DRAFT

October 14, 1993

RAYNAUD'S TREATMENT STUDY

PROTOCOL

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CHAPTER 1

BACKGROUND

1.1 INTRODUCTION

Raynaud's phenomenon is characterized by episodic digital vasospasms that are provoked by cold exposure and/or emotional stress (1). Estimates of its prevalence range from 4.3% - 5.7% of females to 2.6% - 4.3% of males in South Carolina and may be higher in colder climates (2,3). In patients with primary Raynaud's phenomenon, the symptoms cannot be explained by an identifiable disease process such as scleroderma or another collagen vascular disease. In patients with secondary Raynaud's phenomenon, the symptoms occur secondarily to another disease.

1.2 DIAGNOSTIC CRITERIA FOR PRIMARY AND SECONDARY RAYNAUD'S PHENOMENON

The Raynaud's Treatment Study (RTS) is designed to evaluate treatments for primary Raynaud's phenomenon. It is generally assumed that primary Raynaud's phenomenon occurs more frequently than does secondary Raynaud's phenomenon. However, the proportion of patients with primary vs. secondary Raynaud's phenomenon reported in the literature varies greatly, probably because of the referral bias of the investigators (4-7). A random statewide survey in South Carolina of patients with Raynaud's phenomenon found that 32% of patients had primary Raynaud's phenomenon, 8% had scleroderma or another connective tissue disease and 60% had another medical disorder (8).

In 1932, Allen and Brown (9) defined primary Raynaud's phenomenon using the following clinical criteria:

(1) Vasospastic attacks precipitated by exposure to cold or emotional stimuli.

(2) Bilateral symmetrical attacks of the hands and feet.

(3) Absence of gangrene or, if present, limited to the skin of the fingertips.

(4) No evidence of an underlying disease that could be responsible for the vascular attacks.

(5) History of the symptoms for two years.

Grifford and Hines (1957), in a retrospective review of 474 women thought to have primary Raynaud's phenomenon, found that the Allen-Brown criteria were accurate in 95% of their cases (10). However, it is now recognized that patients thought to have primary Raynaud's phenomenon may

develop signs or symptoms of a secondary cause at periods greater than the two-year follow-up period defined by the Allen-Brown criteria (11). It is generally thought that the most common disorder that may present with Raynaud's phenomenon alone is a connective tissue disease. The reported frequency that patients with presumptive primary Raynaud's phenomenon develop a connective tissue disease, however, varies from 0-19% in the current published literature (11-18). The presence of antinuclear antibodies (ANA) and abnormalities of nailfold capillary morphology have proven to be useful predictors of the presence of connective tissue disease, particularly scleroderma (13,15). Therefore, the rigorous definition of primary Raynaud's phenomenon should also include a normal serological profile and normal nailfold capillary morphology.

Although no systematic study has been conducted on the effect of Raynaud's phenomenon on the patient's quality of life, therapeutic trials often use subjective outcome variables in assessing the efficacy of the intervention. These studies provide some insight into the impact that Raynaud's phenomenon has on the patient. Most studies suggest a moderate level of discomfort and loss of function due to vasospasm. Wigley et al, during a trial of nicardipine, scored severity of attacks (scale:1-10) and hand function (scale:1-5) (19). Twenty-five patients (ten with primary Raynaud's phenomenon) had a mean score of 3.3 $\pm$ 0.4 for severity of attacks and 1.7 $\pm$ 0.2 for hand function during the placebo period of the study. In another drug trial, twenty-five patients with Raynaud's phenomenon scored 1.59 $\pm$ 0.38 (scale 1-3) for average severity of the attack (20). During a trial of nifedipine versus placebo, thirteen patients (ten with primary Raynaud's phenomenon) scored severity of pain on a 10cm linear analogue scale (21). Raynaud's phenomenon caused a moderate degree of pain as suggested by the fact that the treatment group scored 4.5 $\pm$ 0.8 at baseline. Finally, the degree of pain and functional limitation was determined on a scale of 1 to 4 (range: 1 = absence and 4 = serious) during a trial of ketanserin versus pentoxifylline (22). Seven of fifteen patients had defined secondary causes for their Raynaud's phenomenon. Subjective scores during placebo administration suggest significant pain (score: 3.53 $\pm$ 0.52) and functional limitation (score: 3.20 $\pm$ 0.77) in these patients. Thus, although none of these trials obtained similar measures from normal control subjects, the results suggest that primary Raynaud's phenomenon has measurable impact on health-related quality of life.

Patients with secondary forms of Raynaud's phenomenon are more likely than patients with primary Raynaud's phenomenon to have major complications such as skin ulceration or ischemic amputation of digits, and therefore they are more likely to have severe impairment of hand function and poor quality of life. A survey of patients with a diagnosis of scleroderma, who have a 97% prevalence of Raynaud's phenomenon, found that 61/94 (65%) had ischemic digital ulcers, 14/94 (15%) had lost at least one digit and 9/94 (10%) had lost more than one digit (23).

1.3 ETIOLOGY

Although the etiology of Raynaud's phenomenon is not known, two main theories have been put forth to explain it. Raynaud (24) hypothesized that exaggerated sympathetic nervous system activity caused an increased vasoconstrictive response to cold, whereas Lewis (25) suggested that a "local fault" rendered small peripheral blood vessels hypersensitive to local cooling. Studies of plasma catecholamine levels in Raynaud's phenomenon patients have generally not supported Raynaud's theory. Studies of plasma epinephrine and norepinephrine in Raynaud's phenomenon patients have found levels that were higher (26), lower (27), or not different (28) from those of normal persons. Moreover, micro-electrode studies of skin nerve sympathetic activity found no differences between patients with primary Raynaud's phenomenon and control subjects during cold pressor tests or other sympathetic stimuli (29).

Recent research has supported the theory of Lewis. No differences were found between patients with primary Raynaud's phenomenon and control subjects in their responses to a variety of sympathetic stimuli, such as reflex cooling, indirect heating, or intra-arterial infusions of tyramine, a compound that causes the indirect release of norepinephrine from sympathetic nerve endings (30). In the same investigation, it was demonstrated that patients had significantly greater digital vasoconstrictive responses to intra-arterial phenylephrine (an alpha-1 adrenergic agonist) and clonidine (an alpha-2 adrenergic agonist) than did normal control subjects. These results suggested that patients with primary Raynaud's phenomenon have increased peripheral vascular and adrenergic receptor density relative to controls (31-33).

In a subsequent investigation, vasospastic attacks were induced in nine of eleven patients with primary Raynaud's phenomenon and in eight of ten patients with scleroderma (34). The attacks were

photographed using an automatic camera and scored by three independent raters. Two fingers on one hand were anesthetized by local injection of lidocaine, and the effectiveness of the nerve blocks was demonstrated by plethysmography. The frequency of vasospastic attacks in nerve-blocked fingers was not significantly different from that in the corresponding intact fingers on the contralateral hand. These findings clearly demonstrate that the vasospastic attacks of Raynaud's phenomenon can occur without the involvement of efferent digital nerves and argue against the etiologic role of sympathetic hyperactivity.

In vitro studies (35-37) have shown that cooling modulates contractile responses medicated by alpha-adrenergic receptors, depending on the species and blood vessels involved. The effects of cooling on adrenergic responses in primary Raynaud's phenomenon patients were therefore studied using brachial artery infusions of adrenergic agonists (38). Clonidine HCl and phenylephrine HCl were administered through a brachial artery catheter while blood flow was measured by venous occlusion plethysmography in cooled and uncooled fingers. Cooling potentiated adrenergic vasoconstriction in the patients but depressed this response in the controls. Vasoconstrictive responses to phenylephrine were not significantly affected by cooling but were significantly greater in the cooled and uncooled fingers of the patients than in the corresponding fingers of the controls. These results suggest that cold-induced sensitization of peripheral vascular alpha-adrenergic receptors constitutes the "local fault" by which cooling triggers the vasospastic attacks of Raynaud's phenomenon. Attacks that are induced by emotional stress can be explained by normal catecholamine elevations acting upon hypersensitive vascular and alpha-adrenergic receptors.

Some studies have examined the physical properties of the blood in primary Raynaud's phenomenon patients, but the results have been inconclusive. One investigation (39) reported increased blood viscosity and red blood cell aggregation in primary Raynaud's phenomenon patients although subsequent investigations failed to confirm these findings (40,41).

In summary, the most recent evidence strongly suggests that the vasospastic attacks associated with Raynaud's phenomenon are locally triggered by peripheral vascular adrenoceptors that are hypersensitive to cold. Moreover, since vascular and adrenoceptors are hypersensitive in primary

Raynaud's phenomenon patients in the basal state, normal catecholamine elevations produced by emotional stress or by reflex cooling can also trigger the vasospastic attacks.

1.4 PHARMACOLOGICAL TREATMENT OF RAYNAUD'S PHENOMENON

Currently, no drug is approved in the United States for the treatment of Raynaud's phenomenon. In fact, avoidance of the cold, reduction of emotional stress and discontinuing vasoconstrictors, such as smoking and caffeine, are the most commonly recommended therapeutic approaches. A number of vasodilators have been used in the treatment of Raynaud's phenomenon, but relatively few well-controlled studies have been done to determine the efficacy of these drugs (42).

Several factors are important when evaluating the literature on therapeutic intervention in Raynaud's phenomenon. It is important to determine if the patient population studied had primary or secondary Raynaud's phenomenon. Primary patients are more likely to respond to vasodilators because of the absence of structurally abnormal blood vessels (43,44). It is also important to distinguish between clinical or self-reported measures and laboratory-based hemodynamic measures of response to treatment. Several studies have reported subjective improvement in the frequency, duration or severity of Raynaud's attacks following drug treatment, but have been unable to objectively measure that positive effect in the laboratory (21,44-48). Lastly, the ideal therapeutic trial should have a double-blind randomized design that is placebo, temperature and activity controlled.

1.4.1 Calcium Channel Blockers

Of the currently available drugs on the market, the calcium channel blockers, because of their vasodilating properties, are the most widely-used agents for the treatment of Raynaud's phenomenon. Nifedipine has been the most widely studied of the available calcium channel blockers (20,21,43,45-47,49-61), but nicardipine (19,62), diltiazem (63-65), verapamil (66), isradipine (67) and nisoldipine (62) have also been investigated.

Three studies with nifedipine have enrolled only patients with primary Raynaud's phenomenon (50,60,69) and two studies enrolled only patients with scleroderma (51,61). The studies of patients with primary Raynaud's phenomenon have reported approximately a 50% reduction in frequency of attacks and a significant reduction in severity of attacks (50,60,69). In the two studies published on the evaluation of nifedipine for the treatment of Raynaud's phenomenon in patients with scleroderma,

subjective improvement was documented (51,61) with digital ulcer healing in one study (51) and improved finger temperature and finger blood flow in the other study (61). In contrast, other studies of nifedipine have shown little or no response among patients with severe or secondary Raynaud's phenomenon (20,43).

While most investigations have shown that nifedipine reduces the frequency and severity of Raynaud's attacks, there has been a lack of correlation between subjective improvement and laboratory measurements of digital blood flow (21,44-47, 49,50). One study showed a reduction in digital blood flow during acute administration of nifedipine as a consequence of the fall in blood pressure that occurred when the patient was not having an attack (70). A decrease in digital blood flow was also reported in patients with scleroderma following nifedipine treatment (71). However, others have reported that nifedipine caused vasodilation of the fingertip blood flow in patients with low baseline flow (55,72), a reduction of cold-induced vasospasm (57), and a decrease in the rewarming time following cold stress test (49). During long-term nifedipine therapy, a trend toward diminished effectiveness was observed over time in patients with primary Raynaud's phenomenon (50) in one study, while long-term benefit was shown in another study (47). One recent study of a sustained release nifedipine preparation showed an impact on Raynaud's symptoms (73).

Nifedipine side-effects, while not serious, are frequent with 30-100% of patients reporting problems (20,43,50,68,69). The most common side effects are headache, flushing, lightheadedness, and edema.

There are a few published studies of the other available calcium channel blockers in the treatment of Raynaud's phenomenon. Nicardipine and placebo therapy was compared in 25 patients with primary and secondary Raynaud's phenomenon. The results failed to show a difference between the two treatment groups with respect to number and severity of attacks, the way in which the attacks occurred, patients' use of their hands in the winter months, patient assessment of medication effectiveness, or objective measurement of finger systolic pressure and critical closing temperature (19). Kahan et al reported that nicardipine reduced the frequency of attacks (mean 29.6 $\pm$ 13.6 attacks per two weeks on placebo vs. 23.1 $\pm$ 17.0 attacks per two weeks on nicardipine; $p<0.05$)

and the severity of Raynaud's phenomenon (mean score 2.2 $\pm$ 0.4 with placebo vs. 1.8 $\pm$ 0.07 with nicardipine; $p<0.05$) (62).

The non-dihydropyridine calcium channel blocker verapamil failed to show clinical benefit in the one published study of 16 patients with Raynaud's phenomenon (66). Diltiazem has been reported to reduce Raynaud's attack frequency and severity in three placebo-controlled studies (63-65). However, one study reported that the improvement was striking in patients with primary Raynaud's phenomenon but did not reach statistical significance in patients with associated systemic disease (64).

In summary, the calcium channel blockers are effective vasodilators and may improve clinical symptoms among patients with Raynaud's phenomenon. There are differences in the effect among different drugs. Differences in response are also likely depending on the underlying cause of the vasospasm. Hemodynamic measurements done in a laboratory-based setting have shown variable response and poor correlation with clinical outcomes. Side-effects are common using intermittent dosing of nifedipine, the most commonly used drug. The new extended release dose nifedipine, Nifedipine XL, with fewer side-effects, does not have well-documented efficacy. Finally, one study suggests that long-term use of nifedipine may be less effective than the reported success of most short-term studies (50), while another reports sustained efficacy (47).

1.4.2 Other Drugs

Many agents other than calcium channel blockers have been used in the treatment of Raynaud's phenomenon, but few controlled studies have been done. In general other agents have been disappointing in their clinical usefulness or they are not available.

Sympatholytic agents including reserpine (74-84), guanethidine (78,85,86), methyldopa (86,87), prazosin (88-92), phenoxybenzamine (93-96), phentolamine (97,98), indoramin (99-100), and tolazoline (101,102) have been used in the treatment of the vasospasm associated with Raynaud's phenomenon. Intra-arterial reserpine was used for the treatment of Raynaud's phenomenon until controlled studies suggested that its effect was no better than that of intra-arterial placebo (78). The adrenergic alpha-1-receptor blocker, prazosin, was reported effective in the treatment of Raynaud's phenomenon (88,90,92). One study suggested that prazosin alone was not effective, but that

successful treatment was seen when prazosin was combined with autogenic training (89). Although prazosin has been shown to reduce symptoms, it is reported to be less effective in secondary Raynaud's phenomenon (92-102) and the clinical improvement may not be sustained with prolonged treatment (76).

Other agents which have been reported in the treatment of Raynaud's phenomenon include angiotensin-converting enzyme inhibitors (103-105), serotonin receptor blockade (48,106-117), thromboxane synthetase inhibitors (20, 118-121), prostaglandins I, (prostacyclin) (122-124), PGE_1 (125-133) and PGE_2 (134), evening primrose oil (135), Iloprost (136-140), and direct-acting vasodilating agents such as nitroglycerin (141-147) and hydralazine (96). The usefulness of these agents, however, is reduced by the high frequency of side-effects, inconvenient route of administration, or lack of effectiveness demonstrated in a placebo-controlled trial.

There have been few studies comparing other agents to calcium channel blockers (51). Thus, nifedipine remains the usual drug of choice in the treatment of Raynaud's phenomenon because of its availability and ease of administration. However, the clinical benefits of this drug have not been clearly demonstrated, and the effectiveness of Nifedipine XL has not been compared to that of behavioral treatment.

1.5 BEHAVIORAL TREATMENT OF RAYNAUD'S PHENOMENON

Behavioral therapies for medical disorders often have involved techniques of stress or arousal reduction. The rationale for such interventions is that the disorder being treated is caused by the effect of "stress." As we have seen in the case of sustained hypertension, the latter notion may turn out to be an oversimplification. It is therefore not surprising that, upon careful scrutiny, stress reduction treatments for hypertension proved to be no more effective than simple attention placebo intervention (148). Ideally, treatments for medical disorders should target the specific underlying pathophysiological mechanisms (149). Using this rationale, biofeedback treatments have been designed in which a specific response is targeted that is thought be abnormal in the disorder in question. For example, electromyographic treatments were designed to treat "tension" headaches believed to be associated with abnormal muscle contraction. As early as 1978, Silver and Blanchard (150) pointed out that these presumably specific biofeedback interventions were no more effective

than simple relaxation/stress reduction techniques, thus frustrating hopes for a collection of specifically-targeted behavioral interventions. The area of treatment for Raynaud's disease, however, may be an exception, as the literature review below will suggest. It is for this reason that a large scale trial focusing on this disorder may have significance for behavioral medicine beyond the specific problem area of Raynaud's disease.

Both observational and experimental studies have demonstrated that peripheral vasoconstriction can be affected by emotional and behavioral factors (148), suggesting the possible role for behavioral interventions in controlling disorders of peripheral vasoconstriction. A number of techniques including general relaxation strategies and suggestive methods such as hypnosis, meditation, autogenic strategies, and biofeedback have been correlated with finger temperature control. Biofeedback and/or autogenic training are the two most frequently used behavioral interventions for the treatment of Raynaud's patients (151). The goal of both interventions is to train Raynaud's patients to voluntarily control their peripheral circulation.

Although temperature biofeedback has demonstrated clinical effectiveness in multiple studies of treatment of a variety of psychophysiological disorders, the mechanism of action is unclear. There is also controversy regarding the necessity of specific feedback in temperature increase training. A number of authors have suggested that biofeedback did not significantly enhance temperature control when compared to autogenic instruction or general relaxation (152-154), while others have demonstrated enhanced efficacy, particularly at post-treatment (155-160).

Multiple studies have demonstrated voluntary control of peripheral blood flow and skin temperature regulation in normal subjects (151,161-164). One of the earliest reports of voluntary control of vasodilation came from the USSR, in which Lisina demonstrated that subjects could increase arm blood flow if allowed to view their plethysmographic records (166). Similarly, other authors reported that normal subjects could learn to control peripheral blood flow and skin temperature using hypnosis and imagery (167-168). However, temperature decreases were easier to produce and were generally larger than temperature increases.

The earliest controlled studies of temperature biofeedback in normal subjects demonstrated that temperature biofeedback with instructions about warming resulted in small, but statistically significant

increases in finger temperature (162,168,169). Finger temperature increases were usually observed early in training, and typically did not increase with additional training. Keefe and Gardner (170) examined the effects of biofeedback treatments of different lengths and found no significant benefits of increased number of sessions. Additionally, experimental studies have suggested that once finger temperature control has been learned, it can be produced in the absence of feedback, generalizes to environments outside the laboratory training sessions, and is maintained over time (171).

The extension of these procedures to Raynaud's phenomenon patients has attempted to teach these patients to increase their finger temperature through peripheral vasodilation, with the goal of reducing vasospastic episodes. Early case studies demonstrated that temperature biofeedback alone, or in combination with various relaxation procedures, reduced the occurrence of vasospastic episodes in patients with Raynaud's phenomenon (172-175). A later multiple-case study indicated that the beneficial effects of temperature biofeedback alone were maintained at a one-year follow-up period (176).

Freedman, Lynn, Ianni and Hale (177) were the first not to include a relaxation component in the biofeedback intervention. In a later controlled outcome study with this method, Freedman, Ianni and Wenig (178) found an average reduction of attack frequency from 21 to 2 per week after 10 biweekly sessions, and this effect persisted at long-term follow-up assessments extending over 1-3 years (179). In later studies, Freedman and coworkers observed that the increased temperature during biofeedback training was associated with increased finger blood flow (155,180). No changes occurred in circulating catecholamines (180), suggesting that the mechanism for temperature feedback did not involve a general reduction in sympathetic outflow. The effect of feedback to increase temperature was blocked by propranolol (181) but persisted even after digital nerve blockade, suggesting that the effect of temperature feedback is related to the local beta-adrenergic mechanism first described by Cohen and Coffman (182).

Temperature biofeedback has frequently been used in combination with different relaxation techniques in the treatment of Raynaud's phenomenon. Autogenic training, which teaches the use of relaxation-inducing self-statements that usually suggest warmth and heaviness (177) is a relaxation strategy that has most frequently been used, either alone or in combination with biofeedback, in the

treatment of Raynaud's phenomenon. One of the first controlled studies with Raynaud's patients demonstrated improvement in responses to cold stress and in the number and intensity of symptoms following autogenic training alone, or in combination with temperature feedback (183). At one-year follow-up, reported symptom improvements were maintained, but responses to cold stress returned to pre-treatment levels (184). Other studies have also demonstrated similar effects of relaxation procedures alone and in combination with temperature biofeedback (185), and similar effects of different types of relaxation procedures on Raynaud's symptoms (186).

Exposure to cold during temperature biofeedback has been demonstrated to enhance the effects of temperature biofeedback alone. In one study, temperature biofeedback combined with cold exposure resulted in greater reductions in Raynaud's symptoms (92.5%) compared to temperature biofeedback alone (66.8%) (148). Both temperature biofeedback groups showed significant finger temperature increases during training sessions and significantly greater reductions in symptoms compared to groups receiving autogenic training (32.6%) and electromyographic (EMG) biofeedback (17.0%). At one year follow-up, both temperature feedback groups showed significant finger temperature increases during a voluntary control test, whereas the EMG and autogenic training groups showed significant temperature decreases during this test (151). A later study indicated that symptom reductions were maintained in the temperature biofeedback groups, two and three years later (187). After three years, however, only the group receiving temperature biofeedback with cold exposure reported significantly fewer attacks overall (187). A similar significant reduction in Raynaud's attacks following temperature biofeedback that was conducted in a cool environment has been reported (179).

Other studies have also demonstrated reductions in vasospastic attacks in Raynaud's patients receiving thermal biofeedback. However, many of these studies utilized thermal biofeedback in combination with a variety of other behavioral interventions, including progressive muscle relaxation and autogenic training, making it difficult to determine the effectiveness of thermal biofeedback alone.

A more traditional classical conditioning paradigm has been examined alone and in combination with temperature biofeedback training to treat Raynaud's phenomenon. The classical conditioning procedure involves pairing the unconditioned stimulus of warm water applied to the hands with a

conditioned stimulus of exposure of the whole body to cold. After repeated pairings, exposure to the cold alone elicits vasodilation in the hands (i.e., the conditioned response). Using this conditioning procedure, patients with Raynaud's phenomenon have been shown to exhibit significant increases in digital temperature during a cold stress relative to untreated control subjects (188). At one-year follow-up, approximately one half of the subjects reported continued positive effects of treatment. Relative to placebo controls, Raynaud's phenomenon patients who received a similar conditioning procedure showed significant improvement in both finger temperature and number of attacks (189). Temperature biofeedback combined with relaxation yielded comparable improvements in finger temperature response to cold stress relative to a similar conditioning protocol (190).

Several investigators have also reported success in uncontrolled trials using temperature biofeedback in the treatment of patients with Raynaud's phenomenon secondary to systemic lupus erythematosus and scleroderma (191-196). However, the only controlled trial with scleroderma patients failed to demonstrate either symptom improvement immediately after treatment or increased finger temperature in response to voluntary control of cold stress (194).

One of the difficulties in evaluating studies of biofeedback is the wide ranging variation in administration of techniques, and the lack of well-controlled evaluations. One complicated factor is that the nature of biofeedback itself appears to require significant patient and therapist interaction, is difficult to evaluate in blinded conditions, and is responsive to experimental demand characteristics. A number of studies have demonstrated the importance of therapist variables in temperature biofeedback (197-200). Additionally, others have suggested the role of motivational factors in superior learning of temperature control (197,201-202). Clearly, motivational factors may be influenced by the therapist's behavior and demand characteristics of the biofeedback situation. Leeb, Fahrion & French (203) found that a positive and warm therapist style was associated with greater increases in temperature than negatively stated or automated instructions.

In summary, a number of controlled studies from several different groups of investigators have demonstrated that temperature biofeedback, either alone or in combination with relaxation techniques, is effective in increasing finger temperature responses to cold challenges and in reducing symptoms of Raynaud's phenomenon (151). Several studies have reported significant improvements that were

maintained for a year or longer. Although more controlled trials have been done with patients with primary Raynaud's phenomenon, these treatments may also benefit patients with secondary Raynaud's phenomenon.

These studies, however, vary widely in their methodological rigor. Only one study that included a no-treatment control group demonstrated the effectiveness of temperature biofeedback (179). Another biofeedback study of Raynaud's phenomenon that included a no-treatment control group demonstrated no differential effectiveness of either temperature or EMG biofeedback relative to the control group (204). While the latter study has been criticized on both conceptual and methodologic grounds (205), the lack of control groups in many of these studies is of major concern, given the high rate of placebo-response demonstrated in pharmacologic studies of Raynaud's phenomenon (20). As is the case in evaluating the pharmacological treatment literature, it is important to distinguish between subjective, symptomatic improvement and objective, physiological improvement. Studies that demonstrated a significant effect on physiological parameters, measured either in the laboratory or in daily life, provide more convincing support for the effectiveness of behavioral interventions than do studies that relied on self-report of symptomatology. Additionally, demonstration that treatment gains were maintained for a minimum of one year following treatment (into another cold season) provide strong support for the effectiveness of behavioral treatments for Raynaud's phenomenon.

In conclusion, as demonstrated in the elegant studies by Freedman and colleagues, temperature feedback training with cold exposure without concomitant training in relaxation, is a specific clinically effective treatment for primary Raynaud's disease (156). It seems important to investigate whether these findings can be replicated in the hands of other therapists and at other sites where the climatic conditions may be different. The reduction in attack frequency reported is impressive. However, the specific mediating factors involved in producing this clinical effect need further study. It is true that during temperature feedback sessions in the laboratory changes opposite to those occurring during vasospastic attacks are induced. However, it remains unknown whether the reduction in attacks in the patient's natural environment is related to the subject's applying the technique specifically for the impending attack. An alternative explanation for the treatment effect might be that patients simply become more sensitized to stimulus conditions that might produce the attacks and thus take

precautions to avoid those situations. For example, data concerning the relationship between individual differences in clinical effect and success at temperature control are either negative or have not been reported. Ambulatory monitoring might contribute to further elucidation of whether clinical effectiveness is related to greater success in avoiding cold triggers. The evidence that secondary Raynaud's disease is amenable to behavioral treatment has not been demonstrated in controlled outcome studies. A controlled outcome study with this population is needed, perhaps using the approach of Stambrook et al (206).

1.6 SUMMARY

From this selective literature review there emerges both a rationale for performance and some implications for the design and conduct of the RTS. Previous studies have not directly compared behavioral and pharmacological therapies for Raynaud's phenomenon. Calcium channel blockers appear to be the most promising among the pharmacological treatments because a beneficial effect in the treatment of Raynaud's phenomenon has been most consistently shown with calcium channel blockers. In the behavioral research literature, temperature biofeedback with cold stress has been reported to have the most beneficial effect on reduction of frequency of symptoms in Raynaud's phenomenon. However, in one study with an untreated control group, there was no beneficial effect of finger temperature biofeedback or frontalis EMG biofeedback.

A comparison of a calcium channel blocker therapy, finger temperature biofeedback, and placebo, using standardized measures of diagnosis, treatment, and evaluation would likely yield much useful information.

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CHAPTER 2

OBJECTIVES AND GENERAL DESIGN OF THE RAYNAUD'S TREATMENT STUDY

2.1. INTRODUCTION

The Raynaud's Treatment Study (RTS) is a multicenter, randomized clinical trial designed to examine the clinical utility of pharmacological and behavioral treatments for patients with primary Raynaud's phenomenon. Treatment with behavioral therapy (temperature biofeedback versus frontalis electromyogram (EMG) biofeedback), and drug therapy (nifedipine XL versus placebo) will be assessed (Figure 2.1). A total of 300 patients will be enrolled in the RTS; the patients will be recruited at five Clinical Units.

The primary end point will be the number of vasospastic attacks experienced by patients. The primary end point will be assessed fifteen months after subjects are enrolled, with an intermediate end point to be assessed three months after enrollment. Adherence-enhancing interventions will be used to minimize loss of patients to follow-up.

A secondary objective of this study is to evaluate the ability of patients to rewarm their fingers following exposure to cold temperatures. To this end, subjects will undergo a physiological "cold box" test at the time of enrollment (baseline), three months after enrollment, and sixteen months after enrollment. Other secondary objectives are described in Section 2.2.

2.2 OBJECTIVES

The primary objective of the RTS is to examine the effectiveness of two treatment strategies relative to appropriate control conditions in reducing the number of vasospastic attacks experienced by patients with primary Raynaud's phenomenon. The treatments are nifedipine XL (a calcium channel blocker) and temperature biofeedback. The control condition for nifedipine XL is placebo; the control condition for temperature biofeedback is frontalis EMG feedback.

Secondary analyses will include, but not be limited to, the following:

1) The number of vasospastic attacks reported by the patients from January 1 through March 31 in 1994 and 1995 for patients enrolled in 1993 and from January 1 through March 31 in 1995 and 1996 for patients enrolled in 1994. (Note that patients who complete their

Treatment Visits after January 1 will begin recording the number of vasospastic attacks one week after completion of Treatment Visits.)

2) The severity of vasospastic attacks.

3) The time it takes for a patient's finger to rewarm after being exposed to 18°C in the physiological cold box test.

4) The reports of quality of life.

2.3 GENERAL DESIGN OF THE RAYNAUD'S TREATMENT STUDY

2.3.1 Introduction

Primary Raynaud's phenomenon is a common condition characterized by attacks of discoloration, especially in the fingers, that are associated with feelings of numbness, tingling or pain. These attacks often occur in response to exposure to cold temperatures. Patients with severe primary Raynaud's phenomenon experience significant degrees of discomfort and behavioral restrictions. The standard treatment of primary Raynaud's phenomenon is nifedipine, a calcium channel blocker. While nifedipine has been shown to be effective in placebo-controlled studies, the therapeutic benefit of the nifedipine XL formulation is unknown. Nifedipine XL has fewer side effects than nifedipine.

A non-pharmacological alternative would be also desirable for treating primary Raynaud's phenomenon. The literature indicates that temperature biofeedback with cold exposure has been associated with reductions in attack rates that exceed those of other behavioral treatments such as relaxation therapy. However, these studies have included only small numbers of patients, and no studies have compared the effects of temperature biofeedback with the effects of nifedipine.

Accordingly, in the proposed study, the effects of temperature biofeedback and nifedipine-XL will be assessed, both individually and in comparison with each other. The effect of each of these treatments will first be established relative to its control condition. In the case of temperature biofeedback (T), the control condition is frontalis EMG biofeedback (E); the difference (T-E) represents the treatment effect of temperature biofeedback. In the case of nifedipine XL (N), the control is placebo (P). The difference (N-P) represents the treatment effect of N. The comparative effectiveness of N and T will be assessed by comparing the treatment effects of T and N, i.e., (T-E)-(N-P).

The specific clinical hypotheses to be addressed by the RTS are:

1. After one year of treatment with nifedipine XL or placebo, there will be significant differences in the average vasospastic attack rates (adjusted for baseline attack rates) between these two groups.
2. After one year of treatment with temperature biofeedback or frontalis EMG feedback, there will be significant differences in the average vasospastic attack rates (adjusted for baseline attack rates) between these two groups.
3. After one year of treatment, there will be significant differences between the treatment effect of nifedipine XL (adjusted for baseline attack rates and for the attack rates in the placebo group) and the treatment effect of temperature biofeedback (adjusted for baseline attack rates and for the attack rates in the frontalis EMG group).

2.3.2 General Approach to Design

The design of the RTS provides appropriate controls for expectation effects and non-specific therapists' effects for the study medication and biofeedback treatment arms. The study treatments will be administered in a manner comparable to what is likely to occur in a clinical setting. The specific treatment arms for the RTS were described in Section 2.3.1.

2.3.3 Recruitment and Eligibility Criteria

There is an implicit requirement that the patients entered into the RTS will be suitable for randomized assignment to any of the planned study treatments. Thus, it may not be possible to enroll patients with a known physiological contraindication to treatment with a calcium channel blocker, patients who could not adhere to a training schedule of biofeedback, or patients with very severe Raynaud's phenomenon which would preclude assignment to the placebo group. In addition to this implicit assumption, sample size considerations require the frequency of attacks prior to treatment to be at least two attacks per day. Details of the inclusion and exclusion criteria for the RTS are provided in Chapter 3, Patient Eligibility.

2.3.4 Randomization

Separate randomization schedules for each Clinical Unit will be prepared. Patients considered to be eligible for the RTS will be scheduled for a Randomization Visit (RV01). If the patient meets the eligibility criteria and is willing and able to participate in the RTS, Clinical Unit staff will request a treatment allocation from the Coordinating Center via the automated telephone randomization system

(ATRS). Once a treatment allocation has been issued for a patient, the patient is enrolled in the RTS. Follow-up of the patient is required and the patient will be included in study analyses, even if he/she never receives study treatment.

The Coordinating Center will produce periodic recruitment reports and will distribute these reports to the Clinical Units and Program Office to aid in the recruitment of Raynaud's patients.

2.3.5 Visit Schedule

The primary end point for the RTS will be the number of vasospastic attacks characteristic of Raynaud's pattern with at least one color change (white or blue) that occur in a one-month period, fifteen months after enrollment. A half-hour period between each attack will be used as a formal dividing point between vasospastic attacks.

A one-month period of data collection for the primary end point has been selected because the burdens associated with keeping daily diaries for longer periods of time might result in non-compliance among patients. A shorter interval of time was not selected because of the potential effect of within-patient variability on the outcome measure.

In addition to the one-month period of primary end point data collection, comparable periods of data collection will be instituted at the time of enrollment (to serve as a covariable for the primary end point analysis), and at three months after enrollment (for intermediate assessments).

Details of the schedule of patient visits are provided in Chapter 10, Patient Visits. A brief description of the visit schedule follows and is summarized in Exhibit 2.2

Each patient will complete at least one Screening Visit for assessment of eligibility to participate in the RTS. Five weeks later the patient will return for the Randomization Visit (RV01). At RV01 the patient's eligibility for and willingness to participate in the RTS will be confirmed. A treatment assignment for the patient will be requested from the Coordinating Center. After the Randomization Visit (RV01), patients assigned to the nifedipine XL and placebo groups will complete five Treatment Visits (TO1 to TO5) over a five-week period for monitoring of blood pressure and adjustment of study medications, as needed (see Chapter 5, Administration of Study Medications). Patients assigned to the Temperature Biofeedback or Frontalis EMG Biofeedback Groups will complete ten Treatment Visits (TO1 to T10) over a five-week period for temperature biofeedback training, followed by a voluntary control session (VC01). In addition, patients in all groups will return to the Clinical Units for six

Monitoring Visits and Follow-up Visits. The Monitoring Visits and Follow-up Visits will include a physical examination, ascertainment of adverse events, and assessment of adherence to prescribed study medication (if pertinent).

Immediately prior to RV01 and after Follow-up Visit (FV01) and Follow-up Visit 3 (FV03), the patients will undergo a one-month period of intense data collection, during which they will use daily calendars to record the occurrence of each suspected vasospastic attack and the color changes associated with each attack (see Chapter 7, End Points).

Procedures to be completed at RV01, Follow-up Visit 2 (FV02) and Follow-up Visit 4 (FV04) include completion of the Quality of Life Form (see Chapter 8, Quality of Life). At RV01, FV02 and FV04 the patient's physiological response to cold exposure will be tested using "cold box" procedures (see Chapter 9, Physiological Measurements).

The patients will also complete daily retrospective calendars, recording the number of attacks that occurred during each day from January 1 to March 31 in 1994 and 1995 for patients enrolled in 1993 or from January 1, 1995 to March 31 in 1995 and 1996 for patients enrolled in 1994. Those patients who complete their Treatment Visits after January 1 will begin completing the daily retrospective calendars one week after the last Treatment Visit.

2.3.6 Adherence Monitoring and Enhancement

Adherence in the RTS will be important in three critical domains: adherence with treatment; adherence with self-monitoring; and adherence with follow-up. Each is discussed separately below.

2.3.6.1 Adherence and Understanding Review Prior to Randomization

Prior to entry into the study a study physician or nurse coordinator will review the study requirements with the potential participant. Issues to be discussed include the study goals and requirements including the Monitoring Visit and Follow-up Visit schedule, randomization procedures, and study treatments. Potential barriers to the patient's full and continuous participation (e.g. transportation difficulties, major life stressor such as pending divorce, etc.) should be reviewed. In addition there should be consideration of the potential participant's willingness to participate in the RTS and his/her confidence that he/she will be able to adhere to the study requirements, regardless of treatment assignment. Participants will only be enrolled into the RTS after a full review of these

issues and a determination by the senior Clinical Unit staff that the patient understands the study requirements and is likely to adhere with the study procedures.

2.3.6.2 General Adherence Enhancing Procedures

Participation in all aspects of the trial should be made convenient for each participant. Free parking should be arranged or travel expenses should be reimbursed; clinic hours should be flexible and accommodate busy work and family schedules; waiting time for all appointments should be eliminated or minimized; and all staff should treat each participant as a valued and important member of the RTS at each study contact.

2.3.6.3 Adherence with Treatment

Participants will be expected to either attend ten sessions of biofeedback training and to practice biofeedback strategies at home or to take study medication each day. As described above, in order to enhance attendance at biofeedback training sessions, each Clinical Unit will attempt to offer sessions at maximally convenient times, including evenings and weekends. Each participant will receive a printed schedule at the start of his/her biofeedback program that lists the date and time of each session, as well as contact telephone numbers. Self-monitoring procedures designed to enhance adherence with practicing biofeedback are described in Chapter 6, Biofeedback.

Participants assigned to the study medication groups will meet individually with Clinical Unit staff once a week for five weeks after initiating drug therapy. At the start of therapy the Clinical Unit nurse will help the participant identify the optimal personal pattern for medication adherence. Pill timing, location of medication consumption and relevant persona and "cues" for use will be discussed and when possible, tailored to the participant's lifestyle. Potential disruptions to the schedule (sleeping in, vacation, weekends, etc) will be identified and plans developed with the participant to minimize the disruption to taking medication. Participants will be asked to return their pill bottles for pill counts and to complete medication use diaries at each Monitoring Visit and Follow-up Visit. The Clinical Unit nurse will review with participants their medication adherence patterns and work with the participants to "troubleshoot" any adherence problems. Telephone follow-up contacts can be used to monitor and encourage study medication use in a supportive, non-evaluative manner.

2.3.6.4 Adherence with Completion of Diaries

Participants will be asked to record information concerning each Raynaud's attack on attack cards over three one-month periods. In addition, the participants will be asked to maintain retrospective diaries of Raynaud's attacks that occur between the Screening Visit (SV01) and RV01 and from January 1 to March 31 in 1994 and 1995 for patients enrolled in 1993 or January 1 to March 31 in 1995 and 1996 for patients enrolled in 1994. (Patients who complete their Treatment Visits after January 1 will start filling out the diaries one week after completion of the Treatment Visits.) In order to enhance adherence with completion of the attack cards and diaries, the diaries will be in a simple format with a pencil attached. The participants will be given practice instruction in completion of the diaries prior to the start of the data collection periods. The participants will be given stamped, addressed mailer envelopes for mailing each week's attack cards and diary to the Clinical Unit at the end of the week. Clinical Unit will contact any participant who fails to return an attack card or diary in a timely fashion.

2.3.6.5 Adherence with Completion of Follow-up Visits

Participants will receive postcards and telephone calls to remind them of their next appointment for a Monitoring Visit or Follow-up Visit. Waiting time and parking will be kept convenient. Clinical Unit staff will call participants who fail to keep Monitoring Visit or Follow-up Visit appointments; home visits may be arranged if necessary and appropriate.

Exhibit 2.1

TREATMENT GROUPS FOR THE RAYNAUD'S TREATMENT STUDIES

Treatment Group	Number of Patients
A. Nifedipine XL	75
B. Placebo	75
C. Temperature Biofeedback	75
D. EMG Frontalis Biofeedback	75
Total	300

Exhibit 2.2

Draft June 22, 1993

Raynaud's Treatment Study

VISIT SCHEDULE FOR THE RAYNAUD'S TREATMENT STUDIES

A. Nifedipine XL and Pill-Placebo Treatment Groups

SV01	RV01	TO1	TO2	TO3	TO4	TO5	FV01	FV02	MO1	MO2	MO3	FV03	FV04
-5 Weeks	0 Weeks	1 Week	2 Weeks	3 Weeks	4 Weeks	5 Weeks*	3 Months	4 Months	6 Months	9 Months	12 Months	15 Months	16 Months

B. Temperature Biofeedback and EMG Frontalis Biofeedback Groups

SV01	RV01	TO1	TO2	TO3	TO4	TO5	TO6	TO7	TO8	TO9	T10*	VC01	FV01	FV02	MO1	MO2	MO3	FV03	FV04
-5 Weeks	0 Weeks	1 Week	1.5 Weeks	2 Weeks	2.5 Weeks	3 Weeks	3.5 Weeks	4 Weeks	4.5 Weeks	5 Weeks	5.5 Weeks	6 Weeks	3 Months	4 Months	6 Months	9 Months	12 Months	15 Months	16 Months

*Treatment visits are ideally completed in five to six weeks, but may be completed in a period as long as ten weeks.

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CHAPTER 3

PATIENT ELIGIBILITY

3.1 INTRODUCTION

This study will include patients with primary Raynaud's phenomenon, defined as episodic digital pallor and/or digital cyanosis with demarcation that is provoked by cold exposure and is reversible on rewarming. Color charts will be used as a guideline for the diagnosis of Raynaud's phenomenon. Raynaud's Treatment Study (RTS) color charts will be used to standardize patient reports of typical color changes, as well as their reports of the hand patterns observed during their Raynaud's phenomenon attacks.

In order to be eligible for enrollment into this study, each patient must satisfy all inclusion criteria and none of the exclusion criteria.

3.2 ELIGIBILITY AND EXCLUSION CRITERIA

3.2.1 Eligibility Criteria

All of the following eligibility criteria must be satisfied for a patient to be eligible for enrollment.

1. The presence of Raynaud's phenomenon as defined by digital pallor and/or digital cyanosis, with demarcation, that is provoked by cold exposure and is reversible on rewarming. The RTS color charts must be used in making the diagnosis of Raynaud's phenomenon.
2. History of Raynaud's phenomenon attacks occurring an average of at least two times daily (average of 14 attacks/week) during the cold season.
3. Nailfold capillary pattern that is within the normal range as determined by capillary microscopy, described in Section 3.4.
4. Absence of a history of digital ulcers or digital gangrene, and absence of digital tip ulcers at the time of the baseline physical examination.
5. History of symptoms of Raynaud's phenomenon for at least two years.
6. Negative antinuclear antibody test (ANA) or titer less than or equal to 1:320, using the HEP-2 substrate.
7. Age 18 years or greater.

8. Has access to telephone for regular contact with Clinical Unit staff.
9. Ability and willingness to give informed consent to participate in the RTS.

3.2.2 Exclusion Criteria

Patients will be excluded if any of the following conditions are satisfied.

1. Evidence of an underlying disease including occlusive arterial disease, trauma, neurogenic lesions, scleroderma, systemic lupus erythematosus, or any other condition that could be responsible for the vascular attacks.
2. Age less than 18 years.
3. Active pregnancy or planning to become pregnant within the duration of the RTS.
4. Breast-feeding.
5. Unreliable due to inability to understand, illicit drug or alcohol abuse, or other factors which are likely to interfere with the conduct of the study.
6. Evidence of any cardiovascular, pulmonary, renal, hepatic, endocrine, neoplastic, psychiatric, neurologic or gastrointestinal disease which is likely to interfere with the conduct of the study.
7. Severe gastrointestinal stricture that might result in an inability to pass the study medication capsule in the feces.
8. Plans to move away from the study area prior to completion of the RTS.
9. Completion of the daily calendars for fewer than three weeks between the Screening Visit (SV01) and the Randomization Visit (RV01).
10. The inability to discontinue concomitant medications thought to have important vasomotor action for at least one month prior to SV01. Medications that must be discontinued prior to enrollment are listed in Section 3.2.3.

3.2.3 Disallowed and Allowed Non-Study Medications

Medications that must be discontinued at least one month prior to SV01 and should not be taken during follow-up include:

alpha methyldopa
beta blockers
calcium channel blockers
clonidine
ergot preparations
guanethidine
hydralazine
minoxidil
nitroglycerine ointment
nicotine resin (or transdermal patch)
pentoxifllyline
prazosin
reserpine

Medications that patients may continue to take prior to and during follow-up include, but are not limited to:

aminophylline and derivatives
analgesics
angiotensin converting enzyme inhibitors
antibiotics
antihistamines
bethanechol
calcitonin
corticosteroids
coumadin
cyclobenzaprine Hcl
diazepam
D-penicillamine
dipyridamole
diuretics
estrogens
fluoxetine (Prozac)
H-2 blockers
immunosuppressants
inhalant bronchodilators
metaclopramide
NSAID's, including ASA
omeprazole
sedatives/hypnotics
sucralfate
thyroid hormone
vitamin supplements

3.3 LABORATORY TESTS

Potential participants will have a physical examination and the following laboratory tests prior to enrollment. The Clinical Unit physician will be responsible for reviewing the results of these laboratory tests and evaluating the suitability of the patient for the RTS prior to enrolling the patient.

3.3.1 Schedule Laboratory Tests

The following laboratory tests will be performed at SV01, Monitoring Visit 1 (M01), and Follow-up Visit 4 (FV04).

Complete Blood Count (CBC) with differential
Platelet count
Electrolytes: Sodium, Potassium, Carbon dioxide, Chloride
Blood uric nitrogen (BUN)/creatinine

SMA-12

Calcium, Phosphorus, Glucose
Magnesium, T. bilirubin, D. bilirubin,
Cholesterol, Uric acid,
Total Protein, Albumin,
Alkaline phosphatase
Aspartate aminotransferase (AST)
Lactate dehydrogenase (LDH)
Creatine Kinase (CPK)
Urinalysis: dipstick and microscopic

In addition, ANA using HEP-2 substrate will be measured at SV01 and at Follow-up Visit 4 (FV04).

3.4 CAPILLARY MICROSCOPY

In order to be eligible for the RTS, the patient must have "normal" capillary microscopy, as described below:

Normal

Nailfold

1. Uniform distribution capillaries, i.e., no disorganization of the overall pattern of capillary distribution.
2. Capillary loop width $< 100\mu$ in the distal row.
3. No marked departure of the basic hair pin shape of the capillary loop, i.e. no marked tortuosity or other deformation.
4. No edematous appearance.
5. Few, if any, capillary hemorrhages (unless related to trauma) with normal outgrowth in the cuticle.
6. No localized avascular areas.

Hands

1. No microvascular abnormalities other than those associate with normal aging.

Capillary microscopy will be repeated at the end of follow-up and classified as "normal" or "abnormal or scleroderma spectrum disease (SDS) pattern" . Criteria for "normal" are described above. The criteria for "abnormal or (SDS) pattern" are described below.

Abnormal or SDS Pattern

Nailfold

Main Features:

1. Capillary loops in the distal row with loop with $>100\mu$ and enlarged in all three portions of the loop (arterial, venous and apical).
2. Localized loss of capillaries consisting of avascular areas of $>0.4mm^2$.

Additional Features:

3. Disorganization of the whole nailfold capillary bed
4. Purplish white background with poorly outlined capillaries of low density proximal to the distal row
5. Numerous capillary hemorrhages in the cuticle with abnormal spreading of hemoglobin breakdown products

Hands

1. Capillary telangiectases.
2. SDS-type capillaries surrounding scars or ulcerations.

Photographs of "normal" and "abnormal" capillary patterns will be provided to each Clinical Unit for reference.

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CHAPTER 4

RECRUITMENT AND ENROLLMENT

4.1 INTRODUCTION

The objectives of a recruitment program are twofold. First, it serves to assure that the recruitment goals of the study are met by each of the participating Clinical Units. Second, it improves the likelihood that all patients with Raynaud's phenomenon within the Clinical Unit's catchment area will have equal access during the recruitment phase of the Raynaud's Treatment Study (RTS), thus avoiding selection biases. To this end, Clinical Unit coordinators will systematically identify potentially eligible patients from a variety of sources, inform them and their physicians about the RTS, and solicit their participation in determining whether they are eligible to enter the RTS.

In order to assist with developing an adequate, study-wide participation of minorities and women, it is planned to track the distribution of patients among the specific target groups, so that adjustments in strategy, if needed, can be made expeditiously. Information will be collected to document: 1) the sources from which RTS candidates are identified; 2) the proportion of patients from specific sources who are determined to be eligible; 3) the exclusion criteria leading to ineligibility; 4) the proportion of eligible patients consenting and enrolling in the RTS; 5) the proportions of women and minorities enrolled in the RTS, as well as the stage at which patients are excluded during the enrollment process.

4.2 PHYSICIAN AND COMMUNITY OUTREACH

A successful program of screening and recruitment requires that the Clinical Units carry out a determined program of informing relevant physicians and nurses about the RTS. The general goals of such a program are to educate the medical and nursing staff about the design and objectives of the RTS, and the criteria which qualify patients for consideration.

During screening, the Clinical Unit staff will actively seek all potentially eligible patients, and discuss with their physicians what participation in the RTS offers their patients. Understanding and acceptance of the goals of the RTS by referring physicians will affect the success with which the Clinical Units will be able to recruit patients. A variety of methods that target the general community as well as physicians may be used for this educational program.

Informing physicians can be accomplished through in-service conferences, Grand Rounds, presentations at local medical societies, editorials in medical journals, or posters and brochures describing the RTS, located at strategic points within the hospital and sent to practicing community physicians.

Approximately 8.6% of the mainland U.S. population (21 million) is comprised of Hispanic-Americans according to 1991 figures from the U.S. Census Bureau. The Hispanic population is expected to grow at 3-5 times the rate of the non-Hispanic population in the U.S. and to reach 25 million by the year 2000. The problems with treating the Hispanic population arise from unfamiliarity and inexperience with the culture and a lack of appropriate access to the Hispanic community. One of the RTS Clinical Units, the UMD-New Jersey Medical School, is presently a recipient of a federally-funded Hispanic Center of Excellence grant which would assist in the development of articles for dissemination to targeted media (newspaper, radio) dedicated to the Hispanic community. Information on the protocol would also be disseminated to the national Sjogren's Foundation which has agreed to publish articles on the RTS focusing on recruitment.

Simultaneous educational efforts directed at patients and the general community will broaden the recruitment base, and help ensure enrollment of minorities. Efforts directed to the general community can include newspaper articles and advertising, interviews on radio talk shows, and similar media campaigns in markets selected to reach minority groups. Institutional public relations departments might be able to assist with these efforts. Patients may contact the Clinical Units directly or through their physicians.

Since most sufferers of Raynaud's phenomenon are women (epidemiological studies identify 60 to 80% of Raynaud's phenomenon patients to be female), achieving adequate gender distribution in recruitment for the RTS is not likely to be difficult, but should be monitored. Previous experience in several of the Clinical Units indicates that enrollment of minorities can be expected to reach 25%.

4.3 ENUMERATION OF POTENTIAL PARTICIPANTS

Any patient with evidence of primary Raynaud's phenomenon is considered a potential candidate for participation in the RTS. Each Clinical Unit will establish procedures for systematic review of

patient records to identify potential participants. Each week, the Clinical Unit Research Coordinator will complete a Weekly Recruitment Summary Form and send it to the RTS Coordinating Center. Information to be reported will include the total number of patient records reviewed and the total number of potential participants identified, according to the sources of the records (e.g., rheumatology department, collaborating referring physician, self-referral). Patients will be considered to be potential participants if their records show they satisfy the RTS eligibility criteria (see Chapter 3, Patient Eligibility). They will be invited to the Clinical Unit for additional evaluation. For those patients who are not eligible for further consideration for participation in the RTS, no additional data will be collected.

4.4 CONFIRMATION OF ELIGIBILITY

The eligibility of patients who contact a Clinical unit directly will be screened by Clinical Unit staff, by telephone or in person, as appropriate. The Research Coordinator will explain the nature of the RTS. If the patient is interested in participating in the RTS, a brief structured questionnaire addressing Raynaud's phenomenon symptoms will be administered to assess his/her eligibility. Patients who seem to meet the eligibility criteria will be asked to complete a more detailed screening questionnaire to be returned to the Clinical Unit, usually by mail. Patients who are still considered to be potentially eligible will be invited to the Clinical Unit for an examination by the research coordinator or Clinical Unit physician.

Once the patient is identified as a candidate for the RTS, he/she will be assigned a name code and patient identification number. The name code and identification number will serve to conceal the patients' identity from RTS Coordinating Center staff. The name code and patient identification number will be recorded on the RTS Candidate Log, which will include the following information necessary for further evaluation of eligibility:

1) date the patient was identified as a potential participant;

2) age;

3) ethnic origin;

4) source of referral (Clinical Unit and affiliates, other collaborating physician, self-referral, or other);

5) whether the patient meets each of the eligibility criteria (see Chapter 3, Patient Eligibility); and

6) exclusion criteria present, if any (see Chapter 3, Patient Eligibility).

If the patient meets more than one exclusion criterion, all the exclusion criteria should be recorded. This information may be used to assess the impact of the exclusion criteria on enrollment in the RTS.

4.5 CORE LABORATORY PROCEDURES

Patients who are apparently eligible for the RTS will be asked to sign the Informed Consent Form. They will be asked to provide a blood sample, to be sent to the Core Laboratory for measurement of antinuclear antibody (ANA) levels.

4.6 RANDOMIZATION

After the RTS Coordinating Center receives the Core Laboratory report of the ANA levels, the Clinical Unit staff will be informed whether or not the patient meets the eligibility criteria, based on information available at the Coordinating Center. Patients considered to be eligible for the RTS will be asked to return to the Clinical Unit for the Randomization Visit (RV01). Prior to RV01 the patient's personal physician must be contacted to obtain his/her agreement for the patient to participate in the RTS. The personal physician must be contacted even if he/she was not involved in referring the patient to the RTS Clinical Unit.

At RV01, the patient's eligibility and willingness to participate in the RTS will be reviewed. If the patient is eligible and willing to participate, Clinical Unit staff will request a treatment assignment from the RTS Coordinating Center, using the automated telephone randomization system (ATRS).

EXHIBIT 4-1

CONSENT TO ACT AS A SUBJECT IN AN EXPERIMENTAL STUDY

TITLE: THE RAYNAUD'S TREATMENT STUDY

INVESTIGATORS: (FILL IN APPROPRIATE INVESTIGATORS FOR EACH CLINICAL UNIT)

You are being asked to join a clinical research study. The doctors at (INSTITUTION) are studying the nature of disease and are attempting to develop improved methods of diagnosis and treatment. This is called clinical research. In order to decide whether or not you should agree to be part of this research study, you should understand enough about its risks and benefits to make an informed judgement. This process is called informed consent, and is meant to tell you about the study and answer any questions you may have.

DESCRIPTION: The (Institution) is part of a nation-wide study in which the effects of 4 treatments for Raynaud's Disease are compared. Sixty patients will be recruited from (INSTITUTION), and a total of 300 patients will be asked to join across the country. You have been asked to join this study because of your report of attacks to your fingers of numbness, tingling and color change, in which blood flow to the hands or feet almost stops, mainly during cold weather.

The study compares the effect of two unlike drug treatments and two unlike non-drug treatments. You will be assigned to one of these four treatments by chance (like the flip of a coin). It is possible that the effectiveness is different for the four treatments. It is likely that some differences in side effects will be found between the four treatments as well. The purpose of this study is to compare the four treatments to find out which, if any, works best. The drug treatments are Procardia XL (nifedipine XL), a drug which dilates the blood vessels to the fingers, or placebo, a pill that contains no drug or medication. If you are assigned to one of the two drug treatments, neither you nor your doctor will know which treatment you are receiving.

The non-drug treatments both involve biofeedback. This is a process in which people learn to change a body function with the help of a device that measures small changes in that function. The two non-drug treatments in this study are temperature biofeedback and muscle tension biofeedback (called EMG biofeedback). If you are assigned to temperature or EMG biofeedback, you will learn mental methods to

Patient's Initials _____

attempt to control Raynaud's symptoms. Unlike the drug treatment conditions, where you and your doctor will not know which drug you are receiving, you and your doctor/therapist will know which biofeedback treatment you are receiving.

Before you can be assigned to one of the four treatments, the fact that you have Raynaud's Disease must be confirmed by a check-up with a doctor, as well as blood and urine tests. The blood test will require a tablespoon (15 cc) of blood to be drawn from a vein in your arm. You will also have a sample of your blood stored for future tests. This sample will require another tablespoon of blood (15 cc) of blood. Should it turn out that you have some other condition causing your Raynaud's Disease, you will not be asked to remain in the study any further. If you are a female, and of child-bearing age, a urine pregnancy test will be performed. If you are pregnant, you will not be asked to remain in this study any further. If you do have Raynaud's Disease, you will be asked to remain in the study. If you are taking drugs for Raynaud's Disease right now, you will be asked to stop taking them at this point. Your complete participation in this study after this initial visit will take about 17 months. After the initial visit, you will enter a one-month phase in which you will record your symptoms, fill out several forms, and take a "cold test" of the hands. All of these tasks will be described in more detail below.

During the four weeks before you enter treatment, you will be asked to keep a diary in which you record each attack, at the time it occurs, on a card designed for this purpose. You are asked to carry this card with you at all times. You will also be asked to record your symptoms each evening on the end-of-the-day report, a quick checklist of your Raynaud's symptoms during that day. During one visit to the clinic, you will be asked to fill out a set of forms that will take about 45 minutes of your time. These forms will ask questions about your Raynaud's symptoms, how you are coping with the symptoms, and how your life is going at this time.

For the cold test of your hands, you will go to a laboratory. You will be asked to place one finger in a cuff. The cuff will be blown up like a blood pressure cuff, and your finger will be cooled for five minutes. When your finger is cool, the pressure in the cuff will be slowly released, and the blood pressure in your finger will be measured. This will be done a total of four times at different temperatures. The temperatures

Patient's Initials _____

will range from room temperature to the temperature inside a refrigerator. This testing session will require about 1-2 hours of your time.

After these tests, you will start one of the four treatments. If you are assigned to a biofeedback treatment, you will be asked to visit a biofeedback therapist twice a week for a total of 10 sessions, or about 5-10 weeks. After a few months, you may be asked to come in for another 4 sessions. If you are assigned to a drug treatment, you will be asked to visit one of the doctors once a week for about 5-10 weeks.

After this, you will continue with the treatment you receive for a little over a year. During that time, you will be asked to return for brief check-ups with a doctor or nurse about every three months. At two of these visits, a blood sample (about two tablespoons) will be taken. In addition, about three months and fifteen months after you start treatment, you will be asked to repeat the assessments that were done before you started treatment: keeping the diary, filling out forms, and taking the cold test. During your first and second winter in the study (January through March), you will again be asked to complete the end-of-the-day-report.

RISKS AND BENEFITS: Risks known to exist with nifedipine treatment include low blood pressure, dizzy spells, heart burn, and swelling of the feet. Biofeedback treatment has no known side effects. If you were taking drugs for your Raynaud's symptoms before you started the study, stopping the drug could result in an increase in these symptoms. Drawing blood from a vein may cause soreness, bruising or swelling at the site of the puncture, and very rarely, it may cause you to feel faint. The cold test of your hand may result in discomfort or return of Raynaud's symptoms from putting your hand in the cold box. Although we cannot assure that benefits will result to you for your joining this study, there is the possibility that your Raynaud's symptoms will decrease as a result of the treatment to which you are assigned.

ALTERNATIVE TREATMENTS: Other treatments used for Raynaud's Disease include avoiding things that make your symptoms worse, relaxation exercises, and drugs such as a short-acting version of nifedipine, diltiazem and prazosin.

Patient's Initials _____

NEW INFORMATION: If new information, either good or bad, about the study treatments comes to your doctor's attention during the course of this study, which may relate to your desire to remain in the study, it will be given to you.

COSTS AND PAYMENTS: You will not be charged for being in this study. There will be no charge for doctor visits, study drugs, or study laboratory (blood and urine) tests. Tests done for other clinical reasons will be charged to you or to your insurance company. You will not be paid for your time in the study.

COMPENSATION FOR ILLNESS OR INJURY: You will not be paid for any injury or illness resulting from this study, but any emergency medical attention which may be necessary will be provided.

PREGNANCY: You will be asked not to become pregnant during the 18 months required to complete the study, and we ask that you use some form of birth-control during this time. There are no well controlled studies evaluating the safety of the drugs being used on pregnant women or women who are breast-feeding. If you should become pregnant, you will be asked to stop treatment while you are pregnant or breast-feeding. We will continue to assess how you are doing once you have stopped your treatment.

RIGHT TO REFUSE OR WITHDRAW: Your participation is voluntary, and you may refuse to join the study, or may stop at any time, without penalty or loss of benefits. Your doctors also have the right to withdraw you from the treatment at any time.

If you choose to withdraw from the treatment, the following procedures will be followed:

- We will contact your primary doctor, regarding your participation in the study and inform him/her of your decision to withdraw, so that he may resume your treatment.

- We will also ask you to continue to participate in brief follow-up interviews, in order to assess how you are doing once you have stopped your participation.

Some of the questions you will be asked during the course of the first meeting and follow-up meetings are of a personal nature. While we would value your full participation, you have the right to refuse to answer questions.

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CONFIDENTIALITY: Every effort will be made to maintain the confidentiality of your study records. Agents of the (Institution), National Heart, Lung and Blood Institute (NHLBI), and the Food and Drug Administration (FDA), will be allowed to inspect those sections of your medical and research records. The data from the study may be published; however, you will not be listed by name. If you desire, the results of the study will be shared with you at the end of the entire study.

INDIVIDUALS TO CONTACT: If you need more information about this study before you decide to join, or if you have any questions about your treatment, or your rights as a research subject, you can contact any of the individuals listed below:

(FILL IN THE INVESTIGATORS/CONTACT PERSONS NAMES AND PHONE NUMBERS).

In case of an emergency, please call (FILL IN THE INSTITUTION'S EMERGENCY NUMBER).

You will receive a copy of this consent form if you agree to participate in this research study.

PATIENT'S STATEMENT OF CONSENT:

I have read the description of the clinical research study in this consent form and understand it. If I have any questions I have talked it over with one of the doctors to my satisfaction. I understand that my participation is voluntary. I know enough about the purpose, methods, risks and benefits of this research study to judge that I want to take part in it. I hereby consent to participate in the Raynaud's Treatment Study.

_____
Patients Signature

_____
Patients Name (Please Print)

_____
Witness' Signature

_____
Date

Patient's Initials _____

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CHAPTER 5

ADMINISTRATION OF STUDY MEDICATIONS

5.1 INTRODUCTION

Patients enrolled in the Raynaud's Treatment Study (RTS) Clinical Trial will be randomly assigned to receive nifedipine XL or its placebo or to receive temperature biofeedback training or frontalis electromyogram (EMG) biofeedback training. All patients assigned to study medications (nifedipine XL or placebo) will initially be prescribed one capsule per day (30 mg per day), to be increased to two capsules per day (60 mg per day) unless contraindicated. This chapter describes the guidelines for prescribing, monitoring, titrating, storing, and disposing of study medications.

5.2 STUDY MEDICATION REGIMENS

Patients with primary Raynaud's phenomenon will be randomly assigned to one of the following study treatments:

1. Nifedipine XL

   At the Randomization Visit (RV01), each patient randomly assigned to the Nifedipine XL Treatment Group will be asked to take one capsule of nifedipine XL 30 mg once a day for one week. At the end of one week, the patient will be asked to take two capsules of nifedipine XL 30 mg once a day during the remainder of the active treatment phase of the study.

2. Placebo

   At the RV01, each patient randomly assigned to the Placebo Treatment Group will be asked to take one placebo capsule once a day for one week. At the end of one week, the patient will be asked to take two placebo capsules once a day during the remainder of the active treatment phase of the study. (The placebo capsule will be identical in appearance to the nifedipine XL capsule. Neither the patient nor the Clinical Unit staff will know if the assigned study medication is nifedipine XL or placebo).

3. Temperature Biofeedback or Frontalis EMG Biofeedback

   Patients randomly assigned to the Temperature Biofeedback Group or the Frontalis EMG Biofeedback Group will not be given any study medication.

During the course of the study, patients in all study groups will be asked to refrain from taking vasodilators or other calcium channel blockers (see Chapter 3, Patient Eligibility, for the list of allowed and disallowed non-study medications). Each patient must have stopped all medications thought to have important vasomotor action at least one month prior to baseline data collection scheduled for the Screening Visit (SV01, see Chapter 3, Patient Eligibility).

5.3 PROCEDURES FOR PRESCRIBING STUDY MEDICATIONS

Each enrolled patient will be assigned a unique medication number; study medication labeled with the patient's assigned medication number will be dispensed to the patient at RV01 and at subsequent Monitoring Visits and Follow-up Visits. Each patient will be assigned only one study medication number.

A sealed tear-off label is attached to each medication label and contains the identification of the contents of the bottle (nifedipine XL or placebo); this label should be detached when the study medication is dispensed to the patient and should be filed unopened at the Clinical Unit. The study medication label should be opened only in case of emergency. To monitor adherence to this procedure, the sealed labels from the bottles distributed to each patient at one visit should be affixed to the Drug Distribution Form which is kept in the patient's file until the patient returns the bottles of medication at the next visit. The Drug Distribution Form with the labels attached is then submitted to the Coordinating Center.

Patients are instructed to take one capsule per day during the first week and two capsules per day thereafter. The study medication may be taken at any convenient time but it is recommended that it be taken after breakfast. Patients should be instructed to drink six ounces of water or other liquids with the study medication.

The patient should be asked to return all empty, opened, and unopened bottles of study medication and all of his/her remaining capsules at each visit to the Clinical Unit. The amount of new supplies of study medication dispensed to the patient should be adjusted to take into account the returned medication which is redispensed.

In extenuating circumstances, study medication may be dispensed by mailing it to the patient. The supply dispensed by mail should be sufficient for one period between scheduled Monitoring Visits or Follow-up Visits or whatever the patient's usual supply has been. The study medication can be

dispensed by mail only if telephone contact with the patient has confirmed that the patient has not had any adverse effects. The study medication should not be dispensed by mail for more than two consecutive Monitoring Visit or Follow-up Visit periods.

5.4 PROCEDURES FOR STORING AND DISPOSING OF STUDY MEDICATIONS

5.4.1 Supplies of Study Medications

Supplies of study medications will be shipped to the Clinical Units before enrollment of patients is scheduled to begin. The medications will be labeled with study medication numbers. The initial supply of medication will be adequate for the entire period of time the patient is scheduled to take study medication. Some "extra" study medication will be provided for emergencies, for example, to replace supplies lost by the patient. Clinical Unit staff are responsible for monitoring the supplies of study medication stored at the Clinical Unit. If remaining supplies for an individual patient are not sufficient, for example, because a substantial quantity was lost or destroyed accidentally by the patient, Clinical Unit staff should alert Coordinating Center staff immediately so that additional supplies can be labeled and shipped to the Clinical Unit.

The Clinical Unit staff are responsible for dispensing the appropriate amount of study medication to the patient at each Monitoring Visit or Follow-up Visit (see Section 5.3, Procedures for Prescribing Study Medications).

5.4.2 Storage and Disposal

Appropriate storage facilities should be provided for study drugs. The Principal Investigator may arrange to have drugs stored in and dispensed from the institution pharmacy. If kept in the RTS Clinical Unit, medications should be stored in a lockable cabinet or closet at a temperature in the range 60° to 80° F and at low humidity. Supplies should be arranged so that bottles are easy to locate by the staff member responsible for dispensing the study medication.

If the study drug bottle label indicates that the expiration of the shelf life of the study drug will occur in the near future, it should not be dispensed to the patient. The procedures for disposal of study medication are as follows:

1. Bottles should be arranged by distinct medication numbers.

2. For each distinct medication number, the labels should be torn off and placed in an envelope and the medication number and the total number of labels written should be on the outside of each envelope. The envelope should be sealed.
3. The study medication bottles now without the labels should be destroyed according to local policy for disposing of medication.
4. The envelopes for each distinct medication number containing the tear-off labels should be mailed to the Coordinating Center.

5.5 METHOD OF MEDICATION ADMINISTRATION AND INITIAL TITRATION

All patients assigned to the study medication groups (nifedipine XL or placebo) will start with one capsule daily to be taken as a single morning dose.

Patients assigned to nifedipine XL or placebo will have the medication titrated to the maximal tolerated dose according to the following procedures:

The patient will be given a supply of study medication at RV01. The patient will be asked to return one week later for a Treatment Visit (T01). At T01, the patient will be asked about the occurrence of side effects. A limited physical examination will be performed which will include vital signs (blood pressure and pulse). If there are no signs or symptoms of side effects or adverse reactions (see below), the patient will be asked to increase the dose of study medication to two capsules once daily in the morning. In another week, he/she will return for a second Treatment Visit (T02). At the second visit, a limited physical examination including blood pressure and pulse will be performed. If there are no side effects or adverse reactions, the patient will continue to take two capsules once daily.

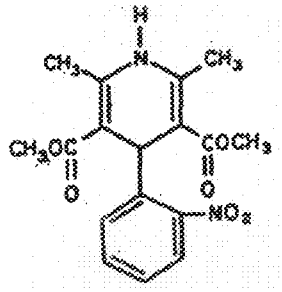
If there are moderate side effects at the second visit (T02), the dose of the study medication will be reduced to one capsule daily. If there are signs or symptoms of severe side effects or an adverse reaction, the medication will be stopped for one week. If the signs and symptoms of the side effect have disappeared at the end of one week, and if the Clinical Unit physician decides that restarting the medication at a lower dose would be safe, the study medication can be restarted at one capsule daily. If the side effect does not resolve, the patient will no longer be prescribed study medication. Even if study medication is

discontinued, the patient will continue to complete his/her scheduled visits to the Clinical Unit and data from the patient will be included in the analyses of study data.

5.6 PHARMOKINETICS OF NIFEDIPINE XL

5.6.1 Description

Nifedipine is a drug belonging to a class of pharmacological agents, known as the calcium channel blockers. Nifedipine is 3,5-pyridinedicarboxylic acid, 1,4-dihydro-2, 6-dimethyl-4 (2-nitrophenyl)-, dimethyl ester, $C_{17}H_{18}N_2O_6$, and has the structural formula:



Nifedipine is a yellow crystalline substance, practically insoluble in water but soluble in ethanol. It has molecular weight of 346.3. Nifedipine XL is a trademark for Nifedipine Gastrointestinal Therapeutic System (GITS); the medication will be referred to as nifedipine XL in this Protocol. Nifedipine XL is formulated as a once-a-day controlled-release tablet (Extended Release Tablet) for oral administration, designed to deliver 30, 60, or 90 mg of nifedipine.

Inert ingredients in the formulations are: cellulose acetate; hydroxypropyl methylcelluiose; magnesium stearate; polyethylene glycol, polyethylene oxide; red ferric oxide; sodium chloride; and titanium dioxide.

5.6.2 System Components and Performance

Nifedipine XL tablets are similar in appearance to conventional tablets. They consist, however, of a semipermeable membrane surrounding an osmotically active drug core. The core itself is divided into two layers; an "active" layer containing the drug, and a "push" layer containing pharmacologically inert (but osmotically active) components. As water from the gastrointestinal (GI) tract enters the tablet, pressure increases in the osmotic layer and "pushes" against the dry layer, releasing drug through the precision laser-drilled tablet orifice in the active layer.

Nifedipine XL tablets are designed to provide nifedipine at an approximately constant rate over 24 hours. This controlled rate of drug delivery into the GI lumen is independent of Ph or GI motility. Nifedipine XL depends for its action on the existence of an osmotic gradient between the contents of the bi-layer core and fluid in the GI tract. Drug delivery is essentially constant as long as the osmotic gradient remains constant, and then gradually falls to zero. Upon swallowing, the biologically inert components of the tablet remain intact during GI transit and are eliminated in the feces as an insoluble shell.

5.6.3 Pharmokinetics and Metabolism

Nifedipine is completely absorbed after oral administration. Plasma drug concentrations rise at a gradual, controlled rate after a dose of nifedipine XL and reach a plateau at approximately six hours after the first dose. For subsequent doses, relatively constant plasma concentrations at this plateau are maintained with minimal fluctuations over the 24-hour dosing interval. About a four-fold higher fluctuation index (ratio of peak to trough plasma concentration) was observed with the conventional immediate release nifedipine capsule at t.i.d. dosing in comparison to a daily dose of nifedipine XL. At steady-state the bioavailability of the Nifedipine XL Extended Release Tablet is 86% relative to nifedipine capsules. Administration of the nifedipine XL tablet in the presence of food slightly alters the early rate of drug absorption, but does not influence the extent of drug bioavailability. Markedly reduced GI retention time over prolonged periods (i.e., short bowel syndrome), however, may influence the pharmacokinetic profile of the drug which could potentially result in lower plasma concentrations. Pharmacokinetics of nifedipine XL tablets are linear over the dose range of 30 to 180 mg in that plasma drug concentrations are proportional to dose administered. There was no evidence of dose dumping either in the presence or absence of food for over 150 subjects in pharmacokinetic studies.

Nifedipine is extensively metabolized to highly water-soluble, inactive metabolites accounting for 60 to 80% of the dose excreted in the urine. The elimination half-life of nifedipine is approximately two hours. Only traces (less than 0.1% of the dose) of unchanged form can be detected in the urine. The remainder is excreted in the feces in metabolized form, most likely as a result of biliary excretion. Thus, the pharmacokinetics of nifedipine are not significantly influenced by renal impairment. Patients in hemodialysis or chronic ambulatory peritoneal dialysis have not reported significantly altered pharmacokinetics of nifedipine. Since hepatic biotransformation is the predominant route for the

disposition of nifedipine, the pharmacokinetics may be altered in patients with chronic liver disease. Patients with hepatic impairment (liver cirrhosis) have a longer disposition half-life and higher bioavailability of nifedipine than healthy volunteers. The degree of serum protein binding of nifedipine is high (92-98%). Protein binding may be greatly reduced in patients with renal or hepatic impairment.

5.6.4 Hemodynamics

Like other slow-channel blockers, nifedipine exerts a negative inotropic effect on isolated myocardial tissue. This is rarely, if ever, seen in intact animals or man, probably because of reflex responses to its vasodilating effects. In man, nifedipine decreases peripheral vascular resistance which leads to a fall in systolic and diastolic pressures, usually minimal in normotensive volunteers (less than 5-10 mm Hg systolic), but sometimes larger. With nifedipine XL tablets (Extended Release Tablets), these decreases in blood pressure are not accompanied by any significant change in heart rate. Hemodynamic studies in patients with normal ventricular function have generally found a small increase in cardiac index without major effects on ejection fraction, left ventricular end diastolic pressure (LVEDP) or volume (LVEDV). Studies have shown some increase in ejection fraction and reduction in left ventricular filling pressure in patients with impaired ventricular function.

5.6.5 Electrophysiologic Effects

Although, like other members of its class, nifedipine causes a slight depression of sinoatrial node function and atrioventricular conduction in isolated myocardial preparations, such effects have not been seen in studies in intact animals or in man. In formal electrophysiologic studies, predominantly in patients with normal conduction systems, nifedipine has had no tendency to prolong atrioventricular conduction or sinus node recovery time, or to slow sinus rate.

5.7 EVALUATION AND MANAGEMENT OF SIDE EFFECTS AND ADVERSE REACTIONS

For the purposes of this study, a side effect is defined as an untoward effect which is distressing or unpleasant, but not harmful to the patient, with the exception of severe side effects which are considered synonymous with adverse reactions. An adverse reaction is defined as an untoward reaction which may be harmful to the patient on either a temporary or permanent basis.

The following are guidelines for decisions about medication dosage:

1. If there are mild side effects, the dose of the study medication will continue to be two capsules daily.

2. If there are signs or symptoms of moderate side effects, the study medication will be reduced to one capsule daily and the patient will continue to take this reduced dose. This patient will be contacted in one week to determine if the side effects have improved or been resolved at the reduced dose. If the side effects have not improved or been resolved, the patient will be seen at an additional visit for evaluation. The Clinical Unit physician will determine if the study medication can be continued at one capsule daily or if it should be stopped.
3. If there are signs or symptoms of a severe side effect or an adverse reaction, the study medication will be stopped for one week. If at the end of one week, the signs and symptoms of the side effect or adverse reaction have disappeared and if the Clinical Unit physician thinks that restarting the medication at a lower dose would be safe, then the study medication can be restarted at one capsule daily. If the side effect or adverse reaction does not resolve, the patient will no longer take any study medication.
4. Even if the study medication is discontinued, the patient will continue to complete his/her scheduled visits to the Clinical Unit and data from the patient will be included in the analyses of the study data.

The following guidelines should be followed during reduction or discontinuation of the study medication.

1. Every attempt should be made to encourage the patient to remain on the study medication unless, in the Clinical Unit physician's judgement, it would be harmful or hazardous to the patient to continue the medication.
2. If it becomes impossible to maintain the patient on full dosage of medication, a reduction in the dose is preferable to complete discontinuation. A record of changes in dose should be kept and reported on the appropriate study form.
3. Whenever the dose of study medication is reduced, the investigator should ascertain and record the effect the reduced dose had upon the undesirable side or adverse effect.
4. If study medication is discontinued, the patient should return all unused study medication to the Clinical Unit.
5. The decision to reinitiate the use of study medication after interruption rests with the Clinical Unit physician.

6. Side effects should be reported to the Coordinating Center on the appropriate study form. If serious adverse reactions develop which the investigator considers to be related to the study medication, they should be reported to the Program Office and RTS Coordinating Center by facsimile transmission or telephone.
7. If the study medication is discontinued, the patient should continue to complete scheduled visits to the Clinical Unit and be followed for the duration of the study.
8. If a patient's study medication is officially unblinded for any reason, the patient's study medication will be permanently discontinued.

5.7.1 Mandatory Interruption of the Study Medication

Discontinuation of the study medication is mandatory in the following circumstances:

1. The patient suspects or confirms that she is pregnant.
2. The patient's treatment regimen has been officially unblinded to either Clinical Unit personnel or the patient.
3. The patient has an intercurrent illness or is hospitalized which in the judgement of the Clinical Unit physician should prompt discontinuation of the study medication.
4. The patient has ischemic digital lesions which are unresponsive to the study medication alone.

If study medication is discontinued because of an intercurrent illness, use of the study medication may be resumed two weeks after resolution of the illness. The patient should take the same dose of study medication he/she was prescribed when the medication was discontinued.

5.7.2 Non-mandatory Interruption of the Study Medication or Reduction of Study Medication Dosage

The evaluation of adverse reactions and side effects, excluding mandatory interruptions of the study regimen, is the responsibility of the Clinical Unit physician and the details of this evaluation are left to this individual. The presence of a side effect does not require discontinuation of the study medication. It is the responsibility of the Clinical Unit physician to determine in each case whether the study medication should be continued or discontinued, temporarily or permanently.

5.7.3 Precautions and Guidelines to the Use of Nifedipine XL

In addition to the initial titration visits, the patients will be seen at Monitoring Visits and Follow-up Visits scheduled at three-month intervals for monitoring safety. The Monitoring Visit and Follow-up

Visit procedures include an interim medical history and a limited physical examination, for example, vital signs (blood pressure and pulse). Blood tests will be performed at baseline, and at six months and fifteen months after enrollment. This information will be recorded on the appropriate study forms. Special attention will be given to the following areas:

1. Nifedipine decreases peripheral resistance and can cause hypotension. Monitoring the blood pressure during initial use and during titration is mandatory. A symptomatic fall in blood pressure of greater than 15 mm Hg or a systolic blood pressure that is less than 95 mm Hg would warrant discontinuation of the study medication.
2. Peripheral edema caused by vasodilation of dependent arterioles may occur while taking nifedipine XL. Mild to moderate edema may not necessitate discontinuation; the investigator must evaluate the cause and nature of the edema and make a decision about dose reduction or discontinuation of the study medication.
3. Patients with a known severe GI stricture should not be enrolled in the RTS. The study medication is contained in a nonabsorbable shell which is eliminated in the feces.
4. Potential interaction with both coumarin and cimetidine have been reported. Increased prothrombin time may occur if the patient is on coumarin. Patients on cimetidine may have increased plasma levels of nifedipine. Nifedipine may increase the plasma level of digoxin. Patients on digoxin should have their blood levels of digoxin monitored.
5. The most common side effects reported with nifedipine therapy include headache, fatigue, dizziness, constipation, and nausea. Other side effects include lightheadedness, flushing, weakness, muscle cramps, nervousness or mood change, palpitations, dyspnea, cough or wheezing. The investigator must evaluate and determine the severity and nature of these symptoms and determine if reduction of the dose of study medication or discontinuation of the study medication is necessary.
6. Safety blood testing, scheduled at the Screening Visit (SV01), Monitoring Visit 1 (M01), and Follow-up Visit 4 (FV04), will include:

   Complete Blood Count (CBC) with differential
   Platelet count
   Electrolytes (Sodium, Potassium, Carbon dioxide, and Chloride)
   Blood uric nitrogen (BUN)/creatinine

SMA-12

Calcium, Phosphorus, Glucose
Magnesium, T. bilirubin, D. bilirubin,
Cholesterol, Uric acid,
Total Protein, Albumin,
Alkaline phosphatase
Aspartate aminotransferase (AST)
Lactate dehydrogenase (LDH)
Creatine Kinase (CPK)
Urinalysis: dipstick and microscopic

In addition, antinuclear antibodies (ANA) using HEP-2 substrate will be measured at SV01 and FV04.

5.7.4 Guidelines for Monitoring Laboratory Parameters

Laboratory tests will be performed prior to enrollment (SV01), six months after enrollment (M01) and at the end of the follow-up period (FV04), as described in Section 5.7.3. The Clinical Unit physician will be responsible for reviewing these data and for determining if there are indications of side effects. The following laboratory parameters would mandate an evaluation by the Clinical Unit physician:

1. Hematocrit less than 30%;
2. Platelet count less than 100,000;
3. Creatinine greater than 2.0 mg%;
4. Urinalysis demonstrates the new onset of proteinuria;
5. New hyperglycemia of greater than 200 mg%;
6. Abnormal liver function tests with new elevations of alkaline phosphatase, SGOT (ALT), or SGPT (AST) levels which the Clinical Unit physician deems significant; or
7. New elevation of the CPK levels.

5.7.5 Blood Specimens for Ancillary Studies

Ancillary studies which are planned can be done on "banked" sera and plasma specimens. A 15 cc tube for sera and a 15 cc tube for plasma will be drawn at SV01, M01, and FV04.

5.8 ADHERENCE

The patient should be asked to bring all empty, opened, and unopened bottles of study medication each time he/she visits the Clinical Unit. The returned study medication will be used for capsule counts for assessment of adherence. The following guidelines should be followed for counting capsules:

1. At each visit the patient should return all unused capsules;
2. The capsules should never be counted in the presence of the patient;
3. It should not be necessary to count every capsule in the bottle--an estimate to the nearest five capsules is sufficient;
4. Unopened bottles should be returned to the patient as part of his/her next study medication supply;
5. Opened bottles can be returned to the patient at the discretion of the investigator, depending on the number of capsules remaining. Wasting study medication is to be discouraged;
6. Unused study medication should never be thrown away in the presence of the patient;
7. Empty bottles should be discarded only at the Clinical Unit.

If the patient has forgotten to bring his/her medication to the Clinical Unit, the patient should be urged to mail empty bottles back to the Clinical Unit as soon as possible. However, if more than two weeks elapse from the date of the visit and the Clinical Unit has not received the empty bottles, then the information should be considered to be missing and recorded as such on the appropriate study form.

5.9 IN CASE OF EMERGENCY

Patients will be informed to call the Clinical Unit staff if any emergency or side effect occurs or if they must deviate from the study protocol. The patients will be given phone numbers of the RTS Clinical Unit investigators for both daytime and nighttime emergencies. An unscheduled emergency visit to the Clinical Unit will be done at any time it is deemed necessary.

If the study medication is taken by a child or another individual, a conservative assumption is that the drug is nifedipine XL and the individual should be treated appropriately. If unblinding must occur, it should be done, if at all possible, without involvement of any member of the Clinical Unit staff. In any case, the RTS Coordinating Center staff should be contacted as soon as possible for advice and/or notification concerning the unblinding.

There are two basic methods of unblinding study medications. The MORE desirable method is for a non-investigator physician to contact the holder of the study medication codes and to act accordingly. The LESS desirable of the two methods is for the sealed bottle label to be opened at the Clinical Unit.

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CHAPTER 6

ADMINISTRATION OF BIOFEEDBACK TREATMENT GROUPS

6.1 INTRODUCTION

Behavioral treatments for Raynaud's phenomenon have been employed since the mid-1970's. These treatments have focused primarily on affecting peripheral vasodilation by increasing digital skin temperature and/or blood flow, and have involved either temperature or electromyogram (EMG) biofeedback procedures alone, or in combination with other relaxation procedures such as autogenic training (1,2,3). Temperature biofeedback procedures involve teaching patients to produce specific changes in peripheral skin temperature and blood flow, while EMG biofeedback involves producing generalized reductions in physiological arousal. Autogenic training involves the use of self-suggestions, in the absence of psychophysiological feedback, and emphasizes both specific physiological sensations associated with relaxation and general feelings of relaxation.

In the first controlled study (1), primary Raynaud's patients were randomly assigned to receive either autogenic training alone or in combination with temperature biofeedback. A wait-list control condition was also utilized, with patients subsequently being randomly assigned to the aforementioned active treatment conditions after four weeks. Overall, the study subjects exhibited an improved vasodilation in response to a cold stress test and reported decreased frequency of attacks (ranging from 10-32%). However, there were no significant differences between treatment groups. A subsequent study (4) compared progressive relaxation, autogenic training, and the two procedures combined, with similar results.

Since previous investigations generally utilized various combinations of procedures (i.e., biofeedback, autogenic and progressive relaxation), a subsequent study was conducted (2) in order to compare the effects of temperature biofeedback alone to either autogenic training or EMG biofeedback. Additionally, temperature biofeedback was administered with and without exposure to a mild cold stress to the finger. There were significant differences among the groups in vasodilation and symptomatic improvement, as well as in muscle tension, heart rate and reported stress. Patients receiving temperature biofeedback with or without cold stress exhibited significant elevations in skin

temperature, as well as significant decreases in reported symptom frequency during the following winter (67% and 93%, respectively). This symptomatic improvement was maintained at two and three year follow-up. Differences in other physiological responses including muscle tension, heart rate, or reported stress were not demonstrated. Patients receiving EMG biofeedback or autogenic training did not exhibit either significant changes in skin temperature or symptomatic improvement (17% and 33%, respectively), however they did exhibit decreases in muscle tension, heart rate and reported stress. Subsequent investigations attempted to replicate these findings, as well as to examine the possible underlying mechanism of action of the treatment procedures (i.e., adrenergic responsivity). The findings of the earlier study were replicated with patients receiving temperature biofeedback reporting significant reductions in vasospastic attacks (80% and 81%, at one-year and two-year follow-up respectively), while patients receiving EMG biofeedback or autogenic changes exhibited little or no symptomatic improvement. There were also significant differences among the groups in the ability to increase skin finger temperature and capillary blood flow (measured by radioisotope clearance), with only the temperature biofeedback group exhibiting significant changes. Finally, intra-arterial propranolol was demonstrated to block a significant proportion of the biofeedback-induced vasodilation, despite use of digital nerve blockade, suggesting a local vascular adrenergic receptor defect. However, in a later study of physiological mechanisms (5), plasma catecholamine (an adrenergic agent) levels did not change during temperature biofeedback or autogenic training for primary Raynaud's patients.

The use of behavioral treatments for secondary Raynaud's phenomenon has been less successful than for the primary form of the disorder, and results have generally been mixed. Several case studies (6) suggested that scleroderma patients treated with temperature biofeedback were able to increase their digital skin temperature and demonstrated some symptomatic improvement. However, these findings have not been reliably replicated. In subsequent controlled investigations (7), 24 patients meeting classification criteria for systemic sclerosis (as defined by the American College of Rheumatology) were randomly assigned to either temperature biofeedback, EMG biofeedback, or autogenic training. Only the patients who received temperature biofeedback exhibited significant increases in their finger temperature during treatment and follow-up. There were no differences among the groups in the frequency of vasospastic attacks or in the physiological data obtained during

ambulatory monitory and laboratory cold stress tests. It is unclear why temperature biofeedback is ineffective in reducing symptoms in scleroderma patients, despite its demonstrated ability to increase finger temperature. However, it is likely that the underlying pathophysiology of secondary Raynaud's phenomenon is different than that of the primary disease.

6.2. RANDOMIZATION

Patients assigned to behavioral interventions (n = 150) will be randomly assigned to either temperature biofeedback (n = 75) or frontalis EMG biofeedback training (n = 75).

6.3 TEMPERATURE BIOFEEDBACK THERAPY

6.3.1 Schedule of Sessions

All patients will receive ten biofeedback training sessions, administered twice per week, over a five-week period. In the event a patient is unable to complete treatment in a five-week period, a maximum of ten weeks will be allowed to complete all sessions. Immediately post-treatment and at the conclusion of the one-year follow-up, the patient will also undergo a voluntary control assessment, at which he/she will be asked to attempt to increase his/her finger temperature in the absence of feedback.

6.3.2 Methods

Biofeedback Training Sessions

All biofeedback sessions will be conducted over approximately 60 minutes, with the exception of the first session, which will require approximately 90 minutes. During this initial session, the patient will be introduced to the biofeedback therapist and the rationale and procedures will be explained.

All sessions will include:

1. A ten-minute adaptation period to allow the patient to accommodate to the environment and for physiological responses to stabilize. No data will be collected during this time.
2. A 16-minute baseline period, during which the patient will be instructed to rest quietly.
3. A 16-minute biofeedback training period, during which the patient will receive auditory and visual analogue feedback of skin temperature. The patients will be instructed to increase his/her finger temperature using any mental means.

Data collected during the baseline and biofeedback periods will be used for within-subject session comparisons. The patient will be asked to rate his/her level of relaxation three times during each session: at the beginning of the session; at the end of the baseline period; and at the end of the session. Ratings will be completed using a 0-100 mm scale (Relaxation Visual Analogue Scale).

The patient will be instructed to practice the techniques on a daily basis.

A test with a minor cold stress will be included in two of the biofeedback sessions (Sessions 6 and 8). All other sessions will be conducted without a cold stressor. The cold stressor will involve localized cooling of the third digit of the dominant hand to 20°C. Cooling will take place for ten minutes, followed by an additional six minutes of feedback in the absence of cooling.

Home Practice

All patients will be asked to practice biofeedback techniques at home, 15 minutes, twice per day during the training period. They will be encouraged to apply the techniques they learned in their natural environment in order to abort or prevent vasospastic attacks. It will be recommended that patients continue to utilize the techniques indefinitely, emphasizing the use as a skill acquisition, which must be practiced to be effective. Compliance with home practice will be assessed utilizing home practice logs to be completed by the patient.

Voluntary Control Sessions

The Voluntary Control Sessions, conducted post-treatment and at one-year later, are designed to assess a patient's ability to produce voluntary changes in skin temperature in the absence of any biofeedback. The sessions will follow essentially the same format as the biofeedback training sessions, including:

1. A 10-minute adaptation period;
2. A 16-minute baseline period; and
3. A 16-minute voluntary temperature control period, during which the patient will be asked to increase his/her finger temperature using any mental means (but without biofeedback). These sessions will not include the use of a cold stressor.

Setting

All sessions will take place in a light and sound-attenuated room. The ambient temperature will be maintained a 23° + 1°C with soft lighting. The recording equipment will be located in a room separate from the patient. When the therapist is not present in the biofeedback room, communication with the patient will be constantly maintained via an intercom.

All patient rooms will be equipped with large reclining chairs. The patient will be asked to sit in a semi-recumbent position, with his/her arms resting on the armrest.

6.3.3 Physiological Recording Equipment and Quantification Procedures

Physiological data recording will include bilateral finger temperature as well as frontalis EMG (see Section 6.4, Frontalis EMG Biofeedback Therapy). Finger temperature will be recorded bilaterally from the distal, palmar surface of the third digit. As previously mentioned, biofeedback will be provided from the dominant hand. Temperature will be recorded minute by minute during the baseline and training periods of all sessions, using two J & J T-68 temperature trainers. Ambient room temperature, and cold stimulus temperature will also be electronically recorded. All patient session data will be stored on a computer disk and sent to the RTS Coordinating Center for analysis. Visual feedback will be provided via a large, visual analogue meter, with the needle movement indicating the degree of temperature change. Auditory feedback will consist of a variable pitch tone, with changes in pitch corresponding to temperature changes.

The cold stressor test will be conducted utilizing Physitemp NTE-2, a commercially available device, which provides localized cooling of the finger and/or hand. This device will be used to cool the third digit of the dominant hand (from which biofeedback is provided) from 30° to 20°C at 1°C/min.

Therapist Characteristics

Because this is a multicenter clinical trial, there will be some variability among the therapists regarding their level of education and prior biofeedback experience. To minimize the effects of this variability, all therapists will meet minimal educational standards. In addition, the therapists will be carefully selected to have high quality interpersonal skills, because therapist characteristics may be important in the conduct of biofeedback (8,9,10). All therapists will be trained to conduct the study at centralized training sessions.

6.4 FRONTALIS EMG BIOFEEDBACK THERAPY

Since frontalis EMG biofeedback therapy has been shown to produce no temperature training effects and no significant reduction in vasospastic attacks in primary Raynaud's subjects (2,11,12), it is included in this study as a control group for the Temperature Biofeedback Group. There is no attempt to include a "blind" procedure or false biofeedback condition since it is relatively easy for both the experimenter and the subject to detect deception in biofeedback studies (e.g., eye blink and swallowing produce brief increases in frontalis EMG). In the only published double-blind study with Raynaud's patients, neither an EMG biofeedback group nor a temperature biofeedback group learned their respective physiological response and not surprisingly, there was no treatment effect for either condition when compared with untreated controls.

6.4.1 Frontalis EMG Training

The schedule of sessions for frontalis EMG biofeedback training will be identical to that for temperature biofeedback training. All patients will receive ten biofeedback training sessions, administered twice per week, over a five-week period. In the event patients are unable to complete treatment in five weeks, a maximum of ten weeks will be allowed to complete all sessions. Immediately post-treatment and one year later, the patients will undergo a voluntary control assessment.

6.4.2 Methods

Biofeedback Training Sessions

All biofeedback sessions will be conducted over approximately 60 minutes, with the exception of the first session, which will require approximately 90 minutes. During this initial session, patients will be introduced to the biofeedback therapist and the rationale and procedures will be explained.

All sessions will include:

1. A ten-minute adaptation period to allow the patient to accommodate to the environment, and for physiological responses to stabilize. No data will be collected during this time.
2. A 16-minute baseline, during which the patient will be instructed to rest quietly.

3. A 16-minute biofeedback training period, during which the patient will receive auditory feedback of frontalis EMG activity. The patient will be instructed to decrease his/her forehead muscle tension as much as possible using any mental means.

Data collected during the baseline and biofeedback periods will be used for within-subject session comparisons. The patient will be asked to rate his/her level of relaxation three times during each session: at the beginning of the session; at the end of the baseline period; and at the end of the session. Ratings will be completed using a 0-100 mm scale (Relaxation Visual Analogue Scale).

The patients will be instructed to practice the techniques on a daily basis.

Home Practice

The patient will be asked to practice biofeedback techniques at home 15 minutes twice per day during the training period. They will be encouraged to apply the techniques they learned in their natural environment in order to abort or prevent vasospastic attacks. It will be recommended that patients continue to utilize the techniques indefinitely, emphasizing the use as a skill acquisition, which must be practiced to be effective. Compliance with home practice will be assessed utilizing home practice logs, to be completed by the patient over the training period.

Voluntary Control Sessions

The Voluntary Control Sessions, conducted post-treatment and at one-year follow-up, are designed to assess a patient's ability to produce voluntary changes in frontalis muscle tension in the absence of any biofeedback. The sessions will follow essentially the same format as the biofeedback training sessions, including:

1. A 10-minute adaptation period;
2. A 16-minute baseline period; and
3. A 16-minute voluntary relaxation period, during which the patient will be asked to relax his/her forehead muscles using any mental means (but without biofeedback).

Setting

All sessions will take place in a light and sound-attenuated room. The ambient temperature will be maintained a $23^{\circ} \pm 1^{\circ}C$ with soft lighting. The recording equipment will be located in a room

separate from the patient. When the therapist is not present in the biofeedback room, communication with the patient will be constantly maintained via an intercom.

All patient rooms will be equipped with large reclining chairs. The patient will be asked to sit in a semi-recumbent position, with his/her arms resting on the armrest. The patient will be instructed to avoid all physical maneuvers such as hand movements, frequent facial movements, or changes in breathing or tensing of muscles.

6.4.3 Physiological Recording Equipment and Quantification Procedures

Physiological data recording will include bilateral finger temperature as well as frontalis EMG. Frontalis EMG will be recorded using a standardized placement of EMG electrodes. Active electrodes will be placed 2.5 cm above each eyebrow and 10 cm apart, with a ground electrode centered between them (1). MBS disposable silver/silver chloride electrodes will be used and electrode gel will be used as the conductant medium. EMG will be recorded using a bandwidth of 20-1000 Hz, rectified, and averaged (RMS) over one-minute periods. Prior to the attachment of electrodes, the patient's skin will be prepared by lightly abrading its surface and cleaning it with alcohol, until resistance is reduced to 10,000 Ohms. The skin temperature will be recorded bilaterally from the distal, palmar surface of the third digit. The temperature will be recorded minute- by-minute during the baseline and training periods of all sessions, with two J & J T-68 temperature trainers. Ambient room temperature will also be electronically recorded. All patient session data will be stored on a computer disk and sent to the RTS Coordinating Center for analysis. Auditory feedback will consist of a continuous tone, which varies in pitch in direct proportion to the extent of muscle contraction in the facial muscles (EMG voltage, rectified and averaged with a time constant of 0.5 seconds).

No cold stressor test will be utilized for the EMG biofeedback conditions.

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CHAPTER 7

END POINT ASSESSMENT

7.1 PRIMARY END POINT

7.1.1 Introduction

The relative effectiveness of several therapies for symptoms of Raynaud's phenomenon will be based on measurements of the frequency of occurrence of Raynaud's phenomenon symptoms. Although a number of features of Raynaud's phenomenon attacks (frequency, severity, duration, threshold for initiation) are possible end points, only the number of attacks per day (frequency) is believed to be counted reliably enough to serve as the primary end point. Therefore, the null hypothesis to be tested is that there are no differences in daily attack rates among groups of patients treated with temperature biofeedback, frontalis electromyogram (EMG) biofeedback, nifedipine XL, or placebo during a one-month period 15 months after initiation of therapy.

The possibility of introducing bias reduces the attractiveness of relying on subjective retrospective report of the daily attack rate, as has been used in previous blinded drug studies (1,2,3). However, devising a completely objective means of determining the frequency of a symptom (in this case attack rate) without relying on the inherently subjective recognition of attacks by subjects is not feasible. Ambulatory electronic monitoring of finger temperature was considered but is believed to be too expensive, cumbersome, and untested to be practical for use in the RTS. A method of counting Raynaud's phenomenon attacks which relies on patient self-reports but gives some safeguards against over-reporting of attacks has been devised and is described below (Section 7.1.2). This method relies on the recognition of the finger and hand color changes that occur as a result of Raynaud's phenomenon, but includes a method by which an observer blinded to treatment group can verify that a characteristic attack occurred. Because this method of counting attacks has face validity, but has not been previously tested as a means of counting the occurrence of Raynaud's phenomenon attacks, a monitoring system will be in place to evaluate its performance after the first 25 patients have had the opportunity to complete it in the period between the Screening Visit (SV01) and the Randomization Visit (RV01). Because a second method of counting attack rate is also included in the study, no data or subjects will be lost if the color identification method is not reliable for some unforeseen reason.

Because of the possible low number of Raynaud's phenomenon events occurring (entry of a subject requires only a minimum of two attacks per day) a relatively long period of counting (one month) has been selected to allow detection of a change in attack rate as a consequence of therapy. There will be three one-month periods: 1) before initiation of biofeedback or drug therapy (immediately before the Randomization Visit, RV01); 2) after biofeedback therapy is completed (immediately after Follow-up Visit 1, FV01); and 3) one year after completion of biofeedback therapy (immediately after Follow-up Visit 3, FV03).

7.1.2 Criteria for Primary End Point

Color changes of the digits are the most often recognized, and indeed, the classical identifying features of Raynaud's phenomenon (4,5). The changes most frequently observed are blanching of digits due to complete arteriolar closure, cyanosis due to sluggish blood flow in the digits, and redness due to reactive hyperemia (4). Of these, the least distinctive is redness because it can be seen on the hands of many normal individuals in response to environmental changes. Therefore, redness is not suitable for definitive identification of Raynaud's phenomenon events. Blanching (whitening) of the fingers, particularly when associated with a clear line of demarcation, is the most distinctive color change and determination of its presence by medical history has been verified as the most reliable identifier of Raynaud's phenomenon (6,7). Cyanosis of digits often follows blanching in Raynaud's phenomenon but may occur without blanching in individuals who suffer Raynaud's phenomenon secondary to a connective tissue disease. Therefore, the patient's recognition of either blanching or cyanosis will be used to identify Raynaud's phenomenon.

7.1.3 Method of Counting Primary End Point

The identification of blanching and/or cyanosis by study participants is the basis for documentation of the occurrence of Raynaud's phenomenon in the RTS. Each patient will be instructed in the method of observing and recording information about attacks. The patient will be instructed to look at his/her fingers and hands when an attack occurs. Doing so obviously requires that the patient recognizes the occurrence of an attack. This may happen in several different ways, all of which are acceptable stimuli for subjects to examine their hands. These stimuli include happenstance recognition of color changes, sensation in the digits, another person's recognition of color changes, or association with environmental conditions that the patient thinks are likely to trigger an attack.

When the patient perceives that an attack is occurring, he/she will compare appearance of his/her digits to a series of nine photographs of digits. These digit photographs depict digits of normal color (five panels) and digits with either blanching (one panel) or cyanosis (three panels) that occurred in Raynaud's phenomenon patients. The patients will also compare their hands with a series of hand panels that represent both normal hands and hands experiencing a Raynaud's phenomenon attack. The study participants will be asked to carry the two groups of photographs (fingers and hands, mounted on a side of a 3" x 5" card) at all times. The panels on the "finger" side of the card will be numbered 1 through 9; the panels on the "hand" side of the card will be lettered A through F.

Although color charts have not previously been used to identify individual Raynaud's phenomenon attacks, they have been used for the diagnosis of Raynaud's phenomenon (6,7). The color charts have been found to be reliable in different nations and across races. This last point requires some emphasis. Although it would seem that individuals with more skin pigmentation might perceive the color changes association with Raynaud's phenomenon attacks differently than do patients with less pigmentation, the same color charts have been used (for diagnosis of Raynaud's phenomenon) with patients of different races without difficulty (Maricq, personal communication). This phenomenon probably results from the fact that the photographs are taken of the palmar side of the digits and hands, which are less pigmented in all individuals, and that the recognition of blanching and pallor in one's own hands may include "filtering out" intervening pigment.

At the time an attack is recognized, the study participant is to complete an "attack card". The attack cards will be supplied in tablet form, attachable to a plastic-encased color chart which has the finger panels on one side and hand panels on the other. The subject will use the attack card to record the date, time, the numbers of the finger panels and the letters of the hand panel which most closely resemble his/her extremities. One card will be completed for each Raynaud's phenomenon attack.

The recorded number and letter will allow a blinded observer to later identify true "gold standard" Raynaud's phenomenon attacks in a more objective manner by counting only those attacks in which blanching or cyanosis was recorded for either fingers or hands. A very important point is that the patients will not be told which of the panels represent true Raynaud's phenomenon attacks.

The package of attack cards and two color charts will be small enough (3" x 5") to be portable since the participants will be asked to keep this device with them constantly for three one-month

intervals so that attacks can be recorded concurrently with their occurrence. The completed cards will be sent to the Clinical Unit on a weekly schedule.

For the purposes of counting the number of Raynaud's phenomenon attacks for the primary end point, a 30-minute interval between times of attacks will be required to count attacks as two separate events. This interval is based on the knowledge that it is often difficult for a patient to be able to identify the cessation of an attack, but that the average duration of an attack is 15 minutes (Freedman R, personal communication). Although some individual attacks may be missed by use of this 30-minute interval, the system allows for distinguishing two attacks from the continuation of one attack. A Raynaud's phenomenon attack will therefore be judged to have taken place when the patient has identified a time of occurrence more than 30 minutes after the time of the last attack and the patient has identified a finger or hand panel which depicts either blanching or cyanosis.

7.2 SECONDARY END POINTS

7.2.1 Introduction

Measurement of features of Raynaud's phenomenon other than the number of attacks will add additional understanding to the study results. These features, including duration, severity (of pain and/or numbness), associated disability, and steps taken by participants to abort or alleviate attacks, have been used in previous studies of effectiveness of therapies (1,2,3,8,9,10,11,12). While many items are of potential interest, only a few will be requested in order to avoid burdening the study participants with lengthy forms that may also lessen overall compliance with the RTS Protocol.

7.2.2 Method of Subject Reporting of Secondary End Points

Secondary end points will include the number of attacks recorded in daily diaries, to be completed at the end of each day for the three-month period between January and March in 1994 and 1995 for patients enrolled in 1993 and between January and March in 1995 and 1996 for patients enrolled in 1994. (Patients who complete the Treatment Visits after January 1 will start recording attacks in the diaries one week after completion of the Treatment Visits.) In order to bolster compliance, these daily diaries will be packaged in booklets sufficient for one week's reporting. Each patient will be instructed to mail the booklets to the Clinical Unit by prepaid mail on a weekly schedule. If the booklets are not received by the Clinical Unit, the patient will be contacted by telephone.

The patients will be asked to use the daily dairies to record the date and time of completion of the diary entry, the number of Raynaud's attacks that occurred during the previous day, the average duration of the attacks, an estimate of the attack severity.

7.3 GLOBAL ASSESSMENTS

7.3.1 Global Assessments by Participants

Broad inquiries regarding the severity, frequency, and consequences of Raynaud's phenomenon attacks will be made of the participants prior to treatment and at three-month intervals throughout the follow-up period. In addition, some information concerning the impact of Raynaud's phenomenon attacks will be ascertained in the self-administered Quality of Life Form (see Chapter 8, Quality of Life).

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CHAPTER 8

QUALITY OF LIFE ASSESSMENT

8.1 INTRODUCTION

This chapter describes the assessment of health Quality of Life (HQL) and important moderators of HQL for patients in the Raynaud's Treatment Study (RTS). The primary purpose of the RTS is to assess the effectiveness of pharmacological and behavioral treatments in reducing the number of vasospastic attacks experienced by patients with primary Raynaud's phenomenon. A subsidiary aim of the RTS is to provide information about the relationship between stress and frequency of Raynaud's phenomenon attacks, including data regarding potential moderators of the stress-attack relationship. The objective of this part of the RTS is to develop an appropriate Health Quality of Life protocol (including measures of stress and moderators of stress and HQL) for this patient population. This objective is achieved by developing a protocol that is based upon existing, standardized instruments, and by modifying and extending those instruments as needed in order to make the protocol more consistent with the needs of the RTS. The RTS provides an opportunity to learn much more about the quality of life, moderators of quality of life, and information about the effects of stress on illness activity among patients with primary Raynaud's phenomenon. This information is of particular importance given the current lack of data on the subject.

8.2 DEFINITION OF HEALTH QUALITY OF LIFE

It is now generally accepted that quality of life is an important dimension for assessing the effectiveness of medical treatments (1). Quality of life has been conceptualized in various ways. According to Shumaker and colleagues, quality of life is a multidimensional construct which refers to a person's overall satisfaction with life and his/her general sense of well-being. Six dimensions are proposed: cognitive; emotional; social; physical; intimacy; and productivity.

8.3 RATIONALE FOR SELECTION OF RELEVANT QUALITY OF LIFE DOMAINS AND SELECTION OF MEASURES FOR EACH DOMAIN

The effects of the disease on the patient's quality of life is viewed as important information to be collected in the RTS. In addition, it is important to assess the changes in quality of life among patients assigned to the different study treatment groups.

Patients with primary Raynaud's phenomenon have variable symptoms, but often they describe feelings of discomfort, numbness, tingling, and pain. They may have a reduced capacity to use their hands, which can interfere with almost any task. Thus, although their ability to manipulate their hands may be impaired, their overall physical functioning is not generally limited. Given the paucity of data, it is not clear whether the vasospastic attacks impact on other domains of the patient's life. However, it seems reasonable to suggest that the occurrence of attacks may be associated with some emotional distress such as anxiety and depression, as well as with minor cognitive disturbances in attention and memory. If patients are concerned about the potential occurrence of an attack in certain problematic situations, it seems plausible that they may avoid those situations (e.g., cocktail parties where they might be expected to hold a cold drink, or shopping in grocery stores near the frozen food section). This could lead to a reduction in the frequency of socializing or at least going out to public situations.

Given the uncertainty surrounding the effects and consequences of primary Raynaud's phenomenon for the patient's physical and emotional functioning, the approach to the assessment of HQL was to assemble a wide range of items, encompassing the entire spectrum of problems and difficulties that patients with primary Raynaud's phenomenon might be expected to face, from minor inconveniences to major problems. In this fashion, the Quality of Life protocol provides enough sensitivity to capture subtle HQL changes as a result of treatment. At the same time, it will be able to capture and assess more severe health threats and consequences should this be an issue among this group of patients.

The SF-36 questionnaire, developed by the Rand Corporation (2), provides the general model guiding the assessment of HQL in the RTS. The questionnaire helps to identify the domains around which Raynaud's-specific assessments are made. In addition, the SF-36 will be administered in its standardized format at the initial screening session to all volunteers for the study. By administering the standardized SF-36 to everyone prior to recruitment it will be possible to collect data that will allow us: (a) to compare Raynaud's patients to other patient groups; and (b) to compare participants in the RTS to nonparticipants using a standardized health quality of life measure. Administration of the standardized SF-36 will allow for comparison of responses to the SF-36 to responses on the Raynaud's specific HQL instrument that was developed expressly for the RTS. At present little is known about

the relationship between disease-specific and global HQL assessments. Nor is there much consensus about which type of assessment is best. The RTS can help provide information on these important points.

HQL dimensions for the Raynaud's specific instrument were selected because it was thought that they might be most affected by symptoms of Raynaud's phenomenon, study medications, as well as by biofeedback. Table 1 shows each quality of life dimension contained on the Raynaud's specific questionnaire, the rationale for its inclusion, and the instruments or items that are proposed to measure it. Each may be affected by the illness, study medication, or by biofeedback treatment. The dimensions to be measured and their rationale are described more fully below.

8.3.1 Cognitive Functioning

Six items have been written to assess memory, concentration, language ability, and spatial orientation. These items are adapted from the Pittsburgh Bypass Project, an NHLBI-funded study examining psychosocial predictors of recovery from coronary bypass graft surgery.

8.3.2 Emotional Functioning

Emotional functioning will be assessed using a core set of items that appears on the SF-36, tapping anxiety, depression, and vigor. These items will be supplemented with two additional anxiety items from Spielberger's (3) State-Trait Anxiety Inventory. In addition, the Quality of Life Questionnaire includes four items taken from the Affect Balance Scale (4) that are designed to assess anger, hostility, and resentment. Finally, a set of six items concerning sleep has been included because of close relationships that have been observed in the past between sleep disturbances and depression and anxiety.

8.3.3 Social Functioning

Two relevant items on the SF-36 were adapted to measure social functioning and activities. We plan to supplement these items with one additional item taken from the Pittsburgh Bypass project, which allows for a direct assessment of perceptions of change in social functioning across time.

8.3.4 Physical Functioning

A set of Raynaud's specific physical functioning items have been prepared for this study. In addition, patients will also respond to the physical functioning items contained on the SF-36. The

instruction for these items contained on the Raynaud's-specific questionnaire have been rewritten to focus the patients' attention on their Raynaud's symptoms. The items on the SF-36 tap more basic activities of daily living, and are perhaps better suited for patients with more severe limitations on physical functioning. Given the lack of information about the level of impairment experienced by primary Raynaud's patients, however, primary Raynaud's phenomenon patients will be asked to complete these more basic physical functioning items as well.

8.3.5 Intimacy/Sexual Functioning

Two items on sexual satisfaction and frequency of sexual activity used in the NHLBI-sponsored Post Coronary Artery Bypass Graft (POST CABG) Studies will be used to assess this category of HQL.

8.3.6 Productivity

The SF-36 contains several items assessing the degree to which the respondents' emotional and physical health have impacted on work and related activities (including activities involved in the maintenance of a home). These items have been revised slightly and expanded to provide the basis for the disease-specific assessment of productivity.

8.4 OTHER ELEMENTS OF HEALTH QUALITY OF LIFE

8.4.1 General Life Satisfaction

In addition to understanding how Raynaud's phenomenon impacts on specific quality of life dimensions, it may also be useful to assess how the illness impacts on the patients' overall life satisfaction. In this way, a determination can be made of the significance of the patients' illness in his/her overall life quality. Overall life satisfaction will be assessed using the Ladder of Life Scale (5) and the Satisfaction with Life Scale (6). Both instruments have been used repeatedly and successfully in the past to assess general life satisfaction in diverse treatment groups and subject populations.

8.4.2 Pain

Pain is an aspect of primary Raynaud's phenomenon, and could impact significantly on other dimensions of quality of life. A number of questions have been assembled to measure the intensity and frequency with which the patients experience pain. This pain-assessment battery also includes questions designed to measure the extent to which the patients' pain interferes with their daily

activities at work and at home. The items for the battery come from a variety of sources, including the Pittsburgh Bypass Project. Some items were also specifically written for the RTS.

8.4.3 Perceived Health Status

Perceived health status reflects the person's general appraisal of his/her overall health. Perceptions of health have proven to be significant predictors of important health outcomes in past research (e.g., 7). The SF-36 contains one item designed to tap perceptions of overall perceived health. Two additional items from the Pittsburgh Bypass Project will be added to the SF-36 item, in order to obtain separate assessments of perceived emotional health and perceived physical health. Associated items ask how satisfied the patients are with their health in these three areas. Together these six items will comprise the measure of perceived health status at baseline. The follow-up questionnaires will contain three additional, parallel items designed to tap perceptions of change in these three health status categories over time.

8.4.4 Symptoms

Raynaud's patients suffer from a variety of different symptoms. The study medication and biofeedback may also add to the symptom experience, through side effects or by sensitizing patients to bodily states and sensations. Symptoms will be assessed using the Cohen and Hoberman Inventory of Physical Symptoms (CHIPS, 8). The CHIPS contains a list of 39 common physical complaints, many of which characterize symptoms of Raynaud's and/or are likely side effects of treatment (see Chapter 5, Administration of Study Medications).

8.5 MODERATORS OF HEALTH QUALITY OF LIFE

8.5.1 Social Support

There are several reasons why it is important to assess aspects of the patients' social support. First, support may act as a moderator of treatment effects. Patients with strong support networks may comply with treatment regimens more thoroughly, thereby leading to larger treatment effects. Second, social support is known to moderate the effects of stress (9). Since there is an interest in understanding how stress relates to frequency of attacks, it is also important to assess moderators of the stress-attack relationship.

Social support is typically assessed in one of two ways (Cohen & Wills, 1985). One way is to measure the person's perception of the amount of support (of various kinds) that is available. Alternatively, support can be operationalized in terms of social integration, the degree to which the person can identify a network of close friends and participates regularly in organized social groups. The distinction is important because the two ways of assessing support are often associated with different patterns of outcomes (9).

Both types of measures will be used in the RTS. Perceived support will be assessed by an abbreviated form of the Rand Social Support Scale (10), a standardized instrument that taps perceptions of various kinds of support. In addition, the positive social support items from the Rand measure will be supplemented with five items that are designed to measure perceptions of negative social support in the Pittsburgh Bypass Project. These items measure the extent to which people are being particularly nonhelpful, or are not helping to the extent that the person thought they would. Social integration will be assessed by four items taken from the POST CABG Studies.

8.5.2 Stress

An important subsidiary purpose of the present trial is to explore the relationship between stress and Raynaud's phenomenon attacks. Stress could impact on the occurrence of vasospastic attacks, most likely through the activation of the sympathetic nervous system. This provides one rationale for including an assessment of stress. Additionally, even if one is not interested in the relationship between stress and attack frequency per se, using stress as a covariate may help to elucidate relationships between treatment and attack frequency that would otherwise go undetected.

Stress is usually assessed in one of two ways: as the number of life events that have transpired and in the form of more generic self-reports of perceived stress. Since both methods tend to produce similar kinds of associations with outcomes, only one measure of perceived stress will be used in the RTS, in order to keep patient burden to a minimum. More concretely, stress will be assessed using the Perceived Stress Scale (11), a well-known and well-used scale of perceived stress.

8.5.3 Coping

If stress is important in predicting Raynaud's phenomenon attacks, then coping responses to stress should moderate the stress-attack relationship. Studying the effects of coping should help enhance

the understanding of the role that stress is playing in producing Raynaud's phenomenon attacks. It is possible to assess coping responses both as a specific set of reactions to specific problems encountered, and as a more stable and general set of coping styles that the person brings to bear across different problem domains (12). Prior research suggests that these two types of coping responses (situation specific vs. generalized) are only moderately related (12), suggesting that each type of coping response may add unique predictive power.

The Coping Orientations to Problems Encountered Scale (COPE, 12) will be used to assess situational and dispositional coping. This scale provides information about 15 different coping categories ranging from problem-focused coping, to positive reinterpretation, to denial and mental disengagement. Prior work (13) suggests that the scale is psychometrically sound (e.g., factor analysis of the scale typically yields 15 factors), and the scale has been successfully used in several prior health-related studies (e.g., Carver et al., in press).

8.5.4 Personality Factors

There are a number of personality factors that could be assessed in clinical trials such as the RTS. Rather than be nonselective, however, an attempt was made to identify personality factors that promise to be most relevant to the nature and goals of the RTS. Five factors were identified. They are: private body consciousness, measured by the Private Body Consciousness Scale (4); private self-consciousness, measured by the Revised Private Self-Consciousness Scale (15); optimism-pessimism, measured by the Life Orientation Test (LOT, 16); self-esteem, measured by Rosenberg's (17) Self-Esteem Scale; and neuroticism, measured by items selected from Eysenck and Eysenck (18) from previously published standardized measures.

These personality characteristics are important for different reasons. Private body consciousness has to do with the extent to which a person focuses on his or her physiology, and is alert to changes in physiological state. Thus, this variable may operate as an important moderator of biofeedback effectiveness. People who tend to focus on their physiology may be better candidates for biofeedback training than those who do not possess this characteristic.

Private self-consciousness is important for two reasons. First, prior research (19) has shown that people high on this characteristic are more committed to the goals they adopt, and are more motivated

to complete tasks successfully than are persons lower in private self-consciousness. This greater commitment may relate to treatment effectiveness in important ways. Second, prior research has shown that private self-consciousness plays a role in reactions to stress. For example, high self-conscious persons seem buffered from the effects of negative life events (20). Private self-consciousness also seems to moderate relationships among stress, optimism-pessimism, and the development of physical symptoms (16).

Optimism-pessimism is important because of its role in moderating reactions to stress (21). To date, this characteristic has been linked to more favorable recovery following coronary artery bypass graft surgery (22), and to less distress following surgery for breast cancer (13). These are not the only beneficial health effects that have been found for this variable. For example, optimism has been shown to be an important variable in dealing with infertility problems (23), and with worries concerning specific health threats (24, 25).

Optimism-pessimism may also play a role in treatment effectiveness. That is, optimists generally expect good outcomes to occur to them. This positivity may carry over to positive expectations regarding the effectiveness of their treatment. This may in turn increase compliance with the treatment regimen, ultimately resulting in greater treatment success.

In addition to the generalized outcome expectancies assessed by the Life-Orientation Test (LOT), four questions were created to assess situation-specific expectancies. These items include two questions which ask patients to indicate their degree of confidence that their Raynaud's phenomenon can be treated successfully with Nifedipine and with biofeedback. Two additional items tap patients' self-efficacy expectancies. These questions assess the degree to which patients feel that they will be able to successfully execute the behaviors necessary to benefit from treatment with Nifedipine and with biofeedback. Researchers have argued that self-efficacy expectancies play a central role in behavior such as coping, and underlie treatment-induced behavior changes (26).

Self-esteem is important for many of the same reasons that optimism-pessimism is important. High self-esteem people may be more likely than low self-esteem people to believe that they have the skills needed to accomplish the biofeedback training successfully. Such beliefs may relate in important ways to actual treatment outcomes. Importantly, there is evidence that self-esteem and

optimism-pessimism are separate constructs (e.g., 27). Thus, each may add unique predictive power to the RTS HQL assessment.

Finally, neuroticism may be an important control variable for use in evaluating the primary outcome measure of interest, the frequency of vasospastic attacks. Strong evidence exists that neuroticism may act as a nuisance variable in studies dealing with self-reported health status (28). That is, people high in neuroticism tend to report heightened symptoms of disease (e.g., angina), even though there is no underlying pathological state (e.g., angiographically- documented coronary artery disease). Inasmuch as the RTS will rely on a self-reported health outcome (the patient's judgment of when a Raynaud's phenomenon attack occurs), controlling for neuroticism when analyzing attack frequency may help identify associations that would otherwise go undetected.

8.6 ABBREVIATED SCALE FORMAT

The Raynaud's-specific quality of life protocol developed for the RTS is broad based, and attempts to assess a wide range of potentially important psychosocial variables of interest. A broad-based approach was needed, relatively little is known about the impact of Raynaud's phenomenon on the patients socio-emotional functioning. The RTS presents the opportunity to collect these data. The breadth of the measures assembled, however, created concerns regarding patient burden because of the time and effort needed to complete the measures. It would be difficult, if not impossible, to administer all of the relevant psychosocial scales in their entirety. Accordingly, abbreviated versions of some of the longer scales of interest will be used. Thus, for example, the number of items measuring self-esteem was reduced from ten to four, and the number of items measuring neuroticism was reduced from twenty to ten. Items were selected for retention either because they had been shown to be good proxies for the overall scale in prior research, or because they had the highest item-total correlations of any of the items on the original scale. Prior research suggests that scales can often be truncated in this fashion without any loss in psychometric quality or predictive power (see, e.g., 11, 22, 29). Thus, the protocol provides a means of obtaining information about a wide range of variables. At the same time, patient burden can be kept to a minimum.

8.7 TIMETABLE FOR INSTRUMENT ADMINISTRATION

The SF-36 will be administered at the Screening Visit (SV01). The Quality of Life Form will be administered at the Randomization Visit (RV01), Follow-up Visit 2 (FV02), and Follow-up Visit 4 (FV04). The length of time for administering the entire Raynaud's specific Quality of Life protocol at RV01 should not be more than 45 minutes. Follow-up questionnaires should not take more than 30 minutes to complete. All questionnaires will be completed at the Clinical Unit. In general, the baseline measures should be administered as soon as possible after the patient enrolls in the study and prior to initiation of study treatment. Follow-up questionnaires should be completed after the patients have completed the monthly daily diaries.

8.8 VARIATIONS AMONG THE MEASURES AS A FUNCTION OF THE TIME OF ASSESSMENT

As noted above, the Raynaud's-specific Quality of Life Form will contain a number of scales and items that are designed to measure stable, enduring patient characteristics. These variables only need to be assessed once at baseline. Thus, follow-up questionnaires will be shorter than the questionnaires completed at baseline. Table 2 summarizes the differences between the Raynaud's-specific instruments to be used at different points in time.

8.9 PILOT TESTS AND REVISIONS OF THE QUALITY OF LIFE FORM

The Quality of Life form will be piloted on at least five healthy, non-Raynaud's participants, to test for acceptability of questions, readability, and length of time for administration. It will also be piloted on five Raynaud's patients at each Clinical Unit. After one year, an analysis will be performed comparing responses on the standardized SF-36 to the health quality of life responses on the Raynaud's specific health quality of life questionnaire. Depending upon the degree of overlap between the two ways of assessing HQL, both will continue to be administered during subsequent years or the protocol will be modified to include only one.

8.10 TABLE 1 - Raynaud's Specific Quality of Life Dimensions

Dimension	Rationale	Instrument	Item
Quality of Life Dimensions			
1. Cognitive	*Impact of pain *Impact of drug	Items adapted from the Pittsburgh Bypass Project re: memory, concentration, spatial ability, language	43,44,46*,48*, 49*,50*
2. Emotional	*Impact of illness *Impact of tx	Items from SF-36 & ABS re: anxiety, depression hostility, and sleep	19a-i,21r, 32a-o,35a-d, 45,46,51*,53*
3. Social	*Impact of illness *Predicting responses to tx	Items from SF-36	21o,25-28,42, 47*
4. Physical	*Impact of illness *Impact of tx	Items from SF-36	20a-j,21a-n q, 52*,
5. Sexual/Intimacy	*Impact of drug	2 items from POST CABG, 1 item from SF-36, and 1 item from Rand Social Support	3b,21p,36,37
6. Productivity	*Outcome of physical & emotional functioning	Items from SF-36	23,24,
Other Elements of Health Quality of Life			
7. General Life Satisfaction	*Summary measure *Provides comparison with individual dimensions	Diener's Satisfaction with Life Scale, and Ladder of Life Scale	126,137,143, 153,159,163
8. Pain	*As sx of illness *Impact of tx	1 item from SF-36 and 5 new items	29-31
9. Perceived Health Status	*Could predict important health outcomes	1 item from SF-36, 2 items from Pittsburgh Bypass Project	12-17,22,14*, 17*,20*
10. Symptoms	*Measure of illness *Measure of side effects of drug	CHIPS	224-263
Moderators of Health Quality of Life			
11. Social Support	*Could moderate impact of stress, tx	Rand Social Support Scale, social integration items, and negative social support items	1-11
12. Stress & Coping	*Coping could moderate impact of stress *Stress could impact freq. & sev. of attacks	Dispositional version of the COPE, situational version of the COPE, Perceived Stress Scale	164-223 107-120, 47-106
13. Personality	*Predict how people cope with attacks *Predict who benefits from tx	Body consciousness, Private self-consc., Self-esteem, Optimism, Specific expectancies, Neuroticism	121-162 38-41

Note: All item numbers refer to item locations in the intake instrument except those denoted by "*." These numbers refer to items that appear only in the follow-up instrument.

8.11 TABLE 2 - Schedule for Administration of Scales

Baseline

Core items

- Social integration
- Rand social support items
  - Negative social support
  - SF-36 (modified or supplemented to reflect Raynaud's specific concerns)
    - 6 items assessing current emotional, physical and overall health
    - 10 items assessing limitation in daily activities
    - 30 items assessing limitation of activities suspected to be influenced by Raynaud's
    - 2 items assessing impact of physical health and emotional health on daily activity and work
    - 2 item assessing impact of health on social activity (1 assessing extent, the other assessing freq.)
    - 1 item assessing impact of pain on productivity
    - 3 items assessing pain experience.
    - 9 items assessing vigor, depression, anxiety
    - 5 items assessing anxiety and hostility
  - Clothing worn or activities done to prevent attacks
  - Sexual activity (2 items)
  - Specific expectancies (self-efficacy)
  - Functional status measure
  - Situational COPE
  - Personality measures
    - Optimism
    - Self-consciousness (introspection)
    - Self-esteem
    - Body-consciousness
    - Neuroticism
  - Quality of life
    - Diener's Satisfaction with Life Scale
    - Ladder of Life
  - Dispositional COPE
  - Symptoms
  - Perceived Stress

3 Month Follow-up

- Core items (with the exception of Self-efficacy, Personality measures and Dispositional COPE)
- 3 items assessing mental, physical and overall health compared to before treatment
- 10 items assessing change in functional status across 9 domains
- 3 items assessing Raynaud's-specific health status

15 Month Follow-up

- Same as 3 month follow-up

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CHAPTER 9

PHYSIOLOGICAL MEASUREMENTS

9.1 COLD STRESS TEST

9.1.1 Rationale

Patients with Raynaud's phenomenon are known to be sensitive to the cold (1, 2). Therefore, several methods have been used to provoke vasospasm by cold exposure. Ideally, therapy which reverses or improves a patient's vascular response to a direct cold challenge would provide objective evidence for benefit of the treatment. In fact, one of the few studies to objectively measure a positive effect of Nifedipine in patients with Raynaud's phenomenon used skin temperature recovery time following a cold stress test (3). Temperature biofeedback has been demonstrated to improve finger temperature responses to cold stress (4, 5).

Cold stress tests have varied from producing a generalized chill (6) to locally cooling one finger during cuff occlusion of the digital blood flow (7). Ice water immersion has been used, but this intense cold challenge is painful and potentially dangerous to the patient. The cold stress test to be used in the Raynaud's Treatment Study (RTS) is a mild painless cold challenge which simulates usual daily cold exposure: it involves placing the hand into a refrigerated chamber. This method was used successfully in a multi-center study of Iloprost in the treatment of Raynaud's phenomenon in scleroderma patients (8). It provides a simple standard method of doing a controlled cold challenge. Skin temperature is closely related to digital blood flow, and it is relatively easy to measure and calibrate and can be performed at comparatively low cost. Information to be collected from this test will include the rate of cooling, the time it takes for the hand to be cooled from 30°C to 18°C, the rate of rewarming, and the time it takes for the hand to rewarm after being challenged in the cold stress box. (9).

9.1.2 Specific Method

Patients will be studied in a quiet room with a stable environmental temperature (27-28°C). The patient will be dressed in loose clothing, placed in a supine position, and a YSI #408 thermistor will be attached to the pad of the left or right middle finger. The patient will acclimate to the room environment during a 30-minute rest period. The cold challenge will then be started. The patient's

finger skin temperature will be warmed to 30° ± 2°C with a small heated blower. This baseline finger temperature will be recorded at two-minute intervals for a maximum of ten minutes. The cold challenge will begin two minutes after two successive stable finger temperature readings are obtained (temperature difference less than 2°C).

The patient's hand will then be inserted into the cold box (maintained at-4 °C) for a maximum period of nine minutes. Skin temperature at each minute and the time at which the finger temperature reaches 18°C will be recorded. If the finger temperature does not reach 18°C, the finger temperature at ten minutes post-insertion will be recorded. The hand will be withdrawn from the refrigerated chamber and the finger temperature will be measured at one-minute intervals for ten minutes. All measurements will be taken with the hand in a horizontal position, level with the right atrium. Patients who have active ulcers on their left hand will use their right hand for these measurements. Patients with active ulcers on both hands will be excluded from this assessment.

Cold tolerance will be assessed by the total time it takes to cool the finger to 18°C, and the change in finger temperature per unit time during cooling. Rewarming will be assessed by rate of change in finger temperature after removal of the hand from cold box into ambient temperature.

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CHAPTER 10

PATIENT VISITS

10.1 INTRODUCTION

Each patient enrolled in the Raynaud's Treatment Study (RTS) will be expected to return to the Clinical Unit on multiple occasions over a period of approximately 18 months. Procedures to be completed include temperature biofeedback or electromyogram (EMG) frontalis biofeedback training for patients assigned to the biofeedback groups, and medication titration for patients assigned to study medication groups (nifedipine XL or placebo). Patients will be monitored for adherence to study treatment and for adverse effects. Intermediate outcome data will be collected three months after enrollment; end point data will be collected fifteen months after enrollment. Details of the Screening Visit, Randomization Visit, Monitoring Visit and Follow-up Visit procedures are described in this Chapter and are summarized in Exhibits 10.1 and 10.2.

10.2 SCHEDULE OF SCREENING VISIT AND RANDOMIZATION VISIT

Each patient will complete at least one Screening Visit (SV01) for assessment of his/her eligibility to participate in the RTS. The Screening Visit procedures include signing the Informed Consent Form, review of the pertinent medical history, and performance of the physical examination and specified laboratory tests. The patient will be instructed in the use of the attack cards and daily diaries for recording the occurrence of Raynaud's attacks (see Chapter 7, End Points). The patient will complete the SF-36, a brief standardized instrument which measures health quality of life. The patient will be asked to complete the attack cards and daily diaries during the four-week to five-week period between SV01 and the Randomization Visit (RV01).

Patients considered to be eligible for the RTS will be asked to return to the Clinical Unit for the Randomization Visit (RV01). If the patient meets the eligibility criteria and is willing and able to participate in the RTS, Clinical Unit staff will request a treatment allocation from the RTS Coordinating Center, via the automated telephone randomization system (ATRS). Once a treatment allocation has been issued for a patient, the patient is enrolled in the RTS. Follow-up of the patient is required and the patient will be included in study analyses, even if he/she never receives study treatment. Other

procedures to be completed at RV01 include the baseline physiological assessment (see Chapter 9, Physiological Measurements) and the Quality of Life Form (see Chapter 8, Quality of Life Assessment).

10.3 SCHEDULE OF FOLLOW-UP VISITS

Participation in the RTS requires patients to complete multiple visits to the Clinical Units over a period of approximately 18 months. Specifically, each patient enrolled in the RTS will be expected to return to the Clinical Unit for five to ten "Treatment Visits" (T01 to T10), and for seven Monitoring Visits or Follow-up Visits thereafter. The schedule of contacts and procedures are summarized in Exhibits 10.1 and 10.2.

During the first five to six weeks after enrollment, patients assigned to the biofeedback treatment groups will return to the Clinical Unit one to two times per week for biofeedback training (see Chapter 6, Temperature Biofeedback). Patients assigned to the biofeedback treatment groups will return to the Clinical Unit for a "Voluntary Control Assessment Visit" (VC01) one week after completing the Treatment Visits, for assessment of their ability to raise the temperature of their fingers.

During the first five weeks after enrollment, patients assigned to the nifedipine XL or placebo groups will return to the Clinical Unit for five Treatment Visits, primarily for medical monitoring and titration of the study medication (see Chapter 5, Administration of Study Medication).

Each scheduled Monitoring Visit and Follow-up Visit will include an interim medical history, with special attention to possible side effects of study medication, general state of well-being, and other pertinent information such as use of non-study medications. At SV01, Follow-up Visit 1 (FV01), and Follow-up Visit 3 (FV03) the patients will be given the attack cards for recording information concerning the occurrence of Raynaud's attacks during the subsequent four weeks. In addition, the patients will be given the daily diaries for recording the occurrence of attacks during the period between SV01 and RV01 and for January 1 through March 31; these daily diaries will be distributed at the Clinic Visits immediately preceding January 1. Physiological "cold box" testing is scheduled at RV01, Follow-up Visit 2 (FV02), and FV04. The Quality of Life Form will be completed at RV01, FV02, and FV04.

Although it would be ideal for each patient to complete visits to the Clinical Units exactly as scheduled, this may not always be possible. Therefore, time windows for Monitoring Visits and Follow-up Visits have been defined, as shown in Exhibit 10-3.

Every effort will be made to maintain contact with the patients so that all participants will have an assessment at the end of the scheduled follow-up period. When a participant fails to keep a scheduled appointment, Clinical Unit staff are expected to contact him/her immediately to reschedule the appointment. If a participant stops returning for scheduled Monitoring Visits and Follow-up Visits, every effort will be made to obtain at least some key information, such as information concerning morbidity.

Any patient who does not complete a scheduled Monitoring Visit or Follow-up Visit within the defined time window for that Visit will be considered as having missed the Visit. A Missed Visit Form will be completed for each missed Visit. The patient will remain in the RTS. Efforts will be made to maintain contact with the patient and to obtain information about the patient's medical status. If a patient is considered to be lost to follow-up, special procedures will be followed to use available resources to ascertain the vital status of the patient.

10.4 SERIOUS ADVERSE EFFECTS

Individual cases of serious adverse effects that are possibly related to study treatments will be reported immediately by the Clinical Unit physician to the Clinical Coordinating Center and to the Program Office by telephone and facsimile (see Chapter 5, Administration of Drug Treatment).

10.5 CLOSE-OUT PROCEDURES

Close-out procedures will be performed at the end of each patient's participation in the RTS (see Chapter 15, Close-out Procedures). In the fall of 1996 patients will be invited to return in groups to the Clinical Units to be informed of their study medication assignment and to review the available study results.

Raynaud's Treatment Study

VISIT SCHEDULE FOR THE RAYNAUD'S TREATMENT STUDIES

A. Nifedipine XL and Pill-Placebo Treatment Groups

SV01	RV01	TO1	TO2	TO3	TO4	TO5	FV01	FV02	MO1	MO2	MO3	FV03	FV04
-5 Weeks	0 Weeks	1 Week	2 Weeks	3 Weeks	4 Weeks	5 Weeks*	3 Months	4 Months	6 Months	9 Months	12 Months	15 Months	16 Months

B. Temperature Biofeedback and Frontalis EMG Biofeedback Groups

SV01	RV01	TO1	TO2	TO3	TO4	TO5	TO6	TO7	TO8	TO9	T10*	VC01	FV01	FV02	MO1	MO2	MO3	FV03	FV04
-5 Weeks	0 Weeks	1 Week	1.5 Weeks	2 Weeks	2.5 Weeks	3 Weeks	3.5 Weeks	4 Weeks	4.5 Weeks	5 Weeks	5.5 Weeks	6 Weeks	3 Months	4 Months	6 Months	9 Months	12 Months	15 Months	16 Months

*Treatment visits are ideally completed in five to six weeks, but may be completed in a period as long as ten weeks.

RTS Schedule of Patient Visits and Procedures

PROCEDURES	VISIT										
	SV01 (-5 weeks)	RV01 (0)	T01 to T05 or T01 to T10* (1 to 10 weeks)	VC01*** (6 to 11 weeks)	FV01 (3 months)	FV02 (4 months)	MO1 (6 months)	M02 (9 months)	M03 (1 year)	FV03 (15 months)	FV04 (16 months)
Clinic Visit	X	X	X	X	X	X	X	X	X	X	X
Clinical Evaluation (blood pressure, pulse, etc.)	X	X			X		X	X	X	X	X
Laboratory tests	X						X				X
ANA levels and capillary microscopy	X										X
Dispense medication** (Titration at T01 to T10)		X	X		X		X	X	X	X	
Medication Adherence**			X		X		X	X	X	X	X
Physiological Assessment		X				X					X
Voluntary Control Assessment***				X							X
Quality of Life Assessment		X				X					X
SF-36	X										
Distribute Attack Cards	X				X					X	
Collect Attack Cards		X				X					X
Distribute Daily Diaries****	X	X						X			
Close-Out Procedures											X

* Patients assigned to the Nifedipine XL (or placebo) Groups will complete five Treatment Visits during the first 5 to 10 weeks after enrollment. Patients assigned to the Biofeedback Groups will complete ten Treatment Visits during the first 5 to 10 weeks after enrollment.

** Patients assigned to the Biofeedback Groups will not be prescribed study medication and so will not be assessed for medication adherence.

*** Patients assigned to the Biofeedback Groups will be assessed for their ability to voluntarily raise their finger temperature.

**** Patients will complete the daily diaries between SV01 and RV01 and during the three-month periods January 1 to March 31 in 1994 and 1995 for patients enrolled in 1993, and January 1 to March 31 in 1994 and 1995 for patients enrolled in 1994.

Exhibit 10.3

Time Windows* for Treatment Visits

	VISIT	IDEAL DATE (Weeks)
Biofeedback Groups	T01	1.0
	T02	1.5
	T03	2.0
	T04	2.5
	T05	3.0
	T06	3.5
	T07	4.0
	T08	4.5
	T09	5.0
	T10	5.5
	VC01	6.0*

	VISIT	IDEAL DATE (Weeks)
Nifedipine XL or Placebo Groups	T01	1
	T02	2
	T03	3
	T04	4
	T05	5*

* Treatment Visits and the Voluntary Control Assessment Visit are ideally completed in a five to six week period, but may be completed in a period as long as eleven weeks.

Exhibit 10.3 Continued

Time Windows* for Follow-up and Monitoring Visits

VISIT	IDEAL DATE (Month)	TIME WINDOW (Weeks)
FV01	3	12 to 15
FV02	4	16 to 25
MO1	6	26 to 38
M02	9	39 to 51
M03	12	52 to 64
FV03	15	65 to 68
FV04	16	69 to 72

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CHAPTER 11

CONDUCT OF THE STUDY

11.1 INTRODUCTION

Achievement of the objectives of this multicenter trial will require the collaboration of many different people (patients, Clinical Unit personnel, consultants, etc.). The investigators will have to be trained in all aspects of the Protocol, the study data will have to be monitored by the Raynaud's Treatment Study (RTS) Coordinating Center staff, periodic data reports will have to be reviewed by special committees, and various ongoing quality control procedures will have to be established.

11.2 TRAINING AND CERTIFICATION

Before the start of the study, training sessions will be organized for Clinical Unit personnel. The Protocol, Manual of Operations and organizational structure of the study will be clearly explained. The training session will cover procedures for collecting patient data, procedures for completing study forms, and instructions in the mechanics of study form edit procedures. With the assistance of Core Laboratory personnel, procedures for collecting and processing study specimens will also be reviewed. If new personnel join the RTS while it is in progress, a special training session could be scheduled at the RTS Coordinating Center or in conjunction with a site visit to the Clinical Unit.

Each Clinical Unit hospital participating in the RTS is required to have one or more individuals on the staff certified to perform the tasks of the physician, nurse-coordinator, biofeedback therapist, and physiological assessment technician. Training and/or experience in addition to completion of specified assignments are required for each individual to become certified.

11.3 DATA EDITING AND MANAGEMENT

The completed and keyed study forms will be edited by computer for several kinds of deficiencies and errors:

1. Unanswered or illegible items.
2. Values of quantitative variables which are outside a preset range.
3. Values of qualitative responses which are not permissible (usually due to data entry errors).
4. Inconsistencies among items within a form.

5. Gross inconsistencies among forms from different visits for specific variables.
6. Patient identification number and name code, follow-up visit number, and follow-up visit date errors or inconsistencies.

For each detected error a correction procedure will be initiated. The Clinical Unit staff will be instructed to complete correction forms and to send them promptly to the RTS Coordinating Center so that the computer data file can be corrected.

A computer inventory of all forms received at the RTS Coordinating Center for each patient will be developed and maintained. This inventory will make it possible to generate a list of study forms which are past due and to send such lists to the Clinical Unit investigators. Another computer file will contain the keyed data from all the study forms received from the Clinical Units and the Core Laboratory. This file will be structured to allow easy addition of new follow-up forms for each patient and will be designed so that all of the forms for a given patient can be linked together to facilitate analysis.

At the time the RTS Coordinating Center receives a form indicating that a patient has been enrolled into the trial, it will generate an Appointment Schedule listing the expected dates and the permissible time windows around these dates for the completion of Monitoring Visits and Follow-up Visits. These schedules will be sent to the Clinical Units to aid in scheduling patient Monitoring Visits and Follow-up Visits. In addition, at the request of the Principal Investigator of a Clinical Unit, the RTS Coordinating Center will attempt to locate patients who have been lost to follow-up for the purposes of collecting final end point information.

Periodically, selected items of data in the computer file will be listed in a compact but readable form, one or two pages per patient, and sent to the appropriate Clinical Unit. Staff at that site will be asked to check whether the data recorded in the RTS Coordinating Center's computer file correspond to the data in the Clinical Unit records. In addition, some investigators may find these lists helpful for patient management purposes.

11.4 QUALITY CONTROL PROCEDURES

11.4.1 Monitoring the Clinical Units

One aspect of quality control will consist of management reports generated by computer about the study forms and their data. The reports will include:

1. Patient enrollment according to Clinical Unit.
2. Number and percentage of forms with detected errors according to Clinical Unit.
3. Number of delinquent forms according to Clinical Unit.
4. Number of missed examinations according to Clinical Unit.
5. Number of delinquent laboratory specimens for analysis by the Core Laboratory according to Clinical Unit.

Other indicators of work performance and adherence to the Protocol will be summarized periodically.

Site visits to participating Clinical Units to resolve problems may be scheduled at the discretion of the Executive and Steering Committees and/or the Data and Safety Monitoring Board and the Program Office.

11.4.2 Site Visits

Staff of the RTS Coordinating Center and the NHLBI Program Office will visit the Clinical Units routinely and when indicated on the basis of the Clinical Unit's performance. The objectives of the site visits are to insure that training has been effective for RTS personnel, to insure that the study equipment is in line with RTS specifications, to train RTS personnel as needed in data collection procedures and to trouble-shoot problems in carrying out patient examinations. Patient examinations must proceed smoothly, in a logical flow which avoids undue burdens upon patients' time and makes effective use of Clinical Unit resources.

Later in the study, return site visits will focus on verification of procedures and data. A random sample of data in the RTS Coordinating Center computer files will be verified against RTS patient records. Study personnel will be recertified.

11.4.3 Monitoring the Core Laboratories

Reliable central coding and reporting procedures and appropriate internal and external monitoring procedures for the RTS Core Laboratory will be developed. Quality control reports on the performance of the Core Laboratory will be prepared periodically for review by the Steering Committee, the Data and Safety Monitoring Board, the NHLBI and any other appropriate groups.

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CHAPTER 12

ORGANIZATIONAL STRUCTURE

12.1 INTRODUCTION

The participating investigators and centers in the Raynaud's Treatment Study (RTS) collaborate through a study organization which is designed to maintain continuity of operations and to facilitate effective communications and cooperation among the various study units. Exhibit 12-1 summarizes the study administration. The participating centers are listed in Exhibits 12-2 and 12-3.

12.2 PARTICIPATING CENTERS

12.2.1 Clinical Units

Five Clinical Units, located at major medical centers/hospitals in the United States, participate in the RTS. Clinical Units are responsible for screening and recruitment of eligible patients and collection of all clinical information and test data required by the RTS protocol.

12.2.2 Clinical Coordinating Center

The Clinical Coordinating Center at the Clinical Trials and Surveys Corp. in Baltimore, Maryland, has primary responsibility for the study's statistical design, data collection and management, and analysis of RTS results. The Coordinating Center staff in cooperation with Clinical Unit Investigators develop the Manual of Operations and pretest all RTS forms. The Coordinating Center staff are also responsible for preparing and distributing regular RTS progress reports and summary notes, preparing reports for the Data and Safety Monitoring Board, preparing data bank study analyses, and ensuring the quality and accuracy of data collection. The Coordinating Center staff assists in the training of Clinical Unit staff.

12.2.3 Biochemistry Core Laboratory

The Core Laboratory is responsible for: 1) developing in cooperation with other RTS investigators standardized procedures for collection of specimens for analysis of biochemical measurements; 2) monitoring specimens submitted by RTS Clinical Units for condition, timeliness and completeness; and 3) performing biochemical assays on all RTS specimens submitted in a timely fashion with documentation that adequate standards of accuracy and precision were maintained.

12.2.4 National Heart, Lung and Blood Institute Program Office

The National Heart, Lung and Blood Institute (NHLBI) Program Office in the Behavioral Medicine Branch is responsible for the overall direction and administration of the RTS. The Program Office staff provide general organizational and scientific guidance for the study and monitor the study's progress for the NHLBI. Statistical guidance is provided by representatives from the NHLBI's Biostatistics Research Branch.

12.3 STUDY ADMINISTRATION

12.3.1 Study Chairman

The Study Chairman, appointed by the NHLBI Director, has major responsibility for the scientific direction and administration of the RTS. The Study Chairman:

1. Advises the NHLBI Program Office on data monitoring and other issues of importance to the overall conduct of the study;
2. Develops and maintains, with advice from other study participants, an internal organizational structure that meets the needs of the RTS and the NHLBI;
3. Is informed on all aspects of study operations and, using the study organization developed, formulates study policy and takes action as necessary to insure the smooth operation of the study;
4. Appoints study participants to appropriate positions and committees as needed;
5. Serves as Chairman of the RTS Steering Committee and Operations Committee; and
6. Serves as an ex-officio, non-voting, member of the Data and Safety Monitoring Board.

The Study Chairman has been appointed to serve for the duration of the study unless other arrangements are made by mutual agreement between the Chairman and the NHLBI Director. In the event that the Study Chairman is unable to serve because of resignation or death, the NHLBI Director will appoint a new Study Chairman.

12.3.2 Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) is comprised of an independent group of experts in relevant biomedical fields, biostatistics and bioethics. The Study Chairman and the Principal and the Co-Principal Investigators from the Coordinating Center, and representatives from the NHLBI Program Office also participate as non-voting members. The DSMB meets at least twice a year. Its primary role

is to advise the NHLBI on all policy matters relating to the RTS. The DSMB has responsibility for protecting the scientific conduct and integrity of the RTS. Its functions include:

1. Review of the RTS Protocol;
2. Review of any changes in the design or operation of the RTS which are recommended by the Steering Committee;
3. Reviewing the RTS performance, progress and findings at regular intervals; and
4. Formulating recommendations for continuation or termination of the RTS based on the enrollment of a sufficient number of patients.

Recommendations made by the DSMB must be approved by the NHLBI prior to implementation.

12.3.3 Steering Committee

The Steering Committee is composed of the Study Chairman and Principal Investigators from each RTS Clinical Unit, the Core Laboratory, the Coordinating Center and the NHLBI Program Office. This committee provides the scientific direction for the study and meets periodically to assess progress. The Steering Committee is responsible for developing the final protocol and for carrying out the protocol. The Study Chairman will represent the Steering Committee on the DSMB. Recommendations by the Steering Committee are subject to approval by the NHLBI.

The following technical subcommittees have been established: Experimental Design, Endpoints, Eligibility, Psychophysiological Reactivity Testing, Biofeedback, Medications, and Quality of Life. These subcommittees were charged with responsibility for developing specific areas of the RTS Protocol.

12.3.4 Operations Committee

The Operations Committee is the operational arm of the Steering Committee, and is composed of the Study Chairman, the Principal Investigators of the Coordinating Center and the Core Laboratory and representatives of the NHLBI Program Office. This committee participates in regularly-scheduled conference calls.

12.3.5 Publications Committee

The Publications Committee is responsible for reviewing all proposals submitted for ancillary studies or data bank studies, and for reviewing and approving all abstracts submitted to scientific meetings and all manuscripts submitted for publication from RTS end point, parallel, data bank or ancillary studies. The members of the Publications Committee are appointed by the Study Chairman.

EXHIBIT 12-1

RTS ADMINISTRATIVE STRUCTURE

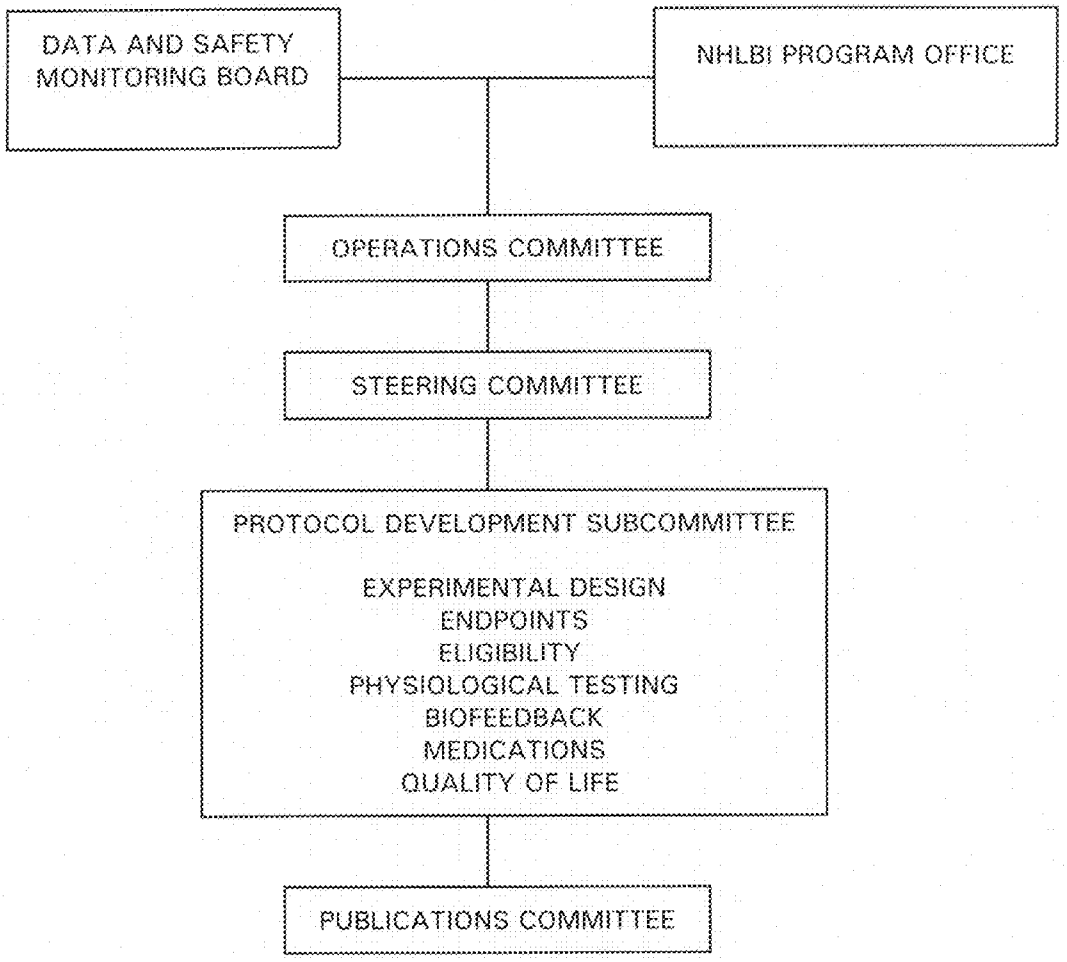

EXHIBIT 12-2

RTS STUDY CLINICAL UNITS		
Clinic Number	**Clinical Unit Name**	**Location**
01	The Johns Hopkins University	Baltimore, Maryland
02	Medical University of South Carolina	Charleston, South Carolina
03	University of Medicine and Dentistry of New Jersey	Newark, New Jersey
04	University of Pittsburgh	Pittsburgh, Pennsylvania
05	Wayne State University	Detroit, Michigan

EXHIBIT 12-3

RTS CENTRAL UNITS

Study Chairman

Dr. Leonard Bielory
University of Medicine and Dentistry of New Jersey
Newark, New Jersey

Coordinating Center

Clinical Trials and Surveys Corp.
Baltimore, Maryland

NHLBI Program Office

Behavioral Medicine Branch
Bethesda, Maryland

Core Laboratory

To be named.

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CHAPTER 13

POLICY MATTERS

13.1 PUBLICATION POLICY

13.1.1 General Statement of Editorial Policy

It is anticipated that Raynaud's Treatment Study (RTS) will generate considerable new data relative to patients with Raynaud's phenomenon. The purpose of the RTS Publications Committee is to foster and guide development of scientific reports originating from data obtained in the RTS. The scientific integrity of the project requires that all data from all RTS sites be analyzed study wide and reported as such. Thus, an individual site is not expected to report and publish data collected from its site alone under the by-line of the RTS. Development of substudies or data bank studies dealing with specific analysis are encouraged. All presentations and publications of any type (RTS or related studies) are expected to protect the integrity of the main objectives of the overall project. Major findings will not be presented prior to release of "mainline" results of the study by agreement of the entire study group of Principal Investigators. The Publications Committee will prepare recommendations concerning the timing of presentation of mainline results (including papers on design and methods) and designation of the meetings at which they might be presented and will submit these recommendations to the Steering Committee for approval.

Publications will be grouped into five general types of papers (see Section 13.1.2). Topics for consideration to be developed into publications will be generated from questions or hypothesis that are submitted to the Publications Committee by investigators, study coordinators and other RTS staff. The Publications Committee will prioritize each request. A writing group with a designated Chairperson will be recommended for each topic and this recommendation will be forwarded to the Steering Committee for approval.

The Steering Committee has primary responsibility for the scientific conduct of the study including all end point, data bank, ancillary, and independent studies (defined below) as well as for all publications and presentations evolving from RTS.

Investigators at all RTS sites, including the Core Laboratory, the Coordinating Center, and NHLBI Program Office have equal status with regard to developing protocols, participating in such studies as

approved by the Steering Committee, and collaborating in the development and publication of research papers based on RTS material. With the approval of the Principal Investigator, study coordinators and other RTS staff at the various sites are encouraged to participate in this process. The Publications Committee will develop standards for regular evaluation of the submission and completion of these protocols.

RTS Investigators at Clinical Units or Central Units proposing studies that require the collaboration of one or more of the RTS Central Units (e.g., Core Laboratory or the Coordinating Center) must contact the appropriate individuals prior to submission of a given proposal. The appropriate staff in the Central Units will participate in drafting the proposal, indicate their willingness to participate, and identify sources of funding to support the level of effort required for the project.

The Coordinating Center staff must be consulted in the development and analysis of protocols that require review of accumulated data from the Clinical Units or data on file at the Coordinating Center. The Coordinating Center staff and NHLBI Program Office staff are available to collaborate in designing and carrying out all RTS research.

13.1.2 Types of RTS Research

RTS research and the resulting presentations and publications may be grouped into the following categories:

1. Design paper(s) and reports on methodology;
2. Major findings;
3. Data bank studies;
4. Ancillary studies; and
5. Independent studies.

Distinctions among these types of studies are given in Section 13.2. Research other than analyses of protocol data may be conducted prior to the end of the RTS investigation and is strongly encouraged, so that the maximum information can be obtained from this study and so that the methods for evaluating and analyzing study data may be refined in preparation for later analyses.

13.1.3 Authorship

The first publication(s) pertaining to the fundamental goals of RTS involving patients enrolled in the RTS will have authorship identified on the byline as "the Raynaud's Treatment Study Group."

Individuals who contributed specific sections of the publication and members of the ad hoc Writing Subcommittee which prepared the manuscript will be identified in appropriate footnotes. An appendix listing all Principal and Co-Investigators in RTS will be included at the end of the manuscript's text. It is intended that there will be more than one publication concerning the major goals; these publications will list the writing team as the authors on behalf of the RTS study group.

13.1.4 Purpose of Procedural Guidelines

The procedures adopted by the RTS investigators for utilization of RTS data are intended to protect the interests of all participants in the study, to assure that study data conform to the requirements of study design and are accurately presented, that authorship is appropriately acknowledged, that the text of each publication is well-written, to ensure that all investigators are aware of ongoing analysis projects, to avoid duplication of analysis projects and to ensure that publication or presentation of RTS data does not occur without the knowledge and approval of the Steering Committee.

13.1.5 Restrictions on Which Data May be Released

RTS findings which might jeopardize the continuation of the project will not be released to RTS Investigators or the public until the end of the study, at a time deemed appropriate by the RTS Data and Safety Monitoring Board, the NHLBI Project Office, and the Study Chairman.

13.2 DESIGN AND METHODS REPORTS, MAJOR FINDINGS, DATA BANK, ANCILLARY, AND INDEPENDENT STUDIES

13.2.1 Design Papers and Reports on Methodology

Manuscripts concerning the overall design, protocol, procedures, or organizational structure of the RTS which do not involve major findings or data collected on RTS patients may be published prior to the end of the study. Such major publications will be developed and reviewed according to the same guidelines used for reports of major findings.

Many public presentations or publications about RTS which do not involve protocol data, data bank or ancillary study data (e.g., grand rounds talks concerning the study's general design and objectives) will not require formal preliminary review and approval by the Publications Committee. However, if there is any doubt, investigators are asked to first consult with the RTS Operations Committee indicating their intention to publish or present the material, in order to avoid the premature release of RTS data or the inappropriate publication of confidential information.

13.2.2 Reports of Major Findings

A report on major findings is one addressing the fundamental goals of RTS or that involves protocol data (such as number of vasospastic attacks) which cannot be released prior to the end of the study. These studies will summarize the findings based on the entire study population and will be written at the conclusion of the project.

13.2.3 Data Bank Studies

A data bank study uses data, specimens, or recordings, which are routinely collected on patients who are logged, screened for entry into, or enrolled in RTS. Analyses of these data are used to answer a specific scientific question. Data used in this research are not directly related to the fundamental goals of the RTS. Data bank studies must be approved by the Publications Committee and Operations Committee and ratified by the Steering Committee. All presentations or publications are to be reviewed following the procedures outlined below.

13.2.4 Ancillary Studies

An ancillary study uses supplementary data that are collected on patients who are logged, screened for entry into, or enrolled in RTS, over and above the data collection required by the RTS protocol. Such studies are restricted to consideration of a specific test technique or involve only supplemental data collected on RTS patients and may be performed by selected Clinical Units rather than at all Clinical Units. Ancillary studies must be reviewed and approved by the RTS Publications and Operations Committees and ratified by the Steering Committee prior to initiation to ensure that they do not conflict with the main protocol. Review by the RTS Publications and Operations Committees is required for presentation or publication of an ancillary study.

13.2.5 Independent Studies

Independent studies of concern to the RTS are studies conducted in patients with Raynaud's phenomenon who enter a RTS Clinical Unit but are not enrolled in the RTS.

It is understood that each Clinical Unit has the right to conduct studies which are independent of the RTS in patients with Raynaud's phenomenon who do not meet criteria for enrollment into the RTS. Independent studies involving patients who meet the RTS eligibility criteria must be disclosed to the Publications Committee. RTS investigators agree not to conduct independent studies which would have a detrimental effect on the conduct of the RTS during the period of recruitment and follow-up of

patients by the RTS. The purpose of such a disclosure is to assure the members of the other participating Clinical Units that recruitment for a new study will not impact on the Clinical Unit's ability to recruit the required number of patients for the RTS, nor on the Clinical Unit's ability to recruit minority patients.

13.3 PROCEDURES FOR INITIATION AND APPROVAL OF STUDIES

13.3.1 Preparation of Proposal for Data Bank and Ancillary Studies

Each proposal for an ancillary or data bank study should contain a brief description of the objectives, methods, analysis plans, significance of the study, and proposed collaborators. The sample size for the proposed study should be justified in terms of meeting the ancillary study objectives. Full details should be given concerning any procedures to be carried out on a study patient such as psychiatric interviews, psychological testing, radiological procedures, etc. Mention should be made of any substances to be injected or otherwise administered to the patients. Any observations to be made or procedures to be carried out on a patient outside of the Clinical Unit should be described. Mention should be made of the extent to which the data bank or ancillary study will require extra visits to the Clinical Unit by the patient or will prolong the patient's usual visits to the Clinical Unit. Information should be given concerning the extent to which the ancillary study will require blood specimens in addition to those presently required for RTS. If blood specimens are to be obtained from the patients, mention should be made of all procedures to be carried out on these specimens.

13.3.2 Reports on Major Findings

Reports on major findings from RTS will generally involve the collaboration of many investigators. Proposals for these reports may be introduced and developed by any member of the Steering Committee. Some Writing Subcommittees will be designated by the Operations Committee on an ad hoc basis for preparation of these abstracts and manuscripts on behalf of the RTS investigators and others on the basis of submission of a proposal.

13.3.2.1 Submission of Proposals

Two copies of each proposal should be submitted to the Coordinating Center for inventory and transmission to the Publications Committee Chairperson. The Chairperson of the Publications Committee will notify the Investigator, the Study Chairman, and the Coordinating Center when the

project is approved, disapproved or, if additional information is needed before a decision can be made.

13.3.2.2 Conduct of this Research

After approval of a proposed end point study, members will be elected or invited to serve on an ad hoc Writing Subcommittee and a Chairperson will be chosen. These investigators will work with the Coordinating Center staff and NHLBI staff to conduct the data analysis needed to investigate the question at hand and to prepare a manuscript based on these findings. Every effort will be made by the Subcommittee to consider and incorporate comments and suggestions from the Steering Committee. Often the Subcommittee members may meet with staff from the Coordinating Center or other RTS Clinical Units for development of these papers.

13.3.2.3 Review and Approval of Manuscripts and Abstracts Prior to Presentation and Publication

Every study manuscript considered suitable for publication will be submitted by the Chairperson of the Writing Subcommittee to the Coordinating Center for distribution to the RTS Publications Committee Chairperson, who will be responsible for arranging and implementing review according to the following procedures.

1. The manuscript will be forwarded promptly to at least two reviewers selected from the members of the Steering Committee or their associates, with the request to respond within two weeks with a detailed critical review of the manuscript. Outside reviewers may be selected when appropriate. Prompt response of reviewers will be strongly urged.
2. Reviews will be forwarded to all members of the ad hoc Writing Subcommittee with a request for appropriate revision and response.
3. The Writing Subcommittee will be expected to respond to the review in a reasonable period of time, forwarding to the Publications Committee Chairman and the Coordinating Center the revised manuscript and a letter commenting on the points raised by the reviewers.
4. After review, the Publications Committee Chairman will return the revised manuscript to the Writing Subcommittee with final approval or recommendations for further changes.
5. If acceptable to the study leadership (NHLBI staff, Operations Committee, and Publications Committee), the completed manuscript will be submitted for publication.

13.3.3 Data Bank Studies

13.3.3.1 Submission of Proposals

Data bank studies must be approved by the Publications Committee. Before beginning a data bank project, a proposal initiated by one or more of the RTS investigators and/or their associates should be submitted to the Publications Committee for consideration. Two copies of each proposal should be submitted to the RTS Coordinating Center for inventory and transmission to the Publications Committee Chairperson. The Chairperson of the Publications Committee will notify the Investigator, the Study Chairman, and Coordinating Center staff when the project is approved, disapproved or additional information is needed before a decision can be made.

13.3.3.2 Conduct of this Research

After approval is given by the Publications Committee, the Principal Investigators (on the data bank project) will work with the Coordinating Center staff and NHLBI staff to conduct the data analysis.

13.3.3.3 Priorities for Work

Because of the routine work load at the Coordinating Center, it will be necessary to establish priorities for data processing and analysis. Therefore, the Coordinating Center staff will, as necessary, conduct analyses on data bank studies in the order in which they have been approved or seek guidance from the Operations Committee for determining priorities for analysis.

13.3.3.4 Authorship

After a data bank study proposal is approved by the Publications Committee, its research and development are the responsibility of the identified investigators on the project. Authorship decisions on RTS data bank studies will take into account the unique cooperative effort that has produced the results. For clinical papers in particular, authorship should be offered to individuals from the Clinical Units, Core Laboratory, Coordinating Center and NHLBI Program Office when their contributions are appropriate. On the other hand, there will be papers of more limited scope which probably do not warrant a large number of authors. The following mechanism will be utilized to determine authorship:

a. The lead author will propose a list of co-authors, based on the above guidelines.

b. The Chairperson of the Publications Committee, and the Study Chairman, will review and approve, or make recommendations regarding alterations in the proposed list of authors.

The names of these investigators will be followed by the designation "and the Raynaud's Treatment Study Group" on the byline.

13.3.3.5 Review and Approval of Manuscripts and Abstracts Prior to Presentation or Publication

The Publications Committee and the Study Chairman's Office, on behalf of the Steering Committee and NHLBI, will review all data bank study abstracts and manuscripts prior to submission for publication or presentation. All abstracts must be received by the Publications Committee members, all co-authors, and the Coordinating Center at least two weeks prior to the submission deadline. Manuscripts produced by data bank studies must be received by these reviewers at least one month (30 days) before the scheduled submission date. After review, the Publications Committee will decide, in consultation with the Coordinating Center staff, if release for publication is appropriate. The Chairperson of the Publications Committee will then notify the authors, the RTS Study Chairman's Office, Coordinating Center, and NHLBI Program Office of its decision within one month of the receipt of a manuscript and within one week of receipt of an abstract. The approved manuscript or abstract may then be submitted.

13.3.4 Ancillary Studies

13.3.4.1 Submission of Proposals

Ancillary study proposals will be reviewed by the Publications Committee and Operations Committee to ensure that the proposed study does not conflict with the primary goals of the study. No further review of ancillary studies is required. Two copies of each proposal should be submitted to the Coordinating Center for inventory and transmission to the Publications Committee Chairperson. The Chairperson of the Publications Committee will notify the Investigator, the Study Chairman, and CCC when the project is approved, disapproved or additional information is needed before a decision can be made.

13.3.5 Independent Studies

Results of independent studies which are approved as acceptable within RTS may be published or presented at the discretion of investigators initiating the independent study.

13.4 CONFLICT OF INTEREST

13.4.1 Introduction

The RTS investigators recognize that bias is a concern for any clinical trial, and the study design has incorporated a number of safeguards against the introduction of bias. In the RTS, these include randomization into one of the four treatment groups, the management and analysis of data by a Coordinating Center, central and blinded interpretation of data by the Core Laboratory, the use of an independent classification system for determination of the primary clinical end point, and an independent Data and Safety Monitoring Board to monitor the study and evaluate the safety and efficacy of the treatments. The RTS will compare different treatments for patients with Raynaud's phenomenon and the results will reflect the comparison of these treatment groups.

Despite these safeguards, the RTS investigators realize that concerns about real or potential conflicts of interest may arise. Where potential conflicts exist, the RTS investigators endorse the task of rational management of conflict according to pre-agreed guidelines and principles. Therefore, the RTS investigators have agreed to a policy on conflict of interest which has few specific restrictions, but a broad indication for disclosure of potential conflicts of interest. The RTS investigators wish to endorse the spirit and content of the 21st Bethesda Conference: Ethics in Cardiovascular Medicine[1] dealing with these issues, and seek to make this policy consistent with the record of that conference.

To address actual or perceived conflict of interest in the RTS Study, the participating investigators voluntarily agree to abide by the guidelines described in the policy statement developed for RTS. See Exhibit 13-1 for a copy of the Financial Disclosure Statement.

13.4.2 Individuals to be Governed by these Guidelines

Members of the RTS Study Group who will be governed by these guidelines include the Study Chairman, the Principal Investigator at each Clinical Center, the principal personnel in the Coordinating Center, and the Principal Investigators of the Core Laboratory. Co-Investigators and other staff who have major responsibility for enrollment, recruitment, follow-up or collection of data for RTS at Clinical Units, affiliated hospitals or Core Laboratory will also be governed by these guidelines. The Principal Investigator for each RTS Center will submit a list of individuals who will be governed by these guidelines at the beginning of the study. The Principal Investigator of each participating unit will review

the guidelines with all appropriate staff prior to the start of patient recruitment and at least annually thereafter.

13.4.3 Time Period of the Policy

The guidelines set forth in this policy will commence at the start of patient recruitment and will terminate at the time of initial public presentation or publication of the principal results. Investigators not privy to end point data who discontinue participation in the trial during recruitment will be subject to these guidelines until their departure from the study.

13.4.4 Financial Guidelines

1. The investigators agree not to own, buy or sell stock or stock options during the aforementioned time period in any pharmaceutical company or related medical equipment companies[1] with products being tested in this trial, or who have provided financial support for the study. In addition, the investigators agree not to have retainer-type consultant positions with these companies for the time period defined above.
2. The Coordinating Center staff will maintain conflict of interest statements updated annually from each investigator.

Activities not explicitly prohibited, but to be reported annually to the Study Chairman and maintained by the CCC include:

1. Ad hoc consultant relationships to companies providing drugs or financial support to the trial.
2. Participation of investigators in any educational activities that are supported by the companies.
3. Participation of investigators in other research projects supported by the companies.
4. Financial interests in these companies, over which the investigators has no control, such as mutual funds or blind trusts.

13.4.5 Reporting of Financial Disclosures and Other Activities

The investigators agree to update their financial disclosures and related activities as described above on an annual basis and submit these data to the RTS Coordinating Center for storage. The

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1 Companies listed for RTS investigators include: Pfizer and the company [to be named] that manufactures biofeedback equipment used in RTS.

This list will be expanded or modified as appropriate for RTS investigators.

Coordinating Center staff will maintain the confidentiality of these records and present them to a review committee, to be constituted by the Study Chairman. In the case of actual or perceived conflict of interest, the Study Chairman will bring it to the attention of the Operations Committee, NHLBI Program Office staff, and the Data and Safety Monitoring Board.

13.4.6 Review of Policy Statement

The investigators agree to review these guidelines on an annual basis and take any additional steps to insure that the scientific integrity of the trial remains intact.

13.4.7 Relationship to Institutional Policies on Conflict of Interest

Since existing policies on conflict of interest may vary between participating institutions, in addition to the above policy, it is expected that investigators will comply with the policies on conflict of interest which exist within their individual participating institutions (medical schools and hospitals). This is the responsibility of each individual investigator.

13.5 ACKNOWLEDGMENT OF NON-FEDERAL FUNDING

In the reports on major findings, data bank and ancillary studies, the financial support of all non-federal groups will be acknowledged at the end of each manuscript.

13.6 REFERENCES

1. Frommer P.L., Ross J., Benson J.A., et al. Task Force IV: Scientific responsibility and integrity in medical research. JACC 1990;16:1-36.

EXHIBIT 13-1

RAYNAUD'S TREATMENT STUDY

INITIAL FINANCIAL DISCLOSURE STATEMENT

I, the undersigned certify that:

1. As of _____, neither I, nor my spouse or dependent children own or will buy or trade stock or stock options in any of the companies[1] providing medication, equipment or financial support in the trial. In addition, I don't have a retainer-type consultant position with any of the companies.*
2. I agree to disclose financial interests as outlined in the RTS Policy on Conflict of Interest during my participation in the RTS Study.

If response is no to question 1 or 2, an explanatory letter is required.

_____ _____

Investigator (type name) Signature

_____

Date

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1 Companies listed for RTS investigators include: Pfizer and the company [to be named] that manufactures the biofeedback equipment used in RTS.

This list will be expanded or modified as appropriate for RTS investigators.

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CHAPTER 14

SAMPLE SIZE CONSIDERATIONS AND DATA ANALYSIS PROCEDURES

14.1 INTRODUCTION

The objectives of the Raynaud's Treatment Study (RTS) are to determine the relative efficacy of two treatment strategies compared to their respective control groups and to each other in reducing the number of vasospastic attacks experienced by patients with primary Raynaud's phenomenon. The treatment groups are: administration of nifedipine XL; temperature biofeedback training; frontalis electromyogram (EMG) biofeedback training (temperature biofeedback control group); and no treatment (placebo).

The number of vasospastic attacks experienced by the patients will be the primary end point collected in this study. The primary end point data will be collected over a one-month period fifteen months after the patient is enrolled into the study. This end point will require that the patient observe at least one of the two color changes (white or blue) in a pattern consistent with the occurrence of a vasospastic attack. A half hour refractory period will be used to formally divide the occurrence of one attack from the next. A count of vasospastic attacks will also be collected from January 1 to March 31 during any cold season that the patient is enrolled in the RTS and will be an important secondary end point.

The study population will include 300 patients. Approximately seventy-five patients will be randomized to each of the four treatment arms. Study enrollment is to take place from October through December of 1993 (Cohort 1) and October through December of 1994 (Cohort 2). Comparisons of treatment effects will be made with respect to a variety of outcome measures in addition to those described above. Analysis techniques in both studies will include tests of differences in mean attack rates, estimation of attack rates, tests of differences in proportions, longitudinal data analysis, and survival analysis.

14.2 ANALYSIS PLANS FOR THE RAYNAUD'S TREATMENT STUDY

14.2.1 Study Monitoring

The RTS Coordinating Center will prepare interim technical and statistical reports for periodic meetings of the investigators and quarterly and annual reports for the NHLBI Project Office staff. The RTS Coordinating Center will analyze the relative frequency of end points of interest and complications across treatment groups and will report these data to the Data and Safety Monitoring Board (DSMB) at approximately six-month intervals. Formal statistical tests (using sequential testing methods) will be included in one of the DSMB reports (at the conclusion of data collection for the first cohort) to assist the DSMB in determining whether observed treatment differences call for consideration of early termination of the study.

Individual treatment arms will be brought to early termination if adverse events accumulate with unexpected rapidity as a result of treatment. Patients will be monitored for the occurrence of adverse events using self-reporting mechanisms and periodic physical exams. Monitoring for safety may be most important for the group of patients assigned to treatment with nifedipine XL, a calcium channel blocker.

14.2.2 Power Evaluations for the Primary End Point

The sample size calculations for the RTS is based on a test for differences among log-normally distributed means. The assumption of constant variance within treatment groups once the logarithmic transformation is made is important for this test to be valid. Many of the study results presented in the literature have reported the standard deviation to be equal to the mean. By taking the logarithm of the estimated attack rate for each patient, the estimated variance in the treatment groups should be stabilized (1). This transformation has the added advantage of being sensitive to the ratio of mean attack rates in the different groups rather than to the difference in attack rates among the different groups.

There are three planned comparisons in the RTS. Let R1, R2, R3, and R4 be the means of the logarithms of the attack rates for the primary end point data for the groups randomly assigned to Nifedipine XL, Temperature Biofeedback, Placebo, and EMG Biofeedback respectively. The planned comparisons are to test: D1 = R1 - R3; D2 = R2 - R4; and D3 = D1 - D2. The comparison D3 will

be used to assess the significance of nifedipine XL treatment versus temperature biofeedback treatment. Two of the planned comparisons are statistically independent (D1 and D2), and the third (D3) is linearly dependent on the other two comparisons. The experiment-wise alpha level will be controlled at 0.05 by performing an F test of H_0:$E(D_1)=0$, $E(D_2)=0$, versus the alternative that the expected value of at least one of the differences is not equal to 0. The significance of the F test will be assess at the 0.05 alpha level; the critical value associated with this alpha level is 3.0. The three planned comparisons will be made only if the global F test is significant. In this case, each planned comparison will be made at the 0.05 comparison-wise alpha level.

Each of the proposed comparisons corresponds to a t-test calculated from a linear contrast across the four means. The contrast matrix is as follows:

	Nifedipine	Temperature Biofeedback	Pill Placebo	EMG Biofeedback
Contrasts				
C1'	1	0	-1	0
C2'	0	1	0	-1
C3'	1	-1	-1	1

The estimate of the three treatment effects (nifedipine XL versus placebo, temperature biofeedback versus frontalis EMG biofeedback, and nifedipine XL versus temperature biofeedback) can be calculated as **Ci'R** where **R** is the vector of means listed above. The variance for each of the proposed contrasts can also be calculated as **Ci'Ci** s^2/n were s^2 is the pooled within group variance estimate and n is 75. The variance estimate for D3 is twice as large as the variance contrast for D1 or D2.

The power of the F statistic is dependent upon the non-centrality parameter ð. The power of the F statistic can be assessed in terms of the two statistically independent planned comparisons (D_1 and D_2) by noting that:

$$F = \frac{T_1^2 + T_2^2}{2} \quad \text{where}$$

$$T_i = \frac{C_i' R}{\sqrt{C_i' C_i \frac{s}{75}}} \quad i=1,2.$$

The non-centrality parameter of the F statistic will be related to the sum of the squared non centrality parameters for each T_i ($i = 1,2$).

Two cases are considered: 1) the case where each contrast contributes equally to the overall F statistic; and 2) the case where only one of the contrasts contributes to the significance of the F statistic.

Case 1) if $T_1 = T_2$ then $F > 3$ when $|T_i| > 1.74$ $i = 1,2$.

By insuring 90% power for each planned contrast to be significant at the 0.05 alpha level, there is at least 80% power that the F statistic will be significant. With the proposed sample size of 75 patients in each treatment group, each planned comparison (D_1 and D_2) has at least 90% power to detect a 38% reduction in the vasospastic attack rate or a 62% increase in the attack rate when comparing a treatment group to its respective control group.

Case 2) if $T_1 = 0$ then $F > 3$ when $|T_2| > 2.45$.

By insuring 80% power for T_2 to be greater than 2.45, there is at least 80% power that the F statistic will be significant. With the proposed sample size of 75 patients in each treatment group, the planned comparison involving D_2 has 80% power to detect a 42% reduction in the vasospastic attack rate or a 71% increase in the attack rate when comparing temperature biofeedback to frontalis EMG biofeedback. Analogous results are obtained when $T_2 = 0$ and $|T_1| > 2.45$.

In summary, if either nifedipine XL or temperature biofeedback are responsible for a true 38 to 42% reduction in vasospastic attacks (eg., from 2 to 1.16 attacks per day) or a 62 to 71% increase in vasospastic attacks (eg., from 2 to 3.42 attacks per day) there will be at least 80% power for the F statistic to be significant.

Power assessments for each of the planned comparisons will be assessed at a comparison-wise alpha level of 0.05. As previously stated, these comparisons will only be made if the specified F statistic is significant. If the null hypothesis for the F statistic test in fact is false, it can be shown that only one of the three null hypotheses for the planned comparisons can in fact be true, and the other two must be false (the alternative hypotheses are true). In considering the alpha level to be used for the planned comparisons, it should be noted that the most conservative estimate that can be made in considering the family of comparisons to be made is that one and only one null hypothesis

can be true once the null hypothesis for the F statistic has been rejected. If the true null hypothesis could be identified, it would be tested at the 0.05 alpha level to prevent a high likelihood of finding in favor of the alternative. Since the specific true null hypothesis cannot be identified, each planned comparison will be tested at the 0.05 alpha level.

The required differences $\Delta = C\mu$ i = 1.2 necessary to have 80% power when testing D_1 and D_2 at the 0.05 α level with 75 patients in each of the treatment groups can be calculated. The estimated variance after applying the logarithmic transformation to the primary end point data is 1. The proposed study size of 300 is sufficient to detect a true 37% reduction in mean attack rates with 80% power when testing at $\alpha = 0.05$. Specifically, if the attack rate in the placebo group is two per day, and the attack rate in the Nifedipine group is 1.2 per day, this treatment effect could be detected with at least 80% power. Likewise, if the attack rate in the EMG biofeedback group is two per day, and the attack rate in the temperature biofeedback group is 1.2 per day, this treatment effect could be detected with at least 80% power.

The proposed comparison between Nifedipine XL and Temperature Biofeedback Treatment Groups is not a two group t test as are the comparisons between nifedipine XL and its placebo and temperature biofeedback and frontalis biofeedback. Patients receiving temperature biofeedback treatment will have different levels of contact with Clinical Unit staff than will patients treated with nifedipine XL. This difference in attention may create a difference in the reporting of vasospastic attacks that is not due the specific treatment effects of the two interventions. To control for this attention difference, the relative difference in attack rates between patients assigned to nifedipine XL and patients assigned to temperature biofeedback will be in relation to the relative difference in estimated attack rates between the patients assigned to placebo and patients assigned to frontalis EMG biofeedback. The difference between the estimated attack rates in patients treated with placebo and patients treated with frontalis EMG biofeedback in effect provide the "null hypothesis" estimate of the difference in reporting vasospastic attacks due to attention differences. Any difference in the attack rates between the Nifedipine XL and Temperature Biofeedback Treatment Groups must be assessed against the "control difference" of placebo versus frontalis EMG biofeedback. Thus, a percent reduction (or increase) mentioned in the following paragraph is relative

to the ratio of the attack rates of the Placebo Treatment group versus Frontalis EMG Biofeedback Treatment group. For instance, if the placebo patients have an average attack rate of two per day, the frontalis EMG biofeedback patients have an average attack rate of 1.7 per day, the nifedipine XL patients have an average attack rate of 1.3 per day, and the temperature biofeedback patients have an average attack rate of 0.5 per day, the nifedipine XL versus temperature biofeedback treatment effect is:

$$E_{NB} = \frac{\frac{1.3}{0.5}}{\frac{2}{1.7}} = \frac{1.3 \times 1.7}{0.5 \times 2} = 2.21$$

rather than $\frac{1.3}{0.5} = 2.6$.

The proposed study size of 300 is sufficient to detect a true 48% reduction (or 1.9 fold increase) in mean attack rates with 80% power when testing at $\alpha = 0.05$.

Additional power for the proposed analyses could be achieved by utilizing an analysis of covariance model (ANCOVA) that incorporates the pre-treatment attack rate for each patient, rather than simply using the post-treatment attack rates for the analysis. A positive correlation of 0.5 has been observed between the pre-treatment and post-treatment attack rates for each individual. Assuming this level of correlation and using an analysis of covariance model with the pretreatment attack rate included as a covariate, the estimated standard deviation for post-treatment attack rates for the RTS would be reduced by approximately 25% and the power to detect any relative difference of Δ or E_{NB} would be increased. Using an Analysis of Covariance Model, and assuming a 25% reduction in the error variance estimate, the sample size of the proposed study is sufficient to detect a true 32% reduction in mean attack rates (or a 48% increase) for a treatment versus its control per day with 80% power when testing at $\alpha = 0.05$. For example, if the attack rate in the placebo group is two per day, and nifedipine XL reduces the attack rate to 1.3 per day, this treatment effect could be detected with at least 80% power when using the ANCOVA design.

Similarly for the planned comparison of nifedipine versus temperature biofeedback ($\mathbf{C}'\boldsymbol{\mu}$), using an analysis of covariance model with the pretreatment attack rate included as a covariate increases the power of the study to detect any absolute difference E_{NB}. By incorporating the pre-treatment

measure into an ANCOVA model, the proposed study sample size is sufficient to detect E_{NB} less than 0.57 or $E_{NB} > 1.75$ with at least 80% power when testing at $\alpha = 0.05$.

14.2.3 Power Evaluations for the Secondary End Points

Many of the secondary outcome measures of interest will be continuous in nature. As such, the methods for calculating power are similar to those for the primary analysis. A "two-tailed" α level 0.01 or less will be used to assess statistical significance of comparison when performing secondary analyses in an effort to reduce the number of spurious associations that could be found to be significant because of the large number of hypotheses that will be tested. Setting $\alpha = 0.01$, the proposed sample size of 75 in each group design could detect true differences between two means as low as 0.55 standard deviation units with 80% power for the comparison of one of the intervention treatments versus its respective control, and 0.79 standard deviation units for the nifedipine versus temperature biofeedback comparison. If a log transformation of data is required, the proposed sample size is sufficient to detect a relative 73% increase or 42% decrease in the attack rate when comparing a treatment to its comparison group, and a 2.2 fold increase versus a 54% reduction in attack rates when comparing nifedipine to temperature biofeedback.

14.2.4 Data Analysis

14.2.4.1 Introduction

Data analyses will be carried out in this study for two main purposes. One is to monitor the performance of the Clinical Units and Core Laboratory. The Raynaud's Study Treatment (RTS) will be monitored with respect to patient recruitment and follow-up, adherence to study protocol, and accuracy and completeness of study data. For this purpose, it is anticipated that performance reports will be generated every three months.

The second main purpose for data analysis is to seek answers to the study research questions and objectives. It is anticipated that research data reports will be generated twice during the conduct of the RTS. The first report will be generated after the primary end point data have been collected for all patients recruited in 1993; the second report will be generated after primary end point data have been collected for patients recruited in 1994.

It is proposed to perform analyses using an intention to treat principle; patient outcomes will be analyzed according to the treatment strategy to which they were assigned. Patients who do not adhere to the treatment protocol will be included in the analyses.

For certain patients enrolled in the study, primary end point data may not be available. Missing data can be the result of informative censoring or uninformative censoring. The amount of missing data in each treatment group will be compared to determine if there may be an informative censoring pattern. If such a pattern is detected, sensitivity analyses will be performed (such as imputing the average control event rate for a nifedipine XL treated patient with missing data) to determine the possible effect that the missing data could have on the overall results.

14.2.4.2 Primary Study Outcome

The primary study outcome will be the number of vasospastic attacks with at least one color change (white or blue) with the characteristic vasospastic attack pattern that occur over a one-month interval. The logarithm of this estimated attack rate will then be taken. The resulting logarithms of the attack rates will be analyzed using the following procedure. The primary end point data will be collected approximately fifteen months after the patient is enrolled into the study. The end point will be standardized for each patient by dividing the number of patient-reported vasospastic attacks during the interval by the number of days the patient was monitored for the occurrence of each defined vasospastic attack. The logarithm of each observation will then be taken.

Statistical analysis of the primary end point will be accomplished using an Analysis of Covariance Model. In performing this analysis, the logarithm of one-month attack rates obtained 15 months after the patient is randomized will be regressed onto the logarithm of the baseline one-month attack rates. The residuals from the regression will then be analyzed using an analysis of variance model (ANOVA). The ANOVA model will include 300 observations of the residuals. Sums of Squares for treatment effects (3 df) will be subtracted from the total sum of squares in order to provide an unbiased estimate of the error variance. An F test will be performed to determine if there are drug treatment effects or biofeedback treatment effects (i.e., H_0: $\Delta_1 = \Delta_2 = 0$ versus H_a: $\Delta_1 \neq 0$ or $\Delta_2 \neq 0$ where $\Delta_1 = E(D_1)$ and $\Delta_2 = E(D_2)$). If the F test is significant at the 0.05 alpha level, specific linear contrasts of the four means will be calculated in order to test each of the three proposed hypotheses.

The t-test value for each linear contrast will be reported along with the unadjusted p-value for the comparison.

14.2.4.3 Data Monitoring Reports

The data monitoring reports will be prepared every six months and will include the following tables:

1. A summary of patient recruitment and follow-up according to study treatment and Clinical Unit, including the number of patients screened, the number of patients recruited, the number of patients at various stages of follow-up, the number of completed scheduled visits, and the number of study measurements completed for each study visit.
2. Tabulations of average number of vasospastic attacks according to study treatment and Clinical Unit, including the number of patients who completed each visit. Treatment differences will be tested using significance levels developed from a sequential monitoring plan (see below).
3. Life table analyses of diagnosis of scleroderma development of digital ulcers, and diagnosis of gangrene by study treatment group.
4. Performance of required biofeedback sessions and patient compliance in taking assigned study medications.
5. Number of patients screened, and proportion of patients screened who were eligible for the RTS by age, sex, race or other demographic characteristics. Number and proportion of patients screened and found ineligible according to the criterion or criteria for eligibility which resulted in their exclusion.

The content of each report will be discussed with the NHLBI Project Office staff and with the study leadership prior to preparation of the report and its distribution to the DSMB. Any other analyses requested by the NHLBI Project Office staff or the DSMB will be prepared and presented at the time of the DSMB meeting.

Interim assessment of the primary outcome measure will be carried out according to the plan described by Jennison & Turnbull (2). One formal interim analysis of the primary end point is proposed. The small number of patients to be enrolled in the RTS, and the seasonal aspects for

collection of the primary end point data (the end point data will be collected during January, February, and March of 1995 for the first group of patients and in January, February, and March of 1996 for the second group of patients) suggests that only one interim monitoring evaluation of the primary end point is required. A wide (nominal $\alpha = 0.001$) boundary will be set for the F statistic for the interim monitoring analysis, and a nominal $\alpha = 0.049$ boundary will be set at the time of the final analysis of the data. If the F statistic is significant at the time of the interim analysis, the planned comparisons D_1, D_2, D_3 will each be performed with the nominal alpha level set at 0.001 for each comparison. Setting such wide monitoring boundaries for the interim analysis has minimal impact on the final nominal α level. The multiple considerations involved in terminating a study early, the low incidence of serious sequelae from primary Raynaud's phenomenon, and the treatment of patients with pill-placebo suggest that the α level for the study should be spent at the conclusion of the RTS, when the chances of finding treatment differences are best.

Using the Bonferroni inequality, one can show that the maximum impact the above monitoring scheme could have on the α level for the entire study would be 0.05.

Early termination of one treatment arm due to adverse effects cannot be ruled out, and calls for continuous review of reported adverse effects. Sequential methods will be used for monitoring the study for the emergence of adverse events, however there will be no attempt to constrain the experiment-wise alpha level for monitoring adverse events to the 0.05 level.

The rationale for this approach is that monitoring methods that increase the power to detect a true difference are preferable to those that preserve the experiment-wise alpha level when monitoring a Clinical Trial for adverse events. Much additional analysis is undertaken to determine if apparent treatment differences in the incidence of adverse events are real or are spurious. These additional analyses alleviate the requirement that the statistical procedures used to identify potential treatment differences in the emergence of adverse events maintain a pre-specified experiment-wise alpha level. One way to increase power to detect treatment differences in the emergence of adverse events is to develop a comparison-wise approach to testing for adverse events rather than an experiment-wise approach to testing for adverse events. Once a potential treatment difference is detected using the comparison-wise approach, it will be the responsibility of the DSMB to discuss the difference, and

develop methods to determine if the difference is due to treatment or is a consequence of normal statistical variation. By adopting this strategy of monitoring for treatment differences in the emergence of adverse events, potential problems can be brought to the attention of the DSMB quicker, and the DSMB can determine if the difference warrants termination of the treatment arm.

Adverse events will be classified by major site of occurrence (e.g. in the cardiovascular system) as well as being uniquely collected (e.g. arrhythmia). Counts of the adverse events (both system wide and unique counts) will be collected in each treatment group. It will be assumed that adverse events are arriving in the treatment groups according to a non-homogeneous poisson process. Blocking factors have been developed in the RTS so that roughly equal numbers of patients will be randomized into the four treatment groups at any given time. This will insure that the group intensity function for each treatment group arrival process is approximately equal across the four treatment groups under the null hypothesis that the individual patient's intensity function for the arrival of adverse events is not dependent upon treatment. Conditioning on the total number of events (in all four groups) that have been observed at each point in time for monitoring the RTS will result in the number of events in each treatment group being distributed according to a multinomial distribution. Under the null hypothesis, of no treatment differences between groups for the occurrence of adverse events, the expected value for the number of adverse events in each treatment group would be one-fourth the total number of events observed.

Using the above model, if four adverse events (such as tachycardia) have been observed in the study at a certain point in time, and all of these events have been observed in one treatment group, the probability of seeing four adverse events in one treatment group when only four have been observed in the entire study is less than 0.02. The Coordinating Center will notify the Chairman of the DSMB if unusual runs of four or more are observed for any end point. The DSMB Chairman will review the data and decide if the full SEMC should be convened to discuss these findings. If unusual runs are not found -- i.e. adverse events are occurring in more than one treatment group, Coordinating Center staff will adopt a sequential testing strategy using a comparison-wise approach to determining the significance of each finding. All tests will be performed at the nominal alpha level of 0.05. Any

statistical test in which the null hypothesis that the events are distributed uniformly across the four treatment groups is rejected will be brought to the attention of the DSMB Chairman.

Coordinating Center staff will also monitor the results of biochemical tests to determine of one or more of the RTS treatments are responsible for raising or lowering these measurements. Coordinating Center staff will perform analysis of variance, on the means of the group measurements as well as Chi-Square analyses for measurements that are denoted as extreme by the Biochemical Core Laboratory.

14.2.5 Secondary End Point Analysis

14.2.5.1 Introduction

For secondary outcome measures, p-values (p) will be included in interim reports for descriptive purposes. It is anticipated that no formal inferences concerning differences among treatment groups on secondary outcomes will be made until data collection has ended. Because of the multiplicity of hypotheses concerning baseline variables or secondary outcome measures which could be tested, a more stringent standard than the $\alpha = 0.05$ alpha level used for each of the primary analysis comparisons should be required for analyses of secondary outcome measures. For tests of secondary hypothesis to be regarded as showing good evidence of treatment group differences, a two-tailed $p \leq 0.01$ will be required; $p \leq 0.001$ will be regarded as strong evidence of treatment group differences.

Additional secondary end point analyses and analyses of the primary outcomes adjusted for covariates will be of interest. These will include, but are not limited to, the following analyses.

1. Further analyses of occurrence of vasospastic attack rates, taking both baseline factors and time-dependent covariates into account.
2. Analysis of secondary outcomes in the trial, including psychosocial factors (e.g. baseline and follow-up measurements of anxiety or depression collected in the Quality Life Form, the severity of vasospastic attacks recorded in daily diaries, and the occurrence of other well-defined outcomes (e.g. diagnosis of scleroderma).
3. Analyses of changes in rewarming times and cooling times in the digits of patients exposed to a cold box stress test.
4. Analyses of adherence to treatment.

5. Analyses of adverse events and toxicities.

14.2.5.2 Secondary End Point Analysis of the Vasospastic Attack Rates

There are two methods that will be used to assess occurrences of vasospastic attacks: attack cards and daily calendars. These are described in detail in Chapter 7, End Points (Section 7.1). Information on attacks collected with these two recording devices will be subject to the following types of secondary analyses:

1. Average attack rates will be calculated at three and 15 months post-randomization according to treatment group, in order to assess changes over time in differences in attack rates among the four treatment strategies. Analyses of variance methods and the Cox proportional (3) hazards model, as extended to counting processes, will be used for these types of analyses.
2. Stratified analyses of the primary outcome measure, using such baseline factors as Clinical Unit, age, sex, and time-dependent covariates such as season of the year will be conducted to investigate the effects of these factors on the attack rates, to gain precision in assessment of treatment effects, and to carry out exploratory analyses to detect differences in treatment effects within subgroups. For studies of this size (N = 300), it is unlikely that there will be serious imbalances in baseline factors that would bias the primary study analyses. Post-stratified secondary analyses taking account of other factors may offer gains in precision in estimation of treatment effects. Analysis of variance or the Cox Proportional Hazards model for counting processes could be used for these analyses. Time-dependent covariates that may be considered in secondary analyses of vasospastic attacks include: adherence to treatment; rewarming times and cooling times of the patient's hands when exposed to a cold box stress test; and psychological measurements (e.g. anxiety, depression, or physical well being) collected during follow-up. Changes in treatment effect over time can be taken into account by including treatment by time interaction terms in the model. The Cox model will also be used for adjusted analyses of other events, such as time to diagnosis of scleroderma.

3. Efforts will be made to classify vasospastic attacks according to severity (pain and action taken to treat an attack), using data recorded in the daily diaries, and to compare treatment groups with regard to the frequency of vasospastic attacks accompanied by different levels of pain among the treatment groups. These data may not be complete, so a categorization of intensity of pain would not be suitable for the primary outcome analyses.
4. Vasospastic attacks may tend to cluster together in a "waxing and waning" manner. The tendency of attacks to cluster and possible treatment effects on clustering can be analyzed by incorporating time since the most recent attack and its interaction with treatment as terms predicting risk of attacks in the Cox models for multiple events, as described above.

14.2.5.3 Analysis of Secondary Outcome Measures

Analyses will be undertaken of a variety of secondary outcomes related to the patient's well-being. These will include, but will not be limited to, the following analyses.

1. The occurrence of certain well-defined events, such as diagnosis of scleroderma.
2. The daily severity of vasospastic attacks and intensity of pain recorded in patient diaries and reflected in patient reports of consumption of analgesics.
3. Repeated psychological measurements collected on the Quality of Life Form (see Chapter 8, Quality of Life).

Comparisons of the frequency of occurrence of fixed events among treatment groups, such as diagnosis of scleroderma, will use standard methods of survival analysis such as the log-rank test or the Cox model (3) for adjusted analyses. The data recorded in diaries will be analyzed by comparing the average number of days during which patients recorded pain above a specified level among treatment groups. Reports for these analyses will take into account the number of days on which patients failed to record any assessment of pain (missing data). Differences among treatment groups in the means over time of the average reported consumption of analgesics per month will be analyzed.

Analyses to measure changes in a patient's quality of life such as the measures of physical well-being will be treated as continuous scales. Repeated measures analysis of variance will be used to compare treatment groups over time.

14.2.5.4 Analyses of Adherence to Treatment

The adherence to assigned medication will be assessed by tablet counts. The proportion of patients reaching a fixed level of adherence (e.g., consume $\geq$ 80% of assigned medication as determined by tablet count) will be presented according to the assigned treatment groups as a function of time since study entry.

After the initial set of ten biofeedback sessions, the patients will not be given additional biofeedback training. Thus, compliance analyses for patients assigned to treatment with biofeedback training will be based on the number of biofeedback sessions attended.

14.3 QUALITY ASSESSMENT PROCEDURES

14.3.1 Introduction

A primary concern for every study is to assure the quality of data being collected and analyzed. The validity of the reports and results produced and published by the study will depend upon the integrity of the data submitted by the Clinical Units and Core Laboratories and upon the appropriateness, thoroughness, and correctness of the data processing and data analysis procedures carried out by the RTS Coordinating Center staff. The first step in assuring quality data is to have the data collectors and observers properly trained and certified. This will be supplemented with various procedures to monitor the performance of these groups with respect to the quality of the study data they have reported. Proposed procedures for monitoring the performance of the Clinical Units, the Core Laboratory, and the RTS Coordinating Center are given in the following sections.

14.3.2 Quality Assessment of the Clinical Units

Performance of the Clinical Units with respect to patient recruitment will be assessed in weekly reports. These reports will include the number of patients randomized to date and the ratio of this number to the number of patients screened for eligibility. Performance in other areas will be assessed by consideration of the following at quarterly intervals.

1. Percentage of patients with missed visits and percentage of patients who are inactive, i.e., patients who are no longer willing or able to complete their regular examinations or visits.
2. Number of study forms which are past due at the RTS Coordinating Center, based on the dates of enrollment.

3. Measurements which are past due at the Core Laboratory.
4. Studies which are called for by the Protocol but were not performed.
5. Number of Protocol violations, such as enrollment of patients who did not meet all of the eligibility criteria or patients who did not provide informed consent.

The RTS Coordinating Center will compare the Clinical Units' performance and quality of submitted material for items such as forms past due, studies not performed, or blood and urine specimens of poor quality. The RTS Coordinating Center will also compare each Clinical Unit's quarterly performance to its past performance and to agreed upon study standards, in order to determine whether the Clinical Unit's performance is outside study standards or whether the Clinical Unit's level of performance has worsened significantly relative to its previous achievement. Study standards will be set by weighing how crucial an item is to the RTS Protocol and the levels of performance which past experience has shown to be attainable.

In addition to the above analyses, quarterly reports will include summary statistics for each Clinical Unit. Large changes in these statistics from quarter-to-quarter within a Clinical Unit may indicate changes in the way the data are being collected. Comparison of these statistics across Clinical Units may indicate that there are differences in how data are collected or differences in the patient population may warrant further investigation.

Performance of both the Clinical Units and the Core Laboratory will be monitored. If too many data are missing for one type of study, for example because the studies were not performed or because the studies were of inadequate technical quality, the analysis of outcomes based on that study may become difficult to interpret and may be biased.

In addition to preparing the Clinical Unit performance monitoring reports, the RTS Coordinating Center staff will help to insure data quality by conducting periodic site visits to the Clinical Units. The data on a patient's chart will be compared to listings of data residing on the main data base at the Clinical Coordinating Center as of the date of the data request. Using the data as of the date of the request should prevent any audit-prompted revisions of study forms. Site visit requests and plans for site visits will be provided to the Study Chairperson and NHLBI Project Office staff on a schedule

developed with the NHLBI Project Office staff. Recertification of Clinical Unit personnel responsible for key areas of data collection may also be necessary on site visits.

14.4 QUALITY ASSESSMENT OF CORE LABORATORY

14.4.1 Introduction

One Core Laboratory for central reading of blood and urine specimens as required by the Protocol is proposed for the RTS. Repeated measurements (totaling 1000 samples) of blood and urine tests may also be planned during follow-up. Execution of this protocol will require reproducible and timely analyses (especially for the antinuclear antibody (ANA) test) by the Core Laboratory. The RTS Coordinating Center will monitor the flow of data from the Core Laboratory and will execute a quality assessment program to insure the reproducibility of these data.

14.4.2 Monitoring the Flow of Data

Blood and urine specimens will be shipped directly to the Core Laboratory from the Clinical Units, with accompanying forms sent to the RTS Coordinating Center. The RTS Coordinating Center will use these records to produce a log of all material sent to the Core Laboratory; the log will be used to mark as delinquent any information not received from the Core Laboratory within two weeks from the date it was shipped to the Core Laboratory. Prompt review of baseline studies will be necessary so that results from the Core Laboratory can be used in establishing the eligibility of patients for the RTS. This is especially important for Core Laboratory ANA results since this test will be used to establish that a patient has primary Raynaud's phenomenon. Specimens submitted for eligibility assessment should be given the highest priority of all specimens received. For the follow-up studies, the Clinical Coordinating Center staff propose that study reports be recorded as delinquent if they are not received within two weeks. The Clinical Coordinating Center will prepare monthly reports on data from the Core Laboratory that are delinquent to indicate the proportion of delinquencies that exceed specified tolerance limits.

14.4.3 Monitoring Data Quality at the Core Laboratory

Two methods will be used to monitor the reliability of test results from the Core Laboratory: 1) examination of means or frequencies of key variables (e.g. results of ANA tests) over time; and 2) blinded resubmission of a sample of study materials. If large changes are noted in means or

frequencies of key variables, an investigation will be undertaken to determine whether the shift represents a change in reporting by the Core Laboratory or a change in the study population. Results of the blinded duplicate readings will be compared to the original readings to assess reliability using Kappa statistics for categorical data, Spearman's rank order correlation coefficient for ordinal data, and Spearman or Pearson correlation coefficients for continuous data.

14.5 QUALITY ASSESSMENT OF THE CLINICAL COORDINATING CENTER

There are certain activities RTS Coordinating Center staff will carry out to insure the quality of the data and analyses.

1. Persons (such as the Principal Investigator and Co-Principal Investigator) not involved in the preparation of the data editing programs will fill out a few study data forms, making deliberate errors. These forms will be keyed and processed through the data editing system to see if all of the errors are detected by the data management system.
2. A sample of original data forms will be compared against the data on the RTS Coordinating Center computer (as part of the site visit procedures described in Section 14.3.2). This procedure will be used not only to detect data entry errors, but also to detect problems with the editing software developed and implemented by the RTS Coordinating Center.
3. For each continuous variable on the data base, a point frequency distribution (i.e., a tabulation of the frequency of occurrence of every distinct value) will be obtained. This will help to identify many types of abnormalities in the continuous data such as: (a) digit preferences; (b) bimodality or other shapes of the distribution; and (c) outliers (i.e., extreme values distinctly separate from the rest of the distribution).

   Once an observation has been identified as a true outlier, the first step will be to go back to the original records and determine whether a recording or keying error was made. If such a value is verified as correct, the question of whether or not to include the value in the data analysis depends upon the nature of the analysis. There is no reason to exclude the value if the analysis is a count of the number of participants having a value exceeding a given cut-point. However, if means and standard deviations are being computed, or if

correlation or regression analyses are being carried out, alternative statistical methods (i.e. non-parametric statistics) will be used to analyze these data.

4. Analysis programs (including those that utilize standard statistical packages such as SAS) will be tested by running these programs on a small subfile of 10 or 20 participants and independently producing the tabulations and statistical calculations from the original data. These procedures help to assure that the correct variables have been selected from the data file, the variables and cut-points have been defined properly, and that transformations of the original variables on the analysis file have been formulated correctly.
5. Different tables which have been produced from a variety of analysis programs will be checked for the consistency of denominators.

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CHAPTER 15

CLOSE-OUT PROCEDURES

15.1 INTRODUCTION

This Chapter describes the procedures for completing data collection and transferring patient care for orderly completion of the Raynaud's Treatment Study (RTS). Procedures to be used by Clinical Unit staff for disposing of medical records and plans for long-term storage of study data are included in the Chapter.

The period during which follow-up of study patients will be concluded is referred to as the "close-out period." At least one Clinic Coordinator should be available in each Clinical Unit until the end of 1996 to respond to Coordinating Center queries and to assist the Coordinating Center staff in editing the data prior to closing the data files. These data files will be used for the data analyses for the reports on major study end points.

15.2 TRANSFER OF PATIENT CARE

One of the most important aspects of the close-out period of the RTS is to arrange for the continued medical care of each patient. The patient should be prepared for termination of the RTS in advance of the last Follow-up Visit. Clinical Center personnel should anticipate whether it will be appropriate and feasible for an individual patient to be followed by Clinical Unit staff or whether this responsibility should be transferred to another physician and/or another clinic.

A personal letter to all referring physicians thanking them for their support of the RTS is highly recommended, whether or not the patient will return to the referring physician for subsequent care. The Coordinating Center staff will supply for each patient a listing of pertinent data collected during the course of the RTS. These listings may be used to assist the Clinical Unit physician in preparing a summary of each patient's history to be provided to the referring physician.

15.3 CLOSE-OUT VISIT

The Close-out Visit procedures should be completed at Follow-up Visit 4 (FV04), scheduled for 69 weeks after enrollment (see Chapter 10, Patient Visits). Patients should discontinue use of the study medication at the Close-out Visit. All unused study medication should be collected at FV04;

all returned bottles of study medication should be destroyed according to Clinical Unit procedures (see Chapter 5, Administration of Study Medications).

15.3.1 Distribution of Close-Out Information to Patients

A letter notifying the patient of the completion of his/her participation in the RTS and offering assistance in arranging for continuing care should be given or sent to each patient. This letter should not be regarded as a substitute for a discussion between the patient and the Clinical Unit physician at the Close-out Visit.

Patients will be invited to return to the Clinical Units in groups in the autumn of 1996 to be informed of their treatment group assignment and to review the available study results. Patients should be apprised of these procedures at the Close-out Visit.

A patient-oriented written description of the RTS findings will be available for distribution at the group sessions in the autumn of 1996 to supplement the information given at these group sessions by the RTS Clinical Unit Principal Investigators. This will be a narrative summary of RTS findings for lay persons and will be available to Clinical Units for distribution. This summary will be prepared by the Operations Committee, with the assistance of Project Office staff.

15.3.2 Inactive Patients

Every effort should be made to contact and examine all inactive patients and, if possible, a Close-out Visit should be performed. If the patient is unable to return to the Clinical Unit for the Close-out Visit, the Clinic Coordinator should arrange for a home visit or examination by the patient's physician. If the patient refuses to be seen by the Clinical Unit personnel, Coordinating Center staff should be notified and provided with a written description of the circumstances. If the patient cannot be located, Coordinating Center staff should be contacted so that efforts may be made to locate the patient through an investigative agency. If the agency is able to locate the patient, information concerning the patient's whereabouts will be forwarded to the Clinical Unit and the Clinical Unit personnel should proceed to attempt to schedule and perform a Close-out Visit for the patient.

15.4 DISPOSAL OF STUDY MEDICATIONS

At the Close-out Visit, any study medications returned by the patients should be destroyed according to Clinical Unit pharmacy procedures. All supplies of study medication in the Clinical Unit

at the end of the close-out period should also be destroyed (see Chapter 5, Administration of Study Medications).

15.5 DISPOSAL OF RECORDS BY INDIVIDUAL CLINICAL UNITS

Clinical Units will maintain patient records that accumulate during the conduct of the RTS. In order to respond to edit messages from the Coordinating Center, study records and patient charts will need to be readily available through December 31, 1996. Information on requirements concerning long-term storage of study records will be distributed at a later date.

15.6 PLANS FOR TOTAL DATA STORAGE

All RTS data will be retained at the Coordinating Center until the period of data analysis has been completed as required by the Food and Drug Administration (FDA).

Recognizing that the observations in the RTS will be collected with great effort and expense, a conscientious effort will be made to summarize and publish the study results. The RTS investigators also believe that the observations should be made available to the general public for reanalysis. The NHLBI Project Officer and the Coordinating Center staff will determine what RTS data should be made available to the general public. The Coordinating Center staff will deliver computer tapes and documentation of these RTS data before funding for the Coordinating Center terminates and in accordance with general NIH guidelines. Any plan for releasing RTS data will maintain patient confidentiality; accordingly, no information which identifies individual patients will be released.