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ORIGINAL PAPER

Informed Consent in Cross-cultural Perspective: Clinical Research in the Tibetan Autonomous Region, PRC

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Abstract Procedures of Informed Consent are considered a high priority for international biomedical research. However, informed consent protocols are not necessarily transferable across cultural, national or ethnic groups. Recent debates identify the need for balancing ethical universals with practical and local conditions and paying attention to questions of cultural competence when it comes to the Informed Consent process for clinical biomedical research. This article reports on the results of a two-year effort to establish a culturally appropriate Informed Consent process for biomedical research in the Tibet Autonomous Region in the People's Republic of China. A team of Tibetan and American researchers, physicians, health professionals and medical anthropologists conducted the research. The Informed Consent was specifically for undertaking a triple-blind, double placebo-controlled randomized clinical trial of a Tibetan medicine compared with Misoprostol for reducing postpartum blood loss. The findings suggest greater need for

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flexibility and cooperation in establishing Informed Consent protocols across cultures and nations.

Keywords Informed consent · Cultural competence · Tibet · Clinical trials protocols

Introduction

Informed Consent in View and Review

> The main thing about this informed consent procedure is to explain in many ways, but also simply. Those of us with education and experience, we can understand, but many others cannot. They have experience in a practical sense, but they do not know how to make sense of these sorts of decisions. First it is good to have a long discussion and then let them decide if they want to participate or not. You might want to then just have them give oral consent.
>
> Patient in a Lhasa hospital (8.03)

Over the past several decades, researchers have paid increasing attention to the complexity of designing informed consent procedures for international clinical trials (Pace et al. 2004; Emanuel et al. 2004; Karim et al. 1998). Societies with no previous experience of human subjects' protection are increasingly involved in clinical research, creating a need for greater discussion about transferability of such efforts across cultures. Indeed, the issues of comprehension and retention of research aims, methods, risks, benefits and informed consent procedures have also been shown to be unevenly understood and accepted in clinical research settings within the US and other countries in the North—and that age, gender and cultural and socio-economic difference and disparity plays a role in this process (cf. Gray 1978; Lerner 2004; Wax 1991; Saldov 1998; Sankar 2004). Dickens and Cook (2003) note that research in resource-poor settings often means recruitment of vulnerable populations who may not understand basic concepts of "research" and who may not benefit themselves from the research. Distinguishing between coercion and voluntarism in settings where subjects are at high risk of mortality from the condition being studied, and ascertaining the meaning of "informed" among subjects who are illiterate and who lack knowledge of clinical research can be

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challenging at best, ethically risky at worst. Researchers concerned with these issues have argued that the ethics of protecting subjects from potentially harmful effects of new drugs or medical procedures should be top priorities, along with ensuring that such research is justified, given the health needs and priorities of target populations (cf. Piquemal 2001; Benatar 2002; Kaufert 1996). Researchers are called upon to make every effort to ensure patients are "informed" about risks and benefits in ways they can understand and to ensure that voluntary consent is obtained (Johns Hopkins Bioethics Institute 2005).

In response to the requirement of informed consent protocols by clinical research institutions across the globe, on the one hand, and questions about the ethical versus legal function of informed consent, on the other (including cultural relevance, potential for miscommunication and coercion and whether or not informed consent is an ideal that can never be achieved), efforts to document and analyze the procedures that work best for establishing culturally appropriate and comprehensible informed consent processes in resource-poor settings are emerging, as are a variety of new approaches and methods to structure the informed consent process. Benitez et al. (2003) note that audiovisual documentation for informed consent surpasses written documentation, in terms of study subject comprehension, in populations with little formal education although this insight is not uniformly borne out across research projects (see Flory and Emanuel 2004). Many studies have found that depictions of research aims, methods and procedures through the use of still photographs, pictures, diagrams and even film help to render research in coherent, ethical, and culturally contextual ways that augment written documentation. Fitzgerald et al. (2003) note that, "research participants in a less-developed country can comprehend a complex consent form if sufficient care is taken to provide them with information" (2003: 1301). Sreenivasan (2003) recommends, "using clear, non-technical language, at an appropriate reading level, in the prospective participant's mother tongue; providing opportunities to ask questions throughout the trial; and using short consent forms" (2003: 2018). Through microbicides trials in South Africa, Freidland et al. (2002) found that sample informed consent documents needed multiple rounds of pre-testing and revision with particular attention to local languages and visual representations before collaborators were confident in their recruitment procedures.

Despite this increasing attention to the context in which research consent is given and the nature of what makes it "informed"(Flory and Emanuel 2004), miscommunication about appropriate informed consent procedures can occur at all levels, from international and national bodies to local cultural and social groups. Different nations do not always agree about their approaches to the protection of human subjects, including who should obtain consent and what sort of protections should be prioritized. Disagreements also occur within nations between specific cultural and social groups who are differently positioned in relation to research efforts (Friedland et al. 2002). This has led some to call for multinational standards that could be used uniformly across cultures, societies and nations (Dickens and Cook 2003). However, Shapiro and Meslin (2001) note, "the particular procedures for obtaining voluntary informed consent in developing countries may need to be tailored to local custom and culture." The very notion of a universal understanding

of "informed consent" belies the ways that this concept, as well as research methods and practices, are culturally, linguistically and ethically embedded. Bhutta (2004), reviewing available literature on the use of informed consent procedures in developing countries, notes that there is little accountability with regard to evaluating the meaning of "informed" among potential participants in cross-cultural encounters.

In this paper, we present research results of efforts to develop a culturally appropriate informed consent process for a clinical trial being carried out in Lhasa, Tibet Autonomous Region (TAR), People's Republic of China (PRC). As described in more detail below, open-ended qualitative interviews and subsequent survey interview data were collected in a four-step process and used to finalize an informed consent document and process for a randomized controlled trial (RCT). Although our research emerges from—and most concretely impacts—Tibetan communities throughout Asia, as well as vulnerable, resource-poor settings more generally, we argue that this case study also helps to elucidate the similarities and differences that play out across national, cultural, and socio-economic boundaries in sites of clinical research. We argue, based on our research findings, and following the lead of Friedland et al. (2002), that there is need for greater flexibility in the form and content that such procedures take across cultures, focusing on the intent of ethical and methodological efforts that might be shared across nations and cultures, rather than specifically on establishing uniform content across cross-cultural research settings.

Project Scope and Design

Developing a Clinical Research Project in the TAR

In 2000, a team of physicians, nurses, midwives and medical anthropologists was asked by the TAR Health Bureau to help develop a maternal and child health (MCH) project, including developing the ability to evaluate MCH policies and programs and to conduct empirical research. In response to this request, the US team members secured a National Institutes of Health (NIH)/National Institute of Child Health and Human Development (NICHD) grant as part of the Global Network for Women's and Children's Health Research.[1] One long-term goal of this effort has been to develop the capacities of Tibetan practitioners and health care institutions to conduct their own clinical research.

When this project began, knowledge about modern western scientific research methods was limited among Tibet's professional and educated classes, and extremely rare among the lay population. Thus, US collaborators realized that potential Tibetan participants involved in the research would have to be educated about research concepts as well as the specifics of this study as part of the informed

[1] NICHD Global Network Research Grant # HD40613 in conjunction with The Bill and Melinda Gates Foundation.

consent process.[2] In conjunction with our collaborating institutions, the TAR Health Bureau and Lhasa Municipal Health Bureau, we selected three maternity hospitals as clinical sites: the Mentsikhang (a Traditional Tibetan Medicine hospital where biomedicine is also practiced), and two biomedical facilities, the Lhasa Municipal Hospital and the Lhasa Maternal and Child Health Hospital. The directors of the three facilities' women's departments, along with representatives from the Tibetan Medical College and the Tibet Drug Administration, formed a Research Committee (RC). Since 2002, this group has worked collaboratively with US investigators in the design and implementation of various stages of a research project, culminating in a randomized controlled trial (RCT) comparing a Tibetan medicine, *zhi byed 11* (hereafter ZB 11), with a Western medicine (Misoprostol)[3] for prevention of postpartum hemorrhage. As with the development of the IC document and process, the development of the research was iterative. When we began contemplating an RCT of a traditional Tibetan medicine vs. a Western medicine, we thought we would first need to compare the traditional Tibetan medicine vs. placebo to obtain an understanding of the effect size. However, given the ethics of testing something that might be effective against a placebo (Kaptchuk, 1998a,b; Harrington 1997), we went from our baseline observational stage directly to the comparison trial.

Reducing postpartum hemorrhage was chosen for our research focus because hemorrhage is the most common direct cause of maternal mortality in Tibet.[4] Moreover, the Tibetan medicine, ZB 11, was well-known among Tibetans in urban and rural areas where it is known colloquially as *skye su ril bu* (birth helping medicine), *skye zug ril bu* (birth pain reducing medicine), and *rgyogs ril* (fast delivery medicine). Misoprostol is available and used in biomedical facilities in Tibet.

[2] Very little modern scientific medical infrastructure exists in Tibet, despite a history of medical entrepreneurialism and experimentation. Tibetan scientific researchers have only been interacting with scientists from more developed regions of the PRC and from other industrialized countries for the past several decades. Tibet's own "science of healing" (*gso ba rig pa*), based on the *rgyud bzhi* (the Four Tantras that form the basis of Tibetan medical theory and structure Tibetan medical education) developed its own research orientations at the Mentsikhang, or Medicine and Astrological Institute (established in 1916). However, while this research was empirical, it is different from the scientific empirical research that emerged over the past century in Western or iomedicine. Tibetan research consisted largely of developing new medical compounds and therapies based on the testing of potencies of various medicinal ingredients, in part through astrological calculations; minimal testing on human patients, and evidence of efficacy was often drawn from clinical observation of small cohorts of patients. Even after the introduction of biomedical hospitals, clinics, and practices in the TAR—first through the British presence in Tibet (McKay 2003), later through Chinese annexation and the training of ethnic Chinese and Tibetans, and, since liberalization and "opening up," also through the introduction of national and international health development agendas—the creation of a medical research infrastructure that resembles anything like that found in developed, industrialized settings remained nascent. Today, medical schools in the region do not train physician researchers in anything but the most elementary research techniques based on simple collection of empirical data.

[3] Brand name Cytotec, prostaglandin E1 analogue, used in biomedicine to contract the uterus (Burns 2001).

[4] This information was provided by the Tibet Autonomous Region Bureau of Public Health, People's Republic of China. The figures provided are as follows: for 2000–467/100,000 deaths/deliveries, with 45% due to postpartum hemorrhage; 2001– 325/100000 with 52% due to PPH; 2003—400/100000 with 49% due to PPH.

The study was divided into three stages. Stage One (2002–2003) consisted of: (1) ethnographic formative research on Tibetan women's beliefs and behaviors during pregnancy and childbirth; (2) quantifying patients' and providers' understandings of "research" concepts and perceived differences between Tibetan and biomedical healing modalities; (3) ethnographic, textual, and clinical research on ZB 11; (4) establishing rates of deliveries and complications and the volume of normal postpartum blood loss at the three hospitals; (5) initial toxicity screening and standardization of ZB 11; (6) initial training of Lhasa providers in all aspects of research; and (7) the commencement of a process through which a culturally appropriate, comprehensible informed consent document and protocol was developed. Stage Two (2003–2004) consisted of the development and trial of data collection tools and protocols, including the informed consent process, which would eventually be used in Stage Three, the actual RCT. Stage Two also comprised ongoing baseline data collection from the three hospitals, as well as episodic trainings for Tibetan providers in data collection and management. The final stage, Stage Three (2004–2006/7) was a triple-blind, double-placebo RCT comparing ZB 11 with misoprostol as prophylaxis for postpartum hemorrhage. Currently the consent rate in this clinical study is 74.8% or 665 consenters out of 888 who were initially asked to enroll.

Informed consent for the first stage of this research, that is, for developing informed consent procedures involving interviews, was obtained using information sheets describing our intent to conduct research and the need to evaluate methods of explaining this research to women so that they could participate with knowledge of what they were participating in and that they could decline to participate. For this stage of research, we obtained verbal agreement for consent rather than written consent because we knew, from prior research experience among several of the authors, that written consent would be difficult with patients who were not literate and could not sign their names. To attempt to ensure that this consent was "informed," we first asked informants if we could interview them to see how much of our informed consent materials made sense to them. We used an information sheet stating this with a place for the interviewer to indicate that verbal agreement for this interview was obtained. With their verbal agreement, we read through each portion of the informed consent documents and asked interviewers to repeat information or explain what they had just been told. This informed consent procedure was designed with our Tibetan co-researchers, and it was vetted by two institutional review boards in the United States (University of Utah and University of California, San Francisco) as well as an Institutional Review Board that was set up (with the help of our research team) in Lhasa.

Once we had a viable and appropriate informed consent procedure for the second and third stages of the research—that is, once we had completed the research described in this article— we used that Informed Consent procedure to obtain informed consent from all participants in second and third stages of the research project. To date, there are 624 women who have been randomized and completed in the third stage of this study. Again, although the second and third stages of research are not the subject of this article, we believe that the relatively high rate of consent in those stages may indicate that we were successful in our goal of developing a

culturally appropriate, understandable—if still imperfect—informed consent process, particularly since we evaluated patient recall of information as a part of the method for developing a final consent instrument (see discussion below).

From the beginning of Stage One, it was clear that designing the informed consent process would take time and a good deal of negotiation in and around cultural patterns. Some of the complexity of designing an informed consent process resulted from the ways that different histories and cultural experiences have engendered different ways of understanding what is being asked of participants in the Tibetan context. Other complexities arose from translation—not simply translating between three languages (Central Tibetan, English and "common dialect" Mandarin), but also accounting for fundamentally different conceptions of the body, health, treatment and disease (Adams et al. 2005a). In the end, US and Tibetan partners (and, significantly, US and Tibetan Institutional Review Boards) were successful in designing an informed consent procedure that would prove to be culturally appropriate and comprehensible, based on the results of qualitative and quantitative research. The methods described below and our lessons learned add to the growing literature on informed consent in cross-cultural perspectives and conducting clinical research in resource-poor settings.

Developing a Culturally Appropriate Informed Consent Process

The development of a culturally appropriate informed consent process took our research team approximately 12–15 months and involved an initial qualitative research period followed by three consecutive pilot studies (taken from Miller et al. 2004a).

In Summer 2003, we conducted an initial round of qualitative interviews at the three hospitals in Lhasa with 24 women and 16 hospital providers to assess their understandings of terms such as "research," "informed consent," and "blinding," their experience with medical research, and their views of birth and delivery. We also interviewed them about the relationship between Tibetan medicine and biomedicine in terms of potency, efficacy and side-effects, as well as their knowledge and beliefs about pregnancy, childbirth and our study medication, ZB 11. This work was also informed by our previous ethnographic research of Tibetan village women's perceptions, cultural practices and beliefs about safe pregnancy and birth (n = 30) (Adams et al. 2005b). In addition to interviews with patients and Lhasa-based providers, we also conducted a focus group with rural health workers aimed at eliciting their definitions and understandings of concepts such as those mentioned above, as well as specific linguistic suggestions (in Chinese and Tibetan) for how to translate concepts in complete and accurate yet uncomplicated ways to Tibetan women.

Based on the results of this initial qualitative research, we developed the first of three informed consent pilot study instruments (Appendix I). Pilot One was then administered to 16 women during September 2003. After these initial two rounds of interviews, we completed a summary document detailing the results of women's responses and then began a several-months process of refining the Informed Consent

document. Pilot Two was conducted in December 2003—January 2004 with 24 patients at the three hospitals. Based on data results from Pilot Two, we further refined the informed consent document. The result of this effort was Pilot Three, conducted in March—April 2004 to 25 patients at the three Lhasa hospitals, and in July—August 2004 with 37 more patients, for a total of 62 patients participating in this final pilot. Based on the results of Pilot Three, as well as approval of this document by US and Tibetan Institutional Review Boards (IRB), we arrived at an informed consent document that we felt we could, with good conscience, use during our clinical study (Appendix II).

Each of the three study instruments used for Pilots One, Two, and Three (all tested during Stage One of the research) were translated into English, Tibetan, and Chinese, with careful back translation and revision, a key component of protocol development. Each piloted version of the document included a brief introduction to the study project, a definition of "informed consent" in simple language, a description of the purpose of the study, the procedures used, risks, benefits, and information on the parameters of the study (e.g., patients have the right to withdraw from the study without penalty, etc.). We also collected demographic information (e.g., age, number of years of schooling completed, community of residence, occupation, etc.) for all participants. The IC documents used in Pilots Two and Three contained black and white illustrations (e.g., of how postpartum blood would be measured) to aid patients' comprehension. Throughout the development process, there was extensive collaboration between the Lhasa-based Research Committee and the foreign investigators, with the Tibetans providing critical input on the phrases used to describe study purpose, procedures, risks and benefits, as well as on the overall ethical, medical and cultural issues surrounding the initial development of such a process in Tibet.

This informed consent development process yielded a number of findings, including: views of "risks" and "benefits" that varied from Western trained researchers' perceptions of these concepts; a lack of familiarity with biomedical research concepts such as blinding and randomization among both patients and providers; challenges in determining ethically sound and culturally appropriate ways of indicating consent; issues of compensation for research participants and perceived associations between participating in research and causality of suboptimum outcomes; general issues of translation as a result of working across three languages; and the impact that the gender and ethnic composition of interview teams had on study results. The following is a discussion of these findings.

Translating "Risks" and "Benefits"

Over the course of this research, many challenges were related to problems of translation, by which we mean, again, not only language, but also how to translate a concept between different culturally specific ways of viewing the body, the causes or prevention of diseases and different understandings of risks and benefits. For example, participants stated that discussing the possibility of bad outcomes in the context of "risks" could bring such bad outcomes into reality. These sentiments are

tied to the Tibetan concept of *rten 'brel*, literally an omen or a portent that can have both positive or negative connotations. Fears surrounding vocalizations of risk are also related to Tibetan ideas that the central humoral "energy" of the body, the *rlung* (wind), will be disturbed by a patient's negative thoughts. If a patient experiences unpleasant emotions, for example, from being told about unpleasant or untoward consequences of labor and delivery, those emotions will agitate *rlung*. Since *rlung* is responsible for all movement in the body (from breathing to muscular movement), agitated *rlung*can account for the production of negative psychophysical effects. Thus, some Tibetans we interviewed believe that if one talks about possible negative outcomes of, for example, childbirth, one can actually generate forces that will bring a negative outcome into reality.

During initial ethnographic interviews, we asked the following suite of questions: "In general, do you think it is a dangerous/risky/ bad idea for women to talk about possible problems that might occur during delivery before she has delivered her baby? If so, why? If not, why not?" Patients responded with answers that affirmed this idea that it was risky. One woman said, "Yes. It is dangerous mostly because it affects the minds of the pregnant woman. If she is not happy, then it can have a negative effect on the health and well being of the baby. It can also make the birth more difficult." Another interviewee related: "Yes, this is dangerous. It is risky to talk about the problems, or even the pregnancy much before because it is scary."

As researchers, we were faced with the question of how to be honest and clear in disclosing possible risks of participating in our project, including reminding women of the causes of obstetric mortality related to hemorrhage, without causing undue distress in patients and possibly agitating their *rlung*. Such disturbances would not only be a problem in the sense that they might discourage women from participating in our research, but, more significantly, they might be perceived as a cause of medical complications (if they occurred) in delivering women, even those who chose not to participate in the study.

This finding is related to a second finding; in all three Pilot Studies, we noticed a difference in responses from postpartum patients compared to prenatal patients. Most of the prenatal patients we interviewed were less inclined than were postpartum patients to answer our questions, or even to listen to the descriptions of the study, including risks and benefits. Perhaps the postpartum patients felt more comfortable answering questions because they had already had their babies and, in that sense, were no longer at risk of disturbed *rlung*.

Given the feedback we received on women's discomfort with lengthy descriptions of risk, and after discussion with our Research Committee, we decreased the discussion of risk factors for postpartum hemorrhage and overly graphic descriptions of hemorrhage itself. Instead, we included general statements about the fact that all women bleed during a normal delivery and stated that if any of our participants appeared to be bleeding excessively they would be given the normal course of treatment for postpartum hemorrhage at that hospital, to ensure their safety. Throughout the three pilot studies, we retained a brief, basic description of the risks or benefits related to the use of ZB 11, according to clinical evidence from Tibetan medical practitioners and Tibetan medical theory. The resulting "risks" section of the final informed consent document became:

> Every woman bleeds during delivery. There are always risks during any delivery, and ways to minimize risks. The medicine we are using, ZB 11, is not a new medicine. It has been used during deliveries for eight hundred years. It is possible that those women who do not get ZB 11 may bleed more than those who get ZB 11. However, the difference in the amount of blood lost for any woman should be small and should not affect her health. Please remember that no matter what capsules you get if you begin to bleed too much then your doctor will give you prompt and appropriate treatment.

While patients seemed to grasp the basic "risks" concept clearly (although their comprehension led them to asking questions about who would pay for treatment if risks did develop into complications, as discussed below), the Tibetan members of the research team were concerned that we include the risk of "greater" bleeding among those study participants who received a placebo as opposed to ZB 11 – a group that had been initially described as the "no medicine" group. Their concern was that since the research participants understood ZB 11 to be effective in reducing blood loss, and since it was used in deliveries in the Tibetan medical hospital, those women who did not receive it, might, in theory, be at greater risk of bleeding more heavily than those who did receive it. Again, the study design initially included a ZB 11 vs placebo-only protocol and this was eliminated before the trials began. In our RCT women either received active ZB 11 and placebo misoprostol OR placebo ZB 11 and active misoprostol. No woman received only placebo, and no woman received two active drugs.

During Stage Two of the development of the informed consent process, however, the Research Committee was convinced that we should mention the fact that "those who receive placebo may bleed more than those who receive ZB 11," but this was weighed against desires to lessen women's fears of participating by eliminating explicit discussion of possible risks. Their suggested solution was to say "under normal clinical circumstances when the amount of blood loss is within normal limits, it should not affect a woman's health" and then offer descriptions of ZB 11 as not a new medicine, and reiterate the fact that neither the doctor nor patient will know which medicine the patient receives. However, as we discovered through Pilot Three, women preferred to have risks expressed simply—in ways that were non-threatening but also clear. After an initial five interviews using the RC's suggested phrasing, we returned to the original phrasing drafted for Pilot Three, quoted above.

In addition to "risk," issues of how "benefit" was conceived proved illuminating. Many women expressed benefits as not only benefits to them, but as benefits to others. For instance, benefits were expressed not in terms of the individual, but from the perspective of being a part of a collective, with a particular emphasis on poor rural women. The Tibetan word for "benefit"—*phen togs*—has religious connotations, along with its secular meaning. Specifically, it is connected to the idea of something being favorable for all sentient beings, or the source of well being for all. For many participants, the idea of being in this study was also tied to ideas of *bka' drin chen bo*, or great gratitude and kindness. When asked what the benefits of the research were, many women said the benefits were not to them now, those in the study, but were for women in the future. As such, *altruism* could serve as an English

language gloss of these concepts of *phen togs* and *bka' drin chen bo*, although these ideas of selflessness and compassion stem from different epistemological and cultural roots. Despite cultural differences, however, this finding parallels research conducted among patient populations in the US who have reported that the desire to benefit others remains a powerful motivator for participating in clinical trials.

Concepts of "Randomization" and "Blinding"

Biomedical research concepts—specifically "randomization" and "blinding"—were also quite difficult to present to potential research participants in understandable yet meaningful ways. There were no direct translations for these concepts in Tibetan. Our US IRB offices recommended that we introduce the idea of randomization by describing it as being like "flipping a coin." The relevant conceptual facts conveyed in this image are that "chance" determines the outcome of the coin toss and the outcome would determine the group to which one would be assigned. But the concept of "flipping a coin" is culturally embedded and has no referent in Tibet.

Consequently, after consulting with an anthropologist colleague and other Tibetan ethnographic sources,[5] we tried explaining randomization using the example of a Tibetan practice of drawing lots, *rgyan rgyab*. This practice is used by Tibetans (particularly nomadic populations) to distribute resources equitably and by chance to a group of families in a community. However, *rgyan rgyab* is more complex than flipping a coin. It involves several steps that, when layered together, ensure a randomization of the chances of being allocated a portion of a given resource—for example access to winter pasture or distribution of meat by nomadic herders. Based on this approximate cultural equivalence of *rgyan rgyab* and "randomization," we initially used this concept in the wording of Pilot Two, as follows: *This process (randomization) is similar to the Tibetan system of "rgyan rgyab." But, unlike rgyan rgyab, you will not know which group you are in.*

As we delved further into the cultural meaning of *rgyan rgyab*,however, we learned that, in other instances such as the selection of candidates for positions of authority, including the Dalai and Panchen Lamas in historical Tibet, *rgyan rgyab*also implied drawing lots from an already select group of choices, and thus is not entirely "random."

Despite these efforts at deriving a culturally meaningful explanation of the randomization concept, many patients from Pilot Two still did not understand the specific ways that selection for either receiving ZB 11 or not would be determined. Only six (of 24) patients were able to remark on the randomization system, mentioning things like "split into two groups" and "draw numbers from envelopes." Although we initially thought the Tibetan concept or *rgyan rgyab* would aid understanding, in practice it often created confusion in women patients for two primary reasons: first, it was sometimes difficult for women to make the leap between the details of this clinical study and cultural concepts that they did not associate with hospitals or the health care system; second, it became clear that although *rgyan rgyab* was a concept familiar to most Tibetans, it is also a type of

[5] Toni Huber.

cultural practice that belongs to a primarily male domain. Therefore, for many women, it still did not aid in their understanding of our study. In an effort to find a culturally appropriate referent for randomization, we might have inadvertently added to participants' confusion over biomedical research concepts.

To aid comprehension of the concept of randomization, we thus used drawings in both Pilot Two and Pilot Three. These drawings showed a Tibetan hospital provider selecting a numbered envelope from a group of envelopes, removing a study medication, and then giving it to a Tibetan woman patient. We described how the envelope was marked with a number that determined if the patient would receive placebo or ZB 11 when she reached full cervical dilation (the optimum timing for administering ZB 11), and then a second envelope with a randomization number that determined if she would be given misoprostol or a placebo after crowning/as the newborn's shoulder emerged (the internationally approved biomedical protocol for administering misoprostol for prophylaxis of postpartum hemorrhage (FIGO/ICM, 2004).

Like "randomization," there was also no easy translation for the concept of "blinding" in Tibetan. Blinding, in biomedical research, refers to the process whereby the patient (in a single blind placebo study), and the provider (in a double blind placebo study), and the researcher (in a triple blind placebo study) do not know who receives either medication or placebo. The assumption underlying blinding is that if a patient does not know whether or not she or he is getting active medicine, there is equal chance that patients in both groups will experience placebo effects similarly. In the case of providers, it reduces bias in treatments given to patients. In the case of researchers, it reduces bias in interpreting or reading data. Attempts to translate blinding for Tibetan research subjects initially ended up with phrases like "keeping in the dark," "obscuring the environment of the research," "like darkness in the middle of the night." When so translated, patients often responded with concerns such as one woman who said: "One should not blind or obscure the meanings/purpose of the research from the patient."

Of course, this is partly what the purpose of "blinding" is, in the sense that it is intended to prevent people from knowing who is getting the intervention medication or the placebo. However, translating the idea of "keeping someone in the dark" as a necessary step to achieving the benefits of research takes time and lengthy digressions back to the basics of Western scientific method. Rather than belaboring the merits of "blinding" as a research strategy, we simplified the concept by noting that neither the patients nor the doctor would know which medicine the patient would receive. This conveyed the concept of blinding without having to translate the precise term, and also evolved in direct relation to the ways we tried to describe randomization. We believe this approach was successful: whereas 50% of study participants in Pilot Two answered "no" to the question "Does the woman know what medicine she will receive?" 100% of women in Pilot Three correctly answered "no."

Education Level, Comprehension and Illustrations

Throughout the development of the informed consent process, we learned that level of comprehension mirrored the study participant's number of years of schooling. These

results were further impacted by whether or not participants were asked to respond to all survey questions at once, after the informed consent document was presented to them (the "recall" study group), or in stages, after each section of the document (the "proximal" study group). Without exception, those in the "proximal" study scored higher than those in the "recall" group (Table 1).

Details of the differences between these methodologies are discussed at length elsewhere (Miller et al. 2004b). Here, suffice it to say that through all three informed consent pilot studies, those who had attained at least a middle school formal education were able to recount the methods, purposes and benefits of research more accurately than those with fewer years of schooling. Similarly, many patients were able to relay information about which medicines would be used, how outcomes would be measured, and the general importance of research regardless of education level.

Yet, there remained through all three pilot studies a fairly high degree of confusion over some issues including randomization, disclosure of risks, etc., particularly in Pilots One and Two, and particularly among women with little or no education. In addition, it was quite common for women with little or no education to say that they "understood" the goal of the research, for instance, but that they could not articulate it in their own words. In general, if women had not received at least a secondary level education, they had a more difficult time understanding terms such as "research methods," and comprehending the details of the study purpose and procedures. However, this did not prevent them from being able to correctly answer questions regarding which medicine would be given, what would be measured and how, what would happen if they bled too much, and if they had the right to refuse to be in the study—core components in making an informed decision about whether or not to participate.

Table 1 Comparison of individual responses Recall Testing vs. Proximal Testing

Question	Recall Group (n = 24)	Proximal Group (n = 62)	P-value
What is the name of the Tibetan medication?	14 (58.3)	47 (78.5)	0.05
What is the purpose of the study?	10 (41.7)	47 (75.8%)	0.006
Does the woman know what capsules she will get?	12 (50)	58 (93.5)	<0.0001
What will be measured?	16 (66.7)	56 (90.3)	0.03
How will it be measured?	9 (37.5)	46 (74.2)	0.004
No matter which group you are in, if you bleed too much, what will the doctor do?	16 (76.7)	52 (84.9)	NS
Are there any risks?	1 (4.2)	16 (25.8)	0.036
Are there any benefits?	9 (37.5)	47 (75.8)	0.002
Can you refuse to participate?	15 (62.5)	58 (93.5)	<0.001
Will you be paid?	18 (75)	58 (93.5)	0.025
Do you have to pay to be in the study?	15 (62.5)	59 (95.2)	0.002

As others (cf. Friedland et al. 2003) have also noted, the use of illustrations and other types of graphics among populations with little or no formal education greatly aided comprehension, and also made it easier for women to imagine being in the study. They could visualize the process they would go through. During Pilot Two and Pilot Three, in which we used illustrations to aid understanding, nearly 100% of participants in both pilots said that the illustrations did help increase their comprehension, even if they still found parts of the research confusing.

Issues of Payment and Responsibility

Perhaps one of the most confusing issues raised during Pilot One and Pilot Two was the question of who would ultimately be financially responsible for treatments for patients enrolled in the study who suffered hemorrhage and who might need medical treatment. Our Tibetan colleagues suspected that some patients would interpret our informed consent disclosures that read, "You will not have to pay to be in this study," to mean that the cost of their medicines—not only the study medications but also any other necessary interventions—would be covered by our research funds. In order to avoid this sort of confusion with patients, in both Pilot Two and Pilot Three we included the following phrase: "If, at any time during the delivery, your blood loss increases beyond safe levels, you will be given the normal treatment for this condition at this hospital regardless of what medicine you receive." We also added the phrase: "The researchers will only pay for the study medications." This would mean, for example, that patients would be expected to pay, or use their health insurance to pay, for all other medications or treatments besides the actual study medication.

These negotiations raised concerns about responsibility and causality among the Research Committee as well as US researchers. We were concerned about the possibility that people enrolled in our study would be denied necessary treatment if they could not pay for it—that is, if they did not have health insurance or funds enough to cover cost of treatment. We had seen patients leave the hospital of their own volition because they assumed they would not get care if they could not pay. Some members of the RC took our initial phrasing—and, more importantly, *their* interpretation of Good Clinical Practices (GCP) in China[6]—to mean that the US researchers and sponsoring agencies would provide a guarantee to all patients that the hospitals or research team would pay for all treatments outside the study medication. For RC members whose hospitals were less financially supported by the TAR government, this seemed like a reasonable request; but for other Tibetan

[6] Good Clinical Practices (GCP) are a set of PRC standards and regulations dictating ethical medical practices, particularly as they relate to clinical trials and the development of new drugs. These GCP practices follow their US FDA and WHO counterparts, with specific additions and changes made in accordance with PRC social and political circumstances. Some of the specific issues covered by the GCP are: assessing clinical safety for drugs intended for long-term treatment of non-life threatening diseases, clinical safety data management, structure and content of clinical study reports, ethical factors in the acceptability of foreign clinical data, and a variety of considerations in the structuring and execution of clinical trials. These data are worthy of a separate article.

counterparts, and to US investigators, this was taken to be a potential violation of research ethics—namely, inviting the possibility of coercion and the hopes that by enrolling in this study, patients would receive free, quality care during their delivery. Both views and both ethical and socio-economic realities, were valid and needed attending to.

After lengthy discussions with members of the Research Committee and the Tibet IRB, we clarified that technically, official government rules of GCP enabled even the poorest Tibetans who had medical identity cards (indicating their poor economic status) to be eligible for hospital subsidization of their treatments. Our goal, then, was to ensure that such state policies were followed for all patients enrolled in our study; our main concern, of course, remained focused on the potential case of life-threatening emergencies and other serious complications. Neither US nor Tibetan counterparts wanted to be involved in a project in which any patient could die because they could not afford appropriate treatment. Yet despite good relations with TAR and Lhasa Municipal Health Bureaus, ultimately the enforcement of TAR government health policy remains outside the realm of what US researchers or sponsoring agencies have authority to address.

Indicating Consent

Another challenge to US and Tibetan researchers was how to demonstrate that illiterate women understood the informed consent process and gave their consent. One suggestion from the US IRB offices was to use a finger or thumbprint. However, qualitative interviews uncovered that many participants feared that our asking for a fingerprint would be a reminder of negative experiences during the Cultural Revolution. Apparently citizens accused of political crimes during the Cultural Revolution (a fate that could potentially befall anyone) were forced to admit their guilt by affixing their thumbprint to a "confession." Going further back into feudal Tibetan history, some Tibetans associated signing with a thumbprint as a negative reminder of relationships such as indentured servitude, which were sealed with a thumbprint. Some of the responses generated to the idea of indicating consent with a thumbprint included: "It is not so good to use the thumbprint method because, before, when we did something that we were punished for by law, then we would have to put our thumbprints. So this might make some people feel bad." We were also told, "Signing the thumbprint does not make me happy. It brings bad memories." Given these responses, we removed the thumbprint as an option for indicating consent and, on all three Pilot Studies, asked for either signature or verbal consent.

A further challenge about indicating consent was whether only a woman could sign for herself, or if a relative could sign the consent for her. According to some study participants, delivering women and recently postpartum women often "lose" their ability to speak. This could be simply a matter of fear and pain, or perhaps one manifestation of what in the US we might call "postpartum blues" in the case of post-delivery. However, this notion was expressed both by participants and by their elder female relatives. In some instances, these elder female relatives "helped" the

post and pre-partum women by answering questions for them. This raised issues for indicating consent: first, the difficulty in gaining consent from women who either feel they cannot speak, or prefer not to speak, in the ensuing time between admission to the hospital and going through the screening and informed consent processes for the study. Second, the role that relatives could play in granting "consent" or in being involved in the consent granting process. Some participants said that they would prefer to have a relative sign for them.

Initially, US researchers were told by Tibetan colleagues that conventionally in China, research projects were able to use signatures or permission from patients' relatives if the patients were unable to sign or consent for themselves, and that current practice in Lhasa hospitals did allow for women to have relatives sign release papers for emergency surgical procedures (Cesarean deliveries). After further discussions with our research committee, we learned that potential participants who did not feel comfortable providing consent to be in the study on their own were not necessarily uninformed or unwilling to participate, but rather that they might be too shy or, in the case of labor, too preoccupied and in pain, to give consent.

Since some of the women entering the study might wish to defer to family members to give consent for them, we initially decided to follow what our colleagues said was the Chinese convention and allow family members to provide consent when a participant was unable or hesitant to provide this herself. However, in early 2004, we found out from our Tibetan researchers that regulations regarding informed consent and use of human subjects were now available in the Chinese GCP regulations. Our research committee interpretation of these regulations was that the only acceptable form of consent was for the woman, and the woman only, to either sign or make a thumbprint indicating consent. Thus, although the Tibet IRB was sympathetic to the possible historical/cultural problems of the thumbprint, and was sensitive to our findings that some women would prefer family involvement and a family member signing the consent for her, they felt now that they were involved in an international research project they must concede to the PRC regulations. Likewise, the Research Committee felt that they should defer to the IRB, and adhere to these TAR/PRC regulations. In the end, the TAR IRB determined that consent must be indicated by a signature, or a thumbprint if the consenting patient were illiterate. The participating US IRBs took their lead from their equivalent Tibetan institution and this protocol was sanctioned by the clinical study's Manual of Operations.

Languages and Translations

Throughout the informed consent development process, language proved to be challenging. We were not only working with one language, but with three (English, Tibetan, and Chinese), and since both Tibetan and Chinese are languages that can differ greatly in their written and spoken form, we had to negotiate across these boundaries to create a document that is both user-friendly and comprehensible, and that can be used as a clear springboard for oral discussion—the real basis of the informed consent process.

A key issue of language and translation is that the majority of patients with secondary and above years of schooling, preferred to have explanations given in a

combination of Tibetan and Chinese. Any biomedical terms, particularly new words such as "capsule" and "placebo" were easier for women with secondary or college education to understand when they were spoken in Chinese. However, for women with no or few years of schooling, understanding these words in Chinese was impossible and explanations were given in Tibetan only.

Furthermore, for our own understanding of the back-translated version of our informed consent documents in English, we needed to adopt a "meaning-based," as opposed to literal, word for word translation. The most significant example of this was in relation to the definition of placebo. In English, placebo is a well-known term. In Tibetan, the word placebo is very new and is translated literally as "mind healing medicine" (*sems gso'i sman*)—most likely an adaptation from the Chinese *an wei ji*, which means roughly the same thing. While in all informed consent document translations (English, Chinese, and Tibetan) placebo was described as "a pill with no medical effects," a literal back translation into English would have read "A mind healing medicine that has no medicinal effect." A phrase that not only would have been confusing (medicine that has no medicinal effect), but might have indicated to US IRBs that we were describing a placebo as having an active ingredient, such as an "anti-anxiety" medication. In our final informed consent document, we added a phrase that alluded to the placebo effect: "placebo is a pill with no medicine in it, but that helps put patients at ease during research."

Gender and Ethnicities in Composition of Interview Teams

Finally, it is important to reflect on the ethnic and gender composition of the interviewing teams. For the most part, teams comprised of only women, for example, one Tibetan and one westerner, worked best. Women said that they felt most comfortable in this environment; our male and female Tibetan staff noticed the same. One male, one female Tibetan teams also worked well, so long as the women did more of the explanations and the men acted as recorders. All male Tibetan teams sometimes provoked shyness or a refusal to participate in the interview. Speaking in Chinese exclusively (either by one of our Tibetan staff or by US researchers) tended to be least productive, sometimes promoting suspicion in the women or their relatives. In addition, translation between English, Tibetan, and/or Chinese often did not work well because it made the overall time of the interview longer—a point that many women raised as a deterrent to both engagement and comprehension. Beyond this, women tended to listen most carefully and respond best when a hospital health provider introduced the study and the team. This bodes well for the actual administration of the Informed Consent process by providers in Stage Two, although it also brings with it a variety of power and authority issues.

Discussion: "Informed" and "Consent" on What Basis?

Our efforts to design and subsequently improve the comprehensibility and cultural appropriateness of our informed consent process proved useful. Respondents

showed increased comprehension about the purpose and the research methods. Moreover, the initial effort to collect basic cultural information about knowledge of research and context for subject participation proved very helpful. An informed consent document was designed that was culturally sensitive and did not offend, frighten, or deter patients from participating in the research. We also found that our efforts to ensure patients were "informed" about the research remained challenging. Even with our use of illustrations and culturally appropriate terms, the patients with the least formal education consistently showed lower levels of comprehension. Still, we noted that in a number of these cases, it was clear that "comprehension" might not mean the same thing as producing correct answers to our pilot questions.

One interesting outcome of the refining of the process is that patient's ability to articulate perceived benefits and risks appeared to be less during Pilots Two and Three than during the initial ethnographic interviews and Pilot One. We believe this may be an artefact of the interview method (moving from open-ended ethnographic discussion of concepts to closed-ended questions). For example, patients being interviewed during Pilot One were nearly all able to articulate some benefits to the research. One woman put it as follows:

> The benefits are potentially of two kinds. First, if people are suffering from a particular problem and the research makes clearer how to get medicines that help, then this is one benefit. The second is that it is more of a benefit for rural people, rather than urban people. The people from the countryside are poor and they don't have good access to good doctors. So if they participate then they will get good care and medicines without having to pay. But the richer people from the city, they will say, "If I participate, what are you going to give me?"

Another participant in Pilot One reflected a similar sentiment: "It will be very beneficial for everyone in the future," she said. "For example, the patient in bed #27, when her child has a baby then that baby, when she gets a baby, it will be beneficial. But for now, we won't directly benefit, but it is still beneficial for the future."

The process of developing this comprehensible informed consent process provoked discussion about the limits to our effort to assess knowledge and level of comprehension. Discussions among the Research Committee posed comparative scenarios: Both Tibetan and US members wondered how many respondents in the United States would be able to remember details of the research process in comparison with our Tibetan respondents, a question also raised by other researchers in different locales (Sreenivasan 2003). Even in resource-rich countries like the United States, response rates might be similar, and that they also reflect varied degrees of formal education, cultural familiarity with concepts of research, issues of race, class, and ethnicity, and so on (Flory and Emanuel 2004).

Furthermore, while we knew that it was important for the process to convey as much information as possible in as comprehensible a fashion as possible, we also wondered what the limits to our ideas about "informed" should be. Voluntary consent in the United States is premised on the assumption that subjects will be able to make informed decisions about their willingness to participate. This means

ensuring that patients are given as much information as possible about the nature of the study, its methods, and possible risks and benefits. While this does mean ensuring that patients understand their rights and options in relation to the research, and while it does imply ensuring that they comprehend what will happen to them (to the extent that the research can disclose this) and what they will be expected to do, it does not necessarily mean that patients understand the *rationale* behind such things as randomization, techniques for measuring or comparing results, or even the nuances of variables that are included in the research. Basing our outcomes on those of Fitzgerald (op. cit.), we believe that our final pilot survey results with 75–100% accurate responses for many of the questions (again, see Table 1) demonstrates that the final informed consent process was adequate for conducting the research and for ensuring that patients who agreed to participate in the research would be sufficiently "informed" for meeting the ethical standards we held for research in our own country.[7] The IC process remains an important component of our research in Tibet. The training involved in working with the Tibetan data collectors/clinicians was a multi-directional experience in learning and cultural exchange. We are also continuing to refine and improve our IC process. We have recently completed a comparison of over 100 postpartum participants for their retention of the information in the IC document by re-asking the same questions 2–3 days after delivery. These data are being analyzed.

Conclusions

Negotiating Consent Across Languages and Cultures

The experience of developing an appropriate informed consent procedure for use in clinical research in the Tibetan context suggests the need for flexibility in negotiations between nations, home institutions, and local research teams across cultural divides. The mandates and models for protecting human subjects from US funding institutions and universities need to play an interesting game of give and take in this process. On the one hand, they need to make every effort to have their researchers meet their own national standards for protecting human subjects, a set of requirements that is largely driven by both ethical and legal infrastructures. On the other, they need to be flexible in their ability to accommodate foreign cultural, national, and ethical priorities.

The issues that are raised by this research on developing an appropriate informed consent process arise not just from cross-cultural differences, but also from the fact that different nations engage in constructing institutions for the protection of human subjects differently. US IRB's (Institutional Review Board's) requirements for inclusion of such things as a "patients bill of rights" or "full disclosure of all possible risks," as well as use of "randomization" and insistence on written consent, may appear unreasonable, not only to patients, but to collaborative research

[7] Fitzgerald et al. (2003) note that 75–80% is an appropriate threshold for comprehension on an oral exam for inclusion in their research.

partners for whom such requirements may not be translatable or, may even be at odds with foreign nations' own conceptions of rights, duties, and obligations of citizens. Insistence on doing things only one way can appear to some collaborating individuals or institutions as acts of intellectual and ethical imperialism.

While the onus falls on the US members of international research teams to convey to their US IRBs the rationale for revising standard protocols for informed consent given specific cultural constraints, it also falls on the US IRBs to respond flexibly to such information. New questions about the protection of human subjects through informed consent processes are being raised by the current international efforts to design research projects, such as the ones described herein. Yet the question remains: When can the US institution relinquish accountability, and to what extent and when and where must they insist on following "home" or "funding" country institutional standards to protect themselves? Can there be international standards and criteria when such "universal" protocols may not be in the best interests of the patients, or the greater clinical and cultural settings in which the research is taking place? If there are not international criteria, what then are the cultural and scientific criteria by which we can reasonably assume that subjects are being protected in their participation in such projects?

Efforts to cultivate a deeper sense of the cultural context within which research is being done should begin with the assumption that "informed" is a concept that should travel in two directions. While researchers want to ensure their subjects are "informed" about the nature, responsibilities, rights and effects of research, so too should researchers make sure they are "informed" about the cultural contexts of the places where they work and make efforts to adapt to these contexts where appropriate. These are the issues raised by current research efforts and are starting to be addressed in places like Tibet.

Appendix I: Informed Consent Form Version 1 with Questionnaire

We are members of a team of Providers and Researchers from the Tibet Autonomous Region (TAR), China, and America who are working together on maternal and child health in the TAR. Our project does two different kinds of work. Our team trains Shang-level health workers in maternal and child health, and delivery skills, using both western/biomedicine (*chi-lu man; gya man*) and Tibetan medicine (*Bod gyi man*). We are also doing research about maternal and child health problems and Tibetan medicine, with a particular focus on helping women with safe delivery.

We will now explain how we are planning to do this research, which will compare ZB 11 (*zhi byed* 11), a Tibetan medicine, with Misoprostol, a Western medicine. You might know this Tibetan medicine by the term "skye su rilbu" as well. We believe that both medicines can help reduce blood loss during delivery. Before that study can be done, we first need to a preliminary study comparing use of ZB 11 to no use of ZB 11. The main goal is to see whether or not ZB 11 reduces the amount of blood lost during pregnancy.

Before we start the research, we must first design a procedure for getting permission from patients to participate. In the West we call this "informed

consent." The first step of the research project will not begin until after a few months. Today, we will just ask you to listen to a description of the project and tell us what you understand or do not understand in this description.

Could we interview you about this process? (check here if verbal consent given)_____

In this research, we will tell women the following:

Purpose of the Study

All women bleed during delivery. This study will test to see if a Tibetan Traditional Medicine, *Zhi B*, works to reduce the amount of bleeding during the final stages of labor.

Procedures

If you choose to participate, here is what will happen:

- you will choose a number from an envelope and this will determine if you will be in the group that gets the medicine or does not get the medicine; this process is like the Tibetan system of "*gyan gyab*."
- your health care during pregnancy and labor will be observed and notes will be taken on your care, but your name will be kept confidential;
- your provider will use a drape to measure blood loss; this means the staff will place a soft plastic receptacle underneath your buttocks to measure the amount of blood that is lost during delivery. Remember that all women lose blood during a normal delivery. We will now show you a picture of the drape. After the blood is measured, it will be safely disposed of. We will compare the amount of blood lost between the two groups.
- if, at any time during the delivery, your blood loss increases beyond safe levels, you will be given the normal treatment for this condition at this hospital even if you are in the "no medicine" group.

Potential Risks and/or Discomforts

We anticipate no risks or discomforts as a result of participation in this study. If you are in the "no medicine group" but your doctors are concerned that there are any complications with your delivery, they will give you the normal course of treatment for such conditions to ensure a safe delivery.

Potential Benefits

There may or may not be any direct benefit to you for participating in this study. Indirect benefits may come to many delivering mothers in Tibet, if we are able to show that Tibetan medicine works to reduce blood loss.

Please note that:

- Your participation in this research is entirely voluntary;
- You may decide not to take part or to withdraw from the study at any time without losing the benefits of your standard medical care;
- Your decision with not affect your care providers
- There is no cost to you for participating in this study
- You will be paid to participate in this study

Other Questions

If you ever have questions about this study, you should contact Pasang Tsering at 6338824.

Consent Page

If you have read the informed consent, or had it read and explained to you, and you understand the information and voluntarily agree to join this study, please sign your name or make your mark below or give verbal consent.

- _____ Yes _____ No

Volunteer's name_____ Volunteer's signature_____ Mark_____ Date_____

Witness' name_____ Witness' signature_____ Date _____

1. After having this read to you, do you feel you understand the research?
2. Would you be nervous or shy about participating?
3. Would you participate?
4. What is the goal of the research?
5. Is medical research important, in general?
6. Why or why not?
7. How is this research going to be done? (explain steps that can be remembered)
   a. What is the selection of patients based on?
   b. What medicine will be given?
   c. What will be measured?
   d. How will this be measured?
   e. Are you concerned about the collection of blood in this way?
8. If you are in the "no medicine" group and if you bleed too much from delivery, what will the doctors do?
9. If you decide you do not want to participate, can you ask to not be included in the study?
10. How much of the details of research should a patient know before participating in this study?
11. What risks will you take if you participate?

12. What benefits will come if you participate?
13. Will you be paid to participate in this research/must you pay to participate?
14. Does any part of the research seem confusing?
15. Do you have any suggestions for the researchers?

Questions for Patient:
Date:
Location:
Patient ID:
Age:
Education:
Language of Interview:
Profession:
Home:
Parity/#live births:
Where delivered last baby:
Current status (antenatal/postpartum):

Appendix II: Feasibility Study of Traditional Tibetan Medicine, *Zhi Byed 11*, to Prevent Post-Partum Hemorrhage: Informed Consent Document

Hello! How are you today? We are members of a team of medical providers and researchers from America and China's Tibet Autonomous Region (TAR), who are conducting research on a traditional Tibetan medicine called zhi byed 11 (ZB 11). You might know this Tibetan medicine by the name "skye su rilbu" as well. It is believed that ZB 11 helps to reduce blood loss after delivery. So we are comparing using ZB 11 to not using ZB 11. The goal is to see whether or not ZB 11 reduces the amount of blood lost after the baby is born."

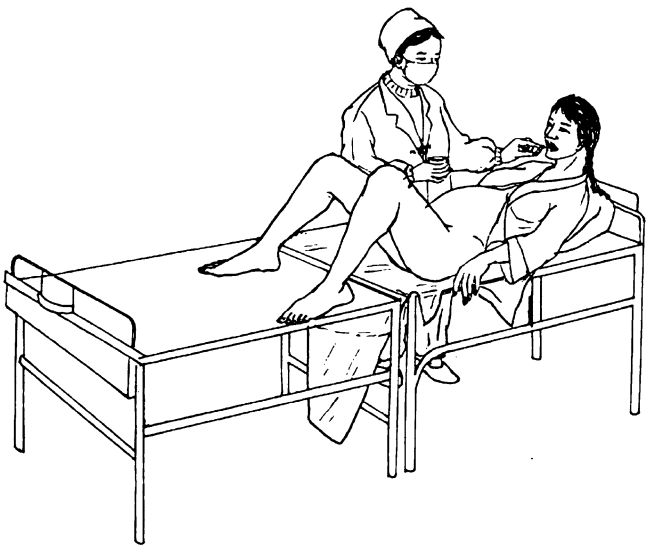
Purpose of the Study

All women bleed during delivery. While some bleeding is normal, too much bleeding can become a problem for the mother. This study will test to see if a Tibetan Traditional Medicine, *Zhi byed 11*, works to reduce the amount of bleeding after the baby is born.

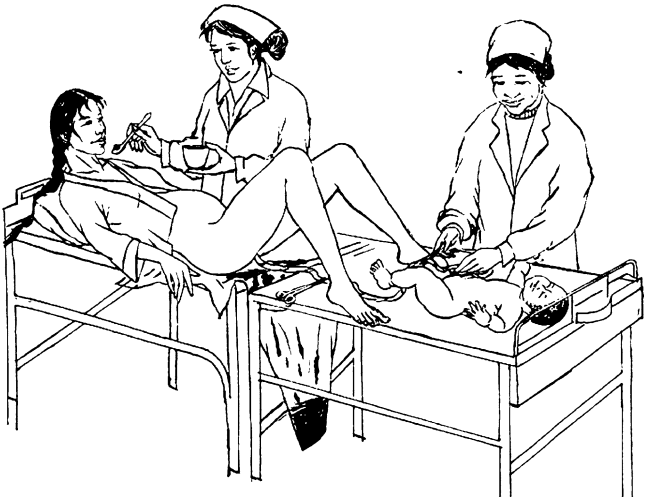
Procedures

If you choose to participate, here is what will happen: when you are ready to have your baby, your doctor will draw an envelope from a box. Some of the envelopes contain ZB 11 and some of the envelopes contain "placebo," medicine that has no medical effect,

but is made to look just like ZB 11. You have twice as much chance of getting the ZB 11 as you do of getting the "placebo." Neither you nor your doctor will know which you get.



Your doctor will give you the medicine when you are ready to have your baby.



Your doctor will use a plastic bag called a "drape" to measure the amount of blood you lose after your delivery

If, at any time during your delivery, your blood loss increases beyond safe levels, you will be given treatment for the condition no matter what medicine you received. At any time during your labor you will receive any medication that your provider believes is necessary for your health and the baby's health.

Potential Risks and/or Discomforts

Every woman bleeds during delivery. There are always risks during any delivery, and ways to minimize risks. The medicine we are using, ZB 11, is not a new medicine. It has been used during deliveries for eight hundred years to help speed and aid childbirth and prevent blood loss. It is possible that those women who do not get ZB 11 may bleed more than those who get ZB 11. However, the difference in the amount of blood lost for any woman should be small. Please remember that no matter what medicine you get, if you begin to bleed too much then your doctor will give you prompt and appropriate treatment.

Potential Benefits

There may or may not be any direct benefit to you for participating in this study. If you get ZB 11, there is the possibility that you will lose less blood after delivery than those who do not get ZB 11. Indirect benefits may come to many delivering

mothers in Tibet, if we are able to show that Tibetan medicine works to reduce blood loss.

Please note that:

- Your participation in this research is entirely voluntary;
- You may decide not to take part or to withdraw from the study at any time without losing the benefits of your standard medical care;
- There is no cost to you for participating in this study;
- You will not be paid to participate in this study;

Do you have any questions now?

Other Questions

If you ever have questions about this study, you should contact Pasang Tsering at 633-5561.

Consent

If you have read the informed consent, or had it read and explained to you, and you voluntarily agree to join this study, please sign your name or make your mark below.

- _____ Yes _____ No

Patient's name_____ Patient's signature or mark_____ Date_____
Witness' name_____ Witness' signature_____ Date_____
Provider/Researcher's name_____ Provider/Researcher's signature_____ Date_____
Provider/Researcher's address and contact information_____

Please note: Women who are consented but subsequently become ineligible before randomization (i.e., develop signs of any exclusion criteria after consent but before being given study drug) will receive only a screening form (ZB 01) and will be treated routinely as per hospital protocol.

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