SUMMARY OF CHANGES
INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:

IMPAACT P1080
(DAIDS ES ID# 10768)

IMPAACT Protocol P1080, “A Pilot Study of Psychiatric and Antiretroviral Medication Concentrations in HIV-1 Infected and Uninfected Children and Adolescents.”

THE AMENDED PROTOCOL IS IDENTIFIED AS:

Version 2.0, Dated 22 April 2014

The information contained in this protocol amendment impacts the IMPAACT P1080 study and must be submitted to site Institutional Review Boards (IRBs) as soon as possible for review and approval. This amendment impacts the study informed consent forms (ICFs); all study sites must prepare updated informed consent forms and obtain IRB approval of the updated forms. Approval must also be obtained from other site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

Upon receiving IRB/EC and any other applicable regulatory entities approvals for this amendment, this amendment is to be implemented immediately and using the updated ICFs.

All study sites must submit an amendment registration packet to the DAIDS Protocol Registration Office (PRO); however, approval from the DAIDS PRO is not required prior to implementing the amendment.

This Summary of Changes, Version 2.0 of the protocol, corresponding site-specific informed consent forms, and all associated IRB correspondence should be retained in each site’s essential document files for IMPAACT P1080.

Summary of Revisions and Rationale

The original design of IMPAACT P1080 was to enable efficient substitution of new psychiatric study drugs of interest through full version protocol amendment. Under Version 1.0, the study drugs of interest were methylphenidate or amphetamine/dextroamphetamine. Under Version 2.0, the study drugs of interest are risperidone; sertraline; citalopram or escitalopram; and fluoxetine or paroxetine. The primary purpose of this full version amendment is to incorporate changes enabling the shifting of focus from the psychiatric study drugs of interest under Version 1.0 to the psychiatric study drugs of interest under Version 2.0.

Modifications throughout the protocol, including updates to the sample size, introduction, psychiatric medications, study visit schedule, study procedures, statistical considerations, and the sample informed consent form have been incorporated for clarity and consistency.

The overall scientific priorities, overall study design, and primary and secondary objective and endpoint remain consistent with Version 1.0.
Detailed Listing of Modifications

Detailed modifications of the protocol text in this summary of changes are indicated by strikethrough (for deletions) and bold (for additions). Unless otherwise stated section numbers reflect the current version of the protocol.

1. Revisions previously included within Clarification Memos #1-5, and Letters of Amendment #01 and #02 have been incorporated.

2. Updates to the protocol version number, date, and roster, as well as minor editorial and typographical edits, including updates to table numbers, page numbering to include appendices and referenced sections have been made.

3. The National Institute of Mental Health (NIMH) has been added as a sponsor on the protocol title page.

4. The following updates have been made to the Protocol Team Roster:
   - Removed: Elizabth Petzold, Janice Hodge, Daniel Hall, Donald Campbell, Mona Farhad, Kennerly Patrick
   - Added: Megan Valentine, Yanling Huo, Alexandria DiPerna, Bobbie Graham, Dorothy Shaw, Julie Ann Hood, Steven D. Douglas
   - Contact details corrected for: Brookie M. Best, Mary E. Paul, Sandra Boyd, George K. Siberry, Patricia Anthony, Suad Kapetanovic

5. Appendices I-B, III-C, and III-D have been added; and the title of Appendices I-A, II, III-A, and III-B have been amended:
   - Appendix I-A: Schedule of Evaluations for subjects enrolled under Version 1.0
   - Appendix I-B: Schedule of Evaluations for subjects enrolled under Version 2.0
   - Appendix II: Pharmacokinetic Sampling Schedule for Selected Psychiatric Medications / Formulations for subjects enrolled under Version 1.0
   - Appendix III-A: DAIDS Sample Informed Consent for HIV-1 Infected Children and Adolescents who enrolled under Version 1.0
   - Appendix III-B: DAIDS Sample Informed Consent for HIV Uninfected Children and Adolescents who enrolled under Version 1.0
   - Appendix III-C: DAIDS Sample Informed Consent for HIV-1 Infected Children and Adolescents who enroll under Version 2.0
   - Appendix III-D: DAIDS Sample Informed Consent for HIV Uninfected Children and Adolescents who enroll under Version 2.0

6. Throughout the protocol, references to methylphenidate or amphetamine/dextroamphetamine have been removed and replaced by “study psychiatric medication” when intended to apply more generally to any study drug of interest

7. In the glossary and in sections 4.6, 6.1, and 7.0, references to the “RCC” have been updated as “RSC” (Regulatory Support Center) and email address likewise been updated.
8. Sample Size, Population, Stratification, Regimen, and Study Duration have been updated in the Protocol Schema as follows:

Sample Size:  **Under Version 1.0, planned accrual was forty-five subjects in each of two arms (Arms 1 and 2) for a total of 90 subjects. Under Version 2.0, forty-five subjects will be enrolled in each of 4 arms, for a total of 180 subjects; total planned accrual in both versions: 270 subjects.**

Population:  HIV-1 infected and uninfected children and adolescents ages ≥6 to <25 years who are currently receiving methylphenidate or amphetamine/dextroamphetamine for treatment of attention deficit hyperactivity disorder (ADHD).

Under Version 2.0, enrolling arms will have HIV-1 infected and uninfected children and adolescents < 25 years who are currently receiving citalopram, escitalopram, risperidone, sertraline, fluoxetine or paroxetine.

Upon receipt of required local IRB approvals of Version 2.0, study sites will cease enrollment into the Version 1.0 study arms (methylphenidate or amphetamine/dextroamphetamine), but subjects in follow up under that version will continue on study to completion as per Appendix I-A.

Stratification:

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Arm: Psychiatric Study Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>15 HIV uninfected subjects</td>
</tr>
<tr>
<td>B</td>
<td>15 HIV-1 infected subjects who are taking concomitant (prescribed) efavirenz</td>
</tr>
<tr>
<td>C</td>
<td>15 HIV-1 infected subjects who are taking a (prescribed) protease inhibitor (PI)* with concomitant ritonavir (at boosting doses) or lopinavir/ritonavir.</td>
</tr>
</tbody>
</table>

*PI may be any of the following: atazanavir, darunavir, fosamprenavir, indinavir, saquinavir or tipranavir

Under Version 1.0, the Study Arms were:
Arm 1: Methylphenidate
Arm 2: Amphetamine/Dextroamphetamine

Under Version 2.0, the Study Arms Open to Enrollment are:
Arm 3: Citalopram or Escitalopram
Arm 4: Risperidone
Arm 5: Sertraline
Arm 6: Fluoxetine or Paroxetine
Regimen: Subjects must already be taking methylphenidate or amphetamine/dextroamphetamine the listed study psychiatric medication for clinical care of ADHD as prescribed by their care provider. Subjects must be on a stable dose of one of these ADHD psychiatric medications for ≥ 12 weeks prior to each of the PK visit (≥ 5 weeks for fluoxetine). This study does not prescribe any therapy or provide medications for study subjects.

Study Duration Subjects enrolled under Version 1.0 will be on study for up to 14 months. Subjects enrolled under Version 2.0 will be on study for up to 2 months.

9. Updates to Schema, Sections 1.19, 2.24, 8.224, 8.4, 8.6, 9.124, and 9.3 to clarify that Secondary Objective #4 only applies to those participants enrolled under Version 1.0:

Schema, Sections 2.24, 8.224, 9.124: To compare the frequency of psychiatric medication dose changes, dose requirement in mg/kg and tolerance between HIV-1 infected and HIV uninfected subjects with routine use of psychiatric medications over one year. (Applies only to subjects enrolled under Version 1.0.)

Section 1.16: Non-invasive Longitudinal Drug Exposure Measures (applicable only to subjects enrolled under Version 1.0)

Sections 8.4, 8.6, 9.3: For the fourth secondary objective, which applies only to participants enrolled under Version 1.0.

10. Additional information on the psychiatric medications under study have been added to the Introduction Section 1.0: Among various classes of psychiatric medications prescribed to adolescents, risperidone and SSRIs were the most commonly used in a survey of P1080 study sites in fall 2011.

11. Within Section 1.14 – 1.16 (Psychiatric Medication Pharmacology, Potential for Antiretroviral and Psychiatric Drug Interactions, and Pharmacogenetics of Antiretrovirals and Psychotropics), Section 5.1 (Drug Regimens, Administration and Duration), and Section 9.11 (Pharmacology Objective), psychiatric study drugs to be studied have been updated, including time requirement for subjects to be on a stable dose.

Section 1.14: Psychiatric Medication Pharmacology

1.141 Current Use of Stimulants

RxList is an internet drug index (www.rxlist.com) owned and operated by WebMD, containing drug information on brand and generic drugs. Each year, it compiles lists of the Top 200 drugs prescribed in the previous year in the U.S. For the calendar year 2007, the following Attention Deficit Hyperactivity Disorder (ADHD) treatment medications were among the top 200 prescribed drugs in this country: Adderall® XR (amphetamine/dextroamphetamine, #36), Concerta® (methylphenidate, #44), Strattera® (atomoxetine, #96), Focalin® XR (dexmethylphenidate, #140), and Methylin® (methylphenidate, #170).

Table 1: Summary of Methylphenidate Formulations in this Study

Dosing and Formulations of Methylphenidate to be studied in P1080

For all formulations described below, both brand name drugs and generics (when available) will be included in this study.
Citalopram is an SSRI approved to treat depression in adults. It is also commonly used off-label for these disorders in children and adolescents, as well as for anxiety disorders, hot flashes and premenstrual dysphoric disorder. When administered orally, the absolute bioavailability is about 80% and is not affected by food. It is about 80% protein bound, and reaches steady-state within about one week with daily dosing. Citalopram is metabolized primarily by CYP 3A4 and 2C19. In patients who are 2C19 poor metabolizers or who are taking 2C19 inhibitors, lower doses are recommended in order to prevent dose-dependent QT-prolongation which can occur with citalopram. The metabolites are much less potent than citalopram. The elimination half-life is about 35 hours, and it is supplied as oral tablets and oral solutions.

Citalopram is a racemic mixture of S and R enantiomers. The S enantiomer is the active moiety, while the R enantiomer is inactive. The active enantiomer is marketed as escitalopram. Escitalopram is approved for depression and generalized anxiety disorder in adults, and for depression in 12 to 17 year olds. A meta-analysis in adults suggested that escitalopram was more effective than citalopram [25] (the postulated mechanism was that the R enantiomer in the racemate antagonized/interfered with the binding of the active S enantiomer), but these findings were not confirmed in subsequent studies. [26] The pharmacokinetic parameters of escitalopram are similar to those of citalopram. Prior pharmacokinetic studies (not efficacy studies) suggest that 20 mg of escitalopram is bioequivalent to 40 mg of citalopram. The elimination half-life is 27 – 32 hours, and it is available in oral solution and oral tablet formulations.

Interestingly, a placebo controlled, randomized efficacy study of escitalopram in 102 HIV-infected adults showed no difference between placebo and escitalopram efficacy in the treatment of depression. The response rate was 62% for escitalopram and 59% for placebo. The authors attributed the lack of difference with placebo to an unusually high placebo response rate. No drug concentrations were reported in this study [27].

Pharmacokinetics of Citalopram/Escitalopram in HIV-uninfected children and adolescents.
For citalopram, a combined report of a prospective and a retrospective study in a total of 44 adolescent subjects under 21 years of age evaluated only trough concentrations [28]. This study found that females had higher trough concentrations than males, and strong serum concentration-dose relationships were found in non-smokers, girls not taking oral contraceptives and girls in the last 14 days of their menstrual cycle.

No pharmacokinetic studies of escitalopram (one of the two enantiomers of citalopram) in HIV-uninfected children or adolescents have been published.

Pharmacokinetics of Citalopram/Escitalopram in HIV-infected children and adolescents.
No pharmacokinetic studies of either citalopram or escitalopram have been published for HIV-1 infected adults, adolescents or children.
1.144 Risperidone

Description

Risperidone is an atypical antipsychotic that is considered a first-line treatment for schizophrenia and related disorders. It is also approved in adults for bipolar disorder. In October 2006, it was approved to treat irritability (for example, aggression towards others, deliberate self-injury, temper tantrums, and labile mood) associated with autism in children and adolescents. In 2007, it was approved for schizophrenia in adolescents and bipolar disorder in children ≥ 10 years.

Risperidone is administered orally or as a long-acting depot intramuscular injection. It is completely absorbed after oral administration, and both risperidone and its metabolites are highly protein bound in the plasma. Risperidone is metabolized by CYP 2D6 to its primary active metabolite, 9-hydroxyrisperidone, which has equal activity to risperidone. It is subject to drug-drug interactions with medications that alter CYP 2D6 activity. The half-life of oral risperidone is 3 hours in extensive metabolizers and 20 hours in poor metabolizers. The half-life of 9-hydroxyrisperidone is 21 hours in extensive metabolizers and 30 hours in poor metabolizers. For oral administration, risperidone is formulated in oral solutions, oral tablets, and orally-disintegrating tablets, all of which are bioequivalent.

Pharmacokinetics of Risperidone in HIV-uninfected children and adolescents.

In a study of 20 children (ages 3 – 10 years) with autistic disorder, a single trough sample was drawn at week 12 to determine risperidone and 9-OH-risperidone concentrations [29]. The authors reported concentrations of these two moieties added together, ranging from 8 – 55 ng/mL. No other pharmacokinetic data are available in the literature on the use of risperidone in children and adolescents.

Pharmacokinetics of Risperidone in HIV-infected children and adolescents.

Pharmacokinetics of risperidone have not been studied in HIV-infected adults, adolescents or children.

1.145 Sertraline

Description

Sertraline is a selective serotonin reuptake inhibitor commonly used to treat major depression, anxiety disorders and premenstrual dysphoric disorder, along with various off-label uses. Sertraline is FDA-approved for obsessive-compulsive disorder in children ≥ 6 years old. Sertraline is administered orally, is highly protein bound (98%), and reaches steady-state in about one week with daily dosing. It undergoes extensive first-pass metabolism by multiple CYP enzymes (2B6, 2C9, 2D6, 3A4, and 2C19). Sertraline weakly inhibits 2D6, but does not affect other enzymes. The primary metabolite, N-desmethysertraline, is much less active than sertraline. The elimination half-life of sertraline is about 26 hours, and the elimination half-life of N-desmethysertraline is about 60 – 100 hours. Sertraline is formulated as immediate release oral tablets or solutions.

Pharmacokinetics of Sertraline in HIV-uninfected children and adolescents.

Two pharmacokinetic studies of sertraline have been performed in children and adolescents [30, 31]. Average sertraline and N-desmethysertraline concentrations were approximately 70 – 85 ng/mL and 110 – 160 ng/mL in 40 patients [31]. A more comprehensive pharmacokinetic assessment was performed in 61 children and adolescents (51 were white, six were black, and 4 were other ethnic origins)[30]. Weight-adjusted sertraline and N-desmethysertraline AUCs were similar between children and adolescents, and were also similar to adults using doses of 50 – 200 mg daily.
Pharmacokinetics of Sertraline in HIV-infected children and adolescents.
Pharmacokinetics of sertraline have not been studied in HIV-infected adults, adolescents or children.

1.146 Fluoxetine
Description
Fluoxetine was the first selective serotonin reuptake inhibitor marketed in the U.S. It is approved to treat depression, obsessive-compulsive disorder, bulimia nervosa, panic disorder and premenstrual dysphoric disorder. Fluoxetine is also approved for pediatric depression and obsessive-compulsive disorder. Fluoxetine is well absorbed after oral administration. It is widely distributed and about 95% bound to alpha-1 acid glycoprotein. Fluoxetine is metabolized to an equipotent active metabolite, norfluoxetine by CYP 2D6 and 2C9. Fluoxetine significantly inhibits multiple CYP enzymes (2D6, 2C19, 3A4, 2C9 and 2C10), and has the potential to alter the pharmacokinetics of many concomitant medications. Both fluoxetine and norfluoxetine have the longest half-lives of all the SSRIs, and steady-state is reached after 3 to 4 weeks of daily dosing. Half-lives are highly variable between patients. After chronic administration, fluoxetine half-life is 4 – 6 days, while norfluoxetine half-life is 8 – 10 days.

Fluoxetine is formulated as oral capsules for daily (immediate release) or weekly (gastro-resistant pellets in capsules) administration. It also comes as immediate release oral solution for daily administration and immediate release oral tablets for daily administration. The once-weekly administration is recommended in adults only.

One population pharmacokinetic study has evaluated HIV-infected adults taking nevirapine and either fluoxetine or fluvoxamine. In seven subjects taking fluoxetine, fluoxetine had no effect on nevirapine exposure, but nevirapine significantly decreased both fluoxetine and norfluoxetine concentrations [32].

Pharmacokinetics of Fluoxetine in HIV-uninfected children and adolescents.
A single population pharmacokinetic study of 11 boys and 10 girls taking 20 mg fluoxetine daily for a depressive disorder or obsessive compulsive disorder reported an oral clearance and apparent volume of distribution of 0.181 L/kg/hr and 37.4 L/kg, respectively [33]. Ten subjects were children (6 – 11 years), and 11 were adolescents (12 – 17 years). Large variability was noted in oral clearance that was not attributable to age or body size measures.

Pharmacokinetics of Fluoxetine in HIV-infected children and adolescents.
Pharmacokinetics of fluoxetine have not been studied in HIV-infected adolescents or children.

1.147 Paroxetine
Description
Paroxetine is a selective serotonin reuptake inhibitor commonly used to treat depression, anxiety disorders, premenstrual dysphoric disorder, and menopause symptoms. Along with the immediate-release tablets and oral suspension, an extended-release tablet formulation is available (although both immediate and extended-release formulations are administered once daily). A bioequivalent salt form, paroxetine mesylate, is also approved.

Paroxetine is completely absorbed after oral administration. It is widely distributed and 93 – 95% protein-bound. Paroxetine is a substrate and potent inhibitor of CYP 2D6. Within the first week or two of dosing, paroxetine saturates the 2D6 pathway, and the steady-state AUC is several fold higher than that predicted from the single-dose due to excess accumulation from this saturation. At steady-state when 2D6 is saturated, paroxetine clearance becomes governed
by alternative CYP enzymes such as CYP 3A4, which does not become saturated. The elimination half-life of the immediate-release product is 21 hours, while the elimination half-life of the controlled-release product is 15 – 20 hours.

**Pharmacokinetics of Paroxetine in HIV-uninfected children and adolescents.**

Paroxetine has been studied in 27 children and 35 adolescents in doses of 10, 20 and 30 mg daily [34]. Oral clearance and volume of distribution were highly dependent on paroxetine dose, CYP 2D6 genotype and weight, but not age or sex. At each dose level, paroxetine systemic exposure was higher in children than in adolescents, but the differences were greatest with the lowest doses. The differences lessened with increasing doses, and disappeared when corrected for weight between the age groups.

**Pharmacokinetics of Paroxetine in HIV-infected children and adolescents.**

Pharmacokinetics of paroxetine have not been studied in HIV-infected adults, adolescents or children.

1.15: Potential for Antiretroviral and Psychiatric Drug Interactions

In addition to a paucity of PK data noted above, drug interactions between ARV and psychiatric medications in HIV-1 infected children and adolescents have not been described. Some of the differences in severity of psychiatric symptoms in these patients as compared to non-HIV-1 infected patients could potentially be due to inadequate or toxic exposure to the psychiatric agents stemming from drug interactions between the psychotropics and the ARVs or the psychotropics and the HIV-1 disease itself […]

The most commonly used psychiatric medication in children, methylphenidate, is hepatically metabolized, but not by oxidation (the method of the cytochrome P450 enzymes).

1.16: Pharmacogenetics of Antiretrovirals and Psychotropics

1.163: […] The metabolic phenotype can provide an initial estimate of CYP 2D6 activity. If CYP 2D6 appears to be important in amphetamine psychotropic metabolism, a genotypic analysis can be explored in this pilot study setting.

Section 4.1: Drug Regimens, Administration and Duration

P1080 will enroll subjects who are receiving specific antiretroviral and/or psychiatric medications that are prescribed by their physician (psychiatric medications are described in sections 5.11 and 5.12). Subjects must have been on the same dose and formulation of these psychiatric study medications for at least ± 2 weeks prior (at least 5 weeks for fluoxetine) to each of the PK visit. HIV-1 infected subjects will have been taking their antiretroviral regimen at the same dose and formulation for at least 4 weeks prior to the two PK visit in this study.

Section 9.11: The primary clinical pharmacology objective of this study is: To assess the steady-state pharmacokinetics of selected psychiatric medications methylphenidate and amphetamine/dextroamphetamine in HIV-1 infected and uninfected pediatric subjects.
12. Section 1.21, Rationale for Psychiatric Medication Study Arms, has been updated:

The psychiatric medications selected for Version 1 of this study protocol, methylphenidate, and amphetamine/ dextroamphetamine, were identified in P1055 as the agents most commonly used by HIV-1 infected children and adolescents for ADHD and related disorders, and those most likely to be used in the near future; however, pharmacokinetic data in HIV-1 infected pediatric subjects is not available. Further, no data exist regarding potentially significant drug interactions between these agents and antiretrovirals.

The formulations selected for this study include immediate release, sustained release, and the commonly used biphasic release (combinations of immediate and sustained release in a single product). While the newer biphasic formulations have been studied in healthy adult volunteers, pharmacokinetic studies have not been reported for HIV-1 infected or HIV uninfected children and adolescents.

The psychiatric medications selected for Version 2 of this protocol are those identified in Site Surveys as the top agents commonly used by HIV-infected adolescents for psychiatric disorders. These include citalopram/escitalopram, risperidone, sertraline, fluoxetine, and paroxetine used for depression and other psychiatric disorders. Specifically, in the fall of 2011, the P1080 team conducted a site survey to assess how many patients ages ≥ 6 to < 12 and ≥ 12 to < 25 years at study sites were taking other psychiatric medications. We queried all sites for use of the following medications: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion, atomoxetine, guanfacine, clonidine, risperidone, quetiapine, lamotrigine, oxcarbazepine and valproate. We also asked open-ended questions to collect any additional psychiatric medications currently being used.

For the 6 – 12 year old age group, the use of these medications was not high. In general, anywhere from 0 to 4 sites (usually 1 or 2 sites) reported having between 1 and 5 patients on each of these individual medications. In subjects from ≥ 12 to < 25 years of age, several drugs were fairly commonly used. In descending order, 22 out of 28 sites reported that they had between 1 and 5 patients taking sertraline. For risperidone, 17 of 27 sites had 1 to 5 subjects taking this medication. For citalopram and escitalopram, 14 of 26 sites, had 1 to 5 patients taking citalopram and 14 of 27 sites had 1 to 5 patients taking escitalopram. For fluoxetine, 13 of 27 sites had 1 to 5 patients taking this drug. For paroxetine, 5 of 24 sites had 1 to 5 patients, and 1 site had 6 to 10 patients taking this drug. No sites reported fluvoxamine use.

Approximately 90% of sites reported that at least some of the subjects taking these various psychiatric medications were concomitantly taking a ritonavir-boosted PI-based ARV regimen. Approximately 60% reported some of the subjects concurrently taking an efavirenz-based ARV regimen.

We would like to collect information on both fluoxetine and paroxetine, as our site survey indicates that these medications are being used in our patient populations, and we have no PK data in HIV-infected youth. Because the numbers of subjects may not be high enough to enroll a full cohort for each of these drugs, we propose enrolling subjects on either drug into a fourth study arm. The anticipated sample size would remain 15 subjects per stratum, and 45 subjects total for that arm, with a maximum of 10 subjects per drug in each stratum. The study team believes that PK data from 15 to 30 subjects on each of these medications would still be an extremely valuable contribution to the biomedical literature, even if a full 45 subjects on each drug will not be enrolled.
Lifetime prevalence rates of major depressive disorder by age 19 are estimated to be 28% [66]. SSRIs are commonly used to treat symptoms of depression and related psychiatric disorders in adolescent patients. Therefore, children and adolescents < 25 years of age who are taking these psychiatric medications will be included. Again, no pharmacokinetic data are available for the use of these agents in HIV-infected populations. Additionally, limited pharmacokinetic data are available in uninfected children and adolescents, particularly for risperidone.

13. Section 1.22, Rationale for Study Strata has been updated:

[…] For the HIV-1 infected subjects, the concomitant antiretroviral medications of efavirenz or ritonavir will be studied, as those are commonly used agents that are most likely to be included in the antiretroviral medication regimen.

In Version 1 of the protocol, we staggered enrollment of HIV-infected subjects, followed by rough selection of appropriate age/sex/race HIV-uninfected subjects, in order to roughly match the demographic characteristics of the two groups. We found that the HIV-uninfected subjects that were submitted for potential enrollment from the study sites did, in fact, fairly closely match the demographics of the HIV-infected group (even if we had not used the selection process), so the complicated screening and staggered enrollment should not be necessary in Version 2 of the protocol. Instead, enrollment of both HIV-infected and HIV-uninfected adolescents will occur simultaneously.

14. Section 1.23, Rationale for Study Design has been updated:

 […] Subjects may be enrolled if they have already been receiving a psychiatric medication of interest for ≥ 2 weeks (≥ 5 weeks for fluoxetine) prior to the pharmacokinetic study assessment. If the psychiatric medication is prescribed on school days (Monday through Friday) the subject will need to have taken all doses for at least two consecutive days prior to the pharmacokinetic assessment to ensure steady-state.

[…] For the arms in Version 2, fewer formulations are available, with the vast majority being simply immediate release oral dosage forms with similar absorption profiles. The clearance of the drug (the primary or gold-standard PK parameter), along with other PK parameters of interest can be estimated from the combined cohort regardless of the included formulations by using population modeling and the corresponding two absorption rates.

The powerful computational power of population analysis essentially accounts or corrects for different subject size and age, doses, and absorption rates (formulations) to estimate pharmacokinetic parameters in the entire cohort taking the drug of interest. There are 2 different sampling strategies (6 hours and 12 hours), depending on the formulation used. The specific sampling times were selected to ensure that the appropriate information will be collected in order to develop the population models.

15. Section 1.24, Summary Rationale has been updated:

Many knowledge gaps exist for the appropriate use of psychiatric medications in children and adolescents. In HIV uninfected children, pharmacokinetic data available for the psychiatric stimulant drugs are limited mainly to immediate release and older, less commonly used, preparations.

[…] Given the current state of knowledge (or lack thereof), predicting psychiatric medication exposure in HIV-1 infected children and adolescents on and off ARVs is fraught with uncertainty.
16. Section 1.25, Summary of Version 1, has been included:

As of January 2014, 82 of 90 subjects in Arms 1 and 2 have been enrolled. 78 subjects have completed the one-year study, and 4 subjects are still on study. Methylphenidate concentrations have been measured in 30 subjects at the first pharmacokinetic (PK) visit (Visit A), and in 24 of those subjects at the final PK visit (Visit B). The mean (range) age was 12.1 (6 – 21) years; weight was 46 (18.6 – 73.5) kg; 18 were male; 24 were Black, 5 White, and 1 mixed race. Nine were HIV-. HIV+ were on efavirenz (EFV; n=6) and ritonavir boosted protease inhibitors (RTV-PI; n=15). Demographics were similar between strata. Subjects took Concerta® (n=22), Metadate CD® (n=3), RitalinLA® or FocalinXR® (n=4), and immediate-release methylphenidate (n=2). The mean (range) daily dose was 32 (10 – 66) mg. Geometric means (coefficients of variation) of selected parameters are summarized in Table 1.

Table 1. Methylphenidate Preliminary Results

<table>
<thead>
<tr>
<th>Group</th>
<th>Uninfected</th>
<th>Infected</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=9, Visit A</td>
<td>n=21, Visit A</td>
<td></td>
</tr>
<tr>
<td>Daily Dose at Visit A</td>
<td>23 (19%)</td>
<td>31 (14%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Average Concentration (ng/mL) Normalized to 36 mg Dose, Visit A</td>
<td>3.8 (95%)</td>
<td>2.4 (90%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Daily Dose at Visit B</td>
<td>25 (17%)</td>
<td>31 (14%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Average Concentration (ng/mL) Normalized to 36 mg Dose, Visit B</td>
<td>4.7 (27%)</td>
<td>2.9 (84%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Overall Average Concentration (ng/mL) per Subject Normalized to 36 mg Dose</td>
<td>5.3 (39%)</td>
<td>2.7 (63%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Overall dose-normalized average concentrations were also significantly different between the strata; 5.3 (39%) in HIV-, 3.0 (65%) in RTV-PI, and 2.3 (47%) ng/mL in EFV subjects (p=0.047). A repeated measures comparison of the average dose-normalized concentration only in subjects who completed both visits was not significantly different by HIV status (p=0.26); Visit A and B geometric mean (%CV) concentrations in HIV- (n=8) were 3.3 (107%) and 4.7 (27%) ng/mL; and in HIV+ (n=16) were 2.6 (84%) and 2.9 (84%) ng/mL.

Our preliminary conclusion is that HIV+ children and adolescents have lower methylphenidate exposure at a given dose than uninfected children. EFV and possibly RTV-PI can induce methylphenidate metabolism; additional study is justified to develop dosing guidance for this population who may require higher doses of methylphenidate to achieve therapeutic systemic exposures. These preliminary results were presented at the Conference on Retroviruses and Opportunistic Infections in Atlanta, GA from Mar 3- 7, 2013.

As of January 2014, the team has been assaying the amphetamine/ dextroamphetamine samples to begin to analyze the pharmacokinetic findings of that study arm. Once the amphetamine assays are completed, the remainder of the methylphenidate samples will be assayed so the findings for both arms can be finalized and published.
17. Section 3.0, Study Design, has been updated: P1080 is a pilot population pharmacokinetic study of HIV-1 infected and uninfected children and adolescents who are taking selected psychiatric medications methylphenidate or amphetamine/dextroamphetamine for the treatment of ADHD. The study subjects in Version 2 will be accrued within a one year period. Subjects will be on study for up to fourteen months. Enrollment progress will be followed by tracking accrual at sites monthly, with a regular review of accrual targets to ensure that enrollment remains on track. **Note: subjects enrolled under Version 1.0 will complete follow up as per Appendix I-A; subjects enrolled under Version 2.0 will complete evaluations and follow up as per Appendix I-B.**

HIV uninfected subjects will be recruited **per the description** in Section 4.6, from the siblings/household members of HIV-1 infected subjects at IMPAACT sites, in a similar fashion to the successful recruitment strategy of P1055 (described in Section 4.6). The group of uninfected subjects will be matched to the group of HIV-1 infected subjects by age, gender and race within each arm. All subjects enrolled in Version 2.0 will have a screening/entry visit, one two PK visit, and three follow-up telephone calls. These two three visits and three follow-up calls are described in Sections 3.1 and 3.2 3.3 and 3.4. On the basis of subjects’ HIV status and medications, **in each arm**, they will be divided into 3 strata as indicated in Table 2 below.

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Arm: Psychiatric Study Drug Methylphenidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>15 HIV uninfected subjects</td>
</tr>
<tr>
<td>B</td>
<td>15 HIV-1 infected subjects who are taking (prescribed) concomitant efavirenz</td>
</tr>
<tr>
<td>C</td>
<td>15 HIV-1 infected subjects who are taking a (prescribed) protease inhibitor (PI)* with concomitant ritonavir (at boosting doses) or lopinavir/ritonavir</td>
</tr>
</tbody>
</table>

*PI may be any of the following: atazanavir, darunavir, fosamprenavir, indinavir, saquinavir or tipranavir

**Under Version 1.0, the Study Arms were:**

- Arm 1: Methylphenidate
- Arm 2: Amphetamine/Dextroamphetamine

**Under Version 2.0, the Study Arms Open to Enrollment are:**

- Arm 3: Citalopram or Escitalopram
- Arm 4: Risperidone
- Arm 5: Sertraline
- Arm 6: Fluoxetine or Paroxetine

18. Section 3.1 (Screening/Entry Visit) has been updated to clarify inclusion criteria 4.15: **Per the inclusion criteria** (section 4.15), the **subject must be taking citalopram, escitalopram, risperidone, sertraline, or paroxetine for at least 2 weeks or fluoxetine for at least 5 weeks prior to enrollment to be eligible for this study.**
19. Updates to study procedures during the Pharmacokinetic (PK) Visit have been included in Section 3.2, 3.2.1, 3.22 and 3.23.

Section 3.2: Week 6 Pharmacokinetic (PK) Visit

Approximately two days prior to the PK visit, the sites will contact subjects/caregivers by phone to verify and encourage reinforce adherence for all medications (ARV and psychiatric) and to confirm that the PK visit can proceed as scheduled (see section 9.2).[...] The PK visit will include a pharmacokinetic assessment (see Section 3.21) with medication history, an adherence survey, a Vanderbilt Scale questionnaire, an electrocardiogram if the subject has not had one for routine clinical care within the past 6 months and a genotypic (see Section 3.22) and phenotypic (see Section 3.23) assessment. [...] Similarly, all subjects must be taking their psychiatric medications consistently for at least 4-2 weeks (at least 5 weeks for fluoxetine) prior to enrollment. Note that subjects must be 100% adherent with psychiatric and (if HIV-1 infected) with antiretroviral medications in the 48 hours prior to the PK visit.

Subjects who are prescribed one of the psychiatric medications under study either methylphenidate or amphetamine/dextroamphetamine for symptomatic control of ADHD will be eligible for this study. Subjects may be taking prescribed methylphenidate or amphetamine/dextroamphetamine either daily or only on certain days of the week. For example, a pediatric subject who takes a stimulant medication as prescribed once daily on Monday through Friday (schooldays) every week will qualify for the study. If the psychiatric medication is prescribed on school days (Monday through Friday), the subject should have taken doses for at least two consecutive days before they are eligible for the PK visit. In the example above, if the subject taking a stimulant on Monday through Friday, the subject would be able to schedule a PK visit on Wednesday, Thursday or Friday.

Additionally, female subjects of child bearing potential will be required to take a pregnancy test, which must be negative for the subject to continue on the study.

Section 3.21: PK Sampling

Each The PK visit should be scheduled so that a witnessed dose of psychiatric and antiretroviral medications will occur on time (according to that subject’s dosing regimen) [...]

[...] Six Either 4 or 5 pharmacokinetic blood samples will be collected according to the schedule in Appendix II, depending on the psychiatric drug formulation that the subject is taking. Sample times are pre-dose, 2, 4, 6, 12 and 24 hours post-dose plus an additional 12 hour post-dose sample for some formulations, e.g. extended release formulations.

3.22: Genotypic Assessment

An additional blood sample will be collected and processed to obtain DNA at the PK visit only from every subject who consents to genetic testing [...]

3.23: Phenotypic Assessment

[...] This void is discarded and NOT included in the collection. [...] All urine produced for the 4 hours after the dextromethorphan dose will be collected. The volume-The date and time of the dextromethorphan dose will be recorded, and this will be the start time of the 4-hour urine collection. All urine produced for the 4 hours after the dextromethorphan dose will be collected. The date and time of the first void within the 4-hour time window should be recorded. The subject should be asked to empty their bladder at the 4-hour time point, and this final sample should be included in the urine collection. The date and time of the final void
within the 4-hour time window should be recorded (even if it occurs earlier than exactly at the 4-hour urine collection time point) as the last collection date and time. All urine collected within the 4-hour window will be pooled as a single specimen. The total volume of that specimen will be measured and recorded, and a 15 mL aliquot will be stored for analysis of dextromethorphan, dextrorphan and 3-hydroxy-morphinan concentrations in the urine.

20. Reference to the Week 24 Pharmacokinetic (PK) Visit and follow-up Telephone calls have been removed in Section 3.3, 3.4, 4.4, and 9.21:

3.3 Week 24 Pharmacokinetic (PK) Visit

The second PK visit will take place at approximately 24 weeks following the study subject’s screening visit. The procedures for the second PK visit will be identical to the first PK visit with two exceptions. First, an additional blood sample for the genotypic assessment is not necessary at the second PK visit. Second, an electrocardiogram is not necessary at the second PK visit. Additionally, female subjects of child bearing potential will be required to take a pregnancy test, which must be negative for the subject to continue on the study. All other procedures will occur as outlined above (in section 3.2).

Section 3.4: Weeks 30, 42 and 52 Telephone Calls

At weeks 30, 42 and 52, the study subjects/caregivers will be contacted by telephone to collect information regarding any dose, drug, or regimen changes, reasons for regimen changes, symptom control using the Vanderbilt Scale, and tolerance for both psychiatric and antiretroviral medications.

Section 4.4: Deferral of Pharmacokinetic (PK) Visits

The Week 6 and Week 24 pharmacokinetic visit may be deferred if needed within the visit window for any of the following reasons, described below.

4.41 If required, the week 6 and Week 24 PK visit may be deferred as needed until the subject is 100% adherent with psychiatric medications and (if HIV-1 infected) with antiretroviral medications in the 48 hours prior to the visit.

4.42 The week 6 PK and Week 24 visit may be deferred as needed if the subject has an intercurrent acute illness that may affect the study outcome.

Section 9.2.1: Deferral of Pharmacokinetic (PK) Visits

The Week 6 and Week 24 pharmacokinetic visits may be deferred if needed within the visit window for any of the following reasons, described below. If the deferral falls outside of the visit window, the site should contact the P1080 team for approval before proceeding with the PK visit.

- If required, the week 6 and/or week 24 PK visits may be deferred as needed until the subject is 100% adherent with psychiatric medications and (if HIV-1 infected) with antiretroviral medications in the 48 hours prior to the visit.

- The week 6 and/or week 24 PK visit may be deferred as needed if the subject has an intercurrent acute illness that may affect the study outcome.
21. Section 3.6, “Early Discontinuation” has been removed:

Subjects who withdraw from the study before the Week 52 call will be requested to return to the clinic for a final visit (See Appendix I).

Refer to Appendix I, Schedule of Evaluations for specific study requirements.

22. Inclusion Criteria has been updated in Sections 4.1 and 4.2:

4.1 Inclusion Criteria for HIV-1 Infected Subjects (Version 2.0)

4.11 Children and adolescents age ≥6 to <25 years at entry.

4.12 Documentation of HIV-1 infection is defined as positive test results from two samples collected at different time points. All samples tested must be whole blood, serum or plasma. Results abstracted from medical records can be used to satisfy this criterion.

Sample #1 may be tested by non-study public program. However, both the result and the assay date must be recorded in subject’s charts. Source documentation {patient’s medical record/chart, Ministry of Health (MOH) registers, laboratory results, etc.} must be available if requested.

Sample #2 must be performed in a CAP/CLIA-approved laboratory (for US sites).

Acceptable Tests

Sample #1 may include be tested using any of the following:

- Two rapid antibody tests from different types of tests listed below, as long as they are positive test results obtained from the 2 manufacturers or based on different samples, principles and epitopes.
- One EIA OR Western Blot OR immunofluorescence OR chemiluminescence
- One HIV-1 DNA PCR
- One quantitative HIV-1 culture RNA PCR ≥5,000 copies/mL (above the limit of detection)
- One qualitative HIV-1 RNA PCR
- One HIV culture (prior to August 2009)
- One total HIV nucleic acid test
Sample #2 may be tested using any of the following:

- **Rapid** antibody test any licensed ELISA test kit. If this option is used in combination with two rapid tests for Sample #1, at least one of the three rapid tests must be FDA-approved and **confirmation by either serum HIV-1 antigen** the third rapid test. HIV-1 antibody test done by must be from a method that is not an ELISA-third manufacturer or based on a third principle or epitope.
- **One EIA OR Western Blot or plasma OR immunofluorescence OR chemiluminesence**
- **One HIV-1 RNA DNA PCR**
- **One quantitative HIV RNA PCR (above the limit of detection)**
- **One qualitative HIV RNA PCR**
- **One HIV culture (prior to August 2009)**
- **One total HIV nucleic acid test**

[...]

4.15 Subject must be taking **citalopram, escitalopram, risperidone, sertraline, or paroxetine** methylphenidate or amphetamine/dextroamphetamine for treatment of ADHD for at least 2 weeks or **fluoxetine for at least 5 weeks** prior to enrollment.

4.151 Allowable **citalopram or escitalopram** methylphenidate formulations include:
- immediate-release oral solution or tablets (Methylin Celexa®, Ritalin Lexapro® or other generic.) Focalin®)
- sustained-release (Ritalin® SR, Metadate® ER or generic), or
- biphasic (Ritalin®-LA, Metadate®-CD, Concerta®, Focalin®-XR)

4.152 Allowable **risperidone** formulations for amphetamine/dextroamphetamine include:
- immediate-release oral solution or tablets (Risperdal®, Risperdal M-Tab® or other generic).

4.153 Allowable **sertraline formulations include**: immediate-release oral solution or tablets (Zoloft® or other generic).

4.154 Allowable **fluoxetine formulations include**: immediate-release oral solution, capsules or tablets (Prozac® or other generic).

4.155 Allowable **paroxetine formulations include**: immediate-release oral suspension, capsules or tablets (Paxil®, Pexeva®, Brisdelle® or other generic) or controlled-release tablets (Paxil CR® or other generic). Adderall®, Adderall® XR, Dexedrine®, Liquadd™, and Dexedrine Spansules® (and any generic equivalents).

4.156 For **all both study arms**, any dose up to the maximum **recommended FDA approved dose by age** (see Section 5.3) will be allowed.
4.2 Inclusion Criteria for HIV Uninfected Subjects

4.21 Children and adolescents age ≥6 to <25 years at entry.

4.22 Subject is not known to be HIV-1 infected.

Note: For perinatally-exposed subjects, definitive exclusion of HIV-1 infection in a non-breastfed infant is based on two or more negative virologic tests, with one obtained at age ≥1 month and one at ≥4 months, or two negative HIV-1 antibody tests from separate specimens obtained at age ≥6 months. Born to an HIV-infected mother will be considered when two separate peripheral blood specimens are drawn on different days and both are negative for HIV DNA or HIV-1 RNA. These tests must be performed in a CLIA-certified laboratory that is approved to perform the assay for protocol testing. Specimens must be drawn at least 4 weeks apart and must be drawn when the infant is four weeks of age or older and has been off antiretroviral drugs for at least two weeks. At least one specimen should be drawn when the infant is greater than 8 weeks of age.

4.23 Subject must be taking citalopram, escitalopram, risperidone, sertraline, or paroxetine for at least 2 weeks or fluoxetine for at least 5 weeks prior to enrollment.

4.231 Allowable citalopram or escitalopram formulations include: immediate-release oral solution or tablets (Celexa®, Lexapro® or other generic).

4.232 Allowable risperidone formulations include: immediate-release oral solution or tablets (Risperdal®, Risperdal M-Tab® or other generic).

4.233 Allowable sertraline formulations include: immediate-release oral solution or tablets (Zoloft® or other generic).

4.234 Allowable fluoxetine formulations include: immediate-release oral solution, capsules or tablets (Prozac® or other generic).

4.235 Allowable paroxetine formulations include: immediate-release oral suspension, capsules or tablets (Paxil®, Pexeva®, Brisdelle® or other generic) or controlled-release tablets (Paxil CR® or other generic).

4.236 For all study arms, any dose up to the maximum recommended dose by age (see Section 5.3) will be allowed.

4.23 Subject must be taking methylphenidate or amphetamine/dextroamphetamine for treatment of ADHD for at least one week prior to enrollment.

4.231 Allowable methylphenidate formulations include: immediate-release (Methylin®, Ritalin® or other generic, Focalin®), sustained-release (Methyltin®-ER, Ritalin®-SR, Metadate®-ER or generic), or biphasic (Ritalin®-LA, Metadate®-CD, Concerta® and Focalin®-XR)

4.232 Allowable formulations for amphetamine/dextroamphetamine include: Adderall®, Adderall®-XR, Dexedrine®, Liquadd™, and Dexedrine Spansules® (and any generic equivalents).

4.233 For both arms, any dose up to the maximum FDA-approved dose by age (see Section 5.3) will be allowed.

4.26 [...] must agree to avoid pregnancy during the entire 144-week trial and to consistently and appropriately use at least two of the following contraception methods: [...]
23. Exclusion Criteria 4.32 has been deleted as not applicable to study drugs of interest under Version 2.0 and criteria 4.31 and 4.35 (under new numbering) have been revised:
   4.31 A positive urine test at screening for use of the following disallowed drugs: methamphetamine; methadone, barbiturates; benzodiazepines; opiates; or phencyclidine; or propoxyphene.
   4.32 Treatment with other routine (medications prescribed for daily and/or consistent use) psychiatric medications concurrently (due to the high likelihood of increasingly complicated and unpredictable drug interactions). Psychiatric medications prescribed for occasional use (such as as-needed anti-anxiety or anti-insomnia medications) will be allowed for study entry, but should not be used in the week prior to the PK Visit (see Disallowed Medications, Section 4.5).
   4.35 Study drugs prescribed above the FDA recommended maximum dose by age (see Section 5.3).

24. Disallowed Drugs have been updated in Section 4.5:

The drugs listed below are disallowed for 1 week prior to the first or second PK visit and the day of the first and second PK visit.
   4.51 Bupropion has been removed from the list
   4.52 and 4.53: Atomoxetine has been removed from both lists
   4.53 For amphetamine/dextroamphetamine, the following drugs are disallowed:
      […]
      • Fluoxetine
      • Paroxetine
      • Quinidine
   4.55 For ritonavir, the following drugs are disallowed:
      […]
      • SSRI: St. John’s Wort (hypericum perforatum)
   4.56 For citalopram/escitalopram, the following drugs are disallowed:
      • Monoamine oxidase inhibitors: isocarboxazid, moclobemide, phenelzine, tranylcypromine, linezolid, selegiline, procarbazine, furazolidone
      • Neuroleptic: pimozide
   4.57 For risperidone, the following drugs are disallowed:
      • Carbamazepine
      • Fluoxetine
      • Paroxetine
   4.58 For sertraline, the following drugs are disallowed:
      • Disulfiram (for the oral concentrate solution)
      • Monoamine oxidase inhibitors: isocarboxazid, moclobemide, phenelzine, tranylcypromine, linezolid, selegiline, procarbazine, furazolidone
      • Neuroleptic: pimozide
4.59 For fluoxetine, the following drugs are disallowed:
   - Monoamine oxidase inhibitors: isocarboxazid, moclobemide, phenelzine, tranylcypromine, linezolid, selegiline, procarbazine, furazolidone
   - Neuroleptic: pimozide
   - Thioridazine

4.510 For paroxetine, the following drugs are disallowed:
   - Monoamine oxidase inhibitors: isocarboxazid, moclobemide, phenelzine, tranylcypromine, linezolid, selegiline, procarbazine, furazolidone
   - Neuroleptic: pimozide
   - Thioridazine

25. Section 4.6, Enrollment Procedures, has been updated:

   [...]Subjects for the HIV-1 infected strata will be recruited from the patients who are routinely evaluated at each domestic IMPAACT site. **Subjects for the HIV uninfected strata can be recruited from members of households with a parent, sibling or other family member who has been infected with HIV-1. [...]** Sites are encouraged to enroll uninfected subjects with similar demographic characteristics (race, sex, age) as the HIV-infected subjects enrolled by that site to the study.

26. Study Treatment has been updated in Section 5.0:

   5.1 Drug Regimens, Administration and Duration

   [...] Subjects must have been on the same dose and formulation of these psychiatric study medications for at least 1 week, 2 weeks prior (at least 5 weeks for fluoxetine) to each of the PK visits. [...] for at least 4 weeks prior to the two PK visits in the study [...]"
5.12 Arm 2: Amphetamine/dextroamphetamine

5.12.1 HIV-1 Infected Pharmacokinetic Sampling Day Dosing Schedule

Single oral dose of dextromethorphan cough syrup will be administered (15 mg for subjects ≥6 to <12 years old, 30 mg for subjects ≥12 to <25 years old).

Observed dose of mixed amphetamine salts (amphetamine/dextroamphetamine) or dextroamphetamine sulfate up to the maximum FDA-approved dose using a formulation listed in 5.2:

Observed dose of one of the following regimens:
- Efavirenz orally at an FDA-approved dose;
- Atazanavir, darunavir, fosamprenavir, indinavir, saquinavir or tipranavir at FDA-approved dose and boosting ritonavir to a maximum of 200 mg twice daily;
- Lopinavir/ritonavir at an FDA-approved dose. Other doses of the protease inhibitor will be considered subject to pre-approval by the protocol chair.

5.12.2 HIV Uninfected Cohort Pharmacokinetic Sampling Day Dosing Schedule

Single oral dose of dextromethorphan cough syrup will be administered (15 mg for subjects ≥6 to <12 years old, 30 mg for subjects ≥12 to <25 years old).

Observed dose of mixed amphetamine salts (amphetamine/dextroamphetamine) or dextroamphetamine sulfate orally up to the maximum FDA-approved dose using a formulation listed in Section 5.2.

Section 5.2: Drug Formulation

For the methylphenidate arm (closed to enrollment in Version 2), the following formulations are allowed in this study […]

For the amphetamine/dextroamphetamine arm (closed to enrollment in Version 2), the following formulations are allowed in this study […]

For the citalopram/escitalopram arm, the following formulations are allowed in this study:
- Celexa® (citalopram hydrobromide) Oral Solution (or generic equivalent oral solution)
- Celexa® (citalopram hydrobromide) Tablets (or generic equivalent tablets)
- Lexapro® (escitalopram oxalate) Solution (or generic equivalent solution)
- Lexapro® (escitalopram) Tablets (or generic equivalent tablets)

For the risperidone arm, the following formulations are allowed in this study:
- Risperdal M-Tab® (risperidone) Orally Disintegrating Tablets (or generic equivalent orally disintegrating tablets)
- Risperdal® (risperidone) Oral Solution (or generic equivalent oral solution)
- Risperdal® (risperidone) Tablets (or generic equivalent tablets)

For the sertraline arm, the following formulations are allowed in this study:
- Zoloft® (sertraline hydrochloride) Concentrate Solution (or generic equivalent concentration solution)
- Zoloft® (sertraline hydrochloride) Tablets (or generic equivalent tablets)

For the fluoxetine arm, the following formulations are allowed in this study:
- Prozac® (fluoxetine hydrochloride) Pulvule (or generic equivalent capsules)
- Prozac® (fluoxetine hydrochloride) Solution (or generic equivalent solution)
- Prozac® (fluoxetine hydrochloride) Tablets (or generic equivalent tablets)
For the paroxetine arm, the following formulations are allowed in this study:

- Paxil® (paroxetine hydrochloride) Suspension (or generic equivalent suspension)
- Paxil® (paroxetine hydrochloride) Tablets (or generic equivalent tablets)
- Paxil CR® (paroxetine hydrochloride) Controlled-Release Tablets (or generic equivalent controlled-release or extended-release tablets)
- Pexeva® (paroxetine mesylate) Tablets (or generic equivalent tablets)
- Brisdelle® (paroxetine mesylate) Capsules (or generic equivalent capsules)

Section 5.3: **Recommended FDA Approved Maximum Daily Doses**

<table>
<thead>
<tr>
<th>Drug Formulation</th>
<th>FDA-approved (or Recommended) Maximum Daily Dose</th>
</tr>
</thead>
</table>
| Methylin® Ritalin® (or generic equivalent), Ritalin® SR, Metadate® ER (or generic equivalent), Ritalin® LA, Metadate® CD | ≥6 to 12 years: 60 mg daily  
>12 years: 60 mg daily |
| Concerta® | ≥6 to 12 years: 54 mg daily  
13 to 17 years: 72 mg daily (not to exceed 2 mg/kg/day)  
>17 years: 72 mg daily |
| Focalin® and Focalin® XR | ≥6 to 12 years: 20 mg daily  
>12 years: 20 mg daily |
| Adderall® Dextedrine® Liquadd™ (or generic equivalent), Dextedrine Spansule CD® (or generic equivalent) | ≥6 to 12 years: 40 mg daily  
>12 years: 60 mg daily |
| Adderall® XR | ≥6 to 12 years: 30 mg daily  
>12 years: 30 mg daily |
| Celexa (or generic equivalent) | >12 years to <18 years: 40 mg daily*  
>18 years: 40 mg daily |
| Lexapro (or generic equivalent) | >12 years: 20 mg daily |
| Risperdal (or generic equivalent) | >12 years to <18 years: 6 mg daily  
>18 years: 6 mg daily (bipolar); 16 mg daily (schizophrenia) |
| Zoloft (or generic equivalent) | >12 years: 200 mg daily |
| Prozac (or generic equivalent) | >12 years to <18 years: 60 mg daily  
>18 years: 80 mg daily |
| Paxil immediate release (or generic equivalent) | >12 years to <18 years: 50 mg daily**  
>18 years: 60 mg daily |
| Paxil CR controlled release (or generic equivalent) | >12 years to <18 years: 50 mg daily**  
>18 years: 75 mg daily |

* Doses of up to 40 mg daily have been studied in adolescents off-label  
** Doses of up to 50 mg daily have been studied in adolescents off-label

27. Toxicity Management has been updated in Section 6.1:  
Protocol participation requires but does not prescribe therapy with methylphenidate oramphetamine salts selected psychiatric medications ("study drugs") [...]

28. Section 6.22 (Vomiting During a PK Visit) has been updated:  
[...] Blood samples will be drawn over **24 hours.** 6 to 12 hours depending on psychiatric drug formulation (see Appendix II).
29. Reporting Requirements have been updated in Section 7.2
   The study agents for which expedited reporting are required are formulations of methylphenidate, amphetamine/dextroamphetamine, citalopram, escitalopram, risperidone, sertraline, fluoxetine and paroxetine and dextromethorphan cough syrup.

30. Statistical Considerations, in Section 8.0, has been updated to account for the additional study arms:
   Section 8.1: General Design Issues

   This is an opportunistic study that will include HIV-1 infected and uninfected subjects who are taking selected common psychiatric medications for symptomatic relief of ADHD.

   The study will enroll subjects who are already taking the study drugs of interest:
   - **Under Version 1.0:** methylphenidate, amphetamine/dextroamphetamine
   - **Under Version 2.0:** citalopram, escitalopram, risperidone, sertraline, fluoxetine and paroxetine.

   Subjects will be replaced if during Week 6 the pharmacokinetic results […]

   Section 8.4 Sample Size and Accrual
   HIV-1 infected subjects will be enrolled first to determine the proportion of HIV-1 infected subjects according to three demographic characteristics: age group (≥6 to < 12; ≥12 to < 25), gender (male; female) and race/ethnicity (white, non-Hispanic; black, non-Hispanic; Hispanic; other). HIV uninfected subjects will then be enrolled in similar proportions to ensure that the groups are comparable. Specifically, individuals in each age category will be counted by gender and by race/ethnicity table for the HIV-1 infected subjects, and will be enrolled in parallel proportion of HIV uninfected subjects (allowing at most a 10% discrepancy per cell). The planned population pharmacokinetic analysis will compare groups of subjects; therefore groups with similar overall demographics would need to be enrolled. Individual paired comparisons are not performed in a population pharmacokinetic analysis, so the protocol will not match specifically on an individual-to-individual basis. Weight information will be collected and incorporated into the pharmacokinetic parameter estimates to account for size.

   Forty-Under Version 1.0, planned accrual was forty-five subjects will be enrolled in each of the two arms (Arms 1 and 2) for a total of 90 subjects. Under Version 2.0, forty-five subjects will be enrolled in each of 4 arms, for a total of 180 subjects; total planned accrual in both versions: 270 subjects. The primary objective is to estimate the mean oral clearance in pediatric subjects for each psychiatric medication. Fifteen subjects with evaluable PK data will be enrolled into each HIV-1 status/psychiatric medication/ARV cell Arms 1 and 2 for each arm, and secondary objectives are to estimate mean oral clearance for each psychiatric medication for HIV-1 infected versus uninfected and in each cell.
Table 4: Published Estimates of the Mean and Coefficient of Variation (CV) for Each Psychiatric Medication

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Clearance (mean)</th>
<th>CV</th>
<th>SD</th>
<th>Estimated width of 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N=5</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>0.4 (L/h/kg)</td>
<td>30%</td>
<td>0.12</td>
<td>±0.15</td>
</tr>
<tr>
<td>Amphetamine/dextroamphetamine</td>
<td>30 (L/h)</td>
<td>30%</td>
<td>9.00</td>
<td>±11.17</td>
</tr>
<tr>
<td>Citalopram</td>
<td>15.2 (L/hr)</td>
<td>10%</td>
<td>1.5</td>
<td>±1.86</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>34.9 (L/hr)</td>
<td>41%</td>
<td>14.2</td>
<td>±17.63</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>0.18 (L/kg/hr)</td>
<td>50%</td>
<td>0.09</td>
<td>0.08</td>
</tr>
<tr>
<td>Paroxetine (20 mg)</td>
<td>0.54 (L/kg/hr)</td>
<td>76%</td>
<td>0.41</td>
<td>±0.51</td>
</tr>
<tr>
<td>Risperidone + 9-OH-risperidone</td>
<td>EM*: 5 (L/h)</td>
<td>40%</td>
<td>2.00</td>
<td>2.48</td>
</tr>
<tr>
<td></td>
<td>PM 3.2 (L/h)</td>
<td></td>
<td>1.28</td>
<td>1.59</td>
</tr>
<tr>
<td>Sertraline</td>
<td>EM: 148 (L/h)</td>
<td>20%</td>
<td>29.60</td>
<td>36.75</td>
</tr>
<tr>
<td></td>
<td>PM: 105 (L/h)</td>
<td></td>
<td>21.00</td>
<td>26.07</td>
</tr>
</tbody>
</table>

*EM = CYP2D6 Extensive metabolizer, PM = CYP2D6 poor metabolizer

Two of the secondary objectives of the study focus on comparing mean clearance between selected cells. Shown below are the required sample sizes in each cell to detect the specified fold difference in ratio of mean clearance with 80% power and a Type I error of 5% for a range of CVs. For example, with 15 subjects per cell, there would be more than 80% power to detect a ratio of 50% difference in means between cells if the CV in each cell was similar to published studies at ≤30% […]

Table 5: Sample Size Required in Each Cell to Detect Specified Ratio of Mean Clearance With 80% Power and a Type I Error of 5% for a Range of CVs.

<table>
<thead>
<tr>
<th>CV%</th>
<th>25%</th>
<th>50%</th>
<th>75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>13</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>30</td>
<td>29</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>40</td>
<td>&gt;30</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>50</td>
<td>&gt;30</td>
<td>26</td>
<td>15</td>
</tr>
</tbody>
</table>

31. Section 9.3, Study Design, Modeling, and Data Analysis, has been updated:

[…] Forty-five subjects will be enrolled in each Arm for a total of 270 subjects across Versions 1.0 and 2.0 of the protocol.

A sample size of 45 pediatric subjects completing a two-pharmacokinetic visit should provide an accurate estimate of the population oral clearance and its variability both between and within subjects for the agents in the study arms. Within-subject variability is typically much less than between-subject variability but might still be clinically relevant. The second PK visit will allow us to estimate this within-subject variability, which is currently unknown.
32. Appendix I-A Schedule of Evaluations for subjects enrolled under Version 1.0, and associated footnotes, has been updated:

<table>
<thead>
<tr>
<th>Screening¹</th>
<th>Entry¹</th>
<th>Week 6 PK visit²</th>
<th>Week 24 PK visit</th>
<th>Week 30³</th>
<th>Week 42³</th>
<th>Week 52³</th>
<th>Early Discont. Visit⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Window</td>
<td>Day 0</td>
<td>+ 4 weeks</td>
<td>± 2 weeks</td>
<td>± 2 weeks</td>
<td>± 2 weeks</td>
<td>± 2 weeks</td>
<td></td>
</tr>
</tbody>
</table>

**CLINICAL EVALUATIONS**

- Informed Consent
  - X
- History⁵
  - X
- Physical exam⁶
  - X
- Adherence Questionnaire⁷
  - X
- Vanderbilt Scale Questionnaire²⁰
  - X
- Instructions and planning for PK Visit
  - X
- Follow-up telephone call
  - X
- Pharmacokinetic Visit (incl. pre-visit phone call)⁹
  - X

**LABORATORY EVALUATIONS**

- Hematology⁹
  - 1mL
- Toxicology Screen¹⁰
  - X
- Chemistries¹¹
  - 2mL
- Electrocardiogram¹²
  - X
- Pregnancy test¹³
  - X
- PBMC pellets for genotypic analysis¹⁴
  - 6mL
- HIV-1 Antibodies, HIV-1/HIV-2, EIA¹⁵
  - 5mL
- HIV-1 RNA PCR¹⁶
  - 3mL
- Lymphocyte subsets¹⁷
  - 1mL
- PK samples¹⁸
  - 24-30mL
- Dextromethorphan Dose and 4-Hour Urine Collection¹⁹
  - X

**TOTAL BLOOD VOLUMES**

| 5mL | 4mL | 37-43mL | 27-33mL |
Footnotes

1. Screening and entry may occur at the same visit or on separate days up to 4 weeks apart. Follow-up visit dates should be calculated from the entry visit.
2. The PK visit should be scheduled as soon as the inclusion/exclusion criteria are confirmed, but may extend to any time within 8 weeks after the entry visit so long as eligibility status does not change.
3. Study subjects/caregivers will be contacted by telephone to collect information regarding any dose, drug, or regimen changes and tolerance for both psychiatric and antiretroviral medications.
4. If subject withdraws from study prior to the 52 week follow-up call, a study discontinuation visit will be done. This should include a physical exam, a detailed medication history and tolerability report from subject/parent.
5. Complete history including source documentation for lifetime exposure to antiretroviral medications; CDC diagnoses; most recent CD4 count and CD4%; most recent viral load and total lymphocyte count (for HIV-1 infected subjects); Tanner stage, neuropsychiatric diagnoses; and lifetime exposure to psychiatric medications for all subjects. A targeted history is sufficient at subsequent visits; includes changes in history from previous visit. The medication history should retrospectively capture the original dose titration and dose modification history of the psychiatric medication to the best extent possible.
6. Physical exam should include height, weight, and vital signs. For the Entry Visit, data may be abstracted from the patient’s medical chart if performed for clinical care within 12 weeks prior to the Entry Visit.
7. Adherence Questionnaire is to be completed by a member of the site staff in a face-to-face interview at the PK visit and over the telephone for the telephone follow-up visits with study subjects (if they are responsible for administering their own medications) or with their parents/primary caregivers (if they are responsible for administering medications). It asks about medications missed over the past three days. The subject (or parent/primary caregiver) will be asked to identify medications taken, frequency of administration, and number of doses missed within the three days prior to the clinic visit.
8. Approximately two days prior to the week 6 and week 24 PK visit, sites should contact subjects/caregivers to review and encourage medication adherence (both to ARV meds and to psychiatric meds), and to determine if the PK visit needs to be rescheduled due to section 9.2.
9. Hematology for Entry Visit should include CBC with differential and platelet count. For HIV-1 positive subjects at the PK visits, WBC and % lymphocytes should be included if needed for dual platform flow cytometer lymphocyte subsets results. For the Entry Visit, data may be abstracted from the patient’s medical chart if performed for clinical care within 12 weeks prior to the Entry Visit.
10. Urine toxicology screen is for disallowed drugs. These include barbiturates, benzodiazepines, opiates, and phencyclidine and propoxyphene, for all study subjects. For methylphenidate arm subjects, amphetamines are also disallowed. Though propoxyphene is not exclusionary, if it is currently part of the sites’ routine screening panel, the result should be recorded on the CRF. It is expected that those on the amphetamine/dextroamphetamine arm will test positive for amphetamines. Further testing for methamphetamine, if not already part of the standard drug screen, is not required prior to enrollment for these participants, and a positive urine test for amphetamines does not exclude them from participation.
11. Chemistries should include AST, ALT, total bilirubin, BUN, electrolytes, glucose, creatinine, total amylase, albumin. For the Entry Visit, data may be abstracted from the patient’s medical chart if performed for clinical care within 12 weeks prior to the Entry Visit.
12. An electrocardiogram will be performed only in study subjects who have not had an EKG in the past 6 months. Abnormal EKG findings should be referred to the subject’s physician for treatment if indicated. Study management of the toxicity should proceed as per section 6.1 of the protocol.
13. Pregnancy test may be either HCG urine or HCG blood serum test and must be performed on all females of childbearing potential within 72 hours of enrollment as well as within 72 hours of the 6 week and 18 24 week PK visits. If the screening and entry visits are completed within 72 hours, a pregnancy test does not have to be repeated at the entry visit.
14. Non-viable PBMC pellets for DNA genotypic analysis should be collected at the first PK visit (Week 6 visit) for all subjects.
15. For HIV-uninfected subjects only: Subjects’ age ≥13 years will have an HIV-1 antibody test at the screening visit to document negative status. A negative HIV-1 test documented in the subject’s medical chart within the past year can be used instead of an HIV-1 screening test at the screening visit to satisfy this inclusion criterion.
16. This is for HIV-1 infected cohort only, and must be performed at a DAIDS VQA-CLIA-certified laboratory.
17. This is for HIV-1 infected cohort only. Lymphocyte subsets include CD4/CD8 counts and percentages. Must be performed at a DAIDS VQA certified–CLIA-certified laboratory. For the Entry Visit, data may be abstracted from the patient’s medical chart if performed for clinical care within 12 weeks prior to the Entry Visit.
18. PK sampling time points are listed by study drug formulation in Appendix II (Pharmacokinetic Sampling Schedule for Selected Psychiatric Medications/Formulations). Sites should contact subjects by telephone for the two days prior to the PK visits (Weeks 6 and 24) to encourage adherence. If the subject reports missing doses in the two days prior to the PK visit day, reschedule the PK visit.
19. 4-Hour urine collection for CYP 2D6 and 3A4 metabolic phenotyping; to include measurement of dextromethorphan, 3-hydroxy-morphinan and dextrorphan. The date and time of the dextromethorphan dose should be recorded, and this is the start time of the 4-hour urine collection period. The date and time of the first void and the final void within the 4-hour period after administration of the dextromethorphan dose should be recorded. See Section 3.23 for further details.
20. The Vanderbilt Scale Questionnaire can be administered via telephone at the Entry Visit.
33. **Appendix I-B Schedule of Evaluations for subjects enrolled under Version 2.0, and associated footnotes, has been added:**

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>Entry</th>
<th>PK visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Window</td>
<td>Day 0</td>
<td>+ 4 weeks</td>
<td>Week 0 - 8</td>
</tr>
</tbody>
</table>

**CLINICAL EVALUATIONS**

- Informed Consent: X
- History: X X
- Physical exam: X X
- Adherence Questionnaire: X
- Instructions and planning for PK Visit: X
- Pharmacokinetic Visit (incl. pre-visit phone call): X

**LABORATORY EVALUATIONS**

- Hematology: 1mL 1mL
- Toxicology Screen: X
- Chemistries: 2mL 2mL
- Pregnancy test: X X X
- PBMC pellets for genotypic analysis: 0-6mL

**Virology**

- HIV-1 Antibodies, HIV-1/HIV-2, EIA: 5mL
- HIV-1 RNA PCR: 3mL

**Immunology**

- Lymphocyte subsets: 1mL 1mL

**Pharmacology**

- PK samples: 30-36mL
- Dextromethorphan Dose and 4-Hour Urine Collection: X

**TOTAL BLOOD VOLUMES**

- 5mL 4mL 49mL
Footnotes

1. Screening and entry may occur at the same visit or on separate days up to 4 weeks apart.
2. The PK visit should be scheduled as soon as the inclusion/exclusion criteria are confirmed, but may extend to any time within 8 weeks after the entry visit so long as eligibility status does not change.
3. Complete history including source documentation for lifetime exposure to antiretroviral medications; CDC diagnoses; most recent CD4 count and CD4%, nadir CD4 count and CD4%; most recent viral load and total lymphocyte count (for HIV-1 infected subjects); Tanner stage, neuropsychiatric diagnoses; and lifetime exposure to psychiatric medications for all subjects. A targeted history is sufficient at the PK visit; includes changes in history from previous visit. The medication history should retrospectively capture the original dose titration and dose modification history of the psychiatric medication to the best extent possible.
4. Physical exam should include height, weight, and vital signs. For the Entry Visit, data may be abstracted from the patient’s medical chart if performed for clinical care within 12 weeks prior to the Entry Visit.
5. Adherence Questionnaire is to be completed by a member of the site staff in a face-to-face interview at the PK visit with study subjects (if they are responsible for administering their own medications) or with their parents/primary caregivers (if they are responsible for administering medications). It asks about medications missed over the past three days. The subject (or parent/primary caregiver) will be asked to identify medications taken, frequency of administration, and number of doses missed within the three days prior to the clinic visit.
6. Approximately two days prior to the PK visit, sites should contact subjects/caregivers to review and encourage medication adherence (both to ARV meds and to psychiatric meds), and to determine if the PK visit needs to be rescheduled due to adherence issues.
7. Hematology for Entry Visit should include CBC with differential and platelet count. For HIV-1 positive subjects at the PK visit, WBC and % lymphocytes should be included if needed for dual platform flow cytometer lymphocyte subsets results. For the Entry Visit, data may be abstracted from the patient’s medical chart if performed for clinical care within 12 weeks prior to the Entry Visit.
8. Urine toxicology screen is for disallowed drugs. These include barbiturates, benzodiazepines, opiates, and phencyclidine, for all study subjects. Though propoxyphene is not exclusionary, if it is currently part of the sites’ routine screening panel, the result should be recorded on the CRF.
9. Chemistries should include AST, ALT, total bilirubin, BUN, electrolytes, glucose, creatinine, total amylase, albumin. For the Entry Visit, data may be abstracted from the patient’s medical chart if performed for clinical care within 12 weeks prior to the Entry Visit.
10. Pregnancy test may be either HCG urine or HCG blood serum test and must be performed on all females of childbearing potential within 72 hours of enrollment as well as within 72 hours of the PK visit. If the screening and entry visits are completed within 72 hours, a pregnancy test does not have to be repeated at the entry visit.

11. Non-viable PBMC pellets for DNA genotypic analysis should be collected at the PK visit for all subjects who have provided consent for genetic testing.

12. For HIV-uninfected subjects only: Subjects’ age ≥13 years will have an HIV-1 antibody test at the screening visit to document negative status. A negative HIV-1 test documented in the subject's medical chart within the past year can be used instead of an HIV-1 screening test at the screening visit to satisfy this inclusion criterion.

13. This is for HIV-1 infected cohort only, and must be performed at a CLIA-certified laboratory.

14. This is for HIV-1 infected cohort only. Lymphocyte subsets include CD4/CD8 counts and percentages. Must be performed at a CLIA-certified laboratory. For the Entry Visit, data may be abstracted from the patient’s medical chart if performed for clinical care within 12 weeks prior to the Entry Visit.

15. PK sampling time points are pre-dose, and 2, 4, 6, 12 and 24 hours post-dose. Sites should contact subjects by telephone for the two days prior to the PK visit to encourage adherence. If the subject reports missing doses in the two days prior to the PK visit day, reschedule the PK visit.

16. 4-Hour urine collection for CYP 2D6 and 3A4 metabolic phenotyping; to include measurement of dextromethorphan, 3-hydroxy-morphinan and dextrorphan. The date and time of the dextromethorphan dose should be recorded, and this is the start time of the 4-hour urine collection period. The date and time of the first void and the final void within the 4-hour period after administration of the dextromethorphan dose should be recorded. See Section 3.23 for further details.
34. The following modifications have been made to the Sample Informed Consent document (Appendices III-A).

**INTRODUCTION**

You are/your child is being asked to re-consent to take part in this research study because you are/your child is infected with HIV-1 and is taking certain antiretroviral (ARV) medications (medication for the treatment of HIV) […]

**WHAT DO I/DOES MY CHILD HAVE TO DO IF I AM/HE/SHE IS IN THIS STUDY?**

Approximately 6 weeks and 24 weeks after your/your child’s entry visit, you/your child will return to the clinic before taking your/your child’s usual medicine. […]

At approximately 30 weeks, 42 weeks and 52 weeks after your /your child’s entry visit, the study staff will call you by phone to see how you/your child is doing. […]

**HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?**

About 270 subjects will take part in this study, across versions 1.0 and 2.0 of the protocol. 60 HIV-1 infected and 30 HIV-uninfected children and adolescents.

**WHAT HAPPENS IF I AM / MY CHILD IS INJURED?**

If you are/your child is injured as a result of being in this study, you / your child will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. The NIH does not provide direct compensation for research related injury. You will not be giving up any of your legal rights by signing this consent form.

35. The following modifications have been made to the Sample Informed Consent document (Appendices III-B).

**INTRODUCTION**

You are/your child is being asked to re-consent to take part in this research study because you are/your child is taking a stimulant medication (methylphenidate or amphetamine/dextroamphetamine) for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

**WHAT DO I/DOES MY CHILD HAVE TO DO IF I AM/HE/SHE IS IN THIS STUDY?**

If you/your child agree(s) to take part in this study, there will be three study visits described below. In addition, you/your child will be contacted by telephone every 3 months to collect any additional information about changes in ADHD medications.

**Screening Visit** (this will take approximately 1½ hours)

- If you are / your child is 13 years of age or older, and have not had an HIV test before in the past year, 1 teaspoon of blood will be drawn to test your blood for the HIV
virus. You / your child will be informed of the results of this test as soon as it is available.

[…] 

Approximately 6 weeks and 24 weeks after your/your child’s entry visit, you/your child will return to the clinic before taking your/your child’s usual medicine.

 […] 

At approximately 30 weeks, 42 weeks and 52 weeks after your /your child’s entry visit, the study staff will call you by phone to see how you /your child is doing. […] 

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY? 
About 270 subjects will take part in this study, across versions 1.0 and 2.0 of the protocol. 60 HIV-1 infected and 30 HIV-uninfected children and adolescents.

WHAT HAPPENS IF I AM / MY CHILD IS INJURED? 
If you are / your child is injured as a result of being in this study, you / your child will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. The NIH does not provide direct compensation for research related injury. You will not be giving up any of your legal rights by signing this consent form.

36. Sample Informed Consent documents (Appendices III-C and III-D) have been added to the protocol.

APPENDIX III-C

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT)

DAIDS SAMPLE INFORMED CONSENT for HIV-1 INFECTED CHILDREN and ADOLESCENTS WHO ENROLL UNDER VERSION 2.0

P1080: A Pilot Study of Psychiatric and Antiretroviral Medication Concentrations in HIV-1 Infected and Uninfected Children and Adolescents
Version 2.0, Dated 22 April 2014

SHORT TITLE FOR THE STUDY: ARV & Psychiatric Medication Concentrations in HIV Infected & Uninfected Children

INTRODUCTION

You are / your child is being asked to take part in this research study because you are / your child is infected with HIV-1 and is taking certain antiretroviral (ARV) medications (medication for the treatment of HIV), as well as a psychiatric medication (citalopram [Celexa®], escitalopram [Lexapro®], risperidone [Risperdal®], sertraline [Zoloft®], fluoxetine [Prozac® or Sarafem®] or paroxetine [Paxil®, Paxil CR®, Pexeva®, or Brisdelle®]). The main purpose of this study is to find out how these psychiatric medications are broken
down in HIV-1 infected and HIV uninfected children and adolescents. The study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator).

Before you decide if you want to be/want your child to be a part of this study, we want you to know about the study. This is a consent form. It gives you information about this study. The study staff will talk with you/your child about this information. You are free to ask questions about this study at any time. If you agree to take part, or allow your child to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

Children and adolescents who are infected with HIV-1 are twice as likely to use psychiatric medications as uninfected children and adolescents. However, there has never been a study to look at the way in which these medicines interact with antiretroviral drugs. This study will look at the way psychiatric medicines are broken down by children and adolescents who are not HIV-1 infected, and compare the results to the way the same psychiatric medicines are broken down by HIV-1 infected children and adolescents who are also taking certain ARVs, such as Ritonavir or Efavirenz. We will look at how your body / your child’s body breaks down both the psychiatric drugs and the ARVs when both are being taken, by drawing some of your /your child’s blood at specific times.

Management of your / your child’s ARV and psychiatric medications will continue to be performed by your regular doctor; this study will not look at whether these medications are right for you / your child or whether they need to be adjusted.

WHAT DO I/DOES MY CHILD HAVE TO DO IF I AM/HE/SHE IS IN THIS STUDY?

If you/your child agree(s) to take part in this study, there may be up to three study visits described below.

**Screening Visit** (this will take approximately 1 hour)
- Once you agree/allow your child to participate in this study, you/your child will be asked some questions about your/your child’s history of exposure to antiretroviral and psychiatric medications to be sure you/your child can participate in this study.

- A urine sample will also be collected to screen for illegal use of drugs, including the following:
  - Methamphetamine (also known as ‘speed’, ‘meth’, ‘crank’, ‘ice’)
  - Barbiturates (also known as ‘downers’, and include Amytal, Nembutal and Seconal)
  - Benzodiazepines (also known as ‘benzos’ and include Valium)
  - Opiates (including morphine, heroin, codeine, hydrocodone, oxycodone)
  - Phencyclidine (also known as ‘PCP’)

If the results of the urine test are positive for any of these drugs, you/your child will not be allowed to participate in the study. [Sites: please clarify procedures in regard to parental notification]. Positive results will NOT be shared with law enforcement.
• If you are/your child is female, of child bearing potential and are/is sexually active, you/your child will be asked to take a pregnancy test. If you are/your child is found to be pregnant, you/your child will not be able to participate in this study. [Sites: please clarify procedures in regard to parental notification].

• If you are/your child is female, of child bearing potential and are/is sexually active, you/your child must also agree to avoid pregnancy during the entire trial and to consistently and appropriately use at least two of the following contraception methods: condoms, diaphragm or cervical cap with spermicide, IUD, hormonal-based contraception.

• The study staff will explain to you/your child the details of what will take place during the next study visit. The screening visit and the entry visit may occur on the same day if the results of the urine and blood tests are available.

Entry Visit (this will take approximately 30 minutes); the Screening and Entry visits may be on the same day.

• Approximately 1 teaspoon of blood will be drawn to check your/your child’s white blood cells (the cells that help your body fight infection) and chemistry levels (tests which help us see how well your liver and kidneys are working). The results of these tests will be shared with you as soon as they are available.

• You/your child will also have a physical exam, a medical history.

• If you are/your child is female, of child bearing potential and are/is sexually active, you/your child will be asked to take a pregnancy test. If you are/your child is found to be pregnant, you/your child will not be able to participate in this study. [Sites: please clarify procedures in regard to parental notification]. Also at this visit, the study staff will explain to you/your child the details of what will take place during the next study visit.

Pharmacokinetic (PK) Visit (this visit will take about 24 hours). Within 8 weeks after your/your child’s Entry Visit, you/your child will return to the clinic before taking your/your child's usual medicine. Approximately two days prior to the PK visit, the staff will contact you/your child by phone to ask about missed doses and to encourage medication adherence. At this clinic visit, the following will take place:

• Approximately 2 teaspoons of blood will be drawn to check your/your child’s white blood cells (the cells that help your body fight infection), chemistry levels (tests which help us see how well your liver and kidneys are working), as well as CD4 or T-cell count and HIV viral load (amount of HIV measured in you/your child’s blood). The results of these tests will be shared with you as soon as they are available.

• You/your child will also have a physical exam, a medical history. Study staff will ask you/your child some questions about medications you have/your child has taken within the three days before the visit.

• Approximately 1 teaspoon of blood will be collected at the visit in order to look at your/your child’s genes (DNA). This will help researchers understand how the genetic differences between people may explain how their body processes and
responds differently to combinations of drugs. You may choose not to have this blood collected if you prefer not to.

- If you are/your child is female, of child bearing potential and are/is sexually active, you/your child will be asked to take a pregnancy test. If you are/your child is found to be pregnant, you/your child will not be able to participate in this study. [Sites: please clarify procedures in regard to parental notification].

- You/your child will be given a single oral dose of cough syrup (dextromethorphan) at the Food and Drug Administration’s (FDA) approved dose. For the 4 hours following the dose of cough medicine, you/your child will be asked to collect your/your child’s urine, so that the urine can be measured, recorded, and analyzed. Analyzing your/your child’s urine after taking the cough syrup will allow the study investigators to predict how you/your child will process different doses of psychiatric medication.

- A total of about 3 tablespoons of blood will be collected to look at how your body breaks down both your psychiatric medications and your antiretroviral medications. This blood will be collected over 24 hours – for this testing about 1 teaspoon will be collected just before you/your child takes(s) your medication; about 1 teaspoon will be collected at 2 hours, 4 hours, 6 hours, 12 hours, and 24 hours, after you/your child takes the medication. To obtain the 24 hour specimen, study staff will discuss with you whether the option of staying overnight is available or you should return the next day. These results will be made available to your healthcare provider upon request.

OTHER INFORMATION

Sometimes a heparin lock (small plastic tube) is used when collecting more than one blood sample over a period of time, such as during a pharmacokinetic visit. It is left in the vein until all of the blood draws are completed, and then it is removed. This allows blood to be taken repeatedly without having to stick you/your child with a needle many times. Any blood samples that remain after tests are run for this study will be destroyed.

GENETIC TESTING

If you provide additional consent, at the pharmacokinetic visit, about 1 teaspoon of blood will be drawn and used for genetic testing, which is a study of your/your child’s genes (DNA). This will help researchers understand how the genetic differences between people may explain how their body processes and responds differently to combinations of drugs. The researchers do not plan to contact you, your child, or the study doctor with the results of these studies. This is because research studies are often done with experimental procedures, and these results should not be used to make decisions about your/your child’s HIV or psychiatric care.

However, in case researchers learn new information that makes them believe that a certain study result is important for your/your child’s HIV or psychiatric care, then your/your child’s study doctor will be informed. If you would like the researchers to also tell you this information in a case like this, then, you/your child will need to tell the study staff if your/your child’s address or phone number change. You/your child may decide that you/your child do not want blood used for genetic testing. You/your child can still be in this study even if you/your child make this decision. Please read the statement below, and mark
your initials in the spaces to indicate whether you agree to allow your /your child’s blood to be used for genetic testing.

I agree to have my blood used for genetic testing as part of this study.

___________ Yes  ___________ No  ___________ Date

I agree to have my child’s blood used for genetic testing as part of this study.

___________ Yes  ___________ No  ___________ Date

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 270 subjects will take part in this study, across versions 1.0 and 2.0 of the protocol.

HOW LONG WILL I/MY CHILD BE IN THIS STUDY?

You/your child will be in this study for up to eight weeks.

WHY WOULD THE DOCTOR TAKE ME / MY CHILD OFF THIS STUDY EARLY?

The study doctor may need to take you/your child off the study early without your permission if:

- The study is stopped or cancelled
- You/your child refuse further participation in the study;
  - You/your child refuse further treatment with ARVs or psychiatric medications
  - The investigator determines further participation would be harmful to your/your child’s health or well-being;
  - You/your child fails to meet study requirements, in a way that would harm you/your child or seriously interfere with the study results;
- The ARVs or psychiatric medications were discontinued or the dose changed such that eligibility status is changed by the prescribing clinician before completion of the study

WHAT ARE THE RISKS OF THE STUDY?

Since you are/your child is already taking the psychiatric and ARV medicines before joining this study, any risks associated with these medicines should be discussed with the doctor who prescribed them.

Cough Syrup Risks
Side effects of a single dose of cough syrup are uncommon, and may include mild sleepiness or dizziness.

Blood Drawing Risks
Blood drawing from a vein may cause some discomfort, bleeding, or bruising where the needle goes into the skin. A small blood clot may form at the site of injection, or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. A feeling of lightheadedness may also occur.

**WILL I RECEIVE ANY COMPENSATION?**

You will receive $XX for each study visit you attend. If you attend all study visits, you may receive up to $XX.

**ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?**

Since no study drugs will be given, there will not be any direct benefit from taking part in this study. Information learned from this study may help others who take psychiatric medications.

**WHAT ABOUT CONFIDENTIALITY?**

Your/your child’s records will be identified only by a coded number and will be kept in a private area to maintain confidentiality.

To help us protect your / your child’s privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you / your child, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you / your child, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

People who may review your / your child’s records include the site IRB (insert name of site IRB), the Office of Human Research Protections (OHRP), the National Institutes of Health (NIH), the National Institutes of Allergies and Infectious Disease (NIAID), study staff, and study monitors and their designees.

You should understand that a Certificate of Confidentiality does not prevent you / your child or a member of your family from voluntarily releasing information about you or your / your child’s participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

**WHAT ARE THE COSTS TO ME?**

Taking part in this study will not lead to added costs to you and your insurance company.

**WHAT HAPPENS IF I AM / MY CHILD IS INJURED?**

If you are/your child is injured as a result of being in this study, you / your child will be given immediate treatment for your injuries. The cost for this treatment will be charged to
you or your insurance company. The NIH does not provide direct compensation for research related injury. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY/MY CHILD’S RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You may choose not to take part/not to allow your child to take part in this study or leave this study/take your child out of the study at any time. Your decision will not have any impact on your/your child’s participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are/your child is otherwise entitled.

We will tell you about new information from this or other studies that may affect your/your child’s health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- name of the investigator or other study staff
- telephone number of above

For questions about your/your child’s rights as a research subject, contact:

- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above
**SIGNATURE PAGE**

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

<table>
<thead>
<tr>
<th>Participant’s Name (print)</th>
<th>Participant’s Signature and Date</th>
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<tbody>
<tr>
<td>Participant’s Legal Guardian (print) (As appropriate)</td>
<td>Legal Guardian’s Signature and Date</td>
</tr>
<tr>
<td>Study Staff Conducting Consent Discussion (print)</td>
<td>Study Staff Signature and Date</td>
</tr>
<tr>
<td>Witness’ Name (print) (As appropriate)</td>
<td>Witness’s Signature and Date</td>
</tr>
<tr>
<td>Father’s Name (If father’s consent is required)</td>
<td>Father’s Signature and Date (If father’s consent is required)</td>
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APPENDIX III-D
DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT)

DAIDS SAMPLE INFORMED CONSENT for HIV UN-INFECTED CHILDREN and ADOLESCENTS

P1080: A Pilot Study of Psychiatric and Antiretroviral Medication Concentrations in HIV-1 Infected and Uninfected Children and Adolescents
Version 2.0, Dated 22 April 2014

SHORT TITLE FOR THE STUDY:  ARV & Psychiatric Medication Concentrations in HIV-1 Infected & Uninfected Children

INTRODUCTION

You are/your child is being asked to take part in this research study because you are/your child is taking a psychiatric medication (citalopram[Celexa®], escitalopram [Lexapro®], risperidone [Risperdal®], sertraline [Zoloft®], fluoxetine [Prozac® or Sarafem®] or paroxetine [Paxil®, Paxil CR®, Pexeva®, or Brisdelle®]). The main purpose of this study is to find out how these psychiatric medications are processed in HIV-1 infected and HIV-uninfected children and adolescents. You are/your child is being asked to take part in this study to allow us see how psychiatric medicines are processed in different people. The study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you/your child decide(s) if you want to be/want your child to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you/your child about this information. You/your child are free to ask questions about this study at any time. If you agree to take part, or allow your child to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

Children and adolescents who are infected with HIV are twice as likely to use psychiatric medications as uninfected children and adolescents. However, there has never been a study to look at the way in which these medicines interact with antiretroviral drugs. This study will look at the way psychiatric medicines are processed by children and adolescents who are not HIV-1 infected, and compare the results to the way the same psychiatric medicines are processed by HIV-1 infected children and adolescents who are also taking other medications. Management of your/your child’s psychiatric medications will continue to be performed by your regular doctor; this study will not look at whether these medications are right for you / your child or whether they need to be adjusted.

WHAT DO I/DOES MY CHILD HAVE TO DO IF I AM/HE/SHE IS IN THIS STUDY?

If you/your child agree(s) to take part in this study, there may be up to three study visits described below.
Screening Visit (this will take approximately 1½ hours)

- Once you agree/allow your child to participate in this study, you/your child will be asked some questions about your/your child’s history of exposure to psychiatric medications to be sure you/your child can participate in this study.

- If you are / your child is 13 years of age or older, and have not had an HIV test in the past year, about 1 teaspoon of blood will be drawn to test your blood for the HIV virus. You / your child will be informed of the results of this test as soon as it is available.

- A urine sample will also be collected to screen for illegal use of drugs, including the following:
  - Methamphetamine (also known as ‘speed’, ‘meth’, ‘crank’, ‘ice’)
  - Barbiturates (also known as ‘downers’ and include Amytal, Nembutal and Seconal)
  - Benzodiazepines (also known as ‘benzos’ and include Valium)
  - Opiates (including morphine, heroin, codeine, hydrocodone, oxycodone)
  - Phencyclidine (also known as ‘PCP’)

If the results of the urine test are positive for any of these drugs, you/your child will not be allowed to participate in the study. [Sites: please clarify procedures in regard to parental notification]. Positive results will NOT be shared with law enforcement.

- If you are/your child is female, of child bearing potential and you are / your child is sexually active, you/your child will be asked to take a pregnancy test. If you are/your child is found to be pregnant, you/your child will not be able to participate in this study. [Sites: please clarify procedures in regard to parental notification].

- If you are/your child is female and of reproductive age, you / your child must also agree to avoid pregnancy during the entire trial and to consistently and appropriately use at least two of the following contraception methods: condoms, diaphragm or cervical cap with spermicide, IUD, hormonal-based contraception.

Entry Visit (this will take approximately 30 minutes); the Screening and Entry visits may be on the same day.

- Approximately 1 teaspoon of blood will be drawn to check your/your child’s white blood cells (the cells that help your body fight infection) and chemistry levels (tests which help us see how well your liver and kidneys are working). The results of these tests will be shared with you as soon as they are available.

- You/your child will also have a physical exam, a medical history.

- If you are / your child is female and of reproductive age, you/your child will be asked to take a pregnancy test. If you are / your child is found to be pregnant, you/your child will not be able to participate in this study. Also at this visit, the study staff will explain to you/your child the details of what will take place during the next study visit.

Pharmacokinetic (PK) Visit (this visit will take about 24 hours.)

Within 8 weeks after your/your child’s entry visit, you/your child will return to the clinic before taking your/your child’s usual medicine. Approximately two days prior to the PK visit, the staff will contact you/your child to encourage medication adherence. At this visit, the following will take place:
- Approximately 1 teaspoon of blood will be drawn to check your/your child’s blood count and chemistry levels (tests which help us see how well your liver and kidneys are working). The results of these tests will be shared with you as soon as soon as they are available.

- You/your child will also have a physical exam, a medical history. Study staff will also ask you/your child some questions about medications you have/your child has taken within the three days before the visit.

- If you are/your child is female, of child bearing potential and you are / your child is sexually active, you/your child will be asked to take a pregnancy test. If you are/your child is found to be pregnant, you/your child will not be able to participate in this study. [Sites: please clarify procedures in regard to parental notification].

- Approximately 1 teaspoon of blood will be collected at the visit in order to look at your /your child’s genes (DNA). This will help researchers understand how the genetic differences between people may explain how their body processes and responds differently to combinations of drugs. You may choose not to have this blood collected if you prefer not to.

- You/your child will be given a single oral dose of cough syrup (dextromethorphan) at the Food and Drug Administration’s (FDA) approved dose. For the 4 hours following the dose of cough medicine, you/your child will be asked to collect your/your child’s urine, so that the urine can be measured, recorded, and analyzed. Analyzing your/your child’s urine after taking the cough syrup will allow the study investigators to predict how you/your child will process different doses of psychiatric medication.

- A total of about 3 tablespoons of blood will be collected to look at how your body breaks down your medication. This blood will be collected over 24 hours - for this testing, about 1 teaspoon will be collected just before you/your child take(s) your medication; about 1 teaspoon will be collected at 2 hours, 4 hours, 6 hours, 12 hours, and 24 hours, after you/your child takes the medication. To obtain the 24 hour specimen, study staff will discuss with you whether the option of staying overnight is available or you should return the next day. These results will be made available to your healthcare provider upon request.

OTHER INFORMATION

Sometimes a heparin lock (small plastic tube) is used when collecting more than one blood sample over a period of time. It is left in the vein until all of the blood draws are completed, and then it is removed. This allows blood to be taken repeatedly without having to stick you/your child with a needle many times. Any blood samples that remain after tests are run for this study will be destroyed.

GENETIC TESTING

If you provide additional consent, at the PK visit, about 1 teaspoon of blood will be drawn and used for genetic testing, which is a study of your/your child’s genes (DNA). This will help researchers understand how the genetic differences between people may explain how their body processes and responds differently to combinations of drugs. The researchers do not plan to contact you, your child, or the study doctor with the results of these studies. This is because research studies are often done with experimental procedures, and these results should not be used to make decisions about your/your child’s psychiatric care.
However, in case researchers learn new information that makes them believe that a certain study result is important for your/your child’s psychiatric care, then your/your child’s study doctor will be informed.

If you would like the researchers to also tell you this information in a case like this, then, you/your child will need to tell the study staff if your/your child’s address or phone number change. You/your child may decide that you/your child do not want blood used for genetic testing. You/your child can still be in this study even if you/your child make this decision. Please read the statement below, and mark your initials in the spaces to indicate whether you agree to allow your/your child’s blood to be used for genetic testing.

I agree to have my blood used for genetic testing as part of this study.

_________ Yes  ___________ No  ___________ Date

I agree to have my child’s blood used for genetic testing as part of this study.

_________ Yes  ___________ No  ___________ Date

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 270 subjects will take part in this study, across versions 1.0 and 2.0 of the protocol.

HOW LONG WILL I/MY CHILD BE IN THIS STUDY?

You/your child will be in this study for up to eight weeks.

WHY WOULD THE DOCTOR TAKE ME / MY CHILD OFF THIS STUDY EARLY?

The study doctor may need to take you/your child off the study early without your permission if:

- The study is stopped or cancelled
- You/your child refuse further participation in the study;
- You/your child refuse further treatment with psychiatric medications
- The investigator determines further participation would be harmful to your/your child’s health or well-being;
- You/your child fails to meet study requirements, in a way that would harm you/your child or seriously interfere with the study results;
- The psychiatric medications were discontinued or the dose changed such that eligibility status is changed by the prescribing clinician before completion of the study;

WHAT ARE THE RISKS OF THE STUDY?

Since you are/your child is already taking the psychiatric medicines before joining this study, any risks associated with these medicines should be discussed with the doctor who prescribed them.

Cough Syrup Risks
Side effects of a single dose of cough syrup are uncommon, and may include mild sleepiness or dizziness.
Blood Drawing Risks
Blood drawing from a vein may cause some discomfort, bleeding, or bruising where the needle goes into the skin. A small blood clot may form at the site of injection, or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. A feeling of lightheadedness may also occur.

WILL I RECEIVE ANY COMPENSATION?
You will receive $XX for each study visit you attend. If you attend all study visits, you may receive up to $XX.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?
Since no study drugs will be given, there will not be any direct benefit from taking part in this study. Information learned from this study may help others who take psychiatric medications.

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WHAT ARE THE COSTS TO ME?
Taking part in this study will not lead to added costs to you and your insurance company or your child’s insurance company.

WHAT HAPPENS IF I AM / MY CHILD IS INJURED?
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  • name of the investigator or other study staff
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SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

_____________________                              __________
Participant’s Name (print)            Participant’s Signature and Date

____________________________                ____________________________________
Participant’s Legal Guardian (print) (As appropriate)  Legal Guardian’s Signature and Date

________________________                        ____________________________________
Study Staff Conducting Consent Discussion (print)  Study Staff Signature and Date

Witness’ Name (print) (As appropriate)            Witness’s Signature and Date

__________________________                ____________________________________
Father’s Name (If father’s consent is required)  Father’s Signature and Date (If father’s consent is required)