TRIAL OF PULSE STEROID THERAPY IN KAWASAKI DISEASE

STUDY PROTOCOL

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Sponsored by the National Heart, Lung, and Blood Institute

Pediatric Heart Network

Trial of Pulse Steroid Therapy in Kawasaki Disease

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TRIAL OF PULSE STEROID THERAPY IN KAWASAKI DISEASE

OVERVIEW (ABSTRACT)

Treatment with high-dose intravenous gamma globulin (IVIG) and aspirin comprise the standard of care for children with acute Kawasaki disease. This multi-center, randomized, double-blind, placebo-controlled trial evaluates the efficacy and safety of pulse steroid therapy, when added to conventional treatment with IVIG plus aspirin, in treatment of children with acute Kawasaki disease.

Subjects must be within 10 days of the onset of disease. After stratification by gender and age (<1 vs. ≥1 years old), patients will be randomly assigned to receive pulse intravenous methylprednisolone (IVMP, 30 mg/kg) plus conventional therapy or placebo infusion plus conventional therapy. IVIG will be given initially at a dose of 2 g/kg over 12 hours and aspirin initially at 80 to 100 mg/kg/day until afebrile for 48 hours, then at an anti-platelet dose of 3 to 5 mg/kg once daily. The protocol includes guidelines for retreatment with IVIG in patients with persistent or recrudescent fever. Study visits will occur at baseline and at one and five weeks after randomization and will include demographics, medical history, laboratory values (CBC, ESR, immunoglobulins, C-reactive protein [CRP], albumin) and echocardiograms. Echocardiograms will be obtained and read according to a predetermined protocol and will also be interpreted at a core reading facility. An ultrasensitive CRP assay will be performed at a core laboratory in addition to a local CRP assay.

The primary aim is to compare the effect of IVMP plus IVIG to IVIG alone on coronary artery outcomes. The primary outcome is the larger of the body surface area (BSA)-adjusted dimensions (z-scores) of the proximal right coronary artery (RCA) or proximal left anterior descending (LAD) artery, measured five weeks after randomization. Secondary aims include comparison of the treatments with respect to systemic inflammation (primary outcomes: duration of fever after completion of IVIG, CRP one week after randomization) and adverse events (primary outcome: incidence of one or more adverse side effects). The total sample size goal is 194 patients, to be recruited over 18 months.

A. SPECIFIC AIMS AND HYPOTHESES

Treatment with high-dose intravenous gamma globulin (IVIG) and aspirin comprise the standard of care for children with acute Kawasaki disease.[1] Even when treated with high-dose IVIG regimens within the first 10 days of illness, approximately five percent of children with Kawasaki disease develop coronary aneurysms and one percent develop giant aneurysms. Indeed, recent analyses adjusting coronary dimension for body surface area (BSA) suggest that a far greater proportion of children with Kawasaki disease have coronary artery dilation in the acute, convalescent, and late phases than would be detected using the Japanese Ministry of Health Criteria.[2] Although one early study showed a detrimental effect of steroid use in Kawasaki disease,[3] others have suggested that steroids may be beneficial in the prevention of coronary artery aneurysms.[4-8] Further studies are needed to assess the risks and benefits of steroid administration to patients with Kawasaki disease.

This multi-center, randomized, double-blind, placebo-controlled trial evaluates the efficacy and safety of pulse steroid therapy, when added to conventional treatment with IVIG plus aspirin, in treatment of patients with acute Kawasaki disease. Subjects will be randomly assigned to receive pulse intravenous methylprednisolone (IVMP) plus conventional therapy or conventional therapy alone.

A.1 Primary Aim: To compare the effect of IVMP plus IVIG to IVIG alone on coronary artery outcomes.

Hypothesis: The addition of IVMP will result in less dilation of coronary arteries and fewer aneurysms.

Primary outcome:

- the larger of the body surface area (BSA)-adjusted dimensions (z-scores) of the proximal right coronary artery (RCA) or proximal left anterior descending (LAD) artery, measured five weeks after randomization.

Secondary outcomes:

- occurrence of coronary artery aneurysms by Japanese Ministry of Health criteria;[9]
- individual z-scores of the left main coronary artery (LMCA), proximal RCA, and proximal LAD coronary artery at one and five weeks;

- changes in absolute coronary dimensions for all coronary artery segments (LMCA, proximal and distal LAD, proximal and distal RCA, posterior descending coronary artery, circumflex artery) from baseline to one and five weeks after randomization

A.2 **Aim**: To compare the effect of IVMP plus IVIG to IVIG alone on severity and duration of systemic inflammation.

Hypothesis: The addition of IVMP will result in lower severity and shorter duration of systemic inflammation.

Primary outcomes:

- total number of days of fever after completion of the initial IVIG infusion;
- C-reactive protein measured one week after randomization.

Secondary outcomes:

- total days of hospitalization;
- requirement for IVIG retreatment as indicated by persistent or recrudescent fever of at least 38.3°C more than 36 hours after completion of the first IVIG treatment;
- laboratory markers of inflammation including C-reactive protein five weeks after randomization and white blood cell count, hemoglobin, and albumin levels measured one and five weeks after randomization.

A.3 **Aim**: To compare adverse reactions occurring with IVMP plus IVIG to those occurring with IVIG alone.

Hypothesis: The addition of IVMP will be associated with few adverse side effects and will reduce the frequency of adverse reactions to the subsequent infusion of IVIG.

Primary outcomes:

- incidence of one or more adverse side effects;

Secondary outcomes:

- incidence of individual adverse reactions believed to be possibly or probably attributable to IVMP and to IVIG.

B. BACKGROUND

B.1 Prior Literature/Studies

B.1.1 Background

Kawasaki disease is an acute illness of childhood characterized by fever, rash, injection of the conjunctivae, inflammation of the mucous membranes, swollen, erythematous hands and feet, and cervical adenopathy.[1,10] Histopathologic features of vasculitis involving arterioles, capillaries, and venules occur in the earliest phase of the disease.[11] Subsequently, the walls of the coronary arteries and other medium-sized muscular arteries may show focal segmental destruction, with coronary artery aneurysms or ectasia developing in approximately 15-25% of affected children.[12-14] More than 30 years after the initial description of Kawasaki disease, its etiology remains elusive despite intense investigation of various candidate agents. Fortunately, better outcomes have been achieved using therapies aimed at reducing inflammation in the coronary artery wall and preventing coronary thrombosis.

In 1984, Furusho *et al.*[15] reported the beneficial effects of IVIG, a finding subsequently confirmed by others.[16,17] Current therapeutic regimens for Kawasaki disease include IVIG and aspirin in various dose regimens and combinations. Recent meta-analyses [17,18] on the efficacy of aspirin and immunoglobulin treatment in preventing coronary artery aneurysms provided some guidance in choice of an optimal therapeutic regimen.

Aspirin was the first medication to be used for treatment of Kawasaki disease, because of its anti-inflammatory and anti-thrombotic effects. Both high-dose (80 - 100 mg/kg/day) and lower-dose regimens have been used in conjunction with IVIG in the acute phase of the illness. In their meta-analysis, Durongpisitkul *et al.*[17] found that high-dose and lower-dose aspirin regimens were associated with a similar incidence of coronary artery abnormalities at 30 and 60 days after disease onset. The meta-analysis of Terai and colleagues[18] similarly reported absence of an effect of aspirin dose on the coronary lesions. Indeed, no prospective study has shown that aspirin decreases the prevalence of coronary artery abnormalities.

In contrast, IVIG administered in the acute phase of Kawasaki disease has well-established efficacy to reduce the prevalence of coronary artery abnormalities.[1] Durongpisitkul's meta-analysis demonstrated that high-dose IVIG (>1 g/kg) was more effective than lower-dose regimens. Furthermore, treatment with a single high dose of IVIG was associated with a lower incidence of coronary abnormalities than administration of multiple doses, as reflected in the prevalence of coronary disease one month after disease onset.

Compared to multiple-dose regimens of approximately equivalent total dose, single-dose regimens deliver a larger total dose of gamma globulin earlier in the course of the disease and result in higher peak serum IgG levels. It is unknown whether the higher peak level or its earlier attainment contributes more to the superior efficacy of the single high-dose regimen. Previous work has shown that the peak adjusted serum IgG level is lower among patients who subsequently develop coronary artery abnormalities and is inversely related to both fever duration and laboratory indices of acute inflammation.[16] This apparent dose-response effect of IVIG forms the theoretical basis for IVIG retreatment of patients who have persistent or recrudescent fever after initial IVIG therapy. In a report of the U.S./Canadian Kawasaki Disease Study Group, approximately 8% of Kawasaki disease patients received at least one additional infusion of IVIG.[19]

Even when high-dose IVIG is administered within the first 10 days of illness, approximately five percent of children with Kawasaki disease develop at least transient coronary artery dilation by Japanese Ministry of Health criteria, and one percent develop giant aneurysms.[1] Recent data have suggested that corticosteroids could have a role in the therapeutic armamentarium for this mysterious illness.[4]

Although corticosteroids are the treatment of choice in other forms of vasculitis, their use has been limited in children with Kawasaki disease. Corticosteroids were used to treat Kawasaki disease long before the first report of IVIG efficacy by Furusho et al. in 1984.[15] Reluctance to employ corticosteroid regimens in acute Kawasaki disease derived from an early study of Kato et al. [3] that demonstrated an extraordinarily high incidence of coronary artery aneurysms (11 of 17 patients) in a group of patients who received oral prednisolone at a dose of 2-3 mg/kg/day for at least 2 weeks, followed by 1.5 mg/kg/day for an additional 2 weeks. In the same study, however, a smaller group of seven patients received prednisolone plus aspirin, and none

developed aneurysms. Nonetheless, based upon this early report, many physicians were hesitant to administer corticosteroids to children with Kawasaki disease. The few subsequent studies on corticosteroids showed either no ill effects or possible benefit. In a randomized trial in 100 children treated with intravenous prednisolone (followed by an oral taper) versus low-dose IVIG (300mg/kg/day for 3 consecutive days), Nonaka and colleagues[20] reported shorter fever duration in the steroid group, but no significant difference in the prevalence of coronary aneurysms. Other studies have suggested that both oral[21] and intravenous[5] steroids may have a beneficial effect on coronary outcome. A case series[6] described four children with Kawasaki disease with recrudescent or persistent fever despite IVIG treatments in whom administration of high-dose intravenous methylprednisolone (30 mg/kg) produced improvement in symptoms; no patients had significant progression of coronary artery abnormalities or adverse effects. A case series by Wallace et al. similarly suggested potential benefits of steroids.[8]

Shinohara et al.[7] reviewed the experience of nearly 300 patients with acute Kawasaki disease treated before the 10th day of illness who presented between 1982 and 1998, and who had coronary artery dimensions under 4mm. Medications were administered in various combinations during routine care, without a prospective protocol. Using regression techniques, the authors found that treatment with prednisolone was associated with a significantly shorter duration of fever after institution of treatment, as well as with a lower prevalence of coronary artery aneurysms. No adverse reactions were recorded for any therapy. This study should be interpreted in light of important limitations. The structure of the study, a retrospective case series, unavoidably introduces the potential for confounding and bias. Furthermore, the dose of IVIG administered to patients in this series was often low and always given over five days, rather than as the single infusion of 2 g/kg recommended by the American Academy of Pediatrics.

Hashino et al.[22] compared the efficacy and safety of additional IVIG therapy with pulse steroid therapy in patients with IVIG-resistant Kawasaki disease. Two hundred and sixty-two consecutive patients had been treated with a single dose of IVIG (2 g/kg) and aspirin (30 mg/kg per day). Thirty-five patients (13.4%) did not respond to the initial IVIG treatment. They received an additional IVIG treatment (1 g/kg) within 36 hours after the initial treatment. Seventeen patients (6.5%) did not respond to the additional IVIG treatment. The investigators randomly divided these patients into two groups: Group 1 consisted of eight patients who were

treated with a single additional dose of IVIG (1 g/kg), and Group 2 consisted of nine patients who were treated with pulse steroid therapy. The IVIG-resistant patients had a high incidence of coronary artery lesions (48.6%). Five patients (62.5%) in Group 1 had coronary abnormalities, including two patients who each had a giant aneurysm and three patients who each had a small aneurysm. Seven patients (77.8%) in Group 2 had coronary abnormalities, including two patients who each had a giant aneurysm, two patients who each had a small coronary aneurysm and three patients who each showed transient dilatation during pulse steroid therapy. There was no significant difference in the incidence of coronary artery abnormalities between the two groups. The duration of high fever in Group 2 (1.4±0.7 days) was significantly shorter than in Group 1(4.8±3.4 days; $P<0.05$). The medical costs for the treatment of patients in Group 2 were significantly lower than those for Group 1 ($P<0.05$). The authors concluded that pulse steroid therapy might be useful in the treatment of patients with IVIG-resistant Kawasaki disease who experience prolonged fever. However, the power of this study was insufficient to determine the influence of steroids on the ultimate fate of the coronary arteries.

B.1.2 Visualization of coronary arteries

In an earlier multi-center, randomized trial,[23] among the total of 1043 follow-up echocardiograms (i.e., studies at two weeks plus those at seven weeks), the proximal right coronary artery was visualized in 99.3% and the distal right coronary artery in 90.0%; the left main coronary artery in 99.6%; the proximal and distal left anterior descending artery in 98.1% and 76.9%, respectively; the circumflex artery in 80.6%, and the posterior descending coronary artery in 79.4%.

B.1.3 Coronary artery z-scores in normal subjects

The use of coronary artery z scores provides a practical method for comparison of treatment strategies in patients with Kawasaki disease. To assess the optimal power transformation of BSA by which to standardize coronary artery dimension, we performed regression analyses predicting the size of the left main, left anterior descending, and right coronary arteries from the untransformed values of body surface area (i.e., $BSA^{1.0}$), the square root of body surface area, and other power transformations between 0.5 and 1. The fits of the models were compared by means of residual plots, coefficients of determination (R^2), and standard errors of regression. Differences were not statistically significant, and the plots appeared virtually identical. Because no model was significantly better than any of the others over the range of BSA in a normal

control group, we standardized coronary artery size to untransformed BSA. The resulting regression models for standardization of coronary artery dimensions with respect to BSA-specific mean dimensions derived from the normal subjects were reported by de Zorzi et al.[2] The z-score for an artery internal lumen diameter measured in millimeters, say X, in a patient with BSA measured in $(meters)^2$ is z=[X-mean]/SD, where the mean and standard deviation (SD) are as shown in Table 1:

Table 1.
Predicted mean and standard deviation of coronary artery dimension in normal subjects

Artery	Mean	SD
Left main coronary artery	1.688+(0.995*BSA)	0.420
Left anterior descending	1.186+(0.820*BSA)	0.356
Right coronary artery	1.503+(0.499*BSA)	0.398

B.1.4 Use of coronary artery z-scores in patients with Kawasaki disease

In 1984, the Japanese Ministry of Health established criteria for coronary artery abnormality in Kawasaki disease.[9] These criteria, applicable to either angiographic or echocardiographic measurement, classify coronary arteries as abnormal if 1) the internal lumen diameter is greater than 3 mm in children younger than age five years or greater than 4 mm in children at least age five years; 2) if the internal diameter of a segment measures at least 1.5 times that of an adjacent segment; or 3) if the coronary artery lumen is clearly irregular. These are the only published criteria that specifically define coronary artery abnormalities in Kawasaki disease, so they have been used internationally to classify coronary artery segments. Indeed, current statistics on the prevalence of coronary artery dilation secondary to Kawasaki disease are based upon these criteria. Although the Japanese Ministry of Health criteria are not strictly based on the body size of the individual patient, coronary artery dimensions in normal children have been shown to increase linearly with indices of body size such as BSA or body length (see Table 1).[24] To determine whether coronary artery dimensions in patients with Kawasaki disease whose vessels are classified as "normal" by Japanese Ministry of Health criteria have a distribution similar to expected population norms when adjusting for body surface area, 125 patients were studied during 4 intervals from onset of illness: (1) 10 days or less, (2) 2 weeks (11 to 21 days), (3) 6 weeks (22 days to 3 months), and (4) 1 year (4 months to 1.5 years).[2]

Using two-dimensional echocardiography, the internal lumen diameter of the left main, proximal left anterior descending, and proximal right coronary arteries were measured. Mean BSA-adjusted dimensions of the proximal left anterior descending and right coronary arteries were significantly larger ($P < .01$) in patients with Kawasaki disease than those in normal subjects in all periods, except for a marginal difference at 6 weeks for the proximal right coronary artery ($P = .02$). For the left main coronary artery, this difference achieved statistical significance in the period of 10 days or less ($p = .002$), with a trend at 2 weeks ($P = .02$), and six weeks ($p = .09$). Among patients classified as having normal coronary arteries on all echocardiograms by the Japanese Ministry of Health criteria, 27% had at least one BSA-adjusted coronary artery dimension more than 2 standard deviations above the expected mean. Coronary artery dilation in Kawasaki disease is thus more prevalent than previously reported, highlighting the need for systematic long-term surveillance of this population.

B.1.5 Intra-observer and inter-observer variability in coronary artery measurements

Intra-observer and inter-observer variability have been assessed in 15 patients by having two ultrasonographers perform repeat measurements at the beginning and end of the exam on each of the three vessels. Intra-observer variability was 0.015±0.17 mm (0.6±6.1%) for the left coronary artery, 0.026±0.13 mm (1.3±5.9%) for the left anterior descending, and 0.053±0.13 mm (2.0±5.9%) for the right coronary artery. The inter-observer variability was 0.061±0.22 mm (2.5±7.7%) for the left coronary artery, 0.031±0.26 mm (0.35±9.9%) for the left anterior descending, and 0.038±0.10 mm (1.8±5.0%) for the right coronary artery.

B.1.6 A pilot randomized trial of pulse IVMP plus high-dose IVIG vs. high-dose IVIG alone

We conducted a prospective randomized trial to determine whether addition of corticosteroids to IVIG might improve outcomes in Kawasaki disease. Subjects were randomized to receive intravenous immune globulin (IVIG), 2 gm/kg over 10 hours, with or without pulsed dose intravenous methylprednisolone (IVMP), 30 mg/kg (maximum 1.5 gm) over 3 hrs. All patients received aspirin, 20 to 25 mg/kg every six hours until afebrile for 48 hours, then 3-5 mg/kg/day. Eighteen subjects received IVMP plus IVIG, and 21 received IVIG alone. Groups were similar in baseline demographic, laboratory data, and coronary artery measurements.

Patients in the IVMP plus IVIG group, compared to those in the IVIG alone group, had shorter mean duration of fever > 38.3º C after initiation of IVIG therapy (1.0 ±1.3 days vs. 2.4 ± 1.9 days, mean ± SD, P = .009); shorter hospital stays (1.9 ± 0.7 days vs. 3.3 ± 2.1 days, P = 0.010), and at six weeks, lower ESR (11.1± 5.7 vs. 19.4 ± 12.4, P= 0.027) and lower median CRP (0.03 vs. 0.08, P = 0.011, Wilcoxon). No significant differences between treatment groups were noted in coronary dimensions at two or six weeks, but statistical power was limited. IVMP was well tolerated; one child developed transient hypertension that did not require treatment. Overall, fewer patients treated with IVMP plus IVIG had adverse events during their hospitalization than did patients treated with IVIG alone.

In summary, treatment of acute KD with IVMP plus IVIG, compared to IVIG alone, resulted in faster resolution of fever, more rapid improvement in markers of inflammation, and shorter length of hospitalization. Adverse effects were infrequent. This study did not have sufficient statistical power to detect the influence of steroid therapy on coronary outcomes.

Data from this pilot study were used in calculation of sample size and power for the current protocol. A full manuscript draft is provided in APPENDIX A.

B.2 Rationale for this trial

A theoretical argument can be made in favor of steroid administration to patients with Kawasaki disease, because coronary artery aneurysms are produced by immune-mediated injury to the arterial wall. In other immune-mediated vasculitides, such as periarteritis nodosa, steroid therapy is effective anti-inflammatory therapy. Indeed, the mechanism of action of IVIG in reducing the prevalence of coronary artery dilation in Kawasaki disease may involve, in part, a generalized anti-inflammatory effect, with reduction of cytokine-induced endothelial activation.[25] The adverse effects of corticosteroids would be minimized by a brief course of therapy.

In view of intriguing initial data suggesting that steroid therapy may be beneficial and that its adverse effects with short-term use are low, we propose a multi-center, randomized, double-blind, placebo-controlled trial to ascertain whether the addition of high-dose IVMP to IVIG further improves outcomes. Because high-dose IVIG has been proven to reduce the likelihood of coronary disease and comprises “standard of care,” this treatment cannot be withheld from any

patient. If effective, the addition of pulse steroids to conventional IVIG therapy could further decrease the likelihood of coronary artery dilation, as well as reduce patient morbidity and hospital stay. Regardless of outcome, the results of such a trial would be important, because administration of pulse steroid therapy to Kawasaki disease patients is becoming common in the United States.

C. STUDY DESIGN AND METHODS

C.1 Overview

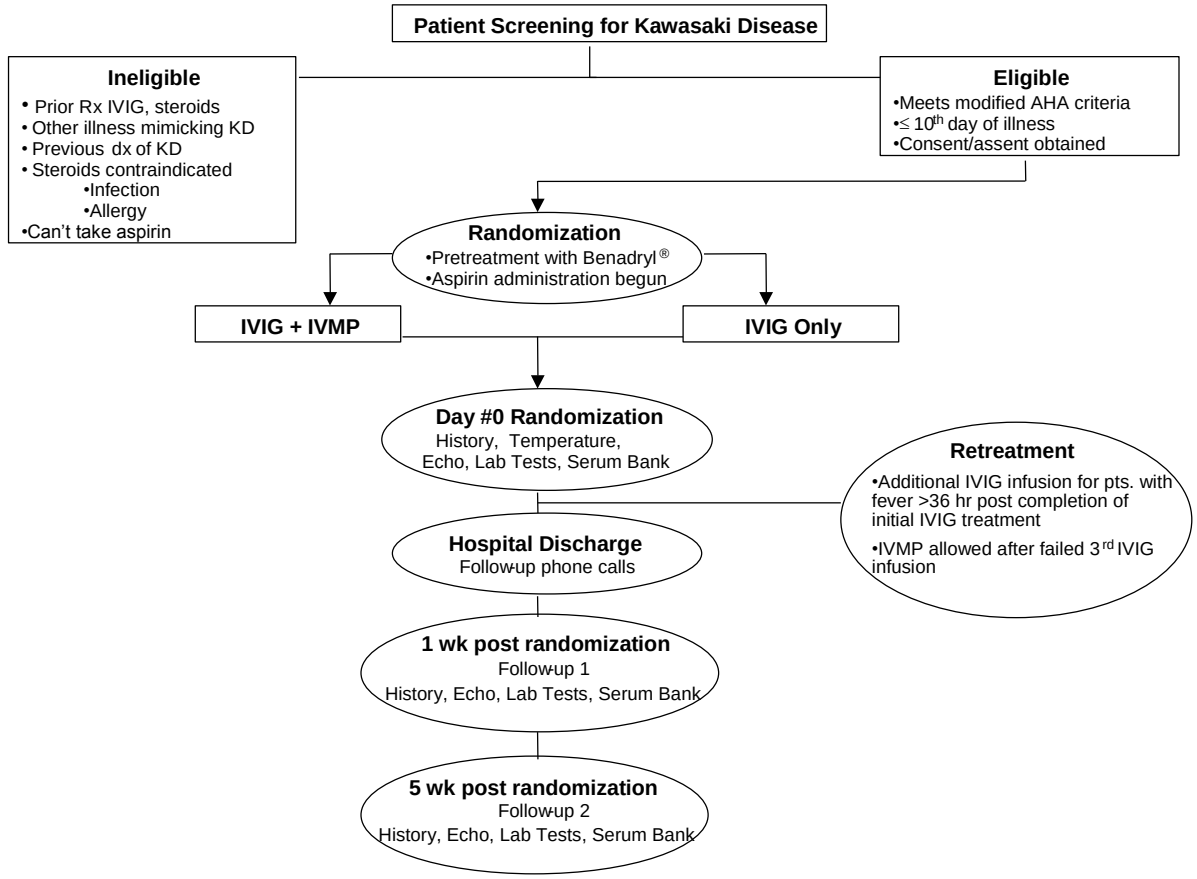
Treatment with high-dose intravenous gamma globulin (IVIG) and aspirin comprise the standard of care for children with acute Kawasaki disease. This multi-center, randomized, double-blind, placebo-controlled trial evaluates the efficacy and safety of pulse steroid therapy, when added to conventional treatment with IVIG plus aspirin, in treatment of children with acute Kawasaki disease.

Subjects must be within 10 days of the onset of disease. After stratification by gender and age (<1 vs. ≥ 1 years old), patients will be randomly assigned to receive pulse intravenous methylprednisolone (IVMP, 30 mg/kg) plus conventional therapy or placebo infusion plus conventional therapy. IVIG will be given initially at a dose of 2 g/kg over 12 hours and aspirin initially at 80 to 100 mg/kg/day until afebrile for 48 hours, then at an anti-platelet dose of 3 to 5 mg/kg once daily. The protocol includes guidelines for retreatment with IVIG in patients with persistent or recrudescent fever. Study visits will occur at baseline and at one and five weeks after randomization and will include demographics, medical history, laboratory values (CBC, ESR, immunoglobulins, C-reactive protein [CRP], albumin) and echocardiograms. Echocardiograms will be obtained and read according to a predetermined protocol and will also be interpreted at a core reading facility. An ultrasensitive CRP assay will be performed at a core laboratory in addition to a local CRP assay. Figure 1 displays patient flow and key measurements for this trial.

The primary aim is to compare the effect of IVMP plus IVIG to IVIG alone on coronary artery outcomes. The primary outcome is the larger of the body surface area (BSA)-adjusted dimensions (z-scores) of the proximal right coronary artery (RCA) or proximal left anterior

descending (LAD) artery, measured five weeks after randomization. Secondary aims include comparison of the treatments with respect to systematic inflammation (primary outcomes: duration of fever after completion of IVIG, CRP one week after randomization) and adverse events (primary outcome: incidence of one or more adverse side effects). The total sample size goal is 194 patients, to be recruited over 18 months.

Figure 1. Kawasaki Disease Trial Protocol



C.2 Participants

C.2.1 Inclusion Criteria

To be eligible for this trial the patient must meet all inclusion criteria including:

Meets any of the following sets of criteria for Kawasaki disease, extrapolated from the American Heart Association guidelines:[1]

- Fever persisting at least 4 days and the presence of at least 4 of the following 5 principal features:
    1. Changes in extremities: Acute changes include erythema and edema of hands and feet; Convalescent changes include membranous desquamation of fingertips
    2. Polymorphous exanthema
    3. Bilateral, painless bulbar conjunctival injection without exudates
    4. Changes in lips and oral cavity: Erythema and cracking of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosae
    5. Cervical lymphadenopathy (≥1.5 cm in diameter), usually unilateral;

OR

- Patients with at least four days of fever and coronary artery disease, defined as either:
    1. Having a z-score in either the proximal right coronary artery or the proximal left anterior descending coronary artery of > 2.5 detected by 2-dimensional echocardiography, as well as:
        - For patients under six months of age, at least two principal criteria
        - For patients at least six months of age, at least three principal criteria.
    2. Meeting Japanese Ministry of Health criteria for coronary aneurysm defined as an internal lumen diameter of >3 mm in children less than 5 years of age or >4 mm in children 5 years of age and older, in either the proximal right coronary artery or the proximal left anterior descending coronary artery and at least one principal criterion.

AND

Enrollment within ten days of the onset of illness, with Day 1 defined as the first day of fever

AND

Informed consent of parents and assent of children who are older than age 7 years and capable of understanding or according to institutional guidelines.

C.2.2 Exclusion Criteria

To be eligible for the trial, a patient must meet none of the following criteria:

1. Treatment with gamma globulin during the current illness prior to potential enrollment.

2. Treatment with steroids, other than inhaled forms, in the two weeks prior to potential enrollment.

3. Has another disease known to mimic Kawasaki disease, such as diseases caused by g*roup A streptococcus* or *staph. aureus*.[1]

4. Previous diagnosis of Kawasaki disease

5. Suspected infection that would contraindicate steroid use, such as *Herpes*

6. Known hypersensitivity to IVMP or one of its components

7. Other contraindications to steroid therapy

8. Unable to take aspirin.

C.2.3 Number of Patients Available for Study

Each Pediatric Heart Network investigator estimated the number of new Kawasaki disease patients at their center per year. The projected total is 265. We project that >50% would be eligible and would provide informed consent. With a target sample size of 194 (see Section 7.1.a), accrual is expected to be complete within 18 months.

C.2.4 Recruitment Protocol

The Principal Investigator at each clinical center, his or her designate, and the nurse-coordinator will have responsibility for case-finding. Study centers will design a system by which Kawasaki disease patients are identified at the earliest possible moment, such as through a Kawasaki disease team that is paged by house staff in the Emergency Department or in-patient wards who are evaluating patients who may have Kawasaki disease. A study investigator or the nurse-coordinator will request informed consent from the parents or legal guardian of all patients who meet study criteria. Data (demographic, eligibility criteria, and informed consent status) will be recorded on a screening form for all patients with Kawasaki disease evaluated at the participating center, regardless of their inclusion in the study, for development of descriptive statistics and definition of the study population.

C.2.5 Human Subjects Considerations

The characteristics of the patient sample and sources of research material are specified in Sections C.2.1-C.2.4. Consent will be obtained from parents at the time of diagnosis of Kawasaki disease, before treatment with IVIG. Consent will be sought by site study investigators, study nurse coordinators, or assigned designates and documented by the parent's witnessed signature of an informed consent document. Assent will be sought from children who are older than age 7 years and capable of understanding or according to institutional guidelines. A sample consent/assent form is included in APPENDIX B.

Measurements made in this study, most of which are obtained routinely during the patient's hospitalization or subsequent clinic visits, will be recorded on study forms.

C.2.5.a Potential Risks

The possible risks or discomforts of the study to the subjects are minimal and include the following:

1. Treatment with pulse IVMP may rarely cause high blood pressure and decreased heart rate. Other adverse effects of steroid use, such as peptic ulcers, mood changes, or hyperglycemia are exceedingly uncommon after a single pulse. During infusion of pulse IVMP, the frequency of vital sign monitoring will be per institutional policy at each Network center.
2. The administration of study drug (pulse IVMP or placebo) will take place in the two hours before IVIG administration. Because of the lag time from ordering IVIG until its preparation, the administration of the study drug is not expected to cause a delay in administration of IVIG.
3. To minimize discomfort, every effort will be made to obtain the blood samples needed for all research laboratory tests with venipunctures that would routinely be performed for the care of the patient. The amount of extra blood drawn in any venipuncture for laboratory tests that pertain only to this study will not exceed 5 mL. The total quantity of extra blood drawn over the 6 weeks of subject participation in the study will be less than 15 mL.
4. The length of the subject's hospital stay will not be affected by any tests involved in this study.

5. All testing that is not part of routine care will be performed free-of-charge.
6. Each patient will be assigned a study identification (I.D.) number so that study information will be confidential. The link between patient name and I.D. number will be stored only at the site where the patient received his/her clinical care.
7. Investigators from the clinical center will have access to the medical record for the acute Kawasaki Disease hospital stay and up to 2 years following enrollment to review the results of follow-up echocardiograms and other relevant studies.
8. Serum will be stored in a central location according to study number and may be used in the future for research questions. No individual results of this testing will be given to families. Of course, DNA testing cannot be performed on serum.

C.2.5.b Potential Benefits

The possible benefits of participation in the proposed study to the subject are as follows:

1. The parents, pediatrician, and primary cardiologist of study participants will receive extensive information about Kawasaki disease and the child's cardiac status.
2. For children randomized to the IVMP treatment arm, potential benefits could be reduction in coronary artery dilation and in adverse reactions to IVIG, as well as shortened fever course and reduced systemic inflammation.

C.2.5.c Risk/Benefit Ratio

The risk/benefit ratio of the study is favorable. Although the individual subject may not directly benefit from study participation, this study should add to general knowledge about the usefulness of pulse steroid therapy in treatment of acute Kawasaki disease. If pulse steroids are found to diminish the prevalence of coronary dilation, its use may benefit children with this relatively common and serious disorder in the future.

If parents decline to participate, their child's medical care will not be adversely affected in any way. If they agree to participate, they are free to withdraw their child from the study at any time.

Patients and their families will be reimbursed for costs associated with participating in the protocol that would not have occurred as part of routine clinical care (e.g., if the patient and family return to the study center for follow-up that otherwise would have been obtained closer to their home). Any compensation above and beyond that will be at the discretion of the individual participating sites and their IRB's; such compensation should be given directly to the child and represent a token of appreciation only.

Patients will be enrolled without regard to gender, race, or ethnicity.

C.3 Trial Enrollment

C.3.1 Stratification

The study design will be a randomized, double-blind, placebo-controlled trial. Both age less than one year and male gender are associated with higher risk of aneurysm formation. Therefore, we will randomize participating patients to treatment groups using randomly permuted blocks within strata according to age (< 1 year vs. ≥ 1 year) and gender. Dynamic balancing by center will be used to ensure that treatment arm totals are balanced within each center.

C.3.2 Blinding

All personnel at each Study Center, other than the research pharmacist, will be blinded to the patient's treatment assignment. Depending upon the policies and procedures at the individual clinical centers, treatment assignment will be obtained via telephone call to the randomization computer at the Data Coordinating Center either by an investigator (or by his/her delegate) or by the responsible pharmacist. A numeric treatment assignment code will be given, rather than the actual treatment assignment. The pharmacist will decipher the code with respect to whether the patient is assigned to the pulse steroid or placebo group. With this procedure, the randomization telephone call can be made by study staff who are to remain blinded to treatment assignment.

C.3.3 Randomization Procedure

Patients will be assigned in a 1:1 ratio to the IVMP plus IVIG or IVIG alone treatment groups. All eligibility criteria must be confirmed, and informed consent obtained before randomization.

Randomization will be accomplished via a telephone call to the randomization computer at the Data Coordinating Center (available 24 hours a day, 7 days a week). There will be a backup sealed envelope system in the event that technical problems prevent telephone randomization. After supplying stratification information (see Section C.3.1) and verifying key eligibility criteria, the randomization computer will return a numeric code that the pharmacist will decipher into treatment group assignment (see Section C.3.2).

Investigators at each institution, together with the research pharmacist where possible, must maintain a log containing the patient's study I.D. and name, date of enrollment, date of treatment, randomization assignment code, and lot number and brand of IVIG received.

C.4 Treatment

C.4.1 Study Drug

C.4.1.a Methylprednisolone

1) Administration: Based upon the patient's body weight, the pharmacist will determine the appropriate dose of IVMP (30 mg/kg, to a maximum dose of 1.0 gm) to be administered over 2 to 3 hours. IVMP will be given in a concentration of 62.5 mg/cc.
2) Indications for withdrawal: Hypertension, bradycardia, or other unexplained symptoms that are significant in the view of the treating physicians.

C.4.1.b Placebo Arm

1) Administration: Patients assigned to the Placebo treatment group will receive a similar volume of placebo (relative to study drug) as 5% Dextrose in Water.
2) Indications for withdrawal: Same as C.4.1.a above, since treating physicians will not be able to distinguish IVMP from placebo.

C.4.1.c Study Drug Preparation and Dispensing

1) Check Dose: 30 mg/kg single dose
2) Determine Dose Volume: Dose to be administered / 62.5 = final volume in mL

3) Prepare Syringe:

- Placebo group: Draw up a volume of Dextrose 5% Water to equal the calculated final volume. (plus 0.1 mL overfill as per department policy)
- Active group: Dilute methylprednisolone with sterile water for injection to a concentration of 62.5 mg/mL.

Table 2 illustrates the standard dilution for Methylprednisolone dosing.

Table 2. Methylprednisolone Dilution Chart

Methylprednisolone vial size	Sterile water to be added
1 gm	16 mL
500 mg	8 mL
125 mg	2 mL

Draw up a volume of methylprednisolone 62.5 mg/ mL to equal the calculated final volume (plus 0.1 mL overfill as per department policy).

4) Label syringe:

Methylprednisolone/placebo in Kawasaki study drug 62.5 mg/mL.
Expiration (48 hrs)
_____mg = _____mL
Patient Name: Division:

C.4.2 Other Treatments

C.4.2.a Intravenous Gamma Globulin (IVIG)

After administration of IVMP or Placebo as above, all patients will receive IVIG, 2 g/kg, over 12 hours (range 8 to 16 hours or longer if patient has significant left ventricular dysfunction). For all subjects, the frequency of vital sign monitoring during infusion will be per institutional policy at each Network center. If a patient develops an adverse reaction (e.g., flushing, hypotension, rigors), the infusion will be stopped immediately. Preparations of antihistamines, steroids, and sympathomimetics will be available for IV administration at the time of gamma globulin infusion; however, the need for steroid

treatment of IVIG adverse reactions is expected to be uncommon. Within each center to the greatest extent possible, investigators should endeavor to use a consistent brand of IVIG in order to diminish variability in adverse reactions secondary to IVIG products, and therefore maximize the likelihood that an effect of steroids on IVIG adverse effects will be detected.

C.4.2.b Aspirin Therapy

All patients will receive acetylsalicylic acid (aspirin), 80 to 100 mg/kg/day, rounded down to the nearest ½ aspirin tablet, until afebrile for 48 hours. Aspirin will be administered every six hours at standardized times (6AM, 12 PM, 6 PM, and 12 AM) to allow comparability of fever data. After the patient has been afebrile (rectal or oral temp < 38.3 °C) for 48 hours, the aspirin will be reduced to an anti-platelet dose of 3 to 5 mg/kg/day given once daily. All children with significant coronary dilation (any coronary artery z-score > 2.5) detected by echocardiography will continue to take low-dose aspirin indefinitely. In children without echocardiographic evidence of coronary abnormalities (all coronary artery z-scores $\leq$ 2.5), aspirin therapy will be terminated at the five-week visit. All adverse reactions will be noted.

C.4.2.c Retreatment with IVIG and/or steroids in patients with persistent or recrudescent fever

In accordance with standard practice,[19] retreatment with IVIG, 2 g/kg, will be administered to any child who, at greater than 36 hours after completion of the initial IVIG treatment, has a fever of at least 38.3°C without another likely source and without administration of additional antipyretics. For example, if a child's dose of aspirin has already been reduced to an anti-platelet dose and fever recrudesces, retreatment may be administered. For the rare patient with recrudescent or persistent fever without another source 36 hours or more after IVIG retreatment, a second retreatment (i.e., a third treatment) with IVIG, 2 g/kg, will be administered. Because steroid treatment does not have proven efficacy for preventing coronary aneurysms in Kawasaki disease, we believe it is justified to withhold steroid therapy other than that administered in the protocol unless a patient has failed the second IVIG retreatment.

Patients with continued fever 36 hours or more after initiation of a third IVIG infusion are a group at especially high risk for coronary aneurysms and for whom no therapies have proven efficacy. They will be treated at the discretion of their center physicians, without a specific protocol.

C.4.2.d Diphenhydramine

In accordance with standard medical practice in administration of IVIG, subjects in both groups will be administered diphenhydramine (Benadryl), 1 mg/kg, one-half hour prior to initiating treatment with IVIG.

C.4.2.e Additional Medications

The use of antibiotics without specific justification will be avoided. Recent data have suggested that concomitant use of ibuprofen antagonizes the irreversible platelet inhibition induced by aspirin.[26] For this reason, patients with recrudescent fever after aspirin dose is lowered will be treated with acetaminophen rather than with nonsteroidal anti-inflammatory drugs (NSAIDs). For patients with significant arthritis but without coronary abnormalities, NSAIDs may be prescribed as necessary for patient comfort. For patients with significant arthritis and coronary abnormalities, NSAIDs may be required for comfort, but may increase the risk of coronary thrombosis. For this reason, addition of another anti-thrombotic medication, e.g., clopidogrel, low-molecular weight heparin, or warfarin, to low-dose aspirin should be considered. Other medications (e.g., furosemide) will be prescribed at the discretion of the study cardiologist at each center and recorded appropriately on the study forms. The use of other medications is expected to be extremely infrequent and to have little effect on coronary artery dilation.

C.4.3 Protocol Deviations in Treatment

All deviations from the above schedules should be noted and described on the Patient Data Collection Form in the section, “Deviations from Protocol.” In addition, for all non-study drugs, the dosage, treatment period, and reason for use will be recorded. For modified and interrupted therapy, the length of and reason for the modification/interruption will be recorded. Every attempt will be made to keep protocol deviations and non-protocol treatment to a minimum.

C.5 Measurement

C.5.1 Schedule of Measurement

C.5.1.a. Overview

Table 3 provides an overview of scheduled tests.

Table 3. Schedule of Measurement

	Day 1 (Treatment)	Discharge	Week 1	Week 5
Demographics	X			
Height/Length	X		X	X
Weight	X		X	X
History/Events/Temperature	X	X	X	X
Echocardiogram	X		X	X
Complete Blood Count	X		X	X
Platelets	X		X	X
ESR	X		X	X
Immunoglobulins	X		X	X
C-Reactive Protein (CRP)	X		X	X
Ultrasensitive CRP	X		X	X
Albumin	X		X	X
Serum bank	X		X	X

Other tests (e.g., urinalysis, blood cultures, ALT) may be added at the discretion of each clinical center depending upon their standard of care for Kawasaki disease patients.

C.5.1.b. Baseline Visits

At baseline, we will obtain demographic information, medical history, laboratory values, and an echocardiogram. All laboratory tests will be conducted prior to infusion of study drug. Echocardiograms will be obtained ideally before or within 24 hours after initiation of study drug; studies obtained more than 48 hours after initiation of study drug will not be used in the primary analysis.

C.5.1.c. Follow-up Visits

Follow-up data will be obtained as follows:

- Hospital Discharge: Discharge assessment form, including all events from time of admission (as listed on events code sheet).

- Subsequent days: Recording of daily temperatures, adverse events, retreatment.
  1. *1 week:* Echocardiogram, laboratory tests, interim medical history.
  2. *5 weeks:* Echocardiogram, laboratory tests, interim medical history.

C.5.1.d. Windows for Visits

The one-week visit will occur 7 days after enrollment, with a window of ± 3 days. For example, if the day of enrollment is considered "Study Day 0," the target date for the first follow-up visit will be "Study Day 7." However, the first follow-up visit cannot occur sooner than three days after the baseline study echocardiogram or before the 11th day of illness. In recognition that these constraints may leave few potential dates for return for patients, visits occurring through Study Day 13 will be included in analyses.

The five-week visit will occur five weeks after enrollment, with a window of ± 1 week. Although we will analyze data that fall within a two-week window of the target, such outliers are strongly discouraged.

Because it is possible that a patient may have more than one echocardiogram or set of laboratory tests within a visit, it is necessary to clarify the rules by which to select data for analysis. Only one echocardiogram per window will be used for analysis. The echocardiogram chosen to represent the findings at a given study window will be chosen as follows:

- Among all <u>complete</u> echocardiograms with blood drawn on the same day, we will submit the echo <u>closest</u> to the target date of the visit.

- If two complete echocardiograms are equally close to the target date, we will use the one that is judged to be better quality.

In rare cases, blood may be drawn on a different day from that on which the echocardiogram is performed. However, the performance of the study echocardiogram and laboratory tests on the same day is strongly encouraged.

Table 4 outlines the time windows for study visits.

Table 4. Time Windows for Study Visits		
Visit Day*	**Protocol-mandated Window**	**Allowable Analyzable "Extended" Window**
Study Day 7 (1 week after enrollment)	Study Day 7 ± 3 days (Study Day 4 through10)	Study Day 4 through 13
Study Day 35 (5 weeks after enrollment)	Study Day 35 ± 7 days (Study Day 28 through 42)	Study Day 21 through 49

* Study Day 0 is the day of Randomization

C.5.1.e. Endpoint of Evaluation

The endpoint of evaluation in this study will be the Week 5 visit. All data on randomized study subjects will be analyzed. Attrition of patients following randomization theoretically could occur because of 1) discontinuation of treatment or withdrawal of consent, 2) failure of the patient to return for follow-up visits, or 3) death. Our experience with previous studies in patients with Kawasaki disease suggests that losses secondary to the first two causes will be rare (< 1%), and we do not anticipate that any subjects will die during the course of the study (the overall mortality rate for acute Kawasaki disease is under 0.3%, including those who present with existing aneurysms). The following assumptions can be made about subjects for whom coronary status is unknown because of loss to follow-up: 1) they all have aneurysms; 2) none have aneurysms; and 3) their incidence of aneurysms is the same as that of their treatment group. We will conduct a sensitivity analysis to assess how these assumptions affect the conclusion of the study.

C.5.2 Outcome Variables

C.5.2.a Coronary Artery Abnormalities

The primary outcome variable will be based on coronary artery z-scores, assessed by two-dimensional echocardiography. For this reason, it will be essential to standardize both the procedure of examination at participating centers and the final interpretation of

the studies. Echocardiograms will be obtained at enrollment and at the one-week and five-week visits. Because coronary artery dilation may be progressive, the enrollment echocardiogram ideally will be obtained prior to initiation of study drug and not longer than 24 hours later. "Enrollment" echocardiograms obtained more than 48 hours after initiation of study drug will not be analyzed in the primary analysis.

To obtain the highest-quality assessments of coronary artery dimensions, children under age two years will be sedated with high-dose chloral hydrate (65 to 100 mg/kg, maximum dose 1000 mg) or other short-acting sedative or hypnotic agents, in accordance with clinical practice recommended by AHA guidelines.[1] Older children who are unable to cooperate may also occasionally require sedation, in accordance with center-specific clinical practice. The cardiac ultrasound examination will be performed using transducers with the highest frequency possible. This typically requires a 7.5-mHz probe in infants, a 5.0-mHz probe in toddlers, and a 3.5-mHz or 5-mHz probe in older children. Studies will be recorded in a dynamic video format, either digitally or in standard 0.5-inch super-VHS tape. Each study must be submitted to the Data Coordinating Center separately (one study for one patient per tape or digital medium).

Echocardiographers will acquire the studies according to a uniform, predetermined protocol. Studies will include a display of the left main, anterior descending, and left circumflex coronary arteries as well as the proximal, middle, and distal segments of the right coronary artery and the posterior descending coronary artery. These vessels will be visualized in multiple planes using a combination of parasternal long-axis and short-axis and apical four-chamber and two-chamber views, as well as subcostal long and short axis projections.

Each coronary artery first will be categorized as nonvisualized or visualized. Primary outcome variables will be derived from on-line measurements of the internal lumen of the proximal right and proximal left anterior descending coronary arteries using electronic calipers during 2-D echocardiography, as previously described in Table 5 (below).[1] Other vessel segments (e.g., the distal left anterior descending, distal right, and posterior descending coronary arteries) will also be measured. Measurements will exclude points of branching, which may normally exceed adjacent vessel diameter.

Table 5*.
Echocardiographic Views of Coronary Arteries in Patients With Kawasaki Disease

- Left main coronary artery: Precordial short axis at level of aortic valve; precordial long axis of left ventricle (superior tangential); subcostal left ventricular long axis
- Left anterior descending coronary artery: Precordial short axis at level of aortic valve; precordial superior tangential long axis of left ventricle; precordial short axis of left ventricle
- Left circumflex: Precordial short axis at level of aortic valve; apical four-chamber
- Right coronary artery, proximal segment: Precordial short axis at level of aortic valve; precordial long axis (inferior tangential) of left ventricle; subcostal coronal projection of right ventricular outflow tract; subcostal short axis at level of atrioventricular groove
- Right coronary artery, middle segment: Precordial long axis of left ventricle (inferior tangential); apical four-chamber; subcostal left ventricular long axis; subcostal short axis at level of atrioventricular groove
- Right coronary artery, distal segment: Apical four-chamber (inferior); subcostal atrial long axis (inferior)
- Posterior descending coronary artery: Apical four-chamber (inferior); subcostal atrial long axis (inferior)

* Modified from Dajani AS, Taubert KA, Gerber MA, Shulman ST, Ferrieri P, Freed M et al. Diagnosis and therapy of Kawasaki disease in children. Circulation 1993; 87:1776-1780.

We will record the maximum dimension of each abnormal segment in order to assess candidacy for fulfilling the Japanese Ministry of Health criteria[9] for coronary aneurysms. These criteria define a coronary artery as abnormal if 1) the lumen diameter (inside to inside) is at least 3 mm in a child under five years or at least 4 mm in a child age five years or older; 2) the internal diameter of a segment measures at least 1.5 times that of an adjacent segment; or 3) the lumen is clearly irregular.

Echocardiograms of each patient will be interpreted blindly and independently by one pediatric echocardiographer in the Echocardiographic Core laboratory. The Data Center

(NERI) will compare measurements obtained by the Core laboratory with those recorded by the clinical center, and an additional reviewer will resolve disagreements about the status of coronary arteries.

Left ventricular function will be assessed by end-systolic and end-diastolic dimensions and shortening fraction (percent change in cross-sectional diameter). These basic parameters of function, although influenced by loading conditions, are more readily measured than complex indexes of contractility.

The presence and degree of valvular regurgitation will be assessed by standard color flow mapping and pulsed Doppler techniques.

The protocol for echocardographic acquisition and interpretation is included in APPENDIX C.

C.5.2.b Fever

Duration of fever is a powerful predictor of coronary artery aneurysms.[27-30] Because duration of fever will be one of the most important secondary study efficacy outcomes, standardization of temperature recording is vital. Hospitalization of patients until they have been afebrile for 24 hours is strongly encouraged. *During hospitalization,* all patients will have rectal or oral temperature determinations every six hours. We will allow axillary temperatures to be recorded if parents or nurses are unable to obtain an oral or rectal temperature, although use of axillary temperatures is discouraged. The site of temperature determination will be recorded. In addition, the maximal daily temperature will be recorded for each 24-hour period. To standardize antipyretic therapy, patients will receive high-dose aspirin every six hours, with doses given at 6 AM, 12 noon, 6 PM, and 12 midnight. Temperature measurements will be made just prior to the administration of aspirin for each of these time points.

Following discharge from the hospital, parents will take temperatures once daily at 6 PM until their child has been afebrile for three consecutive days. In addition, parents may measure and record temperature at any other time that they believe their child is febrile.

We will encourage parents to obtain rectal or oral temperatures, but will accept axillary temperatures or, in older children, tympanic temperatures, if they are unable to obtain rectal or oral temperatures. Parents will be given a digital thermometer prior to hospital discharge and will be instructed regarding its use. All temperatures will be recorded in a home log, which will also include information about the type of temperature measured (e.g., oral). The nurse coordinator will phone families on the first and third day after discharge and encourage parents to complete the log. Patients who are febrile on discharge or whose fever recurs following discharge must be followed by telephone daily by the nurse coordinator until afebrile. The nurse coordinator will keep a concurrent log containing the information obtained from the parents' telephone reports. The patient log will be collected at the one-week follow up visit. Previous trial experience using this method indicates parent compliance with home log recordings of greater than 90%.

C.5.2.c Retreatment

The need for retreatment will be a secondary outcome variable in this study, so uniform criteria for retreatment are essential. See Section C.4.2.c.

C.5.2.d Laboratory Markers of the Inflammatory Response

Laboratory markers of inflammation, including the white blood cell count, hemoglobin, platelet count, and measurements of immunoglobulins, albumin, and C-reactive protein, are broadly reflective of the intensity of infection, severe trauma, or inflammatory states. In Kawasaki disease, they have been shown to contribute significantly to the prediction of coronary artery abnormalities and reflect the severity of coronary vasculitis. [27,31-35] White blood count elevation in non-malignant conditions is almost exclusively attributable to increases in the absolute granulocyte count. The acute phase reaction consists of changes in the rates of synthesis of certain serum proteins during inflammation. In this study, we have chosen to measure two representative proteins: C-reactive protein and albumin. The inflammatory response is accompanied by increased synthesis of C-reactive protein and a decrease in synthesis of serum albumin.

C-reactive protein (CRP) is normally present in the serum at a level of only 1 to 2 µg/ml and may increase to as much as 1 mg/ml or more. C-reactive protein binds to chromatin

and also to C1q, thereby activating complement. C-reactive protein will be measured as is conventional at the clinical centers and as ultrasensitive C-reactive protein by the Core laboratory.

Albumin is the major protein component of serum or plasma. Its concentration ranges from 3.5 to 5.5 mg/dl in normal subjects. It is important in maintaining the osmolarity of the blood and it binds a great many blood constituents, including fatty acids, hormones, bilirubin, and drugs.

As noted above, measurements of ultrasensitive C-reactive protein will be performed in a Core laboratory; however, the other laboratory tests can be measured reliably within each clinical center.

C.6 Adverse Events

C.6.1 Definition

An adverse event is any untoward medical occurrence experienced by a subject. An event constitutes a disease, a set of related symptoms or signs, or a single symptom or sign.

C.6.2 Classification of Adverse Events:

C.6.2.a Relationship

The relationship between study drug (IVMP or placebo) and any adverse event will be determined by the investigator using the following criteria:

Not Related: The event is clearly related to other factors, such as the subject's clinical state, therapeutic interventions or concomitant drugs administered to the subject.

Possibly Related: The event follows a compatible temporal sequence from the time of drug administration, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions or concomitant drugs administered to the subject.

Probably Related: The event follows a reasonable temporal sequence from the time of drug administration, and cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions or concomitant drugs administered to the subject.

C.6.2.b Severity

The severity of clinical adverse events and laboratory abnormalities will be assessed according to the following criteria:

1 = "Not Serious": Any event which:

(a) Results in minimal transient impairment of a body function or damage to a body structure; or

(b) Does not require any intervention other than monitoring.

2 = "Moderately Serious": Any event which:

(a) Results in moderate transient impairment of a body function or transient damage to a body structure; or

(b) Requires intervention, such as the administration of medication or a procedure, to prevent permanent impairment of a body function or damage to a body structure.

3 = "Serious": Any event which:

(a) Is fatal; or

(b) Is life-threatening (the patient was, in the view of the Principal Investigator, in immediate danger of death from the event as it occurred); or

(c) Is severely or permanently disabling; or

(d) Necessitates significant intervention, such as major surgery, to prevent permanent impairment of a body function or permanent damage to a body structure; or

(e) Prolongs hospital admission; or

(f) Involves a drug overdose; or

(g) The Principal Investigator considers to be a serious adverse event.

C.6.3 Data collection procedures for adverse events

Adverse Events (AE) will be recorded according to the date and time of first occurrence, severity, and their duration, as well as any treatment prescribed. Following initiation of study drug dosing, all new or continuing adverse events that were not present at enrollment will be recorded. Any medical condition present at the initial visit, which remains unchanged or improves, will not be recorded as an adverse event at subsequent visits. However, worsening of a medical condition that was present at the initial visit will be considered a new adverse event and reported. Abnormal laboratory values, if felt by the investigator to be clinically significant, will also be recorded on the AE form and assessed in terms of severity and relationship to study drug. Laboratory values that are abnormal at study entry and that do not worsen will not be recorded on the AE form.

C.6.4 Reporting procedures

Reports of all serious adverse events will be submitted to the local Institutional Review Board (IRB) and the DCC within 1 working day of the event. The DCC will report the serious adverse event to the NHLBI as soon as possible and no later than seven calendar days after the event.

C.6.5 Post-study adverse events

All unresolved adverse events at the time of the patient's termination from the study will be followed by the investigators until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained or has stabilized. At the last scheduled contact, the investigator will instruct each parent to report any subsequent event(s) which the parent, or the subject's personal physician, believes might reasonably be related to administration of IVMP or other drugs. Any death or other clinically serious adverse event that may be related to IVMP and that occurs at any time after a subject has discontinued or terminated study participation will be reported as in C.6.3.

C.7 Statistical Methods

C.7.1 Sample Size and Power

C.7.1.a Primary Endpoint

The primary outcome is the larger of the right coronary artery (RCA) and left anterior descending (LAD) artery z-scores, measured at five weeks post-randomization. A difference in treatment group z-score means of 0.5 is considered to be clinically important. This would represent half of the standard deviation among normative controls (children referred for echocardiographic evaluation with no evidence of structural or functional heart disease).[2] Data from a pilot study conducted at Children's Hospital in Boston provide estimates of patient-to-patient variability in the primary outcome among 35 children with Kawasaki disease treated under almost the identical protocol that will be used in the current study (see manuscript in Appendix A). Based on these data, the standard deviation is 1.10. (The standard deviation is very similar when calculated separately among patients on IVIG or IVIG+IVMP.) The sample size required for 85% power to detect a significant treatment difference using a two-sided α=.05 test, when the true mean difference in z-scores is 0.5, is 174 (87 per group).

These calculations assume no loss to follow-up or other missing data. As discussed previously (Section C.5.1.e), loss to follow-up is expected to be minimal. However, a small loss in power results from interim monitoring (Section C.7.1.c). To adjust for this and for other forms of missing data such as uninterpretable echocardiograms, 10% loss is planned and therefore the sample size of 174 will be inflated (174/0.9) to a target of 194 (97 per group).

C.7.1.b Secondary Endpoints

In this section we summarize statistical power for some of the main secondary endpoints with the projected sample size of 87 evaluable patients per treatment group. Two-sided α=.05 tests are assumed throughout.

Z-scores for individual arteries. Table 6 shows estimated standard deviations (SD) for each of the individual z-scores measured at 2 and 6 weeks after the start of illness (i.e., in this study, equivalent to approximately Study Day 7 and 35), from pilot study data. Assuming these standard deviations will be similar in the current study, the power for detecting a difference in mean z-scores of 0.5 is shown in the last column.

Table 6. Standard Deviations of Individual Z-Scores

Artery	Time point	SD	Power
Right Coronary Artery	2 weeks*	.90	96%
Left Anterior Descending Artery		1.08	86%
Left Main Coronary Artery		.78	99%
Right Coronary Artery	6 weeks*	.91	95%
Left Anterior Descending Artery		1.26	74%
Left Main Coronary Artery		.89	96%

* From start of illness.

Coronary Artery Aneurysms (CAA). There will be low statistical power for detecting differences in the percentage of patients who develop CAA because of the expected rate of CAA is very low. Approximately 5% of children with Kawasaki disease treated with a single infusion of 2 g/kg of IVIG within the first 10 days of illness develop CAA by Japanese Ministry of Healthy criteria.[1] With 87 evaluable patients in each treatment group, even if the risk of developing a CAA is reduced 10-fold in the IVMP plus IVIG group, from 5% to 0.5%, the power for detecting this treatment difference statistically is only 27%.

Total Days of Fever. From the pilot study, the standard deviation of number of days with fever was 1.9 days in the IVIG alone group and 1.3 days in the IVIG plus IVMP. Assuming a common value of 1.6, we would have 98% power to detect a mean difference of one day.

Retreatment. There will be low statistical power for detecting differences in the percentage of patients who require retreatment because of the low expected retreatment rate. Approximately 8% of children treated with IVIG require one or more additional IVIG infusions because of persistent or recrudescent fever. With 87 evaluable patients in each treatment group, even if the risk of retreatment is reduced 10-fold in the IVMP plus IVIG group, from 8% to 0.8%, the power for detecting this treatment difference statistically is only 49%.

Adverse Events. In the pilot study, 57% of the IVIG group and 22% of the IVIG plus IVMP group experienced one or more adverse event. The current study will have high power for detecting even smaller treatment differences. For example if the true adverse event rates are 55% and 30%, there will be a 90% chance (90% power) of observing a significant treatment difference.

C.7.1.c Interim Monitoring and Early Stopping

A Data and Safety Monitoring Board (DSMB) has been established by NHLBI to monitor this trial. The DSMB will meet one to two times a year. In addition to routine data reviews (see below) a formal early stopping procedure will be used to monitor the trial for large treatment differences. An O'Brien-Fleming stopping boundary, allowing for flexibility in the exact times of the interim analysis, will be used for this purpose.[36,37] The O'Brien-Fleming plan is conservative in the sense that it is difficult to reach the boundary during the trial. With such a plan, most of the Type I error is conserved for the final analysis and the effect on statistical power is minimal. There will be one such formal interim analysis, when approximately half the patients have reached the Week 5 visit. The Lan-DeMets methodology[37] will be used to adjust the boundary appropriately if the interim analysis does not fall at exactly the halfway point. The primary endpoint will be analyzed and the nominal p-value compared with the stopping boundary to judge the significance of the treatment effect while adjusting for multiple testing. Table 7 shows that if, at the interim analysis with half of the total information (namely, half of the randomized patients have completed the Week 5 visit), the nominal p-value is <0.005, this would represent a statistically significant treatment effect with an overall experiment-wide false positive error rate of α=.05.

Table 7. Interim Analysis

Analysis	**1st (Half of total information)**	**2nd (Final Analysis)**
Nominal p-value to reject null:	0.005	0.048

Even if there is a statistically significant treatment difference at the interim analysis, the DSMB may decide that there is not an ethical imperative to stop the trial. It is common to not consider early stopping guidelines to be hard and fast rules but instead to take a more global view of the trial during data monitoring.[38-40] In order to provide this broader

perspective, the DSMB reports will include summaries of accrual, patient characteristics, adverse events, data quality, primary and secondary endpoints, other information as requested by the DSMB, and any unanticipated special problems that arise during the conduct of the trial.

C.7.2 Analysis Plan

C.7.2.a Primary Analysis

The primary analysis will be according to the intention-to-treat principle. All patients will be analyzed according to their treatment group assignment regardless of actual treatment received. The treatment groups will be compared with respect to the primary endpoint with the t-test. We anticipate that the distribution of this endpoint will be approximately normal even though one might expect a skewed distribution (due to constructing the measure from the maximum of two z-scores). Data from the pilot study support this normality assumption. However, if the assumption is not met, the Wilcoxon rank sum test will be used. The treatment groups will be compared descriptively with respect to demographics and baseline characteristics. Randomization should result in good balance across the two groups. If there are imbalances on covariates that are prognostic for study outcomes, then covariate-adjusted comparisons will be made.

C.7.2.b Secondary Analysis

Several analyses will be conducted using the different coronary dimension outcome measures (both 1 and 5-week time points; individual artery z-scores; absolute measurements; changes in absolute measurements; sum of absolute dimensions of proximal RCA and proximal LAD; etc). These will be analyzed similarly to the primary endpoint. Covariate-adjusted regression models will be used to model the prognostic effects of the baseline covariates themselves.

Dichotomous endpoints such as occurrence of aneurysms, requirement for IVIG retreatment and occurrence of one or more adverse event (as well as occurrence of individual adverse events) will be compared with Fisher's exact test. Covariate-adjusted analyses will use logistic regression and stratified Mantel-Haenszel analyses.

We will also analyze differences between treatment groups after categorizing coronary artery size (largest measurement in any vessel) into small, medium, and large absolute coronary dimension. To partially adjust for body size, this analysis will be stratified by age (< 1 year, 1 – 2 years, 3 – 4 years, 5 – 7 years and ≥ 8 years). For purposes of this study, we will define coronary artery size as follows: small absolute dimension is less than 4 mm; medium absolute dimension is least 4 mm and less than 6 mm; and large absolute dimension is at least 6 mm. The stratified two-sample Wilcoxon test with midrank scores will be used to compare the treatment groups with respect to coronary artery size category, stratifying by age.

Other continuous outcomes include days with fever, days in hospital and laboratory measurements. Some of these outcomes will likely be skewed and we anticipate that logarithmic transformations will bring their distributions more close to normality. Like the coronary artery dimension outcomes, these outcomes will be analyzed with t-tests and regression analyses. The Wilcoxon rank sum test will be used as needed.

In order to confirm that conclusions from the full cohort are not affected by the presence of the ineligible patients, all proposed analyses will be repeated with the exclusion of patients retrospectively found to be ineligible.

C.7.2.c Subgroup Analyses

In order to determine whether the effect of IVMP differs across subgroups, separate treatment comparisons will be made within the following subgroups:

- Gender: males vs. females
- Age: patients <1 year old vs. patients ≥1 year old.
- Coronary Abnormalities at Baseline: patients with and without baseline coronary abnormalities, defined as having a z-score of the proximal RCA or proximal LAD coronary artery of at least 2.5.
- Number of Illness Days at Baseline: patients randomized before day 7 of illness vs. ≥ day 7 of illness.

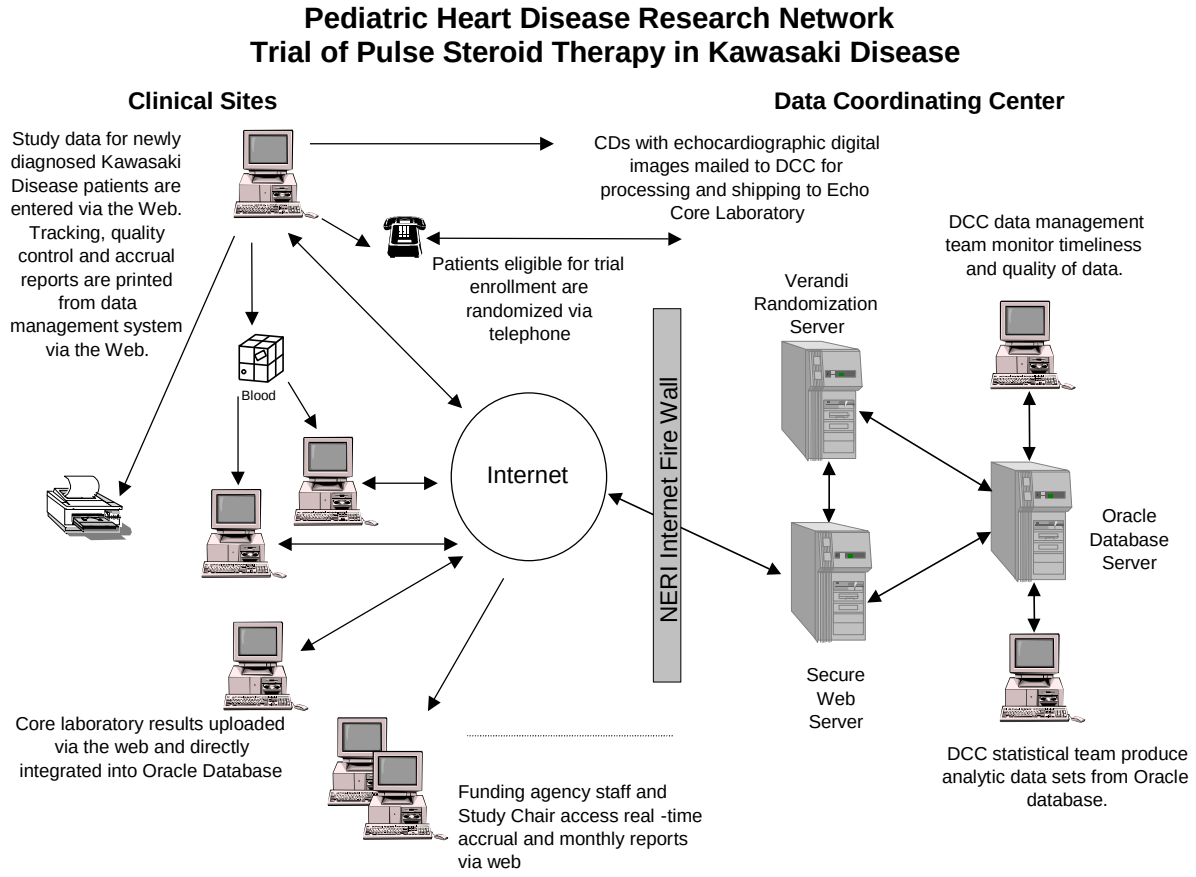
Covariate by treatment interaction tests will be performed to test whether the treatment effect is homogeneous across subgroups.

C.8 Data Management

C.8.1 Information Flow

Data will be received from several sources, including the clinical sites and the Serology and echocardiogram Core Laboratories. The flow of data among the units in this trial is illustrated in Figure 2. Clinical sites will enter data over the Internet using the Advanced Data Entry and Protocol Tracking (ADEPT) software, a customized and secure Web application (see Section C.8.2). The DCC will also be able to perform central data entry and editing to accommodate sites or central labs that submit paper copies of data forms. Sites will send blood specimens directly to the Serology Core Laboratory for central processing, and results of tests performed by these laboratories will be electronically transmitted to the DCC using the ADEPT DMS. Echocardiogram data files from clinical sites may be transmitted to the DCC via the web using NERI's PHN FTP site or submitted on other storage media, such as optical disk or CD-ROM. The DCC will forward the echocardiogram data to the Echocardiogram Core Laboratory either electronically or by FedEx. Results of studies performed by the Echocardiogram Core Laboratory will be directly uploaded to an Oracle database at the DCC or transmitted electronically using the ADEPT DMS.

Figure 2. Data Management System and Information Flow



C.8.2 Overview of data management system

ADEPT uses a "browser-based" user interface together with an Oracle relational database engine which allows direct data entry from multiple study sites or at NERI, and then stores these data centrally at the DCC. Information entered into the data entry system will be by patient study I.D. number; names will not be linked with patient data in the database. Clinical sites will maintain records linking the patient name with the I.D. assigned for the study in locked files. Sites will have full access to their own data and be able to view these data remotely, over the Internet.

The ADEPT data entry system will include real-time field level validations and context sensitive help. Electronic data entry forms will be formatted using HTML to closely resemble the paper-based study instruments. These forms will be enhanced with client side JavaScript code to

ensure rapid data entry, proper validations of all data fields, and proper skip patterns within study data forms. Data will be saved at regular intervals during data entry to prevent loss of information in the event of a disruption of the Internet connection. In the unlikely event of a major disruption of the Internet infrastructure, the ADEPT system has a dial-in backup system to allow for dial-up access to the DMS.

NERI's proprietary VERANDI randomization system, which is capable of supporting blinded medication trials and supports a number of different allocation methodologies, will be used for randomizing patients. Site personnel will randomize patients by telephone.

Key capabilities of the ADEPT system are described below.

C.8.2.a Data entry and editing

The data entry system will include a number of standard features designed to ensure consistently high quality data. Each question on a study form will be associated with a validation, and validations will be executed in real-time during data entry. If the response to a particular question falls outside the range of allowable values specified in the validation for that question, the user will be alerted so that the error can be corrected immediately. Validations will include both inter- and intra-instrument data checks. In addition to alerting the user to invalid entry of items, edit reports will be automatically generated at the completion of data entry for a form. These edit reports will provide the information necessary to correct any data entry errors or resolve questions regarding out-of-range or questionable values. Edit reports will list the participant identification number, instrument name, and a detailed description of why each specific data item was flagged. These edit reports can be printed out and reviewed by a supervisor, or returned to the data collector for resolution.

The ADEPT system will track expected, partially completed, and missing data entry forms by instrument and data collector. Data entry quality will be monitored through a sample based, double data entry quality control system. This quality control system utilizes a self-adjusting algorithm to enforce higher double data entry rates on data entry staff that have higher error rates. This system also allows for a minimum double data

entry rate to be specified for each individual study instrument. This minimum rate of double data entry is adhered to regardless of a data entry staff's error rate.

C.8.2.b Reporting

The ADEPT system will produce visit schedules to assist Clinical Site staff in scheduling or appointments and visit control sheets that will list all of the forms and procedures for a scheduled visit. In addition, the system will produce a variety of reports in both graphical and tabular format, as applicable, to the Study Chair, Program Officer, clinical site and Core laboratory management staff. These will include

- Study Instruments pending entry;
- Study Instrument pending edit resolution;
- Missing data rates;
- Time between collection and entry of data;
- Time to physically key each study instrument;
- Audit logs for all edits to study data;
- Patients with overdue visits;
- Reimbursement information for sites and Core Laboratories.

Other customized reports will be developed within the ADEPT system as needed.

C.8.2.c Data security and integrity

The Web-based components of the data management system utilize several levels of security to ensure privacy and integrity of the study data.

- Web access to ADEPT requires use of assigned user names and passwords;
- Passwords are changed every 90 days;
- Web-based data entry uses secure socket layer (SSL) data encryption;
- Access to any study-specific system features are controlled by Oracle database rights and privileges;
- Oracle archive files are backed up daily;
- There is a full Oracle Back up weekly;
- Backup files are stored off site in safety deposit box;

- Duplicate NT servers are available to replace the Oracle or Web Server;
- Primary Identification is via study I.D. – limited access to ID/Participant linkage;
- Access to electronic linkage limited by Oracle Database Administrator,
- Access to hard copies of linkage kept in locked cabinets by Clinical Center Coordinators,
- NERI firewall limits what internet protocols are allowed to access the web server;
- No direct access is allowed to the Oracle server from the Internet;
- NERI's firewall monitors for unusual (hacker) activity and automatically notifies NERI IS staff

All study data will be stored on NERI's Microsoft Windows NT-based, Oracle server. Access to data on this server (from both inside and outside the data center) is controlled by Oracle's extensive security features. Oracle archiving and backup system ensures minimal data loss, even in the most catastrophic system failure.

C.9 Quality Control

This section describes the quality control program that will be implemented as part of the study to ensure standard implementation of the protocol, protocol compliance, and data integrity. The DCC will develop and update the Manual of Operations (MOO) in collaboration with study investigators and Core laboratory directors. In addition, a Data Management Manual will be developed for clinical site and Core laboratory personnel who will be using the ADEPT data management system. The two manuals will serve as both training and reference manuals and will be accessible on NERI's PHN website.

C.9.1 Clinical center coordinator training

The PHN DCC, working closely with the Program Officer, Study Chair, and the Kawasaki Disease Protocol Subcommittee, will provide central training of clinical center staff in the areas of protocol implementation, data collection and management, specimen collection and handling, collection and handling of imaging data, medical records abstraction, interview techniques, and quality control expectations. Training manuals will be prepared that reflect clearly and succinctly the learning goals for clinical coordinators and represent the skills and protocol

components required to collect quality data. Training follow-up will be completed through conference calls and site visits.

C.9.2 Certification of personnel

Echocardiography personnel at each center will undergo sessions on standardization of technique, and all studies will be read in a Core laboratory. Poor quality echocardiograms may necessitate site visits.

C.9.3 Data monitoring/Site visits

Each clinical site will be visited once by representatives from the DCC and the NHLBI during the study period. The primary roles of the site visit team will be to evaluate general protocol compliance and adherence to Institutional Review Board (IRB) requirements, review site data files for correct filing of copies of consent forms and study forms, audit a random sample of records to assess data integrity, and identify and resolve general problems with study progress. At each site visit, the site monitor will review procedures, observe form completion and data entry (where applicable), and assess adherence to protocols and flow. A random sample of medical records will be reviewed in order to determine whether reporting of data has been accurate and complete. Follow-up actions by the site coordinator or investigator and schedule for completion will be identified at each site visit. An evaluation checklist will be completed at each site visit for inclusion in a Site Visit Report to the investigators. New staff will be trained and existing staff will be retrained, if necessary. Site coordinators will be expected to provide materials and answer questions prior to and during these visits.

The DCC will conduct site visits to each Core Laboratory during the first year to review in-house quality assurance (QA) and quality control (QC) procedures and data transfer to the DCC. Review of central laboratory-related reports will be conducted at least monthly to identify overall or site-specific problems in data or specimen acquisition and reporting of results.

D. STUDY ORGANIZATION

The New England Research Institutes serves as the Data Coordinating Center for the Pediatric Heart Disease Clinical Research Network. The study described in this protocol, “Pulse Steroid

Therapy in Kawasaki Disease" is a research component of this network. Participating clinic sites are: Hospital for Sick Children, Toronto, Ontario; Boston Children's Hospital, Boston; Columbia, New York; Children's Hospital of Philadelphia, Philadelphia, Duke University, Durham, NC; Medical University of South Carolina; and Primary Children's Medical Center, Salt Lake City, Utah. The Network is chaired by Lynn Mahony, MD. Jane Newburger, MD will chair the study. Network committees include the Steering and Publications Committees. The Steering Committee consists of the Network Chair, the DCC Principal Investigator (PI), each clinic site PI, and the NHLBI Project Officer, *ex officio*. The Steering Committee meets in person 2-4 times per year and by teleconference two times per month. The Publications, Presentations, and Ancillary Studies Committee meets once per year and as needed by conference call. The Data and Safety Monitoring Board meets twice per year either in person or by teleconference and consists of 7 members including pediatric cardiologists, a statistician, an ethicist, and a layperson. Its function is to monitor study progress and accomplishment of study aims.

E. STUDY LIMITATIONS

Study limitations include the following:

1. The study may be underpowered for subgroup analysis and some secondary endpoints.

2. Because the latest endpoint is five weeks after randomization, the present study will not show the effect of steroid therapy on later outcomes.

3. The proposed study explores the effect of primary treatment with a single dose of high-dose intravenous methylprednisolone in addition to conventional IVIG. We will not be able to comment on the effect of other steroid regimens for primary treatment or on the effect of steroid therapy for children with persistent fever and/or aneurysms after primary treatment with IVIG alone.

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