This may include documentation of the study drug's chain of custody (seed to bench), chemical content, lack of biological, microbiological and chemical contamination, batch-to-batch reproducibility and stability over time. IRBs increasingly request documentation of adherence to the GAP and GMP guidelines.

3) the safety profile of the study drug is understood. This includes expected side-effects and known drug interactions. For this reason, both government and manufacturer post-marketing surveillance data must be accessible and valid. If study subjects will include persons on prescription medications, IRBs increasingly require documentation of P450 and P-glycoprotein interactions. Significant harm has been demonstrated by negative interactions of prescription agents with the popular herbal medicine *Hypericum perforatum* L.

4) the proposed methodology will achieve statistically-valid results. This requires use of sophisticated modeling to document statistical power and to justify the study design. This requires preliminary data to guide dosing, to calculate sample size needed, and to define the time required for the study. Many studies of complementary and alternative medicine have been rejected solely because of the inadequate methodology (i.e. lack of placebo control, use of non-or poorly-validated instruments, dependance upon vague or subjective outcomes).

IRBs are most concerned with the investigator's justification for placing volunteer human subjects at risk for harm with an experimental medicine. For this reason, if the scientific validity of the proposed research is judged to be sub-optimal, then the IRB will not approve the research.

For the University of Minnesota clinical trial on TJ25 Keishi Bukuryo Gan, we addressed all of these concerns by obtaining approval of the TU025 variant as an investigational new drug (IND) from the US Food and Drug Administration. This several hundred page application took an incredibly long time to produce. Each herbal ingredient must be described in lengthy detail. Each component of each herb must be described in lengthy detail including all safety and toxicity data. For a five herb Kampo formula, this was quite challenging. For a 10 herb formula, I would not want to do this anytime soon.

However, once the application was submitted, it was quickly approved by the FDA. This approval resulted in the University of Minnesota IRB quickly approving this study. The external validation of quality, safety and acceptability of the study by the FDA significantly reduced the IRB committee's workload. Approval of a Kampo formula as an IND may be especially important for committees without much knowledge or experience with herbal medicines.

After IRB approval, we sought to conduct the study at the University of Minnesota's NIH funded General Clinical Research Center (GCRC). Conducting clinical trials at this site comes with many benefits including additional peer-review for scientific and statistical validity. This proved to be the most rigorous component of the process. NIH funding of the GCRC is based,

in part, upon the quality of the peer-review of proposed clinical trials. This review further strengthened the clinical trial but delayed the start of the trial.

As those with clinical trial experience will attest, the greatest challenge for any clinical trial is recruitment of eligible subjects. We have been quite fortunate to have benefited from excellent press coverage in the United States with our trial. However, most potential participants who have expressed interest are not eligible. Thus, careful attention to optimizing the entrance requirements and exclusions is absolutely crucial.

Conclusion

From my perspective, Kampo has many advantages that will support its internationalization. First, Kampo is all-natural and is based upon ancient wisdom. There is much interest internationally in such health products. Second, Kampo is already a prescription agent with government regulation and physician approval in Japan. This is not yet known outside of Japan. Third, much work has been done to understand the mechanism of actions which might explain clinical phenomenon. The best articles should be translated and made available in English. Fourth, quality controls are in place. Every effort should be made to have international third party validation and publicity. Fourth,. a post-marketing surveillance system exists in Japan. Every effort should be undertaken to ensure its robustness.

Key challenges particular to Kampo as I see them are:

1. Absence of data to guide dosing decisions. Clearly, for multi-herb formulas, the amount of any one component in the serum is quite small. Even with quadrapole mass spectroscopy to monitor serum levels, there may be no correlation with efficacy. I do not see any way around this except to conduct dosing trials. For this reason, we are testing two different doses.
2. Absence of a validated means for assessing the subject's sho. The use of subjective assessments that may differ from practitioner to practitioner, and the use of subjective assessments that may differ in the subject from day to day, means that a true trial of Kampo is not likely to be easily approved by a US IRB. For this reason, sho questionnaires or instruments which can quantify the subjective aspects of the physical exam may benefit Kampo research. For this study, we have included a Kampo physical assessment (suidoku/ Oketsu) and basic questionnaire on the sho (hiesho).
3. Absence of data to guide concomitant use of Kampo with prescription medicines. As has been shown with many herbal medicines, use can result in under- or over-dosing prescription medications with resulting patient harm. Additionally, the lack of such information can put the study at risk due to false-positive or false-negative results. For this reason, we have had to exclude women on anti-depressant and/or other prescription medications that can treat hot flashes.
4. The absence of prospective pharmacogenomic data, including P450 and P-glycoprotein data, is not in Kampo's best interest from a patient care and a public relations perspective.

Should a negative result first be found by American physicians or by the American public, all of Kampo would be at risk. Proactive obtaining of such data appears to be in Kampo's long term international interest.

5. The absence of robust clinical trial data in English which would support clinical effectiveness and clinical cost-savings. Should such data be submitted for international review and should it meet international criteria, then Kampo's internationalization will be guaranteed.

On the following pages are key resources for international Kampo clinical trials.

NIH Requirements for Clinical Trials on Botanical Medicines

For single ingredient botanical preparations, information on the raw material and final preparation is needed. For multiple ingredient botanical preparations, identity and quality information (specifications and Certificates of Analysis for all components and for the finished product) is needed for each individual ingredient, as well as for the mixture as a whole.

1. Identification of each study agent using the scientific taxonomic nomenclature (e.g., genus, species, variety-if applicable) and author citation.
2. The name of the study agent supplier of the final study product. If the supplier is a "middle man," the provider of the source material(s) to the supplier. This information should extend back to the raw material harvest, if possible.
3. A letter from the supplier stating commitment to provide product and cooperate with the IND application process, if required.
4. Description of where and how an authenticated reference specimen of the source material is reserved.
5. Identification of the specific pharmacopeial monograph (e.g., U.S. Pharmacopeia) with which the material complies, or a description of suitable tests performed that are specific to the proposed botanical study material and that can be compared to results from an authenticated reference. When no pharmacopeial monograph exists for a study ingredient or in cases where the ingredient does not conform to the existing monograph, specifications should be provided that include all of the same tests found in the monograph.
6. Description (macroscopic) of the parts of the plant from which the product is derived.
7. Information on the geographic source of the material, time of harvest, plant part, and credentials of the person who collected and/or identified the material. If this information is not available, explain how future preparation or acquisition of a reasonably comparable raw material and final or finished study agent can be assured.
8. If the source plant is collected from wild populations, evidence that it was collected in compliance with the WHO Guidelines Guidelines on Good Agricultural and Collection Practices for Medicinal Plants or other national or local guidelines.

9. Description of the extraction procedure (e.g., solvent(s) used, ratio of starting material to finished extract, time and temperature employed, type of extraction, whether fresh or dried material was used, whether any excipient materials were added, what percentage of the extract is native extract, and what percentage is composed of excipients). Define the entire composition of the final extract.
10. Information on the formulation of the final or finished product (e.g., ingredients) and matching placebo, if applicable (see guidance for placebos below).
11. Information regarding active and/or other relevant marker compound(s) used for standardization.
12. Information on the characterization (e.g., chemical profile or fingerprint) of the agent as thoroughly as the state of the science allows. Describe the methods used.
13. Any other information relevant to the standardization process of assuring reasonably consistent material suitable for scientific study (including process control, as well as chemical and/or biological standardization of ingredients).
14. Information on the analysis of the product for contaminants, such as pesticide residues, heavy metals, toxic elements, mycotoxins, microorganisms, and adulterants.
15. The specifications and Certificate of Analysis to show compliance to specifications for purity and content from the supplier/manufacturer or other supporting manufacturer information, relating to the batches to be used in the study.
16. Description of bioavailability, dissolution, disintegration and release if the information is available.
17. Information on short- and long-term stability.
18. Information on storage conditions appropriate for assuring stability during the life of the study and how you plan to store the test agent.
19. If more than one batch will be used for the project, information on batch-to-batch reproducibility.
20. Plans to reserve and analyze product samples from all batches used during the course of the study. Plans should include how and when the samples are selected, how many samples, how the samples are stored, what analyses are conducted, the methods used, and how frequently and by whom the analyses are done. Plans should include tolerances for variability and what will be done if variability exceeds those limits. Sufficient material must be retained from each batch to allow independent analysis, should NCCAM require it.

NIH Requirements for Placebo Controls

1. A letter from the supplier stating commitment to provide product and cooperate with the IND application process, if required.
2. Information on the formulation of the product (e.g., ingredients).
3. Verification that the product is inactive and matches the active product in form, color, smell, taste, or other relevant sensory or physical characteristics.
4. Information on the analysis of the product for contaminants, such as pesticide residues, heavy metals, toxic elements, mycotoxins, microorganisms, and adulterants.

5. The specifications and Certificate of Analysis to show compliance to specifications for purity and content from the supplier/manufacturer or other supporting manufacturer information, relating to the batches to be used in the study.
6. Description of bioavailability, dissolution, disintegration and release if the information is available.
7. Information on short- and long-term stability.
8. Information on storage conditions appropriate for assuring stability during the life of the study and how you plan to store the placebo.
9. If more than one batch will be used for the project, information on batch-to-batch reproducibility.
10. Plans to reserve and analyze product samples from all batches used during the course of the study. Plans should include how and when the samples are selected, how many samples, how the samples are stored, what analyses are conducted, the methods used, and how frequently and by whom the analyses are done. Plans should include tolerances for variability and what will be done if variability exceeds those limits. Sufficient material must be retained from each batch to allow independent analysis, should NCCAM require it.

Resources for International Clinical Research on Herbal Medicines

American Herbal Pharmacopoeia
(http://www.herbal-ahp.org/#)

Australian Government: Therapeutic Goods Administration Questions & Answers for the Identification of Herbal Materials and Extracts
(http://www.tga.gov.au/cm/idherbal.htm)

Complementary Healthcare Council of Australia: Code of Practice for Ensuring Raw Material Quality and Safety
(http://www.chc.org.au/lib/pdf/rawmat.pdf)

Considerations for NCCAM Clinical Trial Grant Applications
(http://nccam.nih.gov/research/policies/clinical-considerations.htm)

Dietary Supplements Health and Education Act
(http://www.cfsan.fda.gov/~dms/dietsupp.html)

European Medicines Agency (EMEA)
(http://www.emea.eu.int/index/indexh1.htm)

CPMP/QWP/2819/00 (EMEA/CVMP/814/00) Note for Guidance on Quality of Herbal Medicinal Products (CPMP/CVMP adopted July 01)
(http://www.emea.eu.int/pdfs/human/qwp/281900en.pdf)

CPMP/QWP/2820/00 (EMEA/CVMP/815/00) Note for Guidance on Specifications: Test procedures and Acceptance Criteria for Herbal Drugs, Herbal Drug Preparations and Herbal Medicinal Products (CPMP/CVMP adopted July 01)
(http://www.emea.eu.int/pdfs/human/qwp/282000en.pdf)

Food Chemical Codex
(http://www.iom.edu/project.asp?id=4585)

Health Canada Natural Health Products Regulations
(http://www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/regs_cg2_tc_e.html)

Herbs of Commerce, 2 nd Edition (2000)
(http://www.herbalgram.org/herbalgram/articleview.asp?a=2222&p=Y)

International Code of Botanical Nomenclature (Saint Louis Code) 2000
(http://www.bgbm.fu-berlin.de/iapt/nomenclature/code/SaintLouis/0000St.Luistitle.htm)

NCCAM Terms of Awards for Clinical Trial
(http://nccam.nih.gov/research/policies/terms-of-awards.htm)

Saskatchewan Herb and Spice Association and the National Herb and Spice Coalition: Good Practices for Plant Identification for the Herbal Industry
(http://www.saskherbspice.org/Good%20Practices%20for%20plant%20identification.pdf)

U.S. Food and Drug Administration: Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements
(http://www.cfsan.fda.gov/~lrd/fr030313.html

U.S. Food and Drug Administration: Guidance for Industry: Botanical Drug Products
(http://www.fda.gov/cder) (regarding the need for and content of an IND for botanical drugs)

U.S. Pharmacopeia – National Formulary monographs for botanical raw materials and extracts
(http://www.uspverified.org/standards/monographs.html

World Health Organization Guidelines on Good Agriculture and Collection Practices for Medicinal Plants
(http://www.who.int/medicines/library/trm/medicinalplants/agricultural.pdf)

World Health Organization Monographs on Selected Medicinal Plants
(http://www.who.int/bookorders/anglais/home1.jsp?sesslan=1)

招待講演 6

漢方薬の臨床試験：チャレンジとレッスン

慶應義塾大学医学部　渡辺　賢治
ミネソタ大学医学部　Gregory Adams Plotnikoff

和文抄録

漢方薬の国際化は、根拠のある臨床試験データがあってこそ可能になる。米国での臨床試験は、治験審査委員会（IRB）による承認を得なければならない。この承認は、治験の登録に必要な全ての要件の基礎となるものであり、その重要性が過度に強調されすぎてはならない。その承認には 1) ヒトでの実験に関する全ての倫理面での問題、2) データの高い信頼性に関わる全ての科学的、統計学的問題について、会議が必要である。米国では、よく知られた単味の西洋ハーブ（*Cimicifuga racemosa* (L.) Nutt.: アメリカショウマ）に関する、大学研究機関での NIH から財源を得ている臨床試験でさえ、IRB の承認がないために 18 ヶ月も遅れてしまった。ましてやよく知られていない、そして複数の生薬からなる、アジアで用いられている薬物に関してはどうであろうか。本発表では、このような問題を防ぐために、米国において開始した、桂枝茯苓丸（TJ-25）の第 2 相臨床試験の経験に基づいた考察を報告し、示唆を与えたい。米国食品医薬品局（FDA）および NIH のガイドラインや、他の関連資料についても紹介する。