Cognitive Effects Snap Shot

Sites Participating: University of Southern California (site #17), University of Michigan (site #18)

Principal Investigator: Robert J. Fontana, MD (University of Michigan)

Co-Investigator: Karen Lindsay, MD (University of Southern California)

Study Name: COGNITIVE EFFECTS OF LONG-TERM PEGYLATED IFN IN PATIENTS WITH CHRONIC HEPATITIS C

Separate Consent Form: Yes

Withdrawal Form: Yes (Form #155)

Eligible Patients: Lead-in, Week 20 Responders, Randomized, Breakthrough/Relapser (Express patients are not eligible)

Visit Schedule (additional data/specimens and forms for AS)

Note: "**X**" means all participating sites take part.

Lead-in Phase

Visit Number →	Form #	S00	W00	W04	W12	W20	W24
Cortisol Results	150		18	18			18
Shipley	151		X				
Neuropsych Test Result	152		X				X
Mod CIDI-12	153						X
Brief Symptoms Index (BSI)	154		X	X			X
Cognitive Effects Withdrawal	155	Can be added to any visit					
Serotonin Results	156		18	18			18
Years of Education	157	X					
Occupational Status	158	X					
Scoring Sheet for NTP Batteries	159	X					

Randomized Phase

Visit Number →	Form #	R00[1]	M12	M18	M21	M24	M27	M30	M33	M36	M42	M45	M48	M54
		B/R												
Cortisol Results	150	18	18			18				18			18	18
Shipley	151													
Neuropsych Test Result	152	X	X			X				X			X	X
Mod CIDI-12	153	X	X			X				X			X	X
Brief Symptoms Index (BSI)	154	X	X	X		X		X		X	X		X	X
Cognitive Effects Withdrawal	155	Can be added to any visit												
Serotonin Results	156	18	18			18				18			18	18

[1] If after the 2nd positive HCV RNA the R00 visit is more than 1 month after the last battery cognitive testing then Form 150, 152, 153, 154, 156 must be completed. Otherwise do not perform the tests. Form 44 Beck scores are always collected at R00 visit.

Week 20 Responders

Visit Number ➔	Form #	W30	W36	W42	W48	W60	W72
Cortisol Results	150				18		18
Shipley	151						
Neuropsych Test Result	152				**X**		**X**
Mod CIDI-12	153				**X**		**X**
Brief Symptoms Index (BSI)	154				**X**		**X**
Cognitive Effects Withdrawal	155	**Can be added to any visit**					
Serotonin Results	156				18		18

Cognitive effects of long-term pegylated IFN in patients with chronic hepatitis C

Principal Investigator: Robert J. Fontana, MD

Co-Investigator: Karen Lindsay, MD

I. Background

The objective of the HALT-C Trial is to determine if long-term pegylated interferon (IFN) can reduce hepatic fibrosis and progression to cirrhosis, hepatic decompensation and/or hepatocellular carcinoma. However, IFN therapy is associated with a broad range of adverse events. Thus, the benefits of long-term IFN therapy must be balanced against the adverse events. Although IFN associated adverse events have been well reported, IFN induced neuropsychiatric toxicity is less well described because most studies have relied on self-reporting by patients or subjective assessment by investigators/study coordinators who are not trained in neuropsychological assessment.

The goal of this ancillary study is to assess the effects of long-term IFN therapy on cognitive function and mood status using objective and validated tools. The specific aims are to:

1. Assess serial changes in cognitive function and mood status in IFN treated patients compared to untreated controls.
2. Identify risk factors associated with IFN induced cognitive changes.
3. Determine if IFN induced cognitive changes are reversible after cessation of therapy.
4. Determine if IFN induced cognitive changes correlate with changes in mood and neurohormone levels.
5. Determine if the frequency, type, severity, and reversibility of IFN induced cognitive changes in W20 virologic responders that receive 48 weeks of PEG + Ribavirin are different from those observed in non-responder controls treated for 6 months with PEG + Ribavirin.

II. Study Protocol

All patients enrolled in the HALT-C Trial at 2 sites (University of Michigan and University of Southern California) will be recruited for enrollment and be prospectively followed per Appendix 1 and Appendix 2. At screen 01, the anxiety, depression, alcohol, and substance abuse modules of CIDI-LT Auto 2.1 diagnostic software program will be self-administered to all participants to assess lifetime psychiatric history per DSM-IV criteria (Appendix 1). Periodically during treatment (week 24, month 12, month 24, month 36, month 48, month 54), the anxiety and depression modules of the CIDI-12 Auto 2.1 will be administered to detect new psychiatric diagnoses.

Cognitive function will be assessed in randomized patients at baseline (W00) and week 24 (W24), randomization visit (R00) - see p.2, month 12 (M12), month 24 (M24), month 36 (M36), month 48 (M48), and month 54 (M54) using a standardized battery of neuropsychiatric tests that will be administered by a trained neuropsychology technician. Test administration and scoring will be supervised by a collaborative psychologist. Mood status will be assessed at baseline, (W00), week 4 (W04), week 12 (W12) and then every 3 months through month 54 using the Beck Depression Inventory-II (BDI-II). The Brief Symptom Inventory (BSI) will be administered at baseline (W00), Week 4 (W04) and every 6 months through month 54 to characterize emotional distress. To determine the potential mechanism(s) of IFN induced neuropsychiatric toxicity, tests of plasma cortisol and whole blood serotonin will be performed on University of Michigan patients at baseline (W00), week 4 (W04), week 24 (W24), randomization visit (R00) - see p.2, month 12 (M12), month 24 (M24), month 36 (M36), month 48 (M48), and month 54 (M54).

In Week 20 Virologic responders, cognitive function will be assessed at baseline (W00), week 24 (W24), week 48 (W48) and week 72 of follow-up (W72) (Appendix 2). Mood status will be assessed at baseline (W00), week 4 (W04), week 12 (W12), week 24 (W24), week 36 (W36), week 48 (W48), week 60 (W60), and Week 72 (W72) using the BDI-II. The BSI will also be administered at baseline (W00), week 4 (W04), week 24 (W24), week 48 (W48), and Week 72 (W72). The CIDI-12 will be administered at week 24 (W24), week 48 (W48) and week 72 (W72). Tests of plasma cortisol and whole blood serotonin will be performed in University of Michigan patients only at baseline (W00), week 4 (W04), week 24 (W24), week 48 (W48), and week 72 (W72). Results of this study will enable us to determine the frequency, pattern, and magnitude of IFN induced neuropsychiatric toxicity, possible biochemical mechanism(s) and/ or risk factors involved**,** and reversibility of cognitive changes.

Inclusion criteria

1. University of Michigan or University of Southern California HALT-C Trial participant
2. Cognitive AS Informed consent obtained at Screening (S00)

Exclusion criteria

1. Unwilling to participate
2. Patients enrolled at other HALT-C clinical centers
3. Express patients

All patients enrolled in the HALT-C Trial at University of Michigan and University of Southern California (135 x 2 = 270) will be recruited into this ancillary study during screening. It is expected that 180 of these patients will be eligible for the Randomized Phase. Patients entering into the randomized phase will continue to be followed in this protocol. The ~90 week 20 virologic responders will be monitored per the Responder protocol through week 72 with ongoing assessment of neuropsychiatric toxicity per Appendix 2.

Randomization Study Visit:
See Appendix 1 and Appendix 2 for overview of study visits.

Breakthrough/ Relapsers re-entering the Randomization Arm of the HALT-C Cognitive Effects Ancillary Study:

1. If after the 2nd positive HCV RNA a patient is eligible to be randomized and the randomization visit (R00) is scheduled more than 1 calendar month after the last battery of cognitive testing, then the standard cognitive battery, CIDI-12, BSI, BDI-II, and blood for WB serotonin and cortisol (UMich patients only) should be collected at the randomization visit (R00). After R00 the next study visit for additional cognitive testing would be the M12 visit.
2. If after the 2nd positive HCV RNA a patient is eligible to be randomized and the randomization visit (R00) is scheduled less than 1 calendar month after last battery of cognitive testing, then no additional cognitive testing will be collected at R00 except for BDI-II (Form #44). Then the next study visit for additional cognitive testing would be the M12 visit.

III. Methods:

A. CIDI

The CIDI Auto 2.1 (**C**omposite **I**nternational **D**iagnostic **I**nterview) is a computerized, self-administered diagnostic interview for the assessment of mental health disorders per DSM-IV and ICD-10 criteria. In this study, the Lifetime (LT) version of the CIDI will be administered to all study subjects at Screen1 (S00) and the 12-month (CIDI-12) version will also be administered at several time points. For respondents incapable of completing the self-administered format of the CIDI, the CIDI can be given by the study coordinator in the INTERVIEWER administered mode.

B. Lifetime CIDI-LT Auto 2.1

1. At Screen 1, the CIDI-LT will be administered to all participants at University of Southern California and University of Michigan (as part of the main HALT-C protocol).
2. The CIDI-LT program will be set-up in the Respondent mode per written instructions (See Appendix 3).
3. Following completion of the tutorial module, the DEMOGRAPHICS (A), ANXIETY (D), DEPRESSION (E), ALCOHOL (J), and DRUGS (L) modules will be completed by the respondent which takes ~20-40 minutes to complete.
4. The CIDI-LT DSM-IV diagnostic data will be entered into Section H of Form #4 Screening Checklist, per the QxQ instructions.
5. The raw data file R[idnumber].ALL and the DSM-IV scoring data file R[idnumber].SCS will be printed out and stored in the patients study record.
6. The CIDI-LT results will be reviewed by a physician investigator to determine if the patient requires further psychiatric assessment during screening

C. 12 month CIDI-12 Auto 2.1

1. The CIDI-12, which captures mental health disorders in the preceding 12 months will be administered at the same time as NPT to randomized study participants at week 24 (W24), randomization visit (R00) - see p.2, month 12 (M12), month 24 (M24), month 36 (M36), month 48 (M48) and month 54 (M54).
2. The CIDI-12 will also be administered at the same time as NPT to week 20 virologic responders at week 24 (W24), week 48 (W48), and week 72 (W72).
3. Only the DEMOGRAPHICS (A), ANXIETY (D), and DEPRESSION (E) modules of the CIDI-12 will be administered which takes ~5-10 minutes.
4. The raw data file R[idnumber].ALL and the DSM-IV scoring data file R[idnumber].SCS will be printed out and stored in the patients case report form.
5. The CIDI-12 DSM-IV diagnostic data will be entered into Form #153 per the QxQ instructions.

D. Neuropsychiatric testing

A battery of neuropsychiatric tests with established validity and reliability will be used to identify changes in selective dimensions of cognitive function. The dimensions of cognitive function that will be tested, the instruments used in the order that they will be administered, and the estimated time of administration is as follows:

Table 1- NPT Test Battery

Dimension	Tests	Time (min)
Verbal Memory and Delayed Memory	Selective reminding test	5-10
Visual Memory	Continuous Visual Memory test	10-15
Speed & efficiency of cognitive processing	Digit Span Digit Symbol Serial Digit Learning	5 3 7
Motor Visuomotor tracking	Simple and Choice reaction time Trail Making test A and B Finger Tapping test	7 7 5
Executive functioning	Wisconsin Card Sorting Test	10-30
Verbal Fluency	Controlled Oral Word Association	5

Because of the need for repeated testing, memory associated tasks have been chosen which have alternate forms to minimize potential practice effects.

NPT administration

1. Patients will be asked to refrain from taking medications known to adversely influence cognitive function for 48 hours before testing (e.g. anti-histamines).
2. NPT testing will be scheduled in conjunction with routine study visits.
3. At baseline (W00), the Shipley Institute of Living Scale (20-25 minutes) will be administered to all patients by a trained technician to assess baseline general cognitive ability. The Shipley will **not** be repeated at subsequent visits.
4. The battery of NPT tests in Table 1 will be administered by a trained neuropsych technician at baseline (W00), week 24 (W24), randomization visit (R00) - see p.2, month 12 (M12), month 24 (M24), month 36 (M36), month 48 (M48), and month 54 (M54) to randomized patients.
5. In week 20 virologic responders, the NPT battery will be administered at baseline (W00), week 24 (W24), Week 48 (W48), and week 72 (W72).

NPT Scoring

1. NPT tests will be scored at each site by the neuropsych technician using the available manuals and scoring instructions.
2. All NPT test results will be reviewed by the collaborative neuropsychologist (Back at University of Southern California and Bieliauskas at University of Michigan) before entry into the Halt -C Trial Data Management System.
3. Completed NPT forms will be stored in the subjects case report forms.
4. Results of the Shipley will be entered into Form #151 Shipley Institute of Living Scale per QxQ instructions.
5. The summary of NPT battery results will be entered into Form #152 Neuropsychiatric Test Results per QxQ instructions.

E. Mood status

Mood disorders including anxiety and depression are common and problematic side effects of IFN. Although IFN induced mood disorders are in part dose and duration of therapy dependent, mood disorders may develop in individuals without a prior psychiatric history and therefore careful monitoring of all IFN treated patients is necessary. Mood disorders may be severe and rarely, even life-threatening requiring IFN dose reductions or discontinuation. Since prospective studies have only followed patients for 6-12 months, the frequency and severity of mood disorders during long-term pegylated IFN are unknown. The BDI-II will be used to assess depressive symptoms in all patients enrolled in the HALT-C Trial per the main protocol. In the cognitive ancillary study, the BDI-II and BSI will be used to assess emotional distress during treatment.

F. Beck Depression Index (BDI-II)

The BDI-II is a 21 item self-administered survey to screen for depressive symptoms corresponding to DSM-IV criteria of major depression. The BDI-II is an updated version of the original Beck. The BDI-II can be scored and interpreted locally and immediately. The BDI-II correlates highly with other depression rating scales such as the Hamilton.

BDI-II administration

1. The BDI-II will be self-administered at baseline (W00), week 4 (W04), week12 (W12), and every 3 months through month 54 in all randomized study participants at University of Southern California and University of Michigan. See page 2 for randomization visit clarification.
2. The BDI-II will also be self-administered to week 20 virologic responders at baseline (W00), week 4 (W04), Week 12 (W12), Week 24 (W24), week 36 (W36), week 48 (W48), week 60 (W60), and week 72 (W72)
3. The BDI-II takes ~5-10 minutes to complete. Individuals with moderate to severe depression may require longer to complete the survey.
4. Item 16 (Changes in Sleeping pattern) and item 18 (Changes in appetite) have 7 options rated in order as 0, 1a, 1b, 2a, 2b, 3a, and 3b to differentiate between increases and decreases in behavior or motivation. Only 1 option should be selected and this item should be scored by the number of the statement selected.
5. It is important that patients complete all of the items on the form. Please ask the patient to complete any missing items after reviewing the form and be certain that each item has a single statement marked.

BDI-II Scoring

1. Each item in the BDI-II is rated on a 4-point scale of 0 to 3.
2. If a patient has made multiple endorsements for an item, the alternative with the highest rating should be used.
3. If a statement was not chosen for a given item, then score it as a 0.
4. The BDI-II is scored by summing the values of the 21 individual items. The range of possible scores is 0 to 63.
5. A respondent's answers to the BDI-II should be entered onto Form # 44 per QxQ instructions immediately following its administration.

BDI-II Interpretation

Researchers should keep in mind that all self-report inventories are subject to response bias. That is, some individuals may endorse more symptoms then they actually have and thus produce spuriously high scores while others might deny symptoms and receive spuriously low scores. In addition, the clinician is cautioned that the BDI-II may simply reflect the degree of depression, not the diagnosis of depression. Determination of the severity of depression and the establishment of a diagnosis of depression requires examination by a clinician (physician or psychologist/ psychiatrist).

Total Score

1. The BDI-II should be scored and assessed following each study visit as follows:

BDI-II Score	**Depression severity**
0 - 10	None to minimal
11 - 14	Mild
15 –19	Moderate
20 – 28	Severe
> 29	Critical

2. Anti-depressants should be considered for patients with moderate to severe depression (BDI-II > 15) before considering IFN dose reduction.
3. Additional follow-up for patients with abnormal BDI-II scores is provided in the Management Guidelines for Depression in the main HALT-C Protocol, Appendix C.1.

Critical Items

Because the BDI-II total score provides only an estimate of the overall severity of depression, it is very important to be attentive to specific items regarding **suicidal ideation**.

1. Patients admitting to suicide ideation **(Item 9**) and hopelessness **(Item 2)** with a **rating of 2 or 3** should be closely scrutinized for suicide potential.
2. In addition to notifying the physician investigator, contact with the local psychiatry collaborator may be indicated.
3. Additional follow-up is recommended for all patients with potential suicidal ideation.

G. Brief Symptom Inventory (BSI)

The BSI is a brief, 53 item, self-administered questionnaire with established reliability and validity that is designed to assess emotional distress in medical and psychiatric patients. The BSI generates 9 symptom scales (e.g. depression, anxiety) and 3 summary scales (e.g. Global Severity Index) after raw scores are converted to T-scores using computerized software that utilizes well-established age and sex matched controls. We plan to use T-scores, which have a mean of 50 with a standard deviation of 10 and a range of 0 to 100 for research analysis.

BSI administration

1. The BSI will be self-administered at baseline (W00), week 4 (W04), and every 6 months through month 54 in all randomized study participants at University of Michigan and University of Southern California.
2. The BSI will be self-administered to week 20 virologic responders at baseline (W00), week 4 (W04), week 24 (W24), week 48 (W48), and week 72 (W72).
3. It takes ~5-10 minutes to complete a paper and pencil version of the BSI.
4. Be certain that respondents complete all 53 items.

BSI scoring

1. Raw scores for each item have a 5-point rating scale of 0 (Not at all) to 4 (Extremely).
2. Raw scores will be entered into the BSI scoring software (MICROTEST Q) per manufacturer's instructions at each center
3. A **Profile Report** containing a graphic profile of the raw and normalized T-scores for all 9 symptom scales and 3 Global indices will be generated by the scoring program.
4. The Profile Report will be entered onto Form #154 Brief Symptom Inventory (BSI), per QxQ instructions.
5. A hard copy of each Profile Report will be stored in the patient's case report form.

H. Blood studies

The biochemical basis of impaired cognition and mood disorders that develop during IFN therapy remains unknown. Although IFN does not readily cross the blood brain barrier, high dose IFN can permeate the periventricular areas of the brain wherein it may exert its CNS effects. Short-term IFN therapy leads to increases in circulating norepinephrine levels in healthy volunteers which are similar to those seen in patients with endogenous depression. Other studies demonstrate marked increases in AM cortisol levels and a failure to suppress cortisol production in patients receiving IFN that is similar to what has been reported in patients with major depression. Other studies suggest that IFN neuropsychiatric toxicity may

be, in part, due to induction of secondary neurotoxic cytokines. Lastly, decreases in serum trypytophan levels have been observed following IFN administration indicating that alterations in serotonergic pathways involved in mood regulation may also be important. This ancillary study provides a rare opportunity to prospectively study the potential biochemical basis of IFN induced neuropsychiatric toxicity.

In this study, AM cortisol levels will be measured as a biological marker of the HPA axis and whole blood serotonin levels will be measured as a marker of serotonergic activity.

Sample collection and processing

1. Preparation - Patients will be asked to take their pegylated IFN dose at **least 2** days before testing to minimize inter-individual variation in the effect of IFN on the circadian rhythm of cortisol secretion.
2. Fasting blood samples will be collected in all randomized University of Michigan patients between 8:00 a.m. and 10:00 a.m. at study visits baseline (W00), week 4, week 24, randomization visit (R00) - see p.2, month 12, month 24, month 36, month 48 and month 54.
3. Fasting blood samples will also be collected in all week 20 virologic responders at University of Michigan between 8:00 AM and 10: 00 AM at study visits baseline (W00), week 4 (W04), week 24 (W24), week 48 (W48) and week 72 (W72).
4. Plasma cortisol
   a. 7 cc of blood collected into a heparinized (green top) tube will be obtained and kept on ice during processing.
   b. Sample will be centrifuged at 3000 rpm x 15 minutes. Plasma will be drawn off and aliquoted to 3 x 1 ml labeled storage tubes and placed in -80 °C freezer per QxQ instructions on Form #150, Cortisol as a Serum Marker of Mood Status.
5. Whole blood serotonin
   a. 10 ml of whole blood will be drawn into a purple top tube and kept on ice during processing.
   b. After mixing well by inverting tube upside down 5 times, 3 x 3 ml whole blood aliquots will be made using labeled storage tubes and placed in -80° C freezer per QxQ instructions on Form #156 Serotonin as a Serum Marker of Mood Status.
6. Plasma and whole blood samples will be transferred to the Research Assays Support Lab at University of Michigan under the direction of Cy Jone and assayed in batches.
7. Plasma cortisol levels will be measured in duplicate using a commercial RIA kit provided by Diagnostic Products Corporation (Los Angeles, CA).
8. Whole blood serotonin levels will be measured in singlet using HPLC with fluorescence detection.
9. Plasma cortisol and whole blood serotonin values will be entered into the HALT-C Trial Data Management System at University of Michigan per QxQ instructions for Form #150 and #156.

I. New forms

Form 157 – Years of Education
Form 158 – Occupational Status
Form 159 – Scoring Sheet for Baseline NPT Batteries Clinician Impairment Ratings

IV. Case Report Forms

Due to the large number of surveys and datasheets, a 3 ring binder CRF will be purchased and used for this ancillary study alone. All original data forms and scoring forms will be filed by date of study visit.

V. Sample size

The proposed studies are designed to detect a difference in the incidence of cognitive impairment between the treated and untreated groups of patients that are randomized. Assuming that 40-50% of the IFN treated group will experience a decline in global cognitive function of one-half of one standard deviation, and that 5-10% of the untreated controls will have similar changes, in order to detect a significant difference of 0.05 (two tailed t-test) with 80% power, the sample size required is 134 or 67 per group. Assuming that attrition will be 5%/ year in each group over the 4 year study, complete data will be available for analysis on ~ 147 of the 180 randomized patients enrolled at the two participating centers.

It is estimated that 45 of the 135 (33%) patients treated in the lead-in phase at each center will be week 20 virologic responders. Assuming that attrition will be 5% per year in week 20 responders, complete data will be available for analysis on 81 of the 90 week 20 responders enrolled at the two participating centers. The frequency, severity, type, and reversibility of cognitive impairment in the 90 virologic responders will be compared to that observed in the 90 patients randomized to the control arm of the HALT-C Trial who only received 6 months of PEG + Ribavirin in the Lead-in Phase.

VI. Data analysis

The primary aim of this ancillary study is to assess serial changes in cognitive function in hepatitis C patients receiving long term IFN and to compare these changes with those observed in untreated controls. The neuropsychiatric tests will be scored and entered into the HALT-C Data Management System. Test scores will be converted to z-scores for each test and to create a global z score, from which z-score changes can be calculated from baseline. Patient groups will be compared by global z-score change in overall test performance from baseline to each interval and endpoint. Specific test performance changes in each measured domain will be done using similar analyses. At baseline and at each test interval, individuals will be classified as cognitively impaired or unimpaired. Cognitive impairment will be defined as performance of one standard deviation below the mean on two or more of the administered tests. Similar criteria have been used by Dr. Bieliauskas and colleagues in studies of early cognitive changes in HIV infection (22,23). Serial test results will be compared using analysis of variance with repeated measures. Intergroup comparisons between treated and untreated randomized controls and patients with and without cirrhosis will be undertaken using analysis of variance step-down test. To determine if changes in cognitive function are reversible, the mean results of neuropsychological tests at the end of the first 2 years of treatment will be compared with baseline, with the scores at the end of the first 4 years of treatment, and with the end of follow-up in the treated and untreated patient groups.

It will be of interest to determine how many subjects in each group of the Randomized Phase demonstrate good versus bad outcomes in terms of neuropsychological test performance. The different groups can be compared in terms of cognitive impairment at baseline and at intervals using chi-square analyses. To identify possible clinical correlates of pretreatment cognitive status, the following variables will be tested using covariate analyses: subject age, gender, educational level, BSI score, Beck score, Ishak inflammation and fibrosis score, pretreatment DSM IV psychiatric profile, and lifetime alcohol consumption.

In week 20 virologic responders who receive PEG + Ribavirin for 48 weeks and are followed for 24 additional weeks post-treatment, global z-score changes from baseline to each subsequent interval and endpoint will be made. Specific test performance changes in each measured domain will be done using similar analyses. Pretreatment baseline variables including subject age, Shipley IQ score, years of education, BDI-II score, BSI score, and global z-score will be tested as predictors of cognitive impairment during anti-viral treatment using univariate and multi-variate analysis. The frequency, type, severity and reversibility of cognitive impairment in the 90 week 20 virologic responders will also be compared to that observed in the 90 patients randomized to the control arm of the HALT-C Trial who only receive 6 months of PEG + Ribavirin in the lead-in phase. The reversibility of cognitive impairment at 6 months following the cessation of anti-viral therapy in the week 20 virologic responders (Week 72) will be compared to that seen in the randomized controls (month 12).

For the analysis of the blood studies, treatment arm, mood states and degree of cognitive impairment will be the independent variables. The dependent variables will be plasma concentration of cortisol and whole blood serotonin. Comparisons between groups will be made using analysis of covariance.

References

1. Wittchen HU. Reliability and validity studies of the WHO Composite International Diagnostic Interview: A critical review J Psychiatric Research 1994; 28: 57-84.
2. Griest JH, Klein MH, Erdman HP, Bires JK, Bass SM, Machtinger PE, Kresge DG. Computer and interviewer administered versions of the Diagnostic Interview Schedule. Hospital Psychiatry 19 38: 1304-1311.
3. Zachary RA. Shipley Institute of Living Scale 1988. Los Angeles: Western Psychological Services.
4. Benton, A.L., Hamsher, K. deS., Varney, N.R. & Spreen, O. Contributions to neuropsychological assessment 1983; New York: Oxford University Press.
5. Lezak MD. Neuropsychological assessment 1995; New York, Oxford Press.
6. Hannay HJ, Levin HS. Selective reminding test: An examination of equivalence of four forms. J Clinical and Experimental Neuropsychology 1985: 7: 251-263.
7. Pavol MA, Meyers CA, Rexer JL, Valentine AD, Mattis PJ, Talpaz M. Pattern of neurobehavioral deficits associated with interferon alfa therapy for leukemia. Neurology 1995; 45: 947-950.
8. Wechsler D. WAIS-R Manual 1981; New York, Psychological Corporation
9. Era P, Jokela J, Heikkinen E. Reaction and movement times in men of different ages: A population study. Perceptual and Motor Skills 1986; 63: 111-130.
10. Martin EM, Pitrak DL, Mullane KM, Pursell KJ, Novak RM, Carson VL, Arruda J, Somerville J, Stern RA. Reaction time performance of HIV-seropositive women. 1997; Natl Conf Women HIV; p 162.
11. Gitlin N, Lewis DC, Hinkley L. The diagnosis and prevalence of subclinical hepatic encephalopathy in apparently healthy ambulant, non-shunted patients with cirrhosis. J Hepatol 1986; 3: 75.
12. Reitan, R.M. and Wolfson, D. The Halstead-Reitan neuropsychological test battery 1993; Tucson, Arizona: Neuropsychology Press.
13. Heaton RK. Wisconsin Card Scoring Test Odessa 1981; Odessa, Florida: Psychological Assessment Resources.
14. Beck A, Ward C, Mendelsohn M, et al. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4: 561-571.
15. Brown C, Schulberg HC, Madonia MJ. Assessing depression in primary care practice with the Beck Depression Inventory and the Hamilton Rating Scale for depression. Psychological Assessment 1985; 7: 59-65.

16. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. Psychological Medicine 1983; 13: 595-605.
17. Roosth J, Pollard RB, Brown SL, Meyer WJ. Cortisol stimulation by recombinant interferona2. Journal of Neuroimmunology 1986; 12: 311-316.
18. Muller H, Hiemke C, Hammes E, Hess G. Sub-acute effects of interferon-a2 on ACTH, cortisol, growth hormone, and prolactin in humans. Psychoneuroendocrinology 1992; 17: 459-465.
19. Butler J, Leonard BE. The platelet serotonergic system in depression and following sertraline treatment. International Clinical Psychopharmacology 1988; 3(4): 343-7.
20. Cleare AJ. Reduced Whole blood serotonin in major depression. Depression and Anxiety 1997; 5; 108-111.
21. Anderson G, Young JG, Cohen D, et al. Liquid-chromatographic determination of serotonin and tryptophan in whole blood and plasma. Clinical Chemistry 1981: 27: 775-776
22. Swanson, B., Bieliauskas, L.A., Kessler, H., Zeller, J.M., and Cronin-Stubbs, D. Infrequent neuropsychological impairment in asymptomatic persons infected with the human immunodeficiency virus. Clin. Neuropsychologist. 1991; 5:183-189.
23. Swanson, B., Cronin-Stubbs, D., Zeller, J.M., Kessler, H.A., and Bieliauskas, L.A. Cognitive changes associated with the acquired immunodeficiency syndrome. App. Nsg. Res. 1992; 5:146-148.

Appendix 1

Cognitive Ancillary study protocol and proposed tests at UMich and USC

Visit	Screen 1	Screen 2	W00	W04	W20	W24	M12	M18	M24	M30	M36	M42	M48	M54
NP Testing														
n (subjects)	270	270	270	270	270	270	180	180	180	180	180	180	180	180
Shipley			x											
NP battery *			x			x	x		x		x		x	x
Mood status														
CIDI **	x													
Mod CIDI-12						x	x		x		x		x	x
Skinner EtOH		x												
BSI			x	x		x	x	x	x	x	x	x	x	x
Beck ^			x	x	x	x	x	x	x	x	x	x	x	x
Serum markers														
n (subjects)			135	135		135	90	90	90	90	90	90	90	90
Blood studies ^^			x	x		x	x		x		x		x	x

* NP battery consists of Selective reminding test, Digit span, Digit Symbol, Serial Digit Learning, Simple and Choice Reaction Time, Trail Making test, Finger tapping test, Wisconsin Card Sorting Test, Controlled Oral Word Association, and Continuous Visual Memory Test

** Baseline CIDI include anxiety, depression, alcohol, drug, and somatization modules; mod CID-I12 includes depression and anxiety modules of the 12 month version

^ Beck to be administered every 12 weeks from month 0 thru 54 per main study protocol

^^ Blood samples for plasma cortisol and serotonin levels to be collected on UMich patients only

Breakthrough / Relapsers re-entering the Randomization Arm: (Express Patients are not eligible for this study)

1. If after the 2nd positive HCV RNA a patient is eligible to be randomized and the randomization visit (R00) is scheduled more than 1 calendar month after the last battery of cognitive testing, then the standard cognitive battery: CIDI-12, BSI, BDI-II, and blood for WB serotonin and cortisol (UMich patients only) should be collected at the randomization visit (R00). After R00 the next study visit for additional cognitive testing would be the M12 visit.
2. If after the 2nd positive HCV RNA a patient is eligible to be randomized and the randomization visit (R00) is scheduled less than 1 calendar month after last battery of cognitive testing, then no additional cognitive testing will be collected at R00 except for BDI-II (Form #44). Then the next study visit for additional cognitive testing would be the M12 visit.

Appendix 2

Proposed tests to be done on Wk 20 Virologic Responders at UMich and USC

Visit	Screen 1	Screen 2	W02	W04	W12	W20	W24	W36	W48	W60	W72
NP Testing											
n (subjects)	45	45	45	45	45	45	45	45	45	45	45
Shipley			x								
NP battery *			x				x		x		x
Mood status											
CIDI **	x										
Mod CIDI-12							x		x		x
Skinner EtOH		x									
BSI			x	x			x		x		x
Beck ^			x	x	x	x	x	x	x	x	x
Serum markers											
n (subjects)			45	45			45		45		45
Blood studies ^^			x	x			x		x		x

* NP battery consists of Selective reminding test, Digit span, Digit Symbol, Serial Digit Learning, Simple and Choice Reaction Time, Trail Making test, Finger tapping test, Wisconsin Card Sorting Test, Controlled Oral Word Association, and Continuous Visual Memory Test

** Baseline CIDI include anxiety, depression, alcohol, drug, and somatization modules; mod CID-I12 includes depression and anxiety modules of the 12 month version

^ Beck to be administered every 12 weeks from month 0 thru 54 per main study protocol

^^ Blood samples for plasma cortisol and serotonin levels to be collected on UMich patients only

Appendix 3

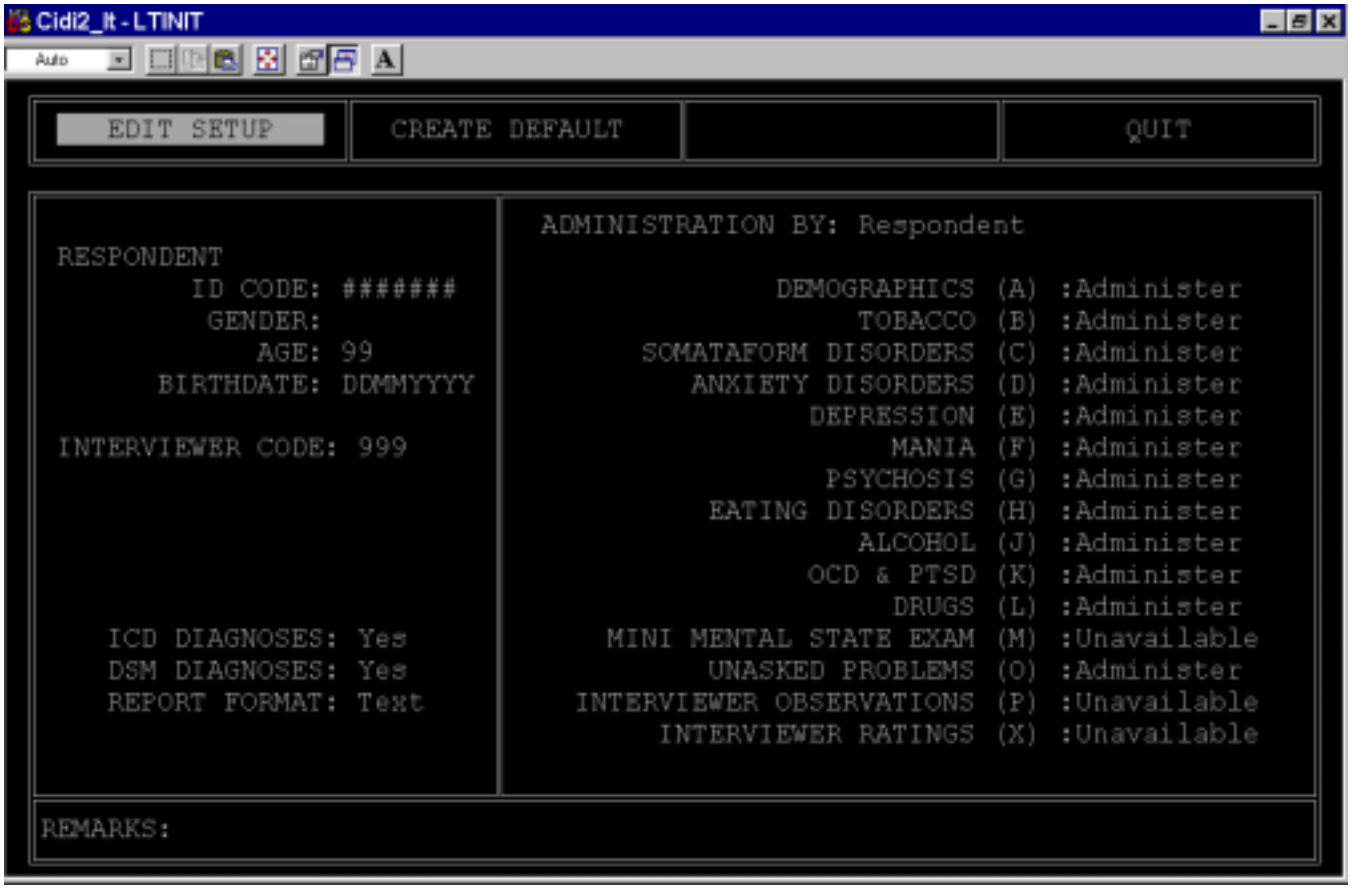
Instructions for using CIDI-LT Auto 2.1

The CIDI-LT Auto 2.1 is a computerized, self-administered diagnostic interview for the assessment of lifetime mental disorders by DSM-IV and ICD-10 criteria. The following instructions are for running the CIDI-LT Auto 2.1 program that has been installed on your computer (See Appendix 4 for installation instructions). If additional questions arise, please refer to the Administrator's Guide and Reference manual.

I. Set-up procedure

The CIDI Auto 2.1 should be administered on a computer in a quiet, private environment with no distractions. The Respondent and Interviewer should be comfortably seated during the process.

1. Double click on the CIDI shortcut Icon on your computer
2. The program will run through several information screens before the interview set-up data entry screen appears as shown below



3. The row of 4 boxes in the menu panel at the top of the screen identifies possible actions to be taken. When a new interview is to be set up only the **EDIT SETUP, CREATE DEFAULT**, and **QUIT** options are available. Pressing [Enter] will cause the highlighted option to be executed. The highlighted option may be changed by pressing either the arrow keys or the tab key.

4. To set-up a new interview, press the highlighted **EDIT SETUP** key. In this window there are two main types of items. The items **ID CODE**, **AGE**, **BIRTHDATE**, **INTERVIEWER CODE**, and **REMARKS** all require the administrator to type in information. All of the other items have a limited set of alternatives from which one is selected by using the arrow keys to scroll through the options. Once the information has been entered or selected the administrator may move on to the next field by typing [Tab] or [Enter]. To move to a previous field, type [Tab] while holding down the [Shift] key The items **ID CODE**, **GENDER**, **AGE**, **BIRTHDATE**, and **INTERVIEWER CODE** must have information entered or an alternative selected or else the program will beep and the **RUN AS SHOWN** option will not be made available.

5. The items in the set-up information window are identified below in their forward entry order:

   ID CODE: A combination of between 1 and 7 letters and digits must be entered into this field. You should use the visit number (**3 letters and digits like S01 for screen 1**) followed by the patient's initials **(3 letters**). If less than 7 characters are entered the program will automatically right justify the code entered and left fill it with zeros until there are 7 characters in the code. For example, the ID code SO1RJF will become 0S01RJF. The Respondent ID Code is used to uniquely identify the output files created by the interview, data transfer and scoring programs. IF a respondent is interviewed on more than one occasion, a unique ID code must be given for each administration. If the same ID code is used on both occasions, the second run will overrun the first.

   GENDER: The interview engine must know the Respondent's GENDER because there are a number of questions within the interview which vary as a function of gender. Using the arrow keys, select either MALE or FEMALE and press [Enter].

   AGE: The Respondent's AGE in years on the day of the interview must be entered in this field. This two digit item is entered by the administrator rather than the respondent for accuracy.

   BIRTHDATE: The respondent's birthrate must be entered in European format: (**DD/MM/YY**) day of the month, followed by the month, and then the year, are all entered as two digit numbers. For example, the date 30th of May 1957 would be entered as 300557. The program will not accept dates in any other format.

   INTERVIEWER CODE: Any number up to 3 digits in length may be entered in this field. A Default value of 999 will appear if you do not specify an interviewer code. It is suggested that an interviewer code be developed at each center to specify which study coordinator administered the Interview (i.e. at UMich, 001= Amy Randall-Ray, 002= Pam Richtmyer).

6. The preceding 5 items must all have a valid value entered before the program will allow the administrator to run the interview. The remaining items in the set-up are initially set to a default value by the program and may be left or unchanged at the administrator's discretion.

   ADMINISTRATION BY: This item has two alternatives: RESPONDENT or INTERVIEWER, either of which may be selected. If the INTERVIEWER option is chosen, some additional text, meant only for the administrator, will be visible on the screen (See Appendix 2). These additional questions should not be asked of the Respondent, so it is important not to choose the INTERVIEWER option if the program is meant to be self-administered by the RESPONDENT.

   DEMOGRAPHICS (A): When setting up a new interview this item has only one option, ADMINISTER. Because the demographics section has several questions which control how later questions in other sections of the interview are asked, it is important that it always be administered.

TOBACCO (B) through **INTERVIEWER RATINGS (X):** These items representing the modules of the CIDI have 3 alternatives: ADMINISTER, DO NOT RUN, or RUN LATER. The three alternatives control which sections of the interview are administered. Choosing ADMINISTER or DO NOT RUN controls whether the section will be administered or not. Choosing RUN LATER will result in the section not be administered in the current session, but the section can be administered in a later session.

For the HALT-C Trial, only the **ANXIETY DISORDERS (D), DEPRESSION (E), ALCOHOL (J),** and **DRUGS (L)** modules should be highlighted as ADMINISTER. All of the other modules should be highlighted as DO NOT RUN. (NOTE: UMich and USC will use the **ANXIETY (D) and DEPRESSION (E)** modules at additional test administrations at week 24 (W24), month 12 (M12), month 24 (M24), month 36 (M36), month 48 (M48), and month 54 (M54) per the Ancillary Study protocol)

ICD DIAGNOSES: This item has two alternatives: YES or NO. Selecting YES will cause the ICD-10 Scoring program to be run. The type of output asked for is controlled by the REPORT FORMAT item described below and the output will be written to a file having the name R[idnumber].ICD. Note that the scoring program can be run later even if this item is coded as NO when the interview is run. For the HALT-C Trial please enter **YES** for this field.

DSM DIAGNOSES: This item has two alternatives: YES or NO. Selecting YES will cause the DSM-IV Scoring program to be run. The type of output asked for is controlled by the REPORT FORMAT item described below and the output will be written to a file having the name R[idnumber].DSM. The initial default value for both ICD DIAGNOSES and DSM DIAGNOSES is **YES**. For the HALT-C Trial, please enter **YES** for the DSM DIAGNOSES field.

REPORT FORMAT: This item has two alternatives TEXT or DATA. This item controls the way in which the output from the Scoring programs appears in the scoring files. Selecting TEXT will cause the output to appear as text describing the diagnoses for which the Respondent met criteria. Selecting DATA will cause the output to appear as data that can be read into statistical analyses packages. Please use the **TEXT** format for respondent's in the HALT-C Trial.

REMARKS: This item allows the administrator to enter up to 40 characters of free form text. It may also be left blank. For the HALT- C Trial , we do not plan to enter any data into this field.

7. The set-up is now complete. If the administrator presses the [Esc] key, all four action options, including **RUN AS SHOWN**, will become available on the menu at the top of the screen. If [Esc] is pressed before having completed entry of the required set-up information, the program will cause the computer to beep and the **RUN AS SHOWN** option will not be available in the menu.

   CREATE DEFAULT: At this point the administrator may choose to use the current selection of Sections to be administered and outputs to be created as the default set-up. Pressing [Enter] with the **CREATE DEFAULT** menu option highlighted will cause the program to create a file named **CIDIA.INI** in the current working directory. This file will contain the information about which sections are to be run and what output is to be created. It will not contain any identifying information about the particular respondent for whom the set-up may have initially been created. On starting the CIDI-Auto, the program will look in the current working directory for **CIDIA.INI**, and if it is found, will use its contents to define the default values for the items. Otherwise, it will use the internally defined default set-up.

RUN AS SHOWN: This menu option runs the program as shown in the set-up screen. Selecting this menu option causes the program to create a file named R[idnumber].INI which contains all the set-up information for that Respondent. This file controls the execution of the interview engine and the data transfer programs.

QUIT: This menu option allows you to quit from the program without saving any of the changes that may have been made in the set-up data or creating any other files.

II. Interview operation

1. Once the set-up procedures have been completed the program will present a screen carrying the CIDI-A logo. Pressing [Enter] will cause the program to continue.
2. If the interview is to be administered by the INTERVIEWER, the program will skip straight into the **DEMOGRAPHICS (A)** section.
3. If the interview is to be self-administered by the RESPONDENT, the program will next present the RESPONDENT with reassurance about the confidentiality of their responses. This is followed by a relatively detailed tutorial.
4. The study coordinator should remain available to assist with completion of the tutorial and entering numerical and letter data into the computer keyboard or attached keypad as needed.

III. Tutorial Module

The tutorial has been designed to teach the RESPONDENT how to answer each type of question they may encounter in the interview. Each type of question is described and in some cases the RERSPONDENT is given a chance to try entering a response to a question of that type.

The Tutorial warns the RESPONDENT to read onset and recency questions carefully. Upon completing the tutorial which takes ~ 5 minutes, the program continues with the interview itself starting at section A.

NOTE: If a RESPONDENT is unable to complete the tutorial section , they will likely encounter great difficulty with many of the more complex questions in the interview. In such cases the administrator is strongly advised to administer the interview to the RESPONDENT in the INTERVIEWER mode (See Appendix 5).

IV. The Interview

The Study coordinator should leave the area to allow the Respondent to complete the program in privacy. However, the Study coordinator should remain nearby to answer questions or troubleshoot problems that may arise.

It should take **20- 40 minutes** for a Respondent to complete the **ANXIETY DISORDERS (D), DEPRESSION (D), ALCOHOL (J)**, and **DRUGS (L)** modules.

A. Types of questions

The following paragraphs describe how responses are entered for each of the different type of questions used in the interview.

1. **Yes/ No questions:** Most of the questions asked require a simple yes or no response. Throughout the interview a **5** is used to indicate YES and a **1** is used to indicate NO. In the tutorial, the RESPONDENT is instructed to answer **No** if they are not sure whether their answer should be Yes or No.

2. **The Go Back key:** Within a Section of the interview, RESPNDENT can go back to a previous question by entering [-] [Enter] (i.e. typing the minus key followed by the [Enter] key). It is possible to back up from the last to the first question within a module. It is not possible to go back to a question within a previous module.

3. **Numerical Answers:** Some questions require users to enter the age of onset or recency of symptoms or to provide some other kind of numerical answer. Answers to such questions are given by typing in the appropriate number followed by [Enter]. These questions also allow users to indicate that they do not know the answer by entering the letters **DK** instead. The program will not accept [Enter] alone. **DK** responses will nearly always be followed with a simple multiple choice question asking the user to choose from a range of broad estimates.

4. **Multiple Response Answers:** A few questions allow users to choose one or more of a number of options as their answer. The most common of these is the question asked about the diagnoses a doctor may have given as the cause of a particular symptom. Users are able to select and deselect options from the list of available options. An option is selected by typing its corresponding letter or number, causing it to be highlighted. To de-select the option, the user types the corresponding letter or number again. Users may select as many of the available options as appropriate.

5. **Text Answers:** Some questions request users to enter text as the answer to the question. Users are only allowed to enter one line of text (~ 60 characters). If they attempt to type beyond the end of the input line the computer will "beep" at them and ignore any further input other than [Enter] or [Backspace].

B. Quitting from a Section or Terminating an Interview

The interview administrator can gain control of the program in order to quit from one section or to terminate the entire interview by typing **[#]** (i.e. [Shift] [3]) from any multiple choice or multiple response questions.

Typing **[#]** causes a message to appear at the bottom of the screen that lists 3 options:

[R] = Resume the interview and return to the current question
[Q] = Quit the current section and go on to the next
[T] = Terminate the whole interview

If the administrator chooses **[Q]** to quit from the current section, the data for that section will be saved but a code will be entered in the R[idnumber].INI file marking that section as partially completed. At the end of the interview, the data transfer program will ignore the data from partially completed sections when it concatenates the data files from each section. This allows the administrator to examine the data but stops the scoring program from making any decisions on the basis of incomplete data.

If the administrator chooses **[T]** to terminate the interview, the data from the current section will not be saved. However, data files from previously completed sections will be concatenated.

Note that a module is complete only after a **5**, indicating move on to the next module, has been entered at the final question of the section. It is only at this point that the results of the Section are written to a file. Terminating the interview at any point within a Section, including the final question of a Section will mean that the results for that Section are not written to a file.

V. Viewing the Interview Results

The Scoring programs read the R[idnumber].OUT created at the end of the interview and create their own results files which will be named either R[idnumber].ICD (if ICD Diagnoses had been called for) or R[idnumber].DSM (If DSM Diagnoses had been called for).

The file **R[idnumber].SCS** contains the results of the scoring program and should be printed out in hard copy format. In the HALT-C Trial, both the ICD-10 and DSM-IV diagnostic data will appear in this file.

A. Data files

Two files, R[idnumber].INI and R[idnumber].OUT, contain all the results of the interview and must be kept. When the data transfer program creates the R[idnumber].OUT file it also creates a compacted version suitable for use as a hard copy of the raw data. This file named **R[idnumber].ALL** contains the same data as that found in R[idnumber].OUT however the information is organized in a compacted format. These files can be found in the CIDI folder in your directory. A hard copy **of R[idnumber].ALL** should be printed out and stored in the patients CRF for future reference.

VI. Inputting CIDI data into the HALT-C Trial database

The DSM-IV diagnoses obtained from a Respondent should be transferred on to section H **of Form #4** of the Screening Checklist. The following parameters for each DSM-IV diagnosis should be transferred per **Form #4** QxQ instructions

a. DSM-IV 5 digit diagnostic code
(e.g. 296.32= Major depressive episode, recurrent, moderate)

b. Number of diagnostic criteria met
Code identifying what level of diagnostic criteria was met.
0= Indeterminate diagnosis
1= Criteria for diagnosis not met
3= The positive criteria for diagnosis are met but exclusion criteria not met
5= All diagnostic criteria are fulfilled

c. 1 digit onset code
Standard CIDI Onset code
1= within last 2 weeks
2= 2 weeks to less than 1 month ago
3= 1 month to less than 6 months ago
4 = 6 months to less than 1 year ago
5=in the last 12 months, DK when
6 = more than 1 year ago

d. 2 digit age of onset if c. is coded

e. 1 digit recency code
Standard CIDI Recency code
1= within last 2 weeks
2= 2 weeks to less than 1 month ago
3 = 1 moth to less than 6 months ago
4= 6 months to less than 1 year ago
5= in the last 12 months, DK when
6 = more than 1 year ago

f. 2 digit age recency if e. is coded

g. DSM-IV diagnosis text

VII. DSM-IV diagnosis text and code

The following DSM-IV diagnoses can be generated from the CIDI Auto 2.1 module of ANXIETY, DEPRESSION, ALCOHOL, and DRUGS.

Anxiety disorders

Specific phobia (300.29)
Social phobia (300.23)
Agoraphobia without history of panic disorder (300.22)
Panic disorder without agoraphobia (300.01)
Panic disorder with agoraphobia (300.21)
Generalized anxiety disorder (300.02)

Depressive disorders

Major depression, single episode mild (296.21)
Major depression, single episode, moderate (296.22)
Major depression, single episode, severe (296.23)
Major depression: recurrent , mild (296.31)
Major depression, recurrent, moderate (296.32)
Major depression, recurrent, severe (296.33)
Dysthymia (300.4)

Alcohol abuse (305.00)

Alcohol dependence (303.90)

Psychoactive substance use disorders; dependence or abuse

Cannabis abuse (305.20)
Cannabis dependence (304.30)
Cocaine abuse (305.60)
Cocaine dependence (304.20)
Hallucinogen abuse (305.30)
Hallucinogen dependence (304.50)
Inhalant abuse (305.90)
Inhalant dependence (304.60)
Opioid abuse (305.50)
Opioid dependence (304.00)
Amphetamine or similar-acting substance abuse (305.70)
Amphetamine dependence (304.40)
Sedative abuse (305.40)
Sedative dependence (304.10)
Stimulants
PCP abuse (305.90)
PCP dependence (304.90)
Other substance abuse (not otherwise specified [NOS]) (305.90)
Other substance dependence (304.90)

Appendix 4

Installation procedure using Windows

1. To install CIDI-LT Auto, open up your Windows File Manager/ Windows Explorer and create a directory folder for the files (Name this new directory CIDI).

2. Copy the program files from the distribution disk into the directory you have just created by dragging the file icons over to the appropriate directory.

3. Once the installation programs have been copied, simply double-click on each of the **LT.EXE** and **12.EXE** file icons, to execute their installation programs. This will result in the extraction of the 8 program files for each version of the CIDI-LTAuto.

4. To run CIDI-LTAuto, merely double-click on the **CIDI2_LT.EXE** file icon in the file Manager/ Windows Explorer for the standard lifetime version of the CIDI-Auto. Or double-click on the **CIDI2_12.EXE** file icon in order to run the 12-months recency version of CIDI-Auto. The CIDI-Auto should then switch the computer to a DOS mode, or open up a DOS window on the screen, which will then run the CIDI-Auto program

5. To setup program access that is more convenient than double-clicking the program icon within the Windows/ Explorer, simply drag the program icon for **CIDI2_LT.EXE** or **CIDI2_12.EXE** from the Windows Explorer directory folder onto the background wallpaper. Note the Explorer will have to be windowed rather than full screen to allow a view of both the Explorer and the Wallpaper. This will automatically generate a shortcut to the program file on your desktop.

Appendix 5

Interviewer Administered CIDI-Lt Auto2.1

The CIDI-LT auto 2.1 may need to be administered by the INTERVIEWER if the RESPONDENT is not capable of performing the self-administered version. Because of the need for stating each question, it is anticipated that an INTERVIEWER administered CIDI will take 30 to 40 minutes to complete.

1. **INTERVIEWER preparation:** Before administering the CIDI-LT Auto 2.1 to a respondent, it is imperative that the INTERVIEWER be familiar with the format, questions, and content of each module. The INTERVIEWER should read all of the sections in the CIDI 2.1 Interviewers Manual before starting an interview. A copy of the actual questions in each module is available in the CIDI Training Reference Questionnaire.
2. **INTERVIEWER instructions:** When the CIDI-LT Auto 2.1 has been set-up in the INTERVIEWER mode, there will be text and instructions addressed to the INTERVIEWER that are set off in brackets and typed in caps. This text should not be read aloud to the patient. These instructions assist the INTERVIEWER.
3. **Cards:** In some of the modules like ANXIETY (D), ALCOHOL (J), and DRUGS (L), the INTERVIEWER will be asked to give the respondent a card for reference to subsequent questions. In these circumstances, give the requested card to the patient before proceeding. At time you will be asked to circle the patient's response for them and then refer back to the circled text. When finished with the interview, keep the completed cards with the computerized data output in the patient's CRF.
4. **Questions:** The principles of asking questions in the standardized interview are essential to maintain the integrity of the survey data. Questions must be read in their entirety and in the order they appear to ensure comparability across respondents. Even slight deviations from wording have been shown to affect responses. Please review pages 9-13 of Interviewer's Manual for exceptions due to grammatical changes, breaking questions into shorter questions, and verifying responses.
5. **Data entry:** Type the respondents response into the computer as a digit or free text into the computer as appropriate to the question. Verify the respondent's answer as needed.

PROBE FLOW CHART: Throughout the CIDI-LT interview, a determination as to whether the reported symptom may or may not be due to a possible Psychiatric condition vs. other cause is assessed. The following line of questioning is used regarding many symptoms or situations.

- **Have you ever had symptom X ?**
    - If Yes
- **Did you tell a doctor ?**
    - If No
- **Did you ever tell any other professional about symptom X ?**
    - If Yes
- **Was symptom ever result of physical illness or injury ?**
    - If No
- **Was symptom ever result of taking medications, drugs, or alcohol ?**
    - If No
    - **Possible Psychiatric symptom**

A psychiatric diagnosis is made when a specified number of positive or inclusion criteria are met and exclusion criteria are eliminated. If a symptom is believed to be due to illness, injury, or medicine, drugs, or alcohol then it will not be classified as a possible psychiatric symptom. To get this information, the PFC is used repeatedly to determine 1) "Did you ever have X symptom ? 2) IF yes, "did you tell a doctor about X symptom ?" 3) If Yes" What was the diagnosis of X symptom ? IF no, "Did you tell another Professional about X symptom ?" 4). "Was X symptom ever the result of physical illness or injury ? " 5) "Was X symptom ever the result of taking medication, drugs, or alcohol ? " 6) If no to 4 and 5,

NOTE: **Doctor** includes psychiatrists, other medical doctors, and osteopaths.
Other Professional includes psychologists, social workers, counselors, nurses, clergy, dentists, chiropractors, healers, and podiatrists .

B. PRB 1 = DID NOT HAVE SYMPTOM
The respondent denies having the symptom, problem or experience, or doesn't remember having it. No further questions will be asked about this symptom. IF PRB 1 = YES then further questions are asked

C. PRB 2 = NOT CLINICALLY SIGNIFICANT
The respondent has had the symptom but the symptom was never severe enough for the respondent to seek professional help or take medication for it more than once, and it did not interfere with his/ her life or activities a lot (i.e. it was not clinically significant).

D. PRB 3 = ALWAYS CAUSED BY MEDICATION, DRUGS, OR ALCOHOL
The respondent has had the symptom and its occurrence met the criteria for clinical significance . Further probing for causes indicated that the symptom was always the result of the respondent's use of medications, drugs, or alcohol.

E. PRB 4= ALWAYS CAUSED BY PHYSICAL ILLNESS OR INJURY
The respondent has had the symptom and its occurrence met the criteria for clinical significance. Further probing for causes indicated that the symptom was always the result of a physical illness or injury or all occurrences were the result of either a physical condition or using medication, drugs, or alcohol.

F. PRB 5 = POSSIBLE PSYCHIATRIC SYMPTOM
The respondent has had the symptom and its occurrence met the criteria for clinical significance. Further probing for causes indicated that all occurrences could not be explained by either using medication, drugs, or alcohol or a physical illness or injury. A PRB 5 question will lead to subsequent questions regarding ONSET and RECENCY.

Appendix 6

Cortisol Radioimmune Assay Procedure

(To be performed at University of Michigan)

All components must be at room temperature (15-28°C) before use.

1. Plain Tubes: Label four plain (uncoated) 12x75 mm polypropylene tubes T (total counts) and NSB (nonspecific binding) in duplicate.

   Because nonspecific binding in the Coat-A-Count procedure is characteristically low, the NSB tubes may be safely omitted without compromising accuracy or quality control.

2. Coated tubes: Label twelve Cortisol Ab-Coated Tubes A (maximum binding) and B through F in duplicate. Label additional Control Ab-Coated Tubes, also in duplicate for controls and patient samples.

Calibrators	µg/dL	Mm/L
A (MB)	0	0
B	1	27.6
C	5	138
D	10	276
E	20	552
F	50	1,380

3. Pipette 25 µL of the zero calibrator A into the NSB and A tubes. Pipette 25 µL of each remaining calibrator, control and patient sample into the tubes prepared. **Pipette directly to the bottom**.

   It is good practice to use a disposable-tip micropipette, changing the tip between samples in order to avoid carryover contamination.

4. Add **1.0 µL** of ^{125}I Cortisol to every tube. Vortex.

   Laboratories equipped with a reliable pipettor-dilutor may handle steps 2 and 3 simultaneously. No more than 10 minutes should elapse during the dispensing of the tracer. Set the T tubes aside for counting at step 6: they require no further processing.

5. Incubate for **45 minutes at 37°C**.

   Use a waterbath: neither an oven nor a heat block is suitable. Longer incubation periods will not significantly affect the assay.

6. Decant thoroughly.

   Removing all visible moisture will greatly enhance precision. Decant the contents of all tubes (except the T tubes) using a foam decanting rack and allow them to drain for 2 or 3 minutes. Then strike the tubes sharply on absorbent paper to shake off all residual droplets.

7. Count for **1 minute** in a gamma counter.

Appendix 7

Whole Blood Serotonin Assay

(To be performed at University of Michigan)

Method:

1. Whole blood is frozen and then diluted with pH 4.5 buffer, thereby lysing the red blood cells.
2. The solution is then put through an ultrafiltration device, and the ultrafiltrate **is** injected info the HPLC system.
3. An HPLC mobile phase of acetate buffer and acetonitrile (88:12) containing heptane sulfonic acid and tetrathylammonium perchlorate is then used to separate serotonin and the internal standard, N-methyl serotonin, from other endogenous compounds in the blood.
4. The analytes are detected by either electrochemical or fluorescence detection. The peak heights of serotonin and N-methyl serotonin are then used **to quantitate** serotonin by the internal standard method.

Sample: 1.5 mL of EDTA whole blood stored in a polypropylene tube at –80 degrees C.

Detection Limit: 1 ng/mL

Linearity: up to 400 ng/mL

Mean Inter-Assay Variation: CV 3.00%

Mean Analytical Recovery: 107%

Specificity: Specific for serotonin. No known interferences.

Appendix 8

Calculation of Standard Scores for Form # 152 (Neuropsychiatric Test Results)

1. Calculate standard scores (SS) for each representative variable according to raw scores and means and standard deviations. The scores will be entered into Form # 152.
2. SS cannot be obtained at this time for reaction times.
3.

Standard Scores Calculations:

X = raw scores on specified items on Form #152

1. Selective Reminding Test (SRT) Recall = Item B2a

SS = (x* - mean for age) (10) + 50
SD for age

*x+5 for males

NOTE: See Table 1 for population means + SD

Table 1 - Selective Reminding Test Normative Data
Age Groups

Variables	18-29	30-39	40-49	50-59	60-69	70-79	80-91
Total Recall *							
Mean	128.18	124.59	125.03	121.62	114.82	105.27	97.96
SD	9.16	13.40	12.00	10.46	15.77	16.67	17.49
LTR							
Mean	122.16	118.14	118.55	112.71	101.52	89.95	77.22
SD	13.12	20.64	17.95	16.10	24.68	29.23	26.26
STR							
Mean	6.14	6.72	6.48	8.96	13.52	17.47	20.74
SD	4.82	7.59	6.72	6.40	9.52	10.47	9.62
LTS							
Mean	124.00	121.62	122.45	116.67	107.00	95.54	87.48
SD	10.47	18.36	15.64	14.52	21.79	24.86	25.26
CLTR							
Mean	115.12	107.93	107.10	101.50	88.92	69.68	54.96
SD	19.67	27.62	26.62	22.39	35.85	38.96	29.04

2. Continuous visual Memory Test (CVMT) Total score = Item B3d

SS = (x* - mean for age) (10) + 50
SD for age

NOTE: See Table 2.

Table 2 - CVMT Norms

Age	Mean Total Score	SD
18-29	82.07	4.05
30-49	79.03	4.78
50-69	75.00	5.50
70+	74.50	5.32

3. Digit Span

a. Digits forward = Item B4a

SS = (x - mean for age) (10) + 50
SD for age

NOTE**:** See Table 3 for population means + SD

b. Digits backward = Item B4b

SS = (x - mean for age) (10) + 50
SD for age

NOTE: See Table 3 for population means + SD

Table 3 - Norms for Digits Forward and Digits Backward
Age Groups

	16-17		18-19		20-24		25-29		30-34	
	Forward	Backward	Forward	Backward	Forward	Backward	Forward	Backward	Forward	Backward
Mean	6.72	4.88	6.66	5.04	6.80	5.10	6.68	5.04	6.61	4.87
SD	1.32	1.44	1.34	1.46	1.27	1.51	1.35	1.63	1.35	1.44

	35-44		45-54		55-64		65-69		70-74	
	Forward	Backward	Forward	Backward	Forward	Backward	Forward	Backward	Forward	Backward
Mean	6.63	4.93	6.57	4.79	6.35	4.55	6.28	4.48	6.14	4.40
SD	1.31	1.49	1.38	1.42	1.45	1.56	1.42	1.44	1.39	1.16

	75-79		80-84		85-89		All Ages	
	Forward	Backward	Forward	Backward	Forward	Backward	Forward	Backward
Mean	6.06	4.31	5.89	4.25	5.69	4.10	6.43	4.70
SD	1.26	1.17	1.26	1.03	1.01	1.05	1.36	1.43

NOTE: For further information pertaining to the sample size for these tests, refer to the WAIS-III manual.

4. Digit symbol= Item B5a

SS = (x - mean for age) (10) + 50
SD for age

NOTE: See Table 4 for population means + SD

Table 4- Digit Symbol Norms

Age	Mean	SD
18-19	81	16
20-24	80	16.25
25-29	78	15.5
30-34	77	16
35-44	75	16.5
45-54	70	15.25
55-64	61	15
65-69	54	15
70-74	51	14.75
75-79	47	14.5

5. Serial digit learning

SS = (x-mean for age/education) (10) + 50
SD for age/education

Education = 6-11		Education = 12-16	
age: 16-64	age: 65-74	age: 16-64	age: 65-74
Mean = 18	Mean = 14	Mean = 20	Mean= 20
SD = 4	SD = 5.5	SD = 4	SD = 7

6. Trails A= Item B9a

SS = (mean for age-x) (10) + 50
SD for age

NOTE: See Table 5 for population means + SD

Table 5 - Trail A and Trail B Narrative Data

		Part A			Part B		
Age	*n*	Mean	SD	Range	Mean	SD	Range
15-17	32	23.4	5.9	15.2-39	47.7	10.4	25.4-81
18-23	78	36.7	9.4	12-60.1	51.3	14.6	23.3-101
24-32	57	24.3	7.6	11.8-46	53.2	15.6	29.1-98
33-40	18	27.5	8.3	16-52.7	62.1	17.5	39-111
41-64	10	29.7	8.4	16.5-42	73.6	19.4	41.9-102

NOTE: If the individual is over 64 years of age, then use the means from the 41-64 age group.

7. Trails B = Item B10a

SS = (mean for age-x) (10) + 50
SD for age

NOTE: See Table 5 for population means + SD

8. Finger tapping Dominant = Item B11a

SS = (x - mean for age/gender) (10) + 50
SD for age/gender

NOTE: See Table 6 for population means + SD

Table 6 - Finger Tapping test Normative Data

Males		Preferred Hand			Non-preferred Hand		
Age	*n*	Mean	SD	Range	Mean	SD	Range
15-17	17	47.6	5.8	38-55.6	43.6	4.9	33.4-51.8
18-23	44	49.5	6.9	26.6-64.6	45.4	6.9	26.8-58.6
24-32	31	50.6	6.6	38.2-66.2	46	6.1	28.8-55
33-40	12	53.4	5.9	39-61	49.8	4.7	41-57.8
41-64	4	44.4	5.8	35.8-48.2	41.4	3.5	36.6-44.4
Females		Preferred Hand			Non-preferred Hand		
Age	*n*	Mean	SD	Range	Mean	SD	Range
15-17	15	42.7	7.9	30.2-54	41.1	6.2	31.6-51
18-23	30	43.6	7.5	30.6-65.6	41.2	6.5	32.8-61.8
24-32	25	45.2	6.7	31-60	40.9	5.7	28.6-53.6
33-40	6	45.8	5.5	40.6-55.6	44.3	4.6	40.6-53.2
41-64	6	40.4	4.8	34.2-48.4	38.6	4.8	32-46.6

NOTE: For both of the proceeding tables, if the individual is over 64 years of age, then use the means from the 41-64 age group.

9. Finger tapping Non-dominant = Item B11b

SS = (x - mean for age/gender) (10) + 50
SD for age/gender

NOTE: See Table 6 for population means + SD

10. Wisconsin Card Sorting Test Categories (WCST) = Item B12a

SS = (mean for age –x) (10) + 50
SD for age

NOTE: See Table 7 for population means + SD

Table 7 – Normative data Means and Standard Deviations for Full Scale IQ and WCST Variables

	< 40 years (n=100)	40-49 years (n=19)	50-59 years (n=16)	> 59 years (n=15)
Full Scale IQ	113.9 (11.7)	112.4 (13.4)	120.3 (9.4)	109.7 (9.9)
Categories Achieved	5.6 (1.0)	4.8 (1.8)	5.6 (1.1)	4.2 (2.0)
Total Errors	21.6 (16.7)	31 (27)	20.9 (12.8)	44.1 (18.9)
Perseverative Errors	10.4 (8)	16 (13.9)	11.3 (6.9)	24.2 (12.8)
% Perseverative Errors	10.2 (5.6)	14.2 (9.6)	11.2 (4.6)	19.6 (9.2)
Nonperseverative Errors	11.2 (11.1)	15.1 (15)	9.6 (6.2)	19.9 (9.1)
Perseverative Responses	13 (9.1)	19.5 (14.9)	14.8 (9.0)	28.9 (13.7)
Trials to 1st Category	12.4 (4.7)	18 (26.7)	12.9 (5.2)	14.3 (7.0
% Conceptual Level Responses	72.8 (14.4)	64.4 (24)	70.7 (13.2)	50 (17)
"Learning to Learn"	-2.4 (4.9)	-5.9 (8.5)	-0.9 (2.0)	-5.7 (8.8)
Failures to Maintain Set	0.8 (1.3)	0.8 (1.5)	0.8 (1.1)	1.0 (1.3)

Data presented as mean (SD)

11. Controlled oral word Association test (COWAT) = Item B13a

A. Adjust score for age and education
   1. If the raw score is greater than or equal to 10 add the appropriate value from Table 8 (x = raw score + value from Table 8)
   2. If the raw score is less than 10 no adjustment is needed to the raw score (x = raw score)

B. $SS = \frac{(x - 37.5)\quad (10) + 50}{10.75}$

NOTE: See Table 8 for age and education adjustment tables

Table 8 - COWAT Narrative Data

Education (years completed)	Age					
	25-54		55-59		60-64	
	Male	Fem	Male	Fem	Male	Fem
Less than 9	9	8	11	10	14	12
9-11	6	5	7	7	9	9
12-15	4	3	5	4	7	6
16 or more	-	-	1	1	3	3

NOTE: If the individual is over 64 years of age, then use the means from the 60-64 age group.