

# ADCS-CGIC

## Protocol 000X

A PHASE III ... SAFETY AND EFFICACY EVALUATION  
OF [DRUG] IN PATIENTS WITH MILD TO MODERATE  
ALZHEIMER'S DISEASE

City, State

Month, Day, Year

# **A New Clinical Global Rating Scale for Alzheimer's Clinical Trials**

Lon S. Schneider, M.D.

University of Southern California

Jason T. Olin, Ph.D.

University of Southern California

Christopher M. Clark, M.D.

University of Pennsylvania

Rachelle S. Doody, M.D., Ph.D.

Baylor College of Medicine

Steven Ferris, Ph.D.

New York University

John C. Morris, M.D.

Washington University, St. Louis

Barry Reisberg, M.D.

New York University

Frederick Schmitt, Ph.D.

University of Kentucky

# National Institute on Aging-Alzheimer's Disease Cooperative Study

Leon Thal, M.D., Principal Investigator

Instrumentation Committee  
Steven Ferris, Ph.D., Chair

Global Scales Committee  
Lon S. Schneider, M.D., Chair

Christopher M. Clark, M.D.  
Rachelle S. Doody, M.D., Ph.D.  
Steven Ferris, Ph.D.  
John C. Morris, M.D.  
Jason T. Olin, Ph.D.  
Barry Reisberg, M.D.  
Frederick Schmitt, Ph.D.

# Protocol xxx, Clinical Global Rating Scale, ADCS-CGIC



- Use of Clinical Global Impressions
  - ◆ History
  - ◆ Standards
- The Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC)
- Validation in Instrumentation Protocol
- Review of Worksheets and CRFs

# Historical Trends



- **1970s--CGIC (Guy 1976)**
  - ◆ Minimal guidelines assume appropriate inferences by clinician
  - ◆ Based on "total clinical experience," or "how much has he changed?"
- **1986-90--NIA Mt. Sinai tacrine trial uses original CGIC (Davis et al 1992)**
  - ◆ Improvement found on ADAS-Cog, none on CGIC
- **1991--Tacrine 30-week trial introduces CIBIC ("CIBI," Knapp et al 1994)**
  - ◆ Informant and patient interviewed at BL with 8 items, follow-up of patient only
  - ◆ "CIBI" detects treatment effect
- **1991--FDA draft guidelines**
  - ◆ CGIC should not include informant information, should remain holistic
- **1992-93--NIA-ADCS, instrument protocol establishes goal to develop new CGIC**
  - ◆ ADCS-CGIC instrument developed

# Current Issues: Global Ratings



- Structure vs. no structure
- Control of information sources (subject vs. informant)
- Severity vs. change measures
- Internal and external validity
- Need for consensus

# Rationale for use of CIBIC




- “If a experienced and unbiased clinician can detect a global change in an AD patient solely on an interview...then that change is assumed to be clinically relevant”
  - ◆ (FDA 1991, P. Leber, and others)

# CIBIC: Global Change Rating



- CIBIC -- based solely on patient interview, was originally recommended by FDA for AD trials
- CIBIC+ -- includes a caregiver interview to provide more complete information on patient status

# CIBIC+ Rating



- Marked improvement (1)
- Moderate improvement (2)
- Minimal improvement (3)
- No change (4)
- Minimal worsening (5)
- Moderate worsening (6)
- Marked worsening (7)

# Development of ADCS-CGIC



- **Consensus identified among clinicians**
  - ◆ **Survey sent to ADCS global raters**
  - ◆ **Clinicians agreed that a CGIC should include:**
    - ☞ Interview of subject and informant
    - ☞ Mental status examination
    - ☞ Take approximately 20 minutes per interview
    - ☞ Assess a common set of areas
- **Format for ADCS-CGIC based on survey results:**
  - ◆ **ADCS-CGIC requires separate interviews of subject and informant**
  - ◆ **Worksheets created**
    - ☞ Include domains with specific areas and sample probes
    - ☞ Content adapted from existing severity rating scales
    - ☞ Space included for notes
    - ☞ Not required to fill out forms or to assess every item
- **Thus, consistency is permitted without forcing a structure on raters**

# ADCS-CGIC Format



## ■ Instructions

- ◆ Note taking as one would clinically
- ◆ Assess mental status
- ◆ Assessment of side effects prohibited
- ◆ 20 minutes recommended per interview
- ◆ Ratings made with reference to baseline

## ■ Baseline

- ◆ Separate interview of subject and informant

## ■ Follow-up

- ◆ Separate interview of subject and informant
- ◆ Interview subject first
- ◆ Global change rating made after 2nd interview

Area	Probe	Notes
<b>Interval history</b> <b>Observation/Evaluation</b> <b>Cognitive</b> <b>Mental/Cognitive State</b> <b>Arousal/Alertness/Attention</b> <b>Orientation</b> <b>Memory</b> <b>Language/Speech</b> <b>Thought content</b> <b>Behavior</b> <b>Hallucinations/Delusions/</b> <b>Illusions</b> <b>Behavior/Mood</b> <b>Sleep/Appetite</b> <b>Neurological/Psychomotor</b> <b>activity</b> <b>Functioning</b> <b>Basic &amp; complex functional</b> <b>activity</b> <b>Praxis</b> <b>Social Function</b>		

# ADCS-CGIC Validation Study

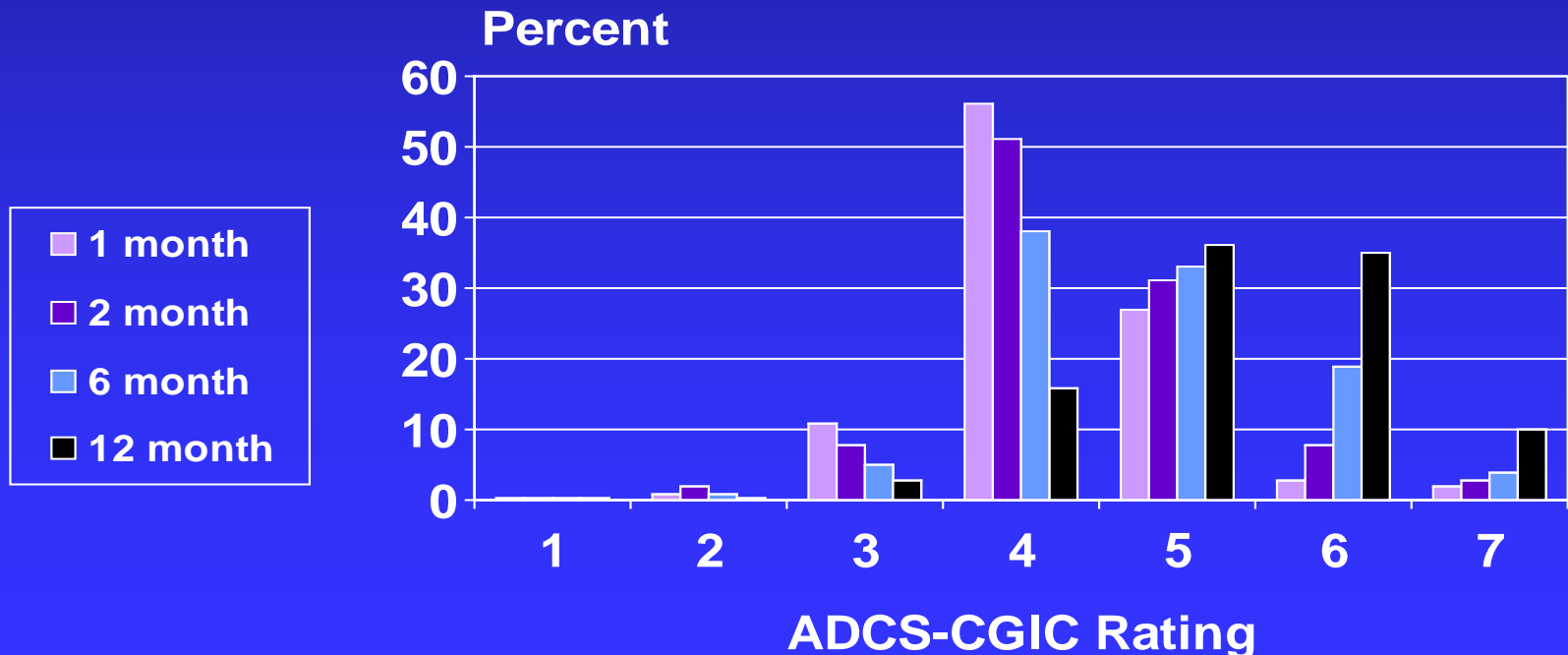


- N=242 AD patients stratified by MMSE and 64 controls
- ADCS-CGIC administered at BL, 1, 2, 6, and 12 months
- MMSE, CDR, GDS, FAST administered at BL and 12 months
- ADCS-CGIC rating made after interview with subject and informant
- Order of interviews randomly assigned for each subject
- Global rating is made after each interview; 2nd is the overall rating

# ADCS-CGIC Results

- ADCS-CGIC distinguished AD subjects from controls ( $F(1,114)=55.86$ ,  $P<0.0001$ )
- ADCS-CGIC significantly worsens over time ( $F(3,240)=68$ ,  $p<0.0001$ )
- Time x level of cognitive impairment interaction ( $F(12,240)=1.93$ ,  $p<0.03$ )
  - ◆ Patients with an MMSE > 10 showed linear worsening
  - ◆ Patients with MMSE < 10 showed the most rapid change at 6 months

## Frequency Distribution over Time

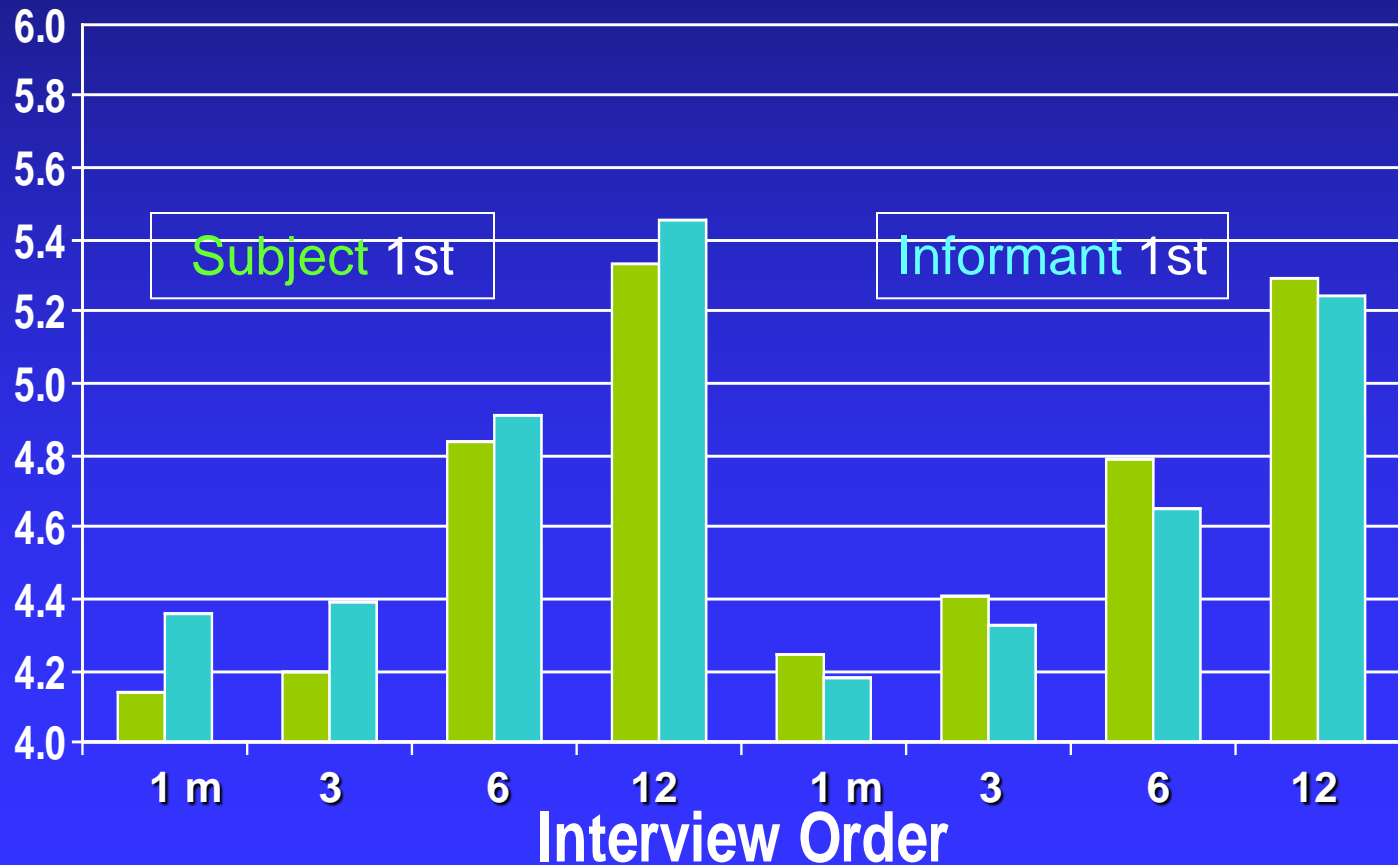


# Interview Order Effect on ADCS-CGIC



- Interview order (subject vs informant) x interview sequence (1st vs 2nd) interaction ( $F(1,80)=5.2$ ,  $p=0.025$ )

## Mean Rating



# ADCS-CGIC

## Correlational Analyses



Measure	MMSE	CDR	GDS	FAST	ADCS-CGIC
MMSE		-0.17	-0.14	-0.21	-0.32
CDR			0.30	0.30	0.23
GDS				0.33	0.21
FAST					0.12

# Conclusions



- Stability over short intervals
- Sensitivity to change over time
- Ratings affected by interview order
  - ◆ Ratings worsened after informant interview
- Effective method for generating a CIBIC+
- Commonly used in clinical trials

# References



- Olin, J.T., Schneider, L.S., Doody, R.S., Schmitt, F.A., Clark, C.M., Morris, J.C., Ferris, S.H., & Reisberg, B. (1996). Clinical evaluation of global change in Alzheimer's disease: Identifying consensus. *Journal of Geriatric Psychiatry and Neurology*, 9, 176-180.
- Schneider, L.S., & Olin, J.T. (1996). Clinical Global Impressions in Clinical Trials. *International Psychogeriatrics*, 8, 277-290.
- Schneider, L.S., Olin, J.T., Doody, R.S., Clark, C.M., Morris, J.C., Reisberg, B., Schmitt, F.A., Grundman, M., Thomas, R.G., & Ferris, S.H. (1997). Validity and reliability of the Alzheimer's Disease Study-Clinical Global Impression of Change (ADCS- CGIC). *Alzheimer's Disease and Associated Disorders*, 11, S22-S32.

# ADCS-CGIC Completion Instructions

## Instructions for Completion

### ALZHEIMER'S DISEASE COOPERATIVE STUDY – CLINICAL GLOBAL IMPRESSION OF CHANGE (ADCS-CGIC)

The trained medically qualified and/or psychologically educated person called the "rater" should have a minimum of 2 years experience or equivalent. If the rater has less than 2 years experience, the investigator must provide documentation to the sponsor supporting why the rater is otherwise qualified to perform this test.

The patient must be interviewed first, the informant afterwards!

The ADCS-CGIC consists of two parts:

Part I: Baseline evaluation (includes information from both patient and informant, i.e. caregiver or someone, who knows the patient well)

Part II: ADCS-CGIC forms for both patient and informant

The overall intent of the ADCS-CGIC is to provide a means to reliably assess global change from baseline in a clinical trial. It provides a semi-structured format to allow examiners to gather necessary clinical information from both the patient and informant in order to make a global impression of clinical change.

Part I is used to record baseline information to serve as a reference for future ratings.

Part II is composed of two sections, a patient interview form and an informant interview form.

These forms are used to record information from separate interviews with both patient and informant from which an impression of change score is made.

#### Method of Administration

##### Part I – Baseline evaluation :

At baseline, the examiner interviews the patient and informant, recording onto Part I notes about baseline status for later reference. At baseline only, clinical information about the patient from any source may be used. The examiner indicates on a checklist the sources of information compiled during the baseline evaluation.

Parts I and II share a similar format for recording relevant clinical information. The column headed "Area" identifies various areas that an examiner might consider while evaluating a patient for potential clinical change, including what might be expected to be assessed in performing an ordinary but brief comprehensive office interview to determine a patient's baseline status and eligibility for a clinical trial. The "Probes" column provides sample items that an examiner might find useful in assessing an area; and are intended as guides for collecting relevant information. The last column provides space for notes. For the baseline form, there are separate spaces for notes taken from the informant and patient interviews. There is no specified amount of time to complete the baseline form.

##### Part II :

Part II is administered at Visit 6. The order of interviews should be the same for all participants, with all patients being interviewed first.

After completing the interviews, the examiner records the clinical impression of change on a 7-point Likert-type scale (from marked improvement to marked worsening). The ADCS-CGIC is a rating of change and not of severity. The examiner may refer to the baseline data in Part I.

The examiner, alone, must make decisions about change, without consulting other staff. The examiner should avoid asking opinions of the interviewee, which may contaminate the ratings, such as opinions regarding change in symptoms or side effects. At the beginning of the interview, the examiner may wish to caution the informant to refrain from mentioning this information.

Suggested guidelines for time allotted for the subsequent ratings of change is 20 minutes each per patient or informant interview. This time was chosen based on the mean time reported by examiners who often assess clinical change.

# ADCS-CGIC: Baseline Worksheet Pg 1

## ALZHEIMER'S DISEASE COOPERATIVE STUDY – CLINICAL GLOBAL IMPRESSION OF CHANGE (ADCS–CGIC)

Used with permission from the NIA Alzheimer's Disease Cooperative Study [NIA Grant AG10483]

### PART I: Baseline Evaluation for both Patient and Informant (*not to be entered into database*)

► *The patient must be interviewed first, the informant afterwards!*

1. Date of examination (dd mon yy) ..... 

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2. Patient's initials (first middle last) ..... 

--	--	--	--

3. Date of birth (dd mon yy) ..... 

--	--	--	--	--	--

► *Use this form to record baseline information for assessing change at a later date. Information can be obtained from all relevant sources, including patient, informant, and staff members. A brief clinical assessment of mental state should be made. No particular format or order is suggested for the interview.*

Area	Probes	Notes
4. Relevant history	recent relevant clinical events, illnesses?	Patient
		Informant
5. Observation/ Evaluation	appearance	Patient
		Informant
Mental/Cognitive state (Structured exam, if used: _____)		
6. Arousal/ Alertness/ Attention/ Concentration	confusion/ clarity excitement reactivity/ state of consciousness	Patient
		Informant
7. Orientation	time place person	Patient
		Informant

▼ To be continued

1

# ADCS-CGIC: Baseline Worksheet Pg 2

ALZHEIMER'S DISEASE COOPERATIVE STUDY – CLINICAL GLOBAL IMPRESSION OF CHANGE (ADCS-CGIC) (cont.)		
Area	Probes	Notes
8. Memory	registration recall long term/remote recall for past events	Patient
		Informant
9. Language/ Speech	fluency/ expressive language receptive language comprehension paraphasia/ word finding naming, amount repetition follows directions	Patient
		Informant
10. Praxis	constructional ability ideational praxis ideomotor/ imitation	Patient
		Informant
11. Judgment/ Problem solving/ Insight	patient's behaviour in situations requiring judgment	Patient
		Informant
Behaviour		
12. Thought content	organisation appropriateness	Patient
		Informant

▼ To be continued

# ADCS-CGIC: Baseline Worksheet Pg 3

ALZHEIMER'S DISEASE COOPERATIVE STUDY – CLINICAL GLOBAL IMPRESSION OF CHANGE (ADCS-CGIC) (cont.)		
Area	Probes	Notes
13. Hallucinations/ Delusions/ Illusions	auditory/ visual misperceptions systematised/ developed	Patient
		Informant
14. Behaviour/ Mood	affect/lability unusual/bizarre uninhibited motivation/energy wandering/getting lost agitation/aggression hostility depression-related anxiety-related appropriateness cooperativeness	Patient
		Informant
15. Sleep/ Appetite	sleep disorder insomnia (type?) nocturnal activity hyper-, hypsomnia appetite/weight change	Patient
		Informant
16. Neurological Psychomotor activity	overall motor activity posture/gait movement disorder unusual motor be- haviour daily patterns	Patient
		Informant
Functioning		
17. Basic and complex (instrumental) functional ability	mobility hygiene/grooming dressing self-feeding shopping household chores/ hobbies finances driving	Patient
		Informant

# ADCS-CGIC: Baseline Worksheet Pg 4

ALZHEIMER'S DISEASE COOPERATIVE STUDY – CLINICAL GLOBAL IMPRESSION OF CHANGE (ADCS-CGIC) (cont.)		
Area	Probes	Notes
18. Social function	participation in: social interactions community activities independence helplessness	Patient
		Informant
19. Notes, comments, summary statement:		
20. Information from other sources:		
<p>The following sources of information were used in completing this form:</p> <p>no (0)    yes (1)</p> <p>21. Interview/examination of patient ..... <input type="checkbox"/>    <input type="checkbox"/></p> <p>22. Interview of informant ..... <input type="checkbox"/>    <input type="checkbox"/></p> <p>23. If yes, describe relationship to patient .....</p> <p>24. Information on neuropsychological test performance ..... <input type="checkbox"/>    <input type="checkbox"/></p> <p>25. General information derived from a staff conference about the patient ..... <input type="checkbox"/>    <input type="checkbox"/></p> <p>26. Other ..... <input type="checkbox"/>    <input type="checkbox"/></p> <p>27. If yes, please specify .....</p>		

# ADCS-CGIC: Instructions Post Baseline

## Instructions for Completion

### ALZHEIMER'S DISEASE COOPERATIVE STUDY – CLINICAL GLOBAL IMPRESSION OF CHANGE (ADCS-CGIC)

The trained medically qualified and/or psychologically educated person called the "rater" should have a minimum of 2 years experience or equivalent. If the rater has less than 2 years experience, the investigator must provide documentation to the sponsor supporting why the rater is otherwise qualified to perform this test.

The patient must be interviewed first, the informant afterwards!

The ADCS-CGIC consists of two parts:

Part I: Baseline evaluation (includes information from both patient and informant, i.e. caregiver or someone, who knows the patient well)

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Part I is used to record baseline information to serve as a reference for future ratings.

Part II is composed of two sections, a patient interview form and an informant interview form.

These forms are used to record information from separate interviews with both patient and informant from which an impression of change score is made.

#### Method of Administration

##### Part I – Baseline evaluation :

At baseline, the examiner interviews the patient and informant, recording onto Part I notes about baseline status for later reference. At baseline only, clinical information about the patient from any source may be used. The examiner indicates on a checklist the sources of information compiled during the baseline evaluation.

Parts I and II share a similar format for recording relevant clinical information. The column headed "Area" identifies various areas that an examiner might consider while evaluating a patient for potential clinical change, including what might be expected to be assessed in performing an ordinary but brief comprehensive office interview to determine a patient's baseline status and eligibility for a clinical trial. The "Probes" column provides sample items that an examiner might find useful in assessing an area; and are intended as guides for collecting relevant information. The last column provides space for notes. For the baseline form, there are separate spaces for notes taken from the informant and patient interviews. There is no specified amount of time to complete the baseline form.

##### Part II :

Part II is administered at Visit 6. The order of interviews should be the same for all participants, with all patients being interviewed first.

After completing the interviews, the examiner records the clinical impression of change on a 7-point Likert-type scale (from marked improvement to marked worsening). The ADCS-CGIC is a rating of change and not of severity. The examiner may refer to the baseline data in Part I.

The examiner, alone, must make decisions about change, without consulting other staff. The examiner should avoid asking opinions of the interviewee, which may contaminate the ratings, such as opinions regarding change in symptoms or side effects. At the beginning of the interview, the examiner may wish to caution the informant to refrain from mentioning this information.

Suggested guidelines for time allotted for the subsequent ratings of change is 20 minutes each per patient or informant interview. This time was chosen based on the mean time reported by examiners who often assess clinical change.

# CGIC: Post-Baseline Worksheet Page 1

## ALZHEIMER'S DISEASE COOPERATIVE STUDY – CLINICAL GLOBAL IMPRESSION OF CHANGE (ADCS-CGIC)

Used with permission from the NIA Alzheimer's Disease Cooperative Study (NIA Grant AG10483)

### PART II (P): Patient's CGIC examination (not to be entered into database)

► The patient must be interviewed first, the informant afterwards!

1. Date of examination (dd mon yy) ..... 

--	--	--	--	--	--
2. Patient's initials (first middle last) ..... 

--	--	--
3. Date of birth (dd mon yy) ..... 

--	--	--	--	--	--

► Use this form to record an ADCS-CGIC rating. You may refer only to the "Part I: Baseline Evaluation Form" to assist in determining clinical change. A brief clinical assessment of mental state should be made. No particular format or order is suggested for the interview. This portion of the CGIC should take close to 20 minutes to complete.

Area	Probes	Notes
4. Interval history	clinical events since baseline	
5. Observation/ Evaluation	appearance	
Mental/Cognitive state (Structured exam, if used: _____)		
6. Arousal/ Alertness/ Attention/ Concentration	confusion/ clarity excitement reactivity/ state of consciousness	
7. Orientation	time place person	

▼ To be continued

# CGIC: Post-Baseline Worksheet Page 2

ALZHEIMER'S DISEASE COOPERATIVE STUDY – CLINICAL GLOBAL IMPRESSION OF CHANGE (ADCS–CGIC) (continuation of patient's CGIC examination)		
Area	Probes	Notes
8. Memory	registration recall long term/ remote	
9. Language/ Speech	fluency expressive language receptive language comprehension paraphasia/ word finding	
10. Praxis	constructional ability ideational praxis ideomotor/ imitation	
11. Judgment/ Problem solving		
Behaviour		
12. Thought content	organisation appropriateness	
13. Hallucinations/ Delusions/ Illusions	auditory/ visual misperceptions systematised/ developed	

# CGIC: Post-Baseline Worksheet Page 3

ALZHEIMER'S DISEASE COOPERATIVE STUDY – CLINICAL GLOBAL IMPRESSION OF CHANGE (ADCS–CGIC) (continuation of patient's CGIC examination)		
Area	Probes	Notes
14. Behaviour/ Mood	affectability motivation/energy agitation/aggression hostility depression-related/ anxiety-related uninhibited appropriateness cooperativeness	
15. Sleep/ Appetite	sleep disorder nocturnal activity appetite/weight change	
16. Neurological/ Psychomotor activity	overall motor activity posture/gait movement disorder unusual motor behaviour	
Functioning		
17. Basic and complex (instrumental) functional ability	mobility hygiene/grooming dressing self-feeding shopping	
18. Social function	interactions community activities	
19. Notes and comments:		

# CGIC: Post-Baseline Informant's Worksheet Page 1

## ALZHEIMER'S DISEASE COOPERATIVE STUDY – CLINICAL GLOBAL IMPRESSION OF CHANGE (ADCS-CGIC)

Used with permission from the NIA Alzheimer's Disease Cooperative Study (NIA Grant AG10483)

### PART II (f): Informant's CGIC interview (not to be entered into database)

► The patient must be interviewed first, the informant afterwards!

1. Date of examination (dd mon yy) ..... 

--	--	--	--	--	--
2. Patient's initials (first middle last) ..... 

--	--	--	--
3. Date of birth (dd mon yy) ..... 

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► Use this form to record an ADCS-CGIC rating. You may refer only to the "Part I: Baseline Evaluation Form" to assist in determining clinical change. It is important to avoid a detailed assessment of side effects or asking the informant's opinion on whether the patient is on active drug. No particular format or order is suggested for the interview. This portion of the CGIC should take close to 20 minutes.

Area	Probes	Notes
4. Interval history	clinical events since baseline changes? illnesses? effects?	
5. Compliance	compliance with protocol problems	
Mental/Cognitive state		
6. Arousal/ Alertness/ Attention/ Concentration	confusion/ clarity excitement/ reactivity state of consciousness	
7. Orientation	time relationships travel find his/her way recognises self/others/objects reacts appropriately	

# CGIC: Post-Baseline Informant's Worksheet Page 2



ALZHEIMER'S DISEASE COOPERATIVE STUDY – CLINICAL GLOBAL IMPRESSION OF CHANGE (ADCS–CGIC) (continuation of informant's CGIC interview)		
Area	Probes	Notes
8. Memory	recall memory past events	
9. Language	expression comprehension word finding naming, amount repetition follows direction	
10. Motor activity	overall activity daily patterns ambulation movement disorder unusual movements	
11. Judgment/ Problem solving	patient's behaviour in situations requiring judgment	
Behaviour		
12. Thought content	organisation appropriateness hostile expression	
13. Hallucinations/ Delusions/ Illusions	auditory/ visual misperceptions	

▼ To be continued

# CGIC: Post-Baseline Informant's Worksheet Page 3

ALZHEIMER'S DISEASE COOPERATIVE STUDY – CLINICAL GLOBAL IMPRESSION OF CHANGE (ADCS–CGIC) (continuation of informant's CGIC interview)		
Area	Probes	Notes
14. Behaviour/ Mood	affect/lability unusual /bizarre/ uninhibited motivation/energy wandering depression-related/ anxiety-related agitation/aggression hostility appropriate/ cooperativeness	
15. Sleep/ Appetite	insomnia (type ?) nocturnal activity hyper-, hypsomnia appetite/weight change	
Functioning		
16. Basic and complex (instrumental) functional ability   Praxis	mobility hygiene/grooming dressing self-feeding shopping household chores/ hobbies finances	
17. Social function	participation in: social interactions community activities independence helplessness	
18. Notes and comments:		

# CGIC: Post-Baseline Summary Sheet

## ALZHEIMER'S DISEASE COOPERATIVE STUDY – CLINICAL GLOBAL IMPRESSION OF CHANGE (ADCS-CGIC) – SUMMARY SHEET

Used with permission from the NIA Alzheimer's Disease Cooperative Study (NIA Grant AG10483)

► Please transfer the information, documented in Part I and Part II and indicate the Clinical Impression of Change.

1. Patient initials (first middle last) .....

### Part I – Baseline Evaluation

2. Examiner initials (first middle last) .....

3. Examiner trial independent (not otherwise involved in the trial) ..... 0 ☐ no 1 ☐ yes

### Part II – Patient's CGIC Evaluation

4. Examiner initials (first middle last) .....

5. Examiner trial independent (not otherwise involved in the trial) ..... 0 ☐ no 1 ☐ yes

### Part II – Informant's CGIC Evaluation

6. Examiner initials (first middle last) .....

7. Examiner trial independent (not otherwise involved in the trial) ..... 0 ☐ no 1 ☐ yes

8. Clinical Impression of Change (indicate one)

Marked improvement ..... 1 ☐

Moderate improvement ..... 2 ☐

Minimal improvement ..... 3 ☐

No change ..... 4 ☐

Minimal worsening ..... 5 ☐

Moderate worsening ..... 6 ☐

Marked worsening ..... 7 ☐