An exploration of the philosophy and environment of a South African randomized, double-blind, placebo-controlled trial of *Lessertia frutescens*

Olajide Oloyede  
Research in Anthropology and Sociology of Health (RASH)  
Department of Anthropology and Sociology  
University of the Western Cape  
Private Bag X17, Bellville, South Africa  
E-mail address: jide.loyede@gmail.com

Abstract
The current paper describes the context setting that was undertaken when designing and conducting the first pilot study of the safety of Sutherlandia (*Lessertia frutescences*), a plant indigenous to South Africa which is generally used, in the country, as a traditional medicine in the treatment of a number of illnesses, including symptoms associated with HIV/AIDS. It asks: Do the researchers who conducted the clinical trial consider the rationale broadly, profoundly and objectively enough? It examines how and why the context setting was undertaken and highlights important aspects of the culture and organization of the clinical trial which might have influenced the participants’ experiences in trial recruitment and participation. The general aim is to build a picture of the environment in which clinical trials were offered and administered. This is because properly conducted clinical trials are key to the knowledge needed by health care bodies to deliver effective, safe and economically sound treatment. The focus is on the organization of the work of the Institute that conducted the clinical trial, the place of trials work within the institute and the beliefs, attitudes and practices of the staff.

Key Words: Sutherlandia, clinical trials, South Africa, SAHSMI, placebo-controlled
Introduction

This paper is the second piece derived from an on-going study of the philosophy, ethics and environment of the clinical trials of herbal medicines which forms part of the wider effort to deal with HIV/AIDS in South Africa. Earlier paper dealt with the epistemological issues that such clinical trials, which are generally concerned with the efficacy and safety of widely used herbs with long history of use by indigenous peoples, throw up (see Oloyede, 2010). The current paper explores the philosophy and environment of the double-blind, placebo-controlled trial of sutherlandia (Lessertia frutescens), a shrub that belongs to the fabrica family. The shrub is indigenous to South Africa and is used to treat such illnesses as cancer, tuberculosis, diabetes, and associated symptoms of HIV/AIDS (Oloyede, 2010). The focus is the context setting that was undertaken when designing and conducting the trials. The aim is to build a picture of the environment in which the clinical trial took place – the organization of the work of the Institute that undertook the trial, attitudes, beliefs and practices of the Institute’s staff, the process of recruitment of trial participants.

The method used to guide the research from which this paper is based is the interview. The choice of this, from the outset, was informed by the thinking that it would allow one to theoretically interpret the information collected. This methodological framework was considered, also, to allow an emphasis on the importance of exploring the issue at hand within a wider context. Because the first trial was conducted before the current study, observation was not possible; observation would similarly have allowed emphasis to be placed on the experience and behavior of the staff, also, within a wider context. Previous research studies of clinical areas in, for example, palliative care where the aim of the research is to understand the environment in which care is provided (Glasser and Strauss, 1965; McIntosh, 1977) provide what would seem to be the evidence of such a research technique. In the present study, data was collected by informal and formal conversation with staff as well as reading documents relating to the trial such as trials’ protocols and informed consent documents. It is essential to point out that the research role adopted and which is still being adopted in the on-going study of which the current paper is derived is that of a peripheral staff member – senior research associate at the Institute. I have been able to interact with those involved in the unit as researchers, clinical investigators and lecturers without actually becoming a full member. The advantage is that I have been able to ask questions freely. The data collected from the informal conversations with staff were supplemented by the formal semi-structured interview with the Director of the Institute. Data from the former were recorded in the form of notes while those from the latter were recorded both in the form of notes and tape-recording. The semi-structured tape-recorded interview consisted of 5 broad areas for discussion: the Institute’s philosophy of clinical research, staffs’ professional background, training and herbal medicine experience, opinions about herbal medicine, knowledge about phases I and II drug trials and how they are managed generally and in the Institute and relationship with members of the multidisciplinary team involved in clinical trials and funders. The paper is in two sections: the first section which describes the wider context of clinical trials in South Africa and the description of the Institute and the second section which describes the conducted trial and the process of the trial.

Conceptually, this paper makes two important points: First, what is described provides support for the idea of the mainstreming of herbal medicine, whereby such medicine is increasingly being seen as a partner with biomedicine in health care. The implication of which is perhaps what one can conceive as a new ‘social order’ in health care whereby medicine becomes more humanized and traditional herbal medicine becomes more rationalized (Ruggie, 2004). Secondly, the description is less about the herb, sutherlandia, than about those who are shaping the process of mainstreaming herbal medicine, which in my view, can be thought of not only as a process of understanding traditional herbal medicine in terms, that perhaps, will be familiar to biomedicine (Ruggie, 2004) but also the bringing to the fore of these medicines and the politics of the enterprise. For if, as Ruggie (2004) rightly points out, clinical trials find that certain herbal medicines are safe and effective, and if the trials explain how these herbs work in terms that biomedical health practitioners can understand, and in addition to these, how traditional herbal health practice differ in theory and practice from conventional medicine in ways that biomedical health practitioners can not only understand but also appreciate, then, we can expect a degree of mutual respect for the differences. Some traditional healers on a UWC CDC-PEPFAR Project in which I am involved anticipate these happy scenarios and welcome mainstreaming for the legitimacy it promises. However, some question the motive for mainstreaming and are concerned about its outcome (Oloyede, 2010, Ruggie, 2004); others focus on the process of mainstreaming demonstrating contesting ideas about nature, disputes about philosophies of knowledge and the appropriate models to test an African traditional medicine (Gibson, in this volume). At a general level, the points made in the current paper and the “messy process” Gibson highlights in this volume both speak to one point: the clinical trial of herbal plant to establish its safety and efficacy is not a straightforward enterprise, whichever way one looks at it.

Clinical Trials in South Africa

One can confidently make the claim that clinical trials of drugs in South Africa have become well established. Though, one must add, it is only of recent that such trials took a firm footing. In fact, within the past ten years of the emergence of the continent as a prominent region for clinical trials, South Africa has become a leading clinical trials-site. Countries in Latin America, Central and Eastern Europe as well as Asia still remain dominant sites for clinical sites as many observers have noted; nevertheless, some
countries in Africa are seen as attractive for such trials by pharmaceutical firms as the cost of developing biopharmaceutical products mounts and subject recruitment for such trials becomes more difficult in the United States and Western Europe, the two leading sources of funding for biopharmaceutical products. The remarkable growth in clinical trials in South Africa has been attributed to two general factors: the strong economy and the regulatory standards for conducting clinical trials (Virk, 2009). Added to this are what effectively attract pharmaceutical firms to Africa for clinical trials: a large diverse population, an essential for clinical trials and the fact that a significant number of those enrolled in clinical trials have not received any previous treatment for their disease, either because, as Virk (2009) notes, it is not available to them or they cannot afford it. There are also what can be referred to as the costs issues: the low cost of recruiting subjects as mentioned earlier and the lower risk of litigation and where litigation arises, the low cost of settlement.

Whilst all the above factors account for the phenomenal growth of clinical trials in South Africa, a highly significant variable that must not escape the mind is disease; the reference here is to those diseases prominent in South Africa such as HIV/AIDS, tuberculosis and diabetes. It is these disease areas that clinical trials occur most (Virk, 2009). HIV/AIDS, as most observers would agree, is an industry in South Africa. This owes to the very high prevalence of the disease in the country. The 2008 UNAIDS Report on the disease put the statistics of those living with HIV/AIDS at 5.7 million as at the end of 2007. Within this industry are epidemiological and clinical studies aimed at developing vaccine against HIV and drugs for the treatment of AIDS and also trials of herbal medicines used by traditional health practitioners to deal with symptoms of HIV/AIDS. Such trials test for efficacy and safety. The attempts to develop HIV vaccine began in 2000 with the establishment of the South African AIDS Vaccine Initiative to co-ordinate the development of HIV vaccines for South Africa. The first such large-scale study to evaluate a candidate for it (HIV vaccine) was started recently by American and South African collaborators (Hutchinson, 2007). The trial involved up to 3000 participants at five sites throughout South Africa and previous Phase I and II trials reveal the vaccine to be safe and effective against HIV in more than half the subjects tested. Very closely associated with HIV is tuberculosis (TB) with up to 60% of adult TB patients diagnosed as HIV-positive according to the 2006 USAID Infectious Disease Report on South Africa. The association of Tuberculosis with HIV/AIDS is more than biological: both are markers of, among other things, social inequality, lack of power and poor or insufficient nutrition in the African context (Gibson, 2010). There are clinical trials aimed at developing vaccine for TB. One of such, which is very advanced, is the proof-of-concept trial at the University of Cape Town which was tested as a Phase III.

A very significant part of the wider environment of clinical trials is the regulatory and ethical framework which is similar in principle to the International Conference on Harmonization for Good Clinical Practice guidelines (ICH GCP). This framework, the South African Good Clinical Practice (GCP) guideline, earlier published in 2000, was strengthened and made tougher in 2006. The approval processes for clinical trials are lengthy and average 12 to 14 weeks but are consistently adhered to by the Medicines Control Council which is responsible for scientific, medical and ethical issues relating to clinical trials applications in the country. This is largely complemented by the non-profit body South African Clinical Research Association (SACRA) and the local Industry/Regulatory Task Group (IRTG) as well as ethical committees of university medical schools. Since there is obviously no clinical trials that does not require subject recruitment, guidelines for this emphasize the need for community engagement, which, within the health field, is often held to be the ‘process of working collaboratively with relevant partners who share common health interests and goals (Tindana et al., 2007). Guidance Point 2 in the 2007 UNAIDS document on ethical considerations in biomedical HIV prevention trials emphasizes the importance of community involvement and meaningful participation to help “ensure the ethical and scientific quality and outcome of proposed research, its relevance to the affected community, and its acceptance by the affected community” (UNAIDS 2007, 10). The clinical trial of sutherlandia for safety and efficacy is part of the wider attempt to deal with the HIV/AIDS pandemic and the regulatory and ethical guidelines referred to above inform the process of the trials. However, one must not assume that all clinical trials necessarily follow the guidelines and regulations irrespective of how tough these are and it becomes essential that individual clinical trial should be examined. Our concern in this paper can be considered as one of such an examination.

Clinical trial of sutherlandia

We start our discussion in this section with what is widely considered the gold standard in clinical investigation – the randomized clinical trials, (RCT). What is presented are the essentials which serve our purpose: to build a picture of the environment of the clinical trial of sutherlandia; a task premised on the understanding that properly conducted clinical trials of herbs are key to the knowledge needed by health care bodies to deliver effective, safe and economically sound treatment.

It would seem to be a general knowledge that scientists hold, generally, that evidence results from the application of scientific methods of research that include the deductive construction of hypotheses and experimental testing. In the medical community, this method takes a different form when applied to biomedical research. The method is the randomized clinical trial (RCT). It is, probably also, a general knowledge that when scientists develop an experimental design, they must first specify their research question and the population and treatment to be studied after which the appropriate methodological techniques are developed to assure that ‘the purported causal relationship...
between the intervention (independent variable) and the outcome (dependent variable) is as free as possible from extraneous factors, which, in some ways, must be “controlled for” to eliminate their intrusion (Ruggie, 2004). What inform this methodological task are not only the research questions but what tends to occasionally slip out of the mind: the preferences and predilections of the scientist. In RCT, as the medical literature shows, the core feature is random assignment ‘of a study population into at least two groups: the experimental group, which receives the treatment being tested and the control group, which receives either another treatment or placebo. The idea is that the random a ‘assignment to the two groups advances the internal validity of the experiment by, presumably, equally distributing the effect of the extraneous factors that might account for the treatment outcome. Related to the technique of randomization into two groups is the expectation that relevant participants are unaware or “blind” to the assignment, both before and after the treatment begins. The idea of blindness was originally intended to refer to patients. The clinicians administering a treatment should also be blind, so also is the investigator evaluating the effects of the treatment. In our case, the trial was double blind, which means that at least two of the participants were blind. The two blind participants were the patient and the investigator.

The population size of our case is small; though, RCT does not require any particular population size, most trials, as the literature shows, tend to recruit a sufficiently large group to allow for greater generalizability or external validity of the results’. As has been variously pointed out in the medical literature, enrolling ‘insufficient numbers of patients may result in a finding of no difference between treatments when in fact there is one, or a finding of equal value when in fact one treatment is superior.’ Small clinical trials are not necessarily useless especially when they show methodological rigour (Sackett and Cook, 1993:25). Their value tends to focus on the early stages of clinical trials, when information is being built about the safety and potential effectiveness of a new treatment.’

RCT as is known is inherently a comparative investigation, usually of the effectiveness of new treatment. The main question that this begs, as some critics would point out, is, what should it be compared with? In most cases, the comparison is with a placebo administered to the control group. It has become a given that once a clinical trial is underway, whenever possible, all the relevant participants remain unaware of who is receiving the experimental treatment and who is receiving the comparison. A failure in blinding can, of course, lead to the study being compromised. What underpins this reasoning is that in so far ‘as a trial is randomized and the administration of the treatment and placebo is blind, all the factors and variables in the “placebo effect” are themselves randomly distributed or averaged and thereby of limited significance, if not insignificant, in the results. McQuay et. al. (1995) suggest that the problem with this is that the “placebo effect” ranges from 0% to 100% on both the positive and negative (nocebo) sides. Reilly (2000) pointed out that patients may react differently to the same placebo administered at different stages in a clinical trial. The point about this is that the placebo effect ‘is not a mere “dummy” variable as is well known, but has a life of its own. This said, the ‘prevailing assumptions about placebo have become routinized and based on these, studies ‘have found that on average about one-third of the people taking a placebo in a clinical trial report a benefit. Does this apply in our case? ‘RCTs now require that treatments under study must perform significantly better than a placebo before they are declared effective. Is this so in our case? What follows in the remaining part of this first section, describes the randomized clinical, double-blind, placebo controlled trial of sutherlandia guided by these two central questions. The description, in summarized form, draws heavily from the published results of the study (see Johnson, et. al. 2007).

What is the safety of sutherlandia? This was the key question of the clinical trial conducted by the South African Herbal Science and Medical Institute (SAHSMI) of the University of the Western Cape in South Africa in 2004. The trial was a pilot study by a team of 5 led by the Director of the Institute and the very first of its type as there was very little evidence relating to safety and none to the efficacy of the herb (Editorial, PLoS Clinical Trials, 2007:002). It was funded by the National Centre for Complimentary and Alternative Medicine (NCCAM) and the Fogarty International Centre (IFIC) at the National Institute of Health of the United States. Whilst both have no role in the study design, collection, analysis and interpretation of the data, the mere involvement of NCCAM at the NIH suggest mainstreaming of medicines other than biomedicine. One could therefore make this specific point, which is one of the key suggestions of the present paper, about the Institute’s clinical trial of sutherlandia. However, this is with caution; the fact that the focus of the Institute is herbal medicine and science signifies that what it embodies stands apart from biomedicine. NCCAM funds research projects that are “sorting out the wheat from the chaff” in, what is referred to as Complementary Alternative Medicine (CAM), establishing which therapies are safe and effective for specific disorders, which are harmful and useless, and why and how certain therapies work. The framework is science. Much of the research is usually conducted through the methodological gold standard of randomized and controlled clinical trials. What informed the study? How was it conceived? To answer these, a close look at the philosophy of the Institute, the profile of which can be found in Oloyede (2010) and Gibson (2011) is necessary.

Fundamentally, the Institute is concerned with what it describes as “scientifically and clinically unlocking the value of traditional medicines in the service of humanity” (SAHSMI document, 2010). In other words, the focus of the Institute’s teaching and research are on promoting healthy lifestyles and focused on scientifically and clinically understanding the quality, safety and efficacy of traditional medicines used for HIV and AIDS, TB, Malaria, Cancer, Diabetes, Depression and Fertility. This, at face value, would seem commonplace. Yet, it is far more than meets the eyes. The figure below, provided by the Director, Quinton Johnson, provides the core of the Institute’s philosophy
The recruitment process (PDR) was embedded in an extended community engagement process. This reflects the philosophy of the Institute, which, apart from adhering to the UNAIDS call for effective community engagement during the "life cycle" of a biomedical HIV prevention trial and beyond (UNAIDS 2007, 8) sees subject recruitment as part of the broad framework of community engagement of the university. The university, it must be said, has a long history of engaging with the community. This history endears it to the disadvantaged communities of the Western Cape province of the country. As such, for the Institute, subject recruitment presents one of the opportunities for involving community members in their research work. It is thus the case that traditional health practitioners were involved in subject recruitment. The involvement of traditional healers in subject recruitment, to some extent, is a variant of what is referred to as "peer-driven recruitment" (PDR) methodology that has gained increasing practice in health sciences in the past 10 years (Abdul-Quader et al, 2006, Bianchy et al. 2003). PDR
and its variants have been utilized in combination with other community engagement activities in the research life cycle (Mosavel et al. 2005) as well as in apparent isolation (Broadhead et al. 2006). PDR works through the tapping of a community member’s social network. Typically, PDR involves identification of a first wave of research subjects who are asked to identify and approach other community members with the option of participating in research. Assuming they are willing, these other community members can then in turn be mobilized as peer recruiters. This process of chain recruitment as aptly described by (Mosavel et al. 2005) continues until the target sample for the research has been achieved.

While approaches differ, the tasks that peer recruiters are normally asked to carry out include seeking potential ‘research subjects, providing them with verbal and or written information about the research (including an informed consent document, if applicable) answering questions about the research and, in some cases, obtaining consent.’ Given these various roles, PDR can be seen as serving both ethical and strictly utilitarian goals as Mosavel et al. (2005) point out. On the utilitarian side, he suggests, PDR is a strategy where the “insider” status and knowledge of peer recruiter can be usefully tapped in an effort to overcome the difficulties that investigators might otherwise face in recruiting and conducting research with individuals or groups who have potentially tangible reasons to mistrust and even avoid outsiders such as illegal workers, injecting drug users and homeless individuals.

The decision was taken early on in the conception of the clinical trial to employ community members to assist with subject recruitment. This was a logical extension of a community consultation process that the Institute viewed as critical given its philosophy that such a process helps to foster mutual trust and support and partnership in the quest for HIV prevention. The Institute views PDR as reflective of a community engagement philosophy in so far as it seeks to mobilize community members to play an active part in the research community process. This decision, which is part of the wider process of the clinical trials that entails not only how the trial was conducted, but also the prelude to the trial, is indicative of the careful thought and meticulous attention to every step of the research process. Part of the philosophy of the Institute is to study those herbal remedies that are widely used by the vast number of the population in South Africa and for which there is a long history of use to suggest, at the very least, a modicum of safety and efficacy to those who prescribe and use them, to justify researching them. As the Director pointed out in the tape-recorded interview, the Institute sees its work as one for the broader audience, one that includes but is not limited to the scientific community; speaks not only to the need for rigorous research guided ethically but also to the politics of knowledge.

The staffs at the Institute are cognizant of the imperatives of scientific objectivity. However, they are also concerned that their research works remain true to the therapy they are studying. The Institute can thus be said to be walking a tightrope. To say this is not to dramatise the situation in which the staff at the Institute probably find themselves within the larger scientific community in South Africa and indeed beyond. It is probably the case that those outside herbal medicine and science might question whether clinical investigators of herbal plants and medicines, by virtue of their deep understanding of its philosophy, would not easily be susceptible to the risk of bias in their research design, leading, ultimately to a somehow exaggerated result. At “issue here is the scientific requirement of “clinical equipoise”, which is a condition of genuine uncertainty on the part of the clinical investigators about the benefits of the trial being conducted. The principle of clinical equipoise or clinical equilibrium as some call it, and its requirements, are well recognized by many clinical investigators and regulators. This issue will not be taken up here other than to state in relation to the pre-clinical trial preparation the Investigators’ application materials, including the protocol, were provided to the University of Missouri Health Sciences IRB which reviewed and approved it as well as to the Stellenbosch IRB and South African Medicines Control Council reviewing agencies. The point about this is the Institute’s commitment to establish the evidence base for the safety and efficacy of sutherlandia. This consideration would seem to have been considered as critical by the Investigators in the clinical trial since passing peer review of the proposed research design is somehow central against skeptics of herbal medicine on the ground that those involved in its clinical trials are steeped in its philosophy thus overly sympathetic to it. Hence, the belief, that the only way to address such a charge was to submit clinical trials of herbal medicine to scientific methods of investigation ‘culminating in well-designed RCTs. Only through gold standard testing, it appears, can the kind of evidence of efficacy be derived to satisfy critics.

Whilst the research design of an RCT focuses ‘on randomization, blinding, and placebo controls, an important issue in relation to providing the legitimacy to the efficacy of herbal plants is how the outcome is measured. In our case, ‘a count was made of the number of participants who reported a particular type of adverse event at least once. The types of events include cardiovascular (e.g. palpitations, nosebleeds), central nervous system (CNS; e.g. headaches, nervousness, insomnia, dizziness), gastrointestinal tract (GIT), infection, allergy, appetite, malaise or general adverse events. A list of the vital physical, haematological, biochemical, and endocrine data were provided by the investigators and these showed no significant differences between the treatment and placebo groups (p>0.05). A large proportion of the vital and physical, biochemical and endocrine endpoints that were measured were within the normal physiological range and not significantly different for the sutherlandia and placebo groups. These were, among others, the diastolic and systolic blood pressure (BP), electrocardiogram (ECG), heart rate, blood temperature (oral), and weight and height, white cell and red cell counts, haemoglobin, haematocrit, mean corpuscular volume (MCV), and red cell diameter and width (RCDW), neutrophil, monocyte, lymphocyte, eosinophil and basophil counts; CD3, CD4, CD8 counts and CD4:CD8 ratio, sodium...
The investigators reported no detection of canavanine in any of the samples. It is clear from the list provided here of the outcome measures of the sutherlandia trial that the scientists involved in the trial relied on the objective measures of biological markers for their proof; however, this does not seem to rule out their concern about the implications of equating bodily sensations that have a large subjective component with biological correlates. I make this point on the basis of the statement by the Director of the Institute in one of our informal discussions that correlates do not fully capture what is happening in the body. Biological correlates, he points out, hardly can explain fully the process of healing, a point that exemplifies the earlier remark about the Institute walking on a tightrope.

Concluding Remarks

This paper, as earlier mentioned, is the second outgrowth of an on-going project which can best be described as a sociology of the clinical trials of herbal plants. The specific focus here is the context setting that was undertaken in the randomized, double-blind, placebo-controlled clinical trial of sutherlandia (Lessertia frutescens), a shrub indigenous to South Africa, which is widely used in the treatment of symptoms of HIV/AIDS. What was described illustrates, in general, the scientific attempt at mainstreaming of traditional herbal medicines. What can be said of this wider attempt at mainstreaming is that traditional herbal medicines do have some benefits and there seems to be the recognition that differences between them and biomedicine notwithstanding, they can co-exist with the latter within the health care system. In a way both seem to co-exist currently; though, as is clearly noticeable and well noted by social science researchers in the field of health, with some measure of inequality reflecting the prevailing system of hierarchies of knowledge where Western knowledge sits at the apex and other knowledges under it.

It can be said with hardly any iota of discomfort that clinical investigators may put in as much effort as possible they will probably not be able to fully explain, through scientific concepts and scientific methods of investigation, the reasons for all the benefits of traditional herbal medicine. Traditional herbal medicine would have to be appreciated for what they are on their own terms. Science, as Ruggie (2004) rightly points out, cannot change traditional herbal medicine – its practice or its mechanisms of action and theories but only possibly change how these are understood. It is in terms of this that the randomized, double blind placebo-controlled clinical trial of sutherlandia described in this paper should be understood, especially, given the philosophy of the Institute that conducted the trial. The use of science, by the scientists at the Institute, as a tool to foreground herbal medicine, to a great degree, contributes to the understanding of herbal medicine in terms that are more familiar to biomedicine. The scientific clinical trial of sutherlandia is, without doubt, a window, so to say, to understand herbal medicine. One can add, at a general level that, such a trial might, in a significant way, affect the role of herbal medicine in health care. Herbal medicine, as is widely known, still remains the source of health care for the majority of South Africans (Oloyede, 2010) and scientific investigations aimed at understanding it, becomes generally helpful. To the extent that it is, one can suggest, as Ruggie (2004) does, that a very significant link will be more likely to be forged between herbal medicine and biomedicine. However, this link begs the question of the relationship that Ruggie (2004) asks in relation to CAM and biomedicine generally: If, for example, certain kinds of herbal medicine help to prevent certain illnesses will these particular treatments be considered complementary or secondary? If considered primary, will biomedical health practitioners be trained in their use? If so, how will this affect the biomedical health practitioners’ approach to medicine? Will pharmaceutical firms “muscle” in, in their (herbal medicines) commodification? Traditional herbal medicine, as is well known, embodies a more holistic approach to its primary goal of healing; biomedicine relies, on the other hand, on scientific validation of its more technological approaches to curing. Will both stand on the same line on the same platform?
References


Glasser, B. G. and Strauss, Anselm. 1965 Awareness of Dying Chicago: Aldine Pub. co


Johnson, Quinton, Syce, James, Nell, Haylene, Rudeen, Kevin and Folk, William, R.,2007. A Randomized, Double-Blind, Placebo-Controlled Trial of Lessertia frutescens in Healthy Adults PLoS Clinical Trials, e16 April

McIntosh, J 1977 Communication and Awareness in a Cancer Ward London: Crom Helm

McQuay, Henry., Carroll, Dawn. and Moore, Andrew. 1995. Variation in the placebo effect in randomized trials of analgesics: All is as blind as it seems Pain, 64, pp. 331-5.


