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Design of the PEDS-C trial: pegylated interferon +/− ribavirin for children with chronic hepatitis C viral infection

Karen F Murray[a], **James R Rodrigue**[b], **Regino P González-Peralta**[c], **John Shepherd**[d], **Bruce A Barton**[e], **Patricia R Robuck**[f], **Kathleen B Schwarz**[g], and **for the PEDS-C Clinical Research Network**

[a]Division of Gastroenterology and Nutrition, Department of Pediatrics, University of Washington, Children's Hospital and Regional Medical Center, Seattle, Washington, USA

[b]The Transplant Center, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

[c]Section of Hepatology and Liver Transplantation, Department of Pediatrics, University of Florida, Gainesville, Florida, USA

[d]Department of Radiology, University of California, San Francisco, California, USA

[e]Maryland Medical Research Institute, Baltimore, Maryland, USA

[f]Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland, USA

[g]Division of Pediatric Gastroenterology and Nutrition, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Abstract

Background—PEDS-C is the first multicenter placebo-controlled trial for the treatment of chronic hepatitis C (HCV) in childhood that has ever been conducted in the United States (USA). Establishment of the research team, protocol, administrative infrastructure, and ancillary contributors for the pediatric trial took years of planning.

Purpose—To study the safety and efficacy of pegylated-interferon alpha (PEG-2a) plus ribavirin (RV) with PEG-2a monotherapy in children aged 5 years through 18 years. To assess the health-related quality of life and growth and body composition in children with chronic hepatitis C infection, before, during, and after treatment.

Methods—Eleven centers of pediatric hepatobiliary clinical research were united in a National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) funded grant with financial support from the Food and Drug Administration (FDA) and a corporate sponsor to conduct the treatment trial.

Limitations—The most important initial limitation in the design of this complex study was securing the financial support and infrastructural organization, a process that took several years. Challenges faced by the study group included identifying the optimal study design given the limited study population, and determining what ancillary studies could be incorporated into the treatment trial.

Author for correspondence: Dr. Karen F. Murray, Division of Gastroenterology and Nutrition, Children's Hospital and Regional Medical Center, 4800 Sand Point Way, NE P.O. Box 5371/Mail stop A5950 Seattle, WA 98105, Tel: 206-987-2587 Fax: 206-987-2527. Karen.murray@seattlechildrens.org.

Conclusions—In this article the process taken to design the study and administrative infrastructure, the lessons learned, and the controversial issues deliberated during the planning process are discussed. The evolution of the study and the considerations taken in the development of the protocol are valuable tools which can be applied to pediatric clinical trials in general.

Background

Chronic infection with chronic hepatitis C (HCV) is a global health problem, with 2.7 million individuals infected in the USA alone. Although the incidence and prevalence of HCV in children is less clear, the virus has been shown to be an important pathogen in the pediatric population [1,2].

Therapy with recombinant interferons normalizes the serum alanine aminotransferase (ALT) and reduces the serum HCV RNA (ribonucleic acid) below detectable levels, but sustained for more than 6 months after therapy (sustained viral response, SVR) in only 8–35% of adults [3]. Review of the equivalent monotherapy in children suggests that the sustained treatment response in children may be 2–3 times higher than that in adults [4,5]. Attempts to improve the SVR have included the addition of ribavirin (RV) to the treatment regimen, and the development of long-acting interferons, including pegylated interferon-2a (PEG-2a).

Aside from well known side effects of RV, a greater concern in treating children with this drug is that it is both a teratogen [6–8] and an embryotoxin [9]. Consequently, great caution must be used in treating females of child-bearing potential. If comparable efficacy of HCV treatment can be achieved in children, without the addition of this teratogenic drug, the public benefit would be great. Efficacy rates in adults given PEG-2a plus RV are vastly improved (SVR up to 56%) in comparison to those administered interferon and RV [10].

Interferon-based side effects unique to pediatric patients have included slow weight gain, and changes in linear growth [11,12]. Whether or not these changes in weight represent changes in body composition with preferential loss of lean body mass or fat, is not known. It is known, however, that preservation and/or augmentation of lean body mass has been linked with improved health outcomes in a number of chronic illnesses including human immunodeficiency virus infection [13] suggesting possible importance in chronic HCV also.

Depression and other psychiatric disorders are among the potentially most serious adverse events facing patients who take interferon-based treatment [14–25], and the addition of RV increases the rates of irritability and depression in adults [19,21,26]. These symptoms can lead to poor compliance and the need to decrease or prematurely stop antiviral therapy [19,22,26]. In addition, HCV itself in adults is associated with decrements in health-related quality of life (QOL) and cognitive functioning [27–31]; the relative impact of interferon and RV on these parameters is unknown [27,28]. Even less is known of the impact of HCV or its treatment on the health-related QOL, cognitive and developmental functioning, or psychological functioning of children.

PEG-2a plus RV is now a standard therapy for chronic HCV in adults. It is possible that PEG-2a monotherapy may be as effective as combination therapy in treating chronic HCV in children, as implied by preliminary studies [32,33]. Moreover, the potential toxicities associated with the use of PEG-2a and RV in children, including possible detrimental effects on the physical and mental health and quality of life warranted further study in this unique group.

Methods

Planning and management

In 1998 the PEDS-C group of 11 investigators was organized to design a prospective, randomized, controlled trial for children with chronic HCV infection, an area where research had been lacking. The investigators were chosen based on demonstrated experience in the management of children with chronic HCV and active clinical research in the area. This group identified government and corporate sponsors, and began protocol development. Since pediatric HCV has a prevalence of <200,000 children in the United States, it is considered a 'rare disease.' Taking advantage of this distinction, the PEDS-C group applied for a FDA Orphan Products (OPD) Grant that underwent standard peer review with NIH advisory council concurrence. As the FDA OPD grants are limited in scope and duration, the NIDDK and the FDA agreed to cosponsor the grant which was converted to an NIDDK cooperative agreement in September 2003. An industry sponsor agreed to supply study drugs and financial support for the central laboratory and data coordinating center.

The primary treatment study was first developed by the PEDS-C group. Evaluation of health related quality of life and intellectual functioning (QOL), and body composition and growth were incorporated into the primary protocol. Experts in hepatic pathology, bone density, body composition and imaging techniques, and pediatric assessment of health related quality of life were identified and joined the PEDS-C group.

To facilitate the conduct of the study, several subcommittees focus on Publications, Ancillary Studies, and Exemptions. These are each chaired by an investigator and include three or four additional investigators and an NIDDK representative.

Study objectives and hypotheses

1. To assess the safety of PEG-2a in combination with RV and PEG-2a alone for the treatment of chronic HCV infection in children.

   Hypothesis 1: PEG-2a and PEG-2a plus RV therapy for children with chronic HCV is safe and well tolerated.

2. To determine whether PEG-2a in combination with RV compared to PEG-2a alone will result in a higher sustained virological response rate in children with chronic HCV.

   Hypothesis 2: The addition of RV to PEG-2a therapy for treatment of chronic HCV in children improves the SVR.

3. To examine the effects of PEG-2a (with or without concomitant RV) treatment on body mass index, body composition, and linear growth in children infected with HCV.

   Hypothesis 3: Children treated with PEG-2a will show growth impairment after 48 weeks of therapy compared to baseline, as assessed by weight for age z scores and lean body mass.

   Hypothesis 4: Children treated with the combination of PEG-2a plus RV will exhibit more growth impairment than those treated with PEG-2a alone.

   Hypothesis 5: Children treated with either therapy will exhibit improved growth during years 2–5 after discontinuation of therapy compared to end of treatment, as assessed by improved weight for age z scores, linear growth velocity, and lean body mass.

Hypothesis 6: Children with SVR will exhibit more growth improvement after discontinuation of therapy than those who do not have an SVR.

4. To characterize short- and long-term outcomes, including health-related QOL, cognitive, developmental, and psychological functioning, and behavior in children treated with PEG-2a (with or without concomitant RV).

Hypothesis 7: Children treated with PEG-2a will show decreased QOL, cognitive and developmental functioning, and psychosocial and/or behavioral functioning during and at the end of treatment when compared to their baseline evaluation.

Hypothesis 8: The decreases in QOL, cognitive and developmental functioning, and psychosocial and/or behavioral functioning will be greater in children treated with PEG-2a plus RV than in children treated with PEG-2a alone.

Hypothesis 9: Children treated with either therapy will exhibit improved QOL, cognitive and developmental functioning, and psychosocial and/or behavioral functioning during years 2–5 after discontinuation of therapy compared to the end of treatment.

Hypothesis 10: The improvements in QOL, cognitive and developmental functioning and psychosocial and/or behavioral functioning after discontinuation of therapy will be greater in children with SVR compared to children who do not have an SVR.

Study design

Treatment—The targeted enrollment is 112 patients 5–18 years of age, to be equally distributed between the 11 sites. Recruitment targets are set to be equal to achieve balance among the sites, and psychosocial factors affecting compliance, such as education and relationship with the coordinator and investigator. However, to optimize enrollment, every center is encouraged to enroll as many patients as possible. After informed consent is obtained from the legal guardian and assent is obtained from the child, subjects are screened for inclusion and exclusion criteria (www.clinicaltrials.gov). Screening procedures are performed as noted in Table 1, and eligible patients randomized and started on therapy within 35 days.

Enrolled patients receive a subcutaneous PEG-2a injection ($180mcg/1.73m^2$) once a week and either placebo or RV tablet(s) given orally twice daily (15mg/kg/day, maximum dose of 1200 mg/day if or equal to 75 kg and 1000mg/day if <75kg). Placebo is provided at an equivalent pill count.

Patients are randomized using a computer generated randomization scheme within clinical sites with stratification by HCV genotypes (1 vs. all others); that is, a separate randomization schedule was generated for the two HCV genotypes within each clinical site. The basis for this randomization scheme was that genotype 1 is the most prevalent HCV genotype in US adults, seen in ≈70% [34], and response rates to interferon-based therapy are lower than for most other genotypes [35]. The ratio of PEG-2a plus RV to PEG-2a plus placebo treatment assignments is 1:1. The randomizations are blocked using random blocking factors of 2 and 4, due to the relatively small sample size within a clinical site (≈10 participants for each of 11 sites) to best balance the groups.

The overall study algorithm is shown in Figure 1. As discussed above, there are two primary treatment arms in this study: PEG 2a + RV (the combination group) and PEG 2a + Placebo (the monotherapy group). The treatment arms proceed as follows.

1. PEG 2a + Placebo treatment is given for 24 weeks, HCV RNA testing is then performed, and treatment continues for 4 more weeks. At week 28, there is a split into two subgroups based on HCV detection:

   a. If virus is still detected, PEG 2a + RV treatment is started and repeat HCV RNA detection determination done 24 weeks into this combination treatment (52 weeks). PEG 2a + RV is given for 28 weeks, then (at week 56):

      • If virus is detected at 52 weeks, treatment is discontinued and untreated follow-up done monthly to week 76.

      • If viral clearance is noted at 52 weeks then treatment is continued for 20 more weeks (to week 76) and then follow-up for 24 more weeks (to week 100).

   b. If viral clearance is noted, continue treatment for an additional 24 weeks (48 weeks), then discontinue therapy and conduct non-treatment follow-up for 24 more weeks (week 72). Families and investigators remain masked to the treatment assignment until week 72 in responders to the initial treatment assignment.

2. PEG 2a + RV are given for 24 weeks, HCV RNA testing is performed, and treatment continues for 4 more weeks. At week 28, there is a split into two subgroups.

   a. If virus is still detected, therapy is discontinued and the patient followed-up for 20 weeks (to week 48). This group is considered a treatment failure.

   b. If viral clearance is noted, the treatment is continued for an additional 20 weeks (to week 48), then discontinued. Follow-up for an additional 24 weeks (to week 72) is then done.

All patients received two additional annual follow-up visits, even if they dropped out of the study for nonresponse, consent withdrawal, treatment intolerance, or investigator withdrawal of the patient.

Baseline and follow-up assessments—Physical examination and laboratory assessments inclusive of hematology, chemistries, and quantitative HCV-RNA are all done at the baseline visit. In addition the health-related QOL, cognitive, developmental, and psychological functioning in all children are assessed as are growth and body composition. Follow-up studies are done as shown in Table 2.

Body composition—Dual energy X-ray absorptiometry (DXA) is a proven tool for measuring body composition in children and thus it was selected as the gold standard for body composition measurements. However, the expense and radiation exposure of this technique makes it less attractive for use in children. Thus, we have included bioelectric impedance (BIA) and anthropometry as well as DXA at all analysis points to determine if these alternative measures can be used in the place of DXA.

Quality of life—Assessment of the child's health-related QOL, also includes cognitive and developmental and psychological functioning. Some of the constructs are measured from multiple sources (e.g., child and guardian) depending on child age. All assessment tools have demonstrated reliability and validity.

Measures to decrease risks to participants—Considering the potential for depression associated with interferon- and pegylated-interferon-based regimens, there are several critical issues that warranted careful consideration. Should children with a history of depression be enrolled; how should depression be monitored throughout the clinical trial; how should children with symptoms of depression be clinically managed; and, should children with clinically elevated levels of depression be withdrawn from the study? In consultation with mental health experts, the risks and benefits associated with each of these questions were evaluated. A plan to reduce the risk of psychological harm to children participating in the clinical trial was developed. The specifics of the plan are as follows:

Children with a history of major depression are excluded from participation in the study because of the potential for significant exacerbation of symptoms secondary to interferon administration. Similarly, children with a history of severe psychiatric disturbance (e.g., psychosis), suicidal ideation, or suicide attempts are also excluded from enrollment. Parents and children are queried about history of depression at the screening visit. They are also administered the Child Depression Inventory (CDI) [36]. Children meeting criteria for major depression [37] at screening are appropriately referred to a child mental health professional for further evaluation and treatment consideration.

Screening for depressive symptoms throughout the clinical trial is also important. Thus, the CDI is administered at baseline, 12 weeks, and 24 weeks, at the end of the study drug, at the end of untreated follow-up, and at each of the annual visits. The Center for Epidemiological Studies Depression scale (CES-D) is used to screen for depression in children who reach the age of 18 years during the study. Both the CDI and CES-D are screening measures of depressive symptoms; however, they do not have adequate specificity and sensitivity to diagnose depression in isolation. Therefore, study participants with a CDI score >19 or a CES-D score > 15 are immediately assessed by the site investigator to further evaluate depressive symptoms.

Two pathways can be utilized to assist the investigator in determining whether a child should be administratively withdrawn from the clinical trial. If the child appears to meet criteria for major depression and meets any of the criteria outlined by the study group (initial episode of depression, recent onset of depression, absence of co-existing condition, ability to make no-suicide contract, high level of family discord, or chronic/recurrent depression), then the child is referred to a mental health provider and study drug administration continues. The investigator monitors the child's mental health treatment closely. If clinical management of depression does not improve within eight weeks of treatment initiation, the study drugs are discontinued and the child is referred to a specialty physician. In this scenario, the child then moves to the first untreated follow-up assessment. In the second clinical pathway, a child who appears to meet criteria for major depression and also develops more significant symptoms or comorbid conditions (e.g., co-existing substance abuse, recent suicide attempt or current suicidal ideation with a plan, psychosis, bipolar disorder, or inability of family to monitor child's safety) is immediately referred to a specialty physician for clinical management of depression and the study drugs are discontinued. The child then moves to the first untreated follow-up assessment.

As multiple ocular conditions can be induced or aggravated by treatment with PEG-2a all patients receive an ophthalmological examination by a study ophthalmologist at screening and at weeks 24 and 48 of therapy.

Outcome measures and endpoints

The primary outcome measurement for the study is the proportion of participants with sustained viral response defined as a non-detectable plasma HCV-RNA (by Roche Cobas

Amplicor HCV Qualitative PCR, v. 2.0, with a detection limit of 60IU/ml) 24 weeks post treatment of 48 weeks duration (72 weeks from initiation of treatment). For purposes of primary outcome determination, the only two groups to be compared will be the two initial randomized arms: monotherapy versus combination therapy. Patients randomized to the monotherapy (PEG-2a plus placebo) arm who fail to exhibit viral disappearance at week 24 will be considered non-responsive for SVR in the intent to treat analysis. The primary outcome will be assessed in a blinded manner.

The secondary outcome measures are sustained biochemical response and safety. Sustained biochemical response is defined as two consecutive normal serum ALT assessments taken 12 and 24 weeks after the completion of therapy. Safety outcomes include vital signs, laboratory tests, and clinical adverse events recorded throughout the study. Changes in QOL and changes in body composition are also secondary endpoints.

Sample-size and power calculations

Based on preliminary pediatric studies, the PEG-2a group would have a primary outcome, a SVR 24 weeks post treatment, of ≈35%. An absolute difference of 30% was assumed between the two treatment groups (35 vs. 65%), which was chosen as a clinically significant difference by the study investigators. Assuming a chi-square test with a two-sided $\alpha = 0.04829$ (to adjust for interim monitoring) and power = 0.80, 51 children per group are needed to detect a true difference of 30%, adjusting for an estimated 15% drop-out rate. Since the clinical centers indicated that they would be able to recruit 112 children, or 56 children in each group, a true difference of 28% will be detected (slightly better than the detectable difference with 51 patients per group) between the percent (proportion) of participants with non-detectable HCV-RNA in the two treatment groups. A sensitivity analysis was also performed to look at the effect of different SVR rates for both treatment groups while keeping the difference between 25 and 35%. It was found that 56 patients in each treatment group always gave at least 0.80 power to detect the specified difference.

Analysis strategy

The primary outcome for this study will be the proportion of participants with non-detectable serum HCV-RNA (SVR) 24 weeks after completing treatment. Each patient will have a binary outcome (no detectable serum HCV-RNA or detectable serum HCV-RNA). Therefore, the primary analysis will be a chi-square test of the frequencies of the contingency table formed by treatment group and SVR (yes/no). If the assumptions for the chi-square test are violated due to low rates of SVR, Fisher's Exact Test will be used. Prior to the primary analysis, a Breslow-Day test for homogeneity of treatment effect between the two strata will be conducted. If this test indicates a non-significant difference of treatment effect, the primary analysis will be of the combined strata. If there is a significant difference of treatment effect, the results will be reported separately. The primary analysis will be conducted using intention-to-treat principles with all patients analyzed in the treatment group in which they were randomized. It is unlikely that there will be missing SVR information because patients can be described as treatment failures at week 24 of the study, long before any tests are performed for SVR. Patients who are not treatment failures are seen frequently for study drug resupply and for follow-up visits so that drop-outs will not be common.

Secondary analyses of the primary outcome will utilize logistic regression to investigate the effect on the treatment effect of baseline factors as well other factors measured during the course of treatment. Secondary outcomes for this study include sustained biochemical response defined as two consecutive normal serum ALT assessments taken at weeks 60 and 72. Safety outcomes, also secondary outcomes, will include vital signs, laboratory tests, and

clinical adverse events recorded throughout the study. For the analysis of ALT at weeks 60 and 72, the main analysis will be initially analyzed with a chi-square analysis of proportions of patients with normal ALT at these two measurement points and, for adjusted analyses, with logistic models. For safety outcomes, there will be multiple measurements at various points during the study, which will be analyzed using mixed models to adjust for the multiple measurements.

During the course of the study, the primary outcome will be monitored by the DSMB using monitoring limits for both efficacy and futility. For efficacy, an alpha-spending function [38] is used based on an O'Brien-Fleming strategy [39]. For futility, a beta-spending function is used based on a Pampillona-Tsiatis strategy [40]. If the study results cross one of the monitoring limits for either efficacy or futility, the DSMB then has the option of recommending early termination of the trial to the NIDDK.

For analysis specific to growth and body composition, the outcome variables are change in weight for age z scores, linear growth velocity, and lean body mass, all evaluated at 48 weeks. Data will be examined for skewness and log-transformed for analysis if necessary. For analysis specific to health-related QOL and behavioral functioning, the outcome measures are change in scores on psychological tests, evaluated before treatment and at treatment weeks 24, 48, and at 24 weeks after discontinuation of treatment. As there are multiple measurements, mixed models are used to investigate correlates of changes in body composition during treatment.

The relationship among measurements of body composition made by DXA, BIA, and skinfold thickness will be analyzed by regression methods, aided by the Bland-Altman graphical technique of plotting difference versus average [41].

Procedures

Screening

At screening the patient is assigned an identification number and three letter identification code utilizing an Automated Telephone Response System (ATRS) at the DCC/CRO. This system uses a touch-tone phone to enter information about a new participant, including age, gender, ethnicity, race, HCV genotype, and a check on eligibility and informed consent. Access to the system is over an 800 number using Personal Identification Number (PIN) numbers and passcodes assigned to each clinic coordinator.

If a screened patient failed to meet eligibility criteria and the site investigator thought an exemption should be granted to allow admission of the patient to the trial, (e.g., borderline laboratory abnormality which was not clinically significant) the investigator submitted an Exemption Request form to the Exemptions Committee. The Committee was composed of five members other than the investigator submitting the request. The Committee circulated the request and voted by email. Choices were 'accept, deny, or discuss by conference call.' Decisions were returned within 24h of submission of the Exemption Request.

Baseline visit and randomization

The randomization assignment is obtained by a second call by the study personnel to the ATRS system with stratification by clinical site and HCV genotype. Information as to which medication packages to dispense is verbally conveyed to the caller. Additionally, faxes are automatically sent to the coordinator and the clinical site pharmacy by the ATRS system. The resulting randomization schedules are stored in the ATRS database for reference by the system.

All of the study medications are packaged with unique medication numbers on each package, including the PEG-2a that all subjects received. The local pharmacy at each clinical site prepares the medications for distribution with the patient number and a three-letter identifier prior to distribution to the patient/caregiver.

Study visits and post-treatment follow-up visits

All adverse events are recorded and any considered possibly related to study medication are scored a toxicity grade. The Pediatric AIDS toxicity table [42] is used as a guide for grading severity of adverse events. Medication compliance is assessed with the coordinator review of the medication diary filled out by the parent/caregiver. This diary is modeled on the Pediatric AIDS adherence tool [43]. Pill and vial counts are determined by the research coordinator and/or the investigational pharmacist. Study medication dose adjustments are standardized for laboratory and non-laboratory toxicities according to predetermined thresholds. If, despite maximal dose reduction, an adverse event continues, the medication is discontinued.

Measures of body composition

Anthropometry (skinfold, SF)—Lange skin calipers (Lange, Cambridge MD USA) are used to measure the skin fold thickness (mm) in three regions: left tricep skinfold thickness, right tricep skinfold thickness, subscapular. A sum, *triscap,* is derived from these measures and used to calculate% fat using the following equation:% $Fat_{SF} = (1.33*triscap) - (0.013*tris\text{-}cap*triscap) - 2.5$. For triscap values >35cm:% $Fat_{SF} = (0.546*triscap) + 9.7$. Percentiles of age- and sex-adjusted % fat_{SF} were derived from the Ten State Nutrition Survey for infants and children [44].

Bioimpedance analysis (BIA)—Bioimpedance Analysis (BIA) measures the relative electrical resistance and reactance between fat and muscle. Simple adhesive electrodes (two at each location) are placed on the left hand and foot as per manufacturer instructions. The BIA method reports a resistance in mhos, a reactance in mhos, and a phase angle in degrees, for a constant current source of 50kHz and 1mA. Total body resistance and reactance are measured in the supine position using a single-frequency 50-kHz tetra polar four terminal impedance analyzer (RJL Systems, Detroit, MI, USA). Measures are taken in the morning following an overnight fast.

There are two primary measures derived from BIA, fat free mass (FFM_{BIA}, where FFM is in kg) and percent fat mass (%Fat_{BIA}). %Fat_{BIA} was defined as%$Fat_{BIA}= [(1 - FFM)/W]*100$. Both FFM and %$Fat_{B}IA$ are directly comparable to the DXA equalent measures. Each BIA derivation will be compared to DXA as well as relationships deriven directly from the study data.

Dual X-ray absorptiometry—The DXA whole body scan takes <10min and exposes the child to ≈5 μSv effective radiation dose. The 11 clinical centers involved in this trial have a variety of DXA systems. Eight centers have Hologic systems (7 – Discovery/A and 1-Discovery/W) while three have GE Healthcare devices (2-Prodigy, 1-Prodigy Advance). For pooling data across system types, baseline calibration measures were acquired on all systems at the beginning of the trial using the Hologic Whole Body Phantom, European Spine Phantom (ESP), and the Hologic Block Phantom. Each phantom was scanned 10 times without repositioning. The systems' bone mineral density (BMD in g/cm^2) and bone mineral content (BMC in g) calibration were adjusted to agree with one another using the ESP and Block phantom scans and multiplicative correction terms. One system for each manufacturer was chosen as the reference site based on stability and being closest to the mean phantom values. The BMD and BMC measures were then adjusted for known manufacturer-specific

differences by converting the BMD to standardized BMD (sBMD) units using the equations in Genant *et al.*[45]. Additional manufacturer-specific corrections were applied to the whole body composition measures to remove residual differences between sites from the whole body phantom baseline scans. After the above cross-calibration procedures, the accuracy of each system was monitored over the course of the study using local quality control phantoms, (the Hologic Anthropomorphic Spine Phantom for the Hologic systems and the GE Lunar Aluminum Spine Phantom for the GE Lunar Prodigy systems). Adjustments were made to the BMD and BMC results using the cumulative statistics method (CUSUM) such that statistically significant changes from the cross-calibration accuracy were removed using multiplicative factors [46]. The common assumption that changes in the spine phantom BMC and BMD are reflected in the whole body values as well was used. Lastly, the radiographic uniformity of the whole body scans without a phantom was monitored, coined 'air scans', to insure that there were no region of interest specific inaccuracies.

Health related quality of Life—Health-related quality of life is measured using the Child Health Questionnaire (CHQ), which assesses physical functioning, role and social limitations, general health, bodily pain and discomfort, guardian impact, self-esteem, mental health, general behavior, and family impact [47]. The CHQ-PF50 is completed by every study parent. Children who are at least 10 years old complete the CHQ-CF87. Cognitive functioning is measured using the Behavior Rating Inventory of Executive Function (BRIEF), a paper-and-pencil 86 item questionnaire, that assesses emotional and behavioral dysregulation, difficulties with response inhibition, working memory, and the ability to quickly transition into new situations or tasks [48]. Both the preschool version and a version normed for older children and adolescents are used in this clinical trial. To assess behavioral and emotional outcomes, guardians also complete the Child Behavior Checklist (CBCL), which permits an assessment of child adaptation across both internalizing (e.g., depression, anxiety) and externalizing (e.g., conduct problems, aggression) domains [49]. Participants who are at least 19 years of age will be administered the Adult Behavior Checklist (ABCL) [50]. An assessment of life stress and quality of life for caregivers (parents/guardians) is also utilized [51]. Specifically, caregivers complete the Life Events Checklist (LEC), which measures their perception of 46 life events and the degree to which they represent positive or negative stressors. Caregivers also complete the MOS 36-Item Short-Form Health Survey (SF-36) to assess their physical and mental health status, including: physical functioning, role functioning (physical and emotional), social functioning, pain, general health, vitality, and mental health [52].

Infrastructure

The functions of the DCC include: (1) development of case report forms (CRFs), (2) the data management system based on telefaxing of the CRFs, (3) the ATRS randomization system, 4- the adverse event reporting system, and, (4) monitoring the study. The DCC facilitates the monthly teleconferences of the PEDS-C Executive Committee and the Steering Committee, both of which are chaired by the PI.

The central laboratory (Covance Central Laboratory Services, Inc., Indianapolis, Indiana) distributes the visit kits, performs all laboratory testing on the patients (except as specified below) and promptly communicates test results to the sites and to the DCC. The central laboratory study database is electronically transferred to the DCC. The central laboratory also ships 'deidentified' research plasma and serum samples to the NIDDK Repository on a quarterly basis.

As the study proceeded it was necessary to modify the protocol to allow performance of certain laboratory assessments in CLIA-approved laboratories geographically closer to the

patient than the study site. The 'local lab tests' were allowed for two reasons: (1) assessments that needed to be done more frequently than the original visit schedule because of safety indications (most commonly weekly complete blood counts for assessment of neutropenia) and (2) patient convenience in the event that a certain test had to be repeated because of issues at the central laboratory such as 'quantity not sufficient' or tube breakage.

Discussion

The challenges in designing this study include the limited subject population and the use of potentially toxic treatments in a pediatric population. Additionally, the incorporation of two fundamentally important ancillary studies into the primary study was felt to be necessary, but created new challenges. There were many decisions to consider during the design of this study. All investigators agreed that a prospective randomized controlled trial should be done. However, there was debate as to the need for an untreated observation group. Although such a group would have been of scientific interest in clarifying the natural history of HCV in children, the concept was abandoned because most investigators believed that parents would not be willing to enroll children in a study if there were a chance of receiving no treatment.

The rationale for adding RV in case of inadequate viral clearance with PEG-2a monotherapy, at 24 weeks, was the adult experience that treatment with the combination of PEG-2a plus RV is associated with the highest SVR. Additionally, RV is available in the marketplace. The authors therefore believed that recruitment would be impossible without the provision to add RV.

The study was designed as a double-blind study both because this was considered to be the gold standard approach for clinical trials in general and also for the practical consideration that RV is available in the marketplace. There was concern that the families who learned their child was taking monotherapy would manage to obtain RV so as to provide the children with combination therapy.

Another point of discussion during the study design focused on the timing of the treatment discontinuation/change decision point at week 24 rather than week 12, as is commonly done in adults. Although adult trials have shown that a two log drop in viral load by week 12 is predictive of SVR, [53], in the small pediatric pilot study some of the children who had a SVR did not respond until after week 12–24 weeks. Therefore, the presence of virus at week 24 was used as a more conservative marker of treatment failure.

Another question was whether or not to include early time points for later determination of viral kinetics. There were questions about the trauma of frequent venipunctures, the increased blood volume requirements, and the inconvenience of frequent visits. Ultimately there was agreement that if the early viral kinetics could accurately predict the likelihood of SVR, that knowledge was of sufficient value to offset the above concerns. Management of depression was a major area of concern, particularly given the risk of suicide in adolescents treated with selective serotonin receptor inhibitors, which was published [53] as the protocol was being developed. Patients with pre-existing psychiatric disease were excluded and the protocol was detailed extensively as to early diagnosis and management of depression, including a stopping rule for management of severe depression.

When the trial was presented to the FDA, questions were raised about a six month treatment for Genotype non-I, as is recommended for adults [54] and about the use of hematopoetic growth factor to treat anemia and neutropenia as is done in adults [55]. However, the group responded that the small sample size precluded deriving any useful conclusion about the utility of these practices for the pediatric age group; the protocol was then given FDA

approval without these modifications. The FDA also recommended that the Pediatric AIDS adherence modules be incorporated for determination and documentation of medical compliance, and this was done.

The DSMB recommended exclusion of siblings based on concerns about genetic similarities in immune response and similarities in compliance to treatment. The DSMB also recommended the addition of anti-thyroperoxidase antibody in monitoring for hypothyroidism, and the exclusion of subjects with positive tests.

Once the antiviral trial was finalized, the next major decision was what ancillary studies proposed by PEDS-C members should be incorporated into the trial. The group voted to incorporate health related quality of life and body composition and growth into the main protocol. Quality of life, cognitive functioning, and psychological sequelae were included because, (1) the impact of both the disease process and drug therapies on these neuropsychological parameters in children is unknown, (2) it is important to examine the differential effects on these variables of the two therapies used, and (3) identifying the complete range of morbidity associated with HCV and PEG-2a and RV therapies may facilitate the development and implementation of possible psychotherapeutic interventions aimed at attenuating morbidity in these children.

Perhaps the most significant lessons learned in the development of PEDS-C were the length of the timeline (13 years from start to projected finish – see Table 3), the importance of having the community of interested pediatric subspecialists effectively and forcefully articulate the need for a particular trial, and of then developing solid financial support from both government and industry. The ultimate success of any clinical trial for children depends on the development of a highly functional organization of pediatric subspe-cialists and their colleagues (research coordinators, investigational pharmacists, GCRC), and a DCC/CRO, all of whom can work together with government and industry scientists. Such collaboration is essential in order to achieve the very important goal of improving child health by establishing safety and efficacy of pharmacotherapeutic agents in this age group. Finally, pediatric clinical trials must be performed with careful attention to the unique physiological and psychological needs of both the young subjects enrolled and those of their families as well.

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Appendix

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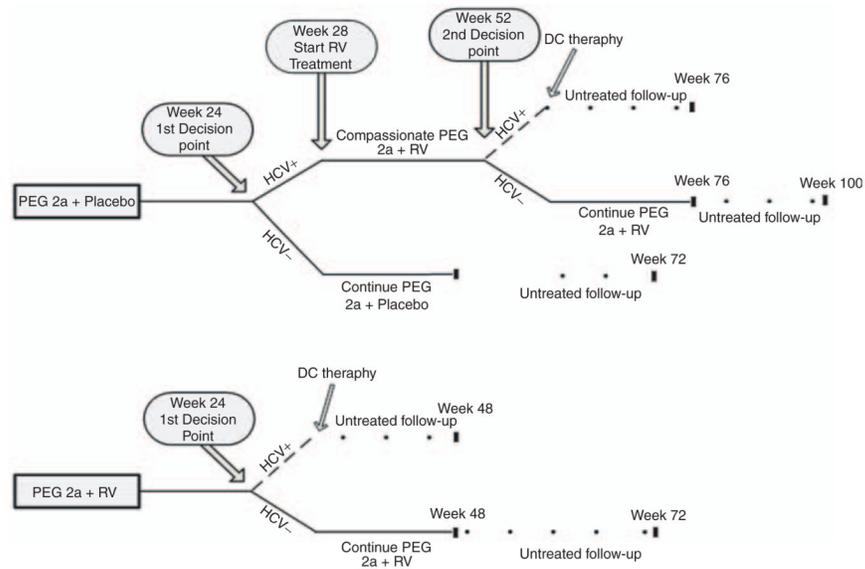
Figure 1. Diagram of overall study design

Table 1

Screening assessments

Medical history and physical exam	Body weight, height, vital signs, body temperature, complete medical history and concomitant medications, Depression screen (CDI)
Immunology	Ceruloplasmin, alpha1-antitrypsin, anti-HBc IgM Ab, anti-HAV IgM Ab, HBsAg, anti-HCV Ab, anti-mitochondrial Ab, anti-nuclear Ab, anti-smooth muscle Ab, anti-HIV Ab, anti-LKM Ab
Hematology	Complete blood count (hemoglobin, hematocrit, WBC, platelets), including differential, prothrombin time, partial thromboplastin time, INR
Hematology	Hemoglobin A_1C
Chemistry	ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, total protein, albumin, BUN, creatinine, creatinine phosphokinase, uric acid, calcium, phosphorus, cholesterol, triglycerides, glucose, sodium, chloride, and potassium
Virology	Clinical:HCV genotype, qualitative and quantitative HCV-RNA
Thyroid function tests	TSH, Free T4, Thyroid Peroxidase Antibody
Serum bank	Samples will be stored in a serum bank in the event some tests need to be repeated or additional testing is warranted and for the NIDDK repository
Pregnancy test	Serum pregnancy test to be performed in fertile or potentially fertile females only
Urinalysis	Urine sample to be sent to central lab for analysis
Ophthalmology	Complete ophthalmologic exam with slit lamp exam and dilation (dilation recommended but not required)

HB – hepatitis B; HAV– hepatitis A virus; Ab – antibody; Ag – antigen; HIV– human immunodeficiency virus; LKM – liver kidney microsomal; WBC– white blood cell; INR– international normalized ratio; AST– aspartate aminotransferase; BUN– blood urea nitrogen; TSH– thyroid stimulating hormone.

Table 2

Schedule of assessments in a subject who completes 48 weeks of therapy without the need for a treatment change

Assessment	Screen days	Study treatment period (weeks)									Untreated follow-up (weeks)												Annual visits
	−35 to −1	BL	1	3	5	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	
Follow-up week #																	4	8	12	16	20	24	
Informed consent and child assent	×																						
Complete medical history	×																						
Vital signs and physical exam	×															×						×	×
Vital signs and symptom directed physical		×	×	×	×	×	×	×	×	×	×	×	×	×	×		×	×					
Telephone assessment	×										×				×					×	×		
Immunology	×																						
Hematology	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×		×			×	×
PT/PTT	×	×								×						×						×	×
Chemistry	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×		×			×	×
HCV-RNA clinical	×[1]	×[1]					×[2]			×[2]						×[2]			×[2]			×[2]	×[2]
HCV-RNA research	×	×					×			×						×						×	
Thyroid function Tests	×					×				×			×			×						×	
HCV genotyping	×																						
Serum bank	×	×					×			×				×		×			×			×	×
Pregnancy test Serum	×	×		×		×	×		×	×	×	×		×	×	×		×	×			×	×
Pregnancy test urine	×	×						×												×			
Urinalysis	×									×			×			×						×	
Ophthalmology Exam	×									×						×							
Adverse events, concomitant medications, and compliance	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Depression screen	×	×								×						×						×	×
Growth/body composition	×	×								×						×						×	×
QOL/outcomes	×	×								×						×						×	
Patient diary review	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×						

[1] Quantitative.

[2] Qualitative.

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Shaded area - assessment for all patients.

Table 3

Timeline for the PEDS-C study

1996	Viral Hepatitis Working Group, NIH – presentation of the problem of Pediatric HCV, invitation to submit concept proposal for treatment trial
1997	NIH Consensus Conference on HCV – absence of pediatric data
1998	Formation of PEDS-C group
	Initial development of the protocol
	Identification of the industry sponsor
2000	Pegylated interferon PK study
	Approval of the protocol by industry Scientific Review Board
	Submission of the IND to the FDA
	Identification of the DCC/CRO and central laboratory
2001	Submission of the FDA Orphan Products grant
	Approval of the protocol by the FDA
2002	Revision and resubmission to the FDA Orphan Products grant
	Consolidation of the FDA OPD and NIDDK support in an interagency agreement
2003	Award of the NIH Cooperative Agreement and industry grant
2004	Completion of the site and DCC/CRO subcontracts
	Continued protocol development
	Organization of the sites: research coordinator, GCRC, investigational pharmacist
	Organization of PEDS-C: Medical Safety, E×emptions, Publications and Ancillary Studies Committees
	Organization of the DCC including randomization, CRFs, database, website, monitors
	Approval of the protocol by the IRBs and GCRCs of 11 sites, the DCC, and the DSMB
	Screening of first patient
2004	Enrollment of first patient
	Solicitation of ancillary studies
2005	Recruitment of patients
2006	Enrollment of last patient
2008	Conclusion of antiviral trial 6 months followup
2009	Conclusion of annual followups and all ancillary studies

PK – Pharmacokinetics; CRF – Case Report Forms; GCRC – General Clinical Research Center.