DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Minneapolis District Office
Central Region
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July 22, 2005

Stephen C. Olson, M.D.
Clinical Investigator
2450 Riverside Avenue
F282-2A West-B
Minneapolis, Minnesota 55454

Dear Dr. Olson:

We enclose a copy of the Establishment Inspection Report (EIR) for the inspection conducted at your premises at Minneapolis, MN, on January 3-6, 11, 19, 21 and 26, 2005, by Investigator Sharon L. Matson of the Food and Drug Administration (FDA). This procedure is applicable to EIRs for inspections completed on or after April 1, 1997. For those inspections completed prior to the above date, a copy of the EIR may still be made available through the Freedom of Information Act (FOIA).

The Agency is working to make its regulatory process and activities more transparent to regulated industry. Releasing the EIR to you is part of this effort. The copy being provided to you comprises the narrative portion of the report; it may reflect redactions made by the Agency in accordance with the FOIA and 21 CFR Part 20. This, however, does not preclude you from requesting and possibly obtaining additional information under FOIA.

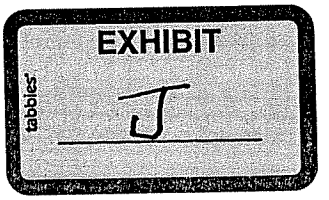
If there is any question about the released information, feel free to contact me at the address indicated on the letterhead.

Sincerely,

For W. Charles Becoat
Director
Minneapolis District

CCL/ccl

Enclosure: EIR, 1/3-6,11,19,21,26/05



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SUMMARY OF FINDINGS

I conducted this clinical investigator inspection and data audit per a For Cause assignment from the Center for Drug Evaluation and Research (CDER/HFD-46), dated 12/14/04 to follow-up on Division of Scientific Investigations Complaint #1006 (Attachment #1 and 2).

This is the first FDA inspection of this clinical investigator.

The study assigned for audit is titled "Efficacy and Tolerability of Olanzapine, Quetiapine and Risperidone in the Treatment of First Episode Psychosis: A Randomized Double Blind 52-Week Comparison" aka "CAFÉ Study", protocol number 5077IL/0114, IND 32,132 sponsored by AstraZeneca (Attachment #3).

No FD 483 List of Observations was issued. I noted several items verbally. No evidence of misconduct or significant violation of the protocol or regulations was found in this inspection. See heading **DSI Complaint #1006**. Questions regarding psychiatric diagnosis would have to be addressed through medical review at CDER.

I used Compliance Program 7348.811 for this inspection and report.

ADMINISTRATIVE DATA

Inspected firm: Stephen C. Olson, MD
Location: 2450 Riverside Avenue

F282-2A West-B
Minneapolis, MN 55454
Phone: 612/273-9763
FAX: 612/273-9779
Mailing address: (same as above)
E-mail: olson403@umn.edu

Dates of inspection: 1/3/2005, 1/4/2005, 1/5/2005, 1/6/2005, 1/11/2005, 1/19/2005, 1/21/2005, 1/26/2005

Days in the facility: 8

Participants: Sharon L. Matson, Investigator

HISTORY OF BUSINESS

Stephen C. Olson, MD started at the University of Minnesota (UMN) in December 2000 as an Associate Professor of Psychiatry. He has been involved in clinical research as a principal and co-investigator since about 1986 and those studies are listed in his CV, attached as Exhibit #1.

Besides teaching and research, Dr. Olson's responsibilities include:

- Director, Schizophrenia Program within the UMN Academic Health Center
- Attending Psychiatrist on **Station 12**, FUMC-R (further described below)
- Facilitating some group therapy sessions at the FUMC-R **Day Treatment** (")
- and, providing private outpatient practice services.

"Station 12" is a psychosis specialty unit at Fairview University Medical Center –Riverside hospital (FUMC-R, same address as referenced) which opened on 4/1/03. Station 12 was described as a "state of the art" inpatient unit with dedicated staff to treat patients with psychotic disorders. The Medical Director for this unit is John Vuchetich, MD – one of Dr. Olson's co-investigators on this study. When asked about his responsibilities for Station 12, Dr. Olson said he is an Attending Psychiatrist on that unit and was involved in the planning of it.

"Day Treatment" is an outpatient Adult Mental Health Day Treatment Program at FUMC-R aka Day Treatment. Patients are referred to this program from mental health care providers in the Twin Cities area or by self-referral but all must be "admitted" by a physician with privileges at FUMC-R. A Treatment Plan is made that includes combinations of group or individual therapy, occupational therapy, education, and other activities. Progress Notes are made throughout the treatment period and recommendations/a plan is made before discharge.

Dr. Olson is compensated through both University of MN Physicians (UMP) as an independent licensed physician, and through UMN research funds.

PERSONS INTERVIEWED and INDIVIDUAL RESPONSIBILITY

This inspection was unannounced. I showed up at the referenced address, showed credentials, and issued a FD 482 Notice of Inspection to **Stephen C. Olson, MD, Clinical Investigator** and person most responsible for this study. I explained this is a For Cause inspection to follow-up on a complaint and that it would include a full audit of the referenced study. Dr. Olson answered all questions asked and was available upon request throughout this inspection.

Dr. Olson had a patient scheduled within a half hour of my arrival and so after obtaining preliminary information he brought me to the **Ambulatory Research Center (ARC)** located in the Riverside Professional Building (606 24th Ave, Suite #602, Minneapolis, MN 55454) which is attached by skyway to FUMC-R. ARC is administratively within the UMN Department of Psychiatry. At ARC Dr. Olson introduced me to:

Jean Kenney, LICSW, Study Coordinator
Scott Lenz, Assistant Director, ARC
Elizabeth Lemke, Community Program Specialist.

Together, Dr. Olson and Ms. Kenney provided access to the study records, in- and outpatient medical records, and answered all questions asked.

Dr. Olson is the principal investigator on this study. He attended the Investigator's Meeting in Chapel Hill, NC 1/21-24/02. He enrolled the majority of subjects on this study. Dr. Olson's responsibilities for this study include communications with the sponsor, monitor, and IRB; making diagnoses; participating in informed consent; determining subject eligibility; seeing subjects at each visit, reviewing evaluations, and determining whether subjects should continue; and, overseeing study staff.

Dr. Olson's co-investigators on this study are:

S. Charles Schulz, MD, and Head of the UMN Department of Psychiatry
John Vuchetich, MD, and Medical Director of FUMC-R Station 12

Their CVs are attached as Exhibit #2 and 3. Dr. Vuchetich enrolled and regularly assessed about 4 subjects on study. Otherwise all were seen by Dr. Olson. Dr. Schulz did not enroll any subjects and was a back-up only if one of the other physicians was out. Dr. Schulz did see Subject #13/DRM, the subject of DSI Complaint #1006 on 11/29/03 as an attending on Station 12.

Administratively, as UMN psychiatry staff Dr. Olson reports to Dr. Schulz who reports to Deborah Powell, MD, Dean, Medical School, UMN → Frank Cerra, MD, Senior VP, Academic Health Center, UMN → Robert Bruininks, President, UMN, 100 Church St., Rm 202 Morrill Hall, Minneapolis, MN 55108.

Jean Kenney became the study coordinator in 6/02 after the original coordinator – Ruth Thomson, left. Ms. Kenney's responsibilities for this study include evaluating patients ability to consent; explaining the study to prospective subjects and obtaining informed consent; seeing subjects at each visit; performing evaluations; receipt, dispensing, and accounting for test articles; entering data collected into electronic case report forms; participating in monthly study coordinator telephone conferences; and, overseeing other staff that perform some of the above. Ms. Kenney is 40% paid through UMP as an independent licensed social worker at FUMC-R, outpatient. She is 60% paid through UMN research funds. She reports to Dr. Olson. Her CV is attached as Exhibit #4.

A number of study staff besides Ms. Kenney were trained and certified to perform evaluation scales such as the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), Positive and Negative Symptom Scale (PANSS), and Clinical Global Impressions (CGI) per review of records: Elizabeth Lemke, Julie Pearson, Tanya Adelman, Angela Guimaraes, and Christa Surerus-Johnson. They also were involved in explaining the study to subjects and obtaining and/or witnessing signed consent. Their CVs are attached as Exhibit #5 - 9.

I spoke to several other persons by phone in the course of this inspection and complaint follow-up:

Bill Andersen, Eagan Counseling Clinic (a memo of telecon is attached, Attachment #4)
Adrienne Baranauskas, Director of Research, FUMC-R
Keith Dunder, Attorney, Office of the General Counsel, AHC, UMN (Attachment #5)
Norm Isaacson, Investigator, MN Dept. of Human Services (Attachment #6)
Tyna Isaacson, Deputy Director, Dakota County Social Services
Moira Keane, Director, Research Subjects' Protection Programs, UMN (Attachment #7)
Peggy Mattingly, Director, Day Treatment Program, FUMC-R
Pat Murphy, Program Manager, Station 12, FUMC-R
Eric Peterson, Administrator, Boston Health Care, Theodore I home (Attachment #8)
S. Charles Schulz, MD, Co-investigator and Head, Dept. of Psychiatry, UMN (Attachment #9)
Jo Zillhardt, Medical Review Coordinator, MN Office of the Ombudsman for Mental Health & Mental Retardation (Attachment #10)

I attempted to meet and/or talk to the following persons in follow-up to the subject complaint:

David Pettit, Case Manager/Mental Health Social Worker, Dakota County
Theodore I residence/group home staff that actually interacted with DRM
Dan Buse, psychotherapist, Day Treatment Program, FUMC-R

Through their directors I was told they could not speak to me without a signed consent from a living relative. Consent was not pursued at this time per consultation with the assignment contact.

DSI Complaint #1006

This complaint involves the death/suicide of DRM, Subject #13 in the referenced study. DRMs Death Certificate shows he was found dead on 5/8/04 due to "sharp force injuries to the neck and chest" with a contributing condition of "history of mental illness", and manner of death "suicide". His Death Certificate, Autopsy Report, and Serious Adverse Event report are attached as Exhibit #10, 11, and 12.

The main points of the complaint and follow-up are as follows.

1) **DRM did not have the diagnosis under study, i.e. schizophrenia, schizophreniform disorder, or schizoaffective disorder.**

DRM was admitted to FUMC-R on 11/12/03 after transfer from Regions Hospital, St. Paul, MN where he had been brought in handcuffs and placed on a 72-Hour Hold. Medical records showed that DRM presented on admission to FUMC-R as grandiose, agitated, and having sleep problems. He was placed on Station 12. He was diagnosed with "Psychosis NOS" [not otherwise specified] throughout his admission until discharge on 12/8/03. Initial notes include differential diagnoses of possible mood disorder and bipolar as well as schizophrenia. The differential is schizophrenia by the time of discharge. DRMs inpatient medical records are attached as Exhibit #13, and the following chronology is provided for reference.

11/12/03 Admission Note, Diagnoses, Axis I:

1. Psychosis, not otherwise specified
2. Mood disorder, not otherwise specified
3. Rule out bipolar affective disorder with psychosis
4. Rule out schizophrenia

11/13/03 Attending Admission Note [by Dr. Olson], Diagnosis: Axis I: Psychosis NOS. Differential diagnosis includes paranoid schizophrenia, schizoaffective disorder, and bipolar with manic psychosis. General medical condition needs to be ruled out.

Started Risperdal, 3 mg for psychosis

Internal medicine consult - TSH normal, hyperlipidemia, elevated total bilirubin, otherwise normal.

11/14/03 Psychosis NOS, DSM code 298

Examiner's Statement in Support of Petition for Commitment by Dr. Olson states psychosis NOS: paranoid schizophrenic vs. psychotic mania vs. psychosis due to medical condition per examination 11/13/03.

11/15/03 Psychosis NOS

11/17/03 Attending Note states MRI and thyroid studies normal, Diagnosis: Psychosis NOS

Pre-Petition Screening Program Report recommends commitment due to "mentally ill", diagnosed Psychosis NOS, Mood Disorder NOS, R/O Bipolar, R/O Schizophrenia.

11/18/03 Psychosis NOS -- schizophrenia vs. mania
Neuropsychological evaluation - normal functioning

11/19/03 Psychosis NOS
11/20/03 Psychosis NOS

11/20/03 Note stating mother called and questions medication compliance. Mouth checks are started.

11/21/03 Psychosis NOS
Chemical Dependency Evaluation

Evaluation to Sign Consent Form obtained by Jean Kenney and witnessed.
Study Consent Form signature obtained by Ms. Kenney and witnessed.
Exhibit #14 and 15

11/24/03 Psychosis NOS
DRM began study screening. "Schizophrenia" per Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) – Exhibit #16

11/25/03	Psychosis NOS
11/28/03	Psychosis NOS
11/29/03	Psychosis NOS
12/1/04	Psychosis NOS, probable paranoid schizophrenia
12/2/04	Psychosis NOS
12/3/04	Psychosis NOS
12/4/04	Psychosis NOS
12/5/04	Psychosis NOS, probable paranoid schizophrenic Baseline visit with Ms. Kenney, DRM to begin test article that evening
12/8/04	Discharge Diagnoses, Axis I: Psychosis NOS Probable schizophrenia Questionable history of alcohol abuse versus dependence

As noted, DRM met criteria for schizophrenia on 11/24/03 per Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) – Exhibit #16. He retains the diagnosis of schizophrenia throughout outpatient study visits – records attached as Exhibit #17.

In evaluating a new, psychotic patient Dr. Olson described the first things they look at to rule out are a medical condition, drugs, and then mood disorder. When asked how bipolar psychosis was ruled out Dr. Olson described that they took a detailed history from the mother. Neither mom nor DRM could identify anyone that could provide first hand accounts of his behavior while living in California [for about 3 years] other than brief visits by the mother on 2 occasions. DRM did not report any manic episodes – question A16, SCID (Exhibit #16). Dr. Olson described that ultimately DRM did not meet the criteria/show symptoms indicating a mood disorder.

Dr. Olson and Jean Kenney volunteered that they were aware DRMs mother was not happy with his diagnosis or treatment and believed he was not getting better. She sent several letters regarding this which were in DRMs file and are attached for reference as Exhibit #18. Dr. Olson suggested getting a second opinion and that is noted in several places: mothers letter to Dr. Schulz (no date), Dr. Schulz response, and study progress notes 4/15/04 attached as Exhibit #18 page 1, 11 and Exhibit #17 page 18, respectively. The mother also had concerns about DRMs thyroid, possible gluten intolerance, and nutritional supplements that might be affecting him and these concerns were addressed, i.e. tests and consults were performed.

In summary, questions regarding psychiatric diagnosis would have to be addressed through medical review at CDER.

2) **DRM was court ordered to get medical treatment and instead was put in a study.**

Court and court-related documents are attached as Exhibit #19. A petition for commitment was filed for DRM 11/17/03. A stay of commitment was court ordered 11/20/03 for 6 months under agreed upon terms and conditions that included (Exhibit #19 page 13):

- remain hospitalized and cooperate with treatment until medically discharged;
- enter, participate, and complete an inpatient/outpatient treatment program and aftercare recommendations as determined by social worker;
- cooperate and follow rules at any living facility arranged by social worker;
- take drugs or medications only as prescribed; and,
- cooperate with social worker as determined.

The terms of the stay of commitment and conditions of discharge are arrived at by a patient's treatment team that includes a psychiatrist and county Case Manager, in this case David Pettit. I was not able to meet/talk/review records with Mr. Pettit as noted above but a 12/11/03 progress note states that he was supportive of DRM being in the CAFÉ Study - Exhibit #17 page 12.

Before discharge from Station 12, arrangements for after care are discussed and made. The choices for DRM included participating in a study or receiving **standard medical care.** When asked what "standard care" is Dr. Olson described that most patients would be prescribed medication and asked to return within a couple weeks of discharge and on some regular basis after that. He said the wait for a new patient to get in with a psychiatrist is about 4 – 6 weeks. Standard care was described similarly by several others (telecons noted above) - patients see a psychiatrist for medication tolerance checks about each 3 months for 5 – 10 minutes. Dr. Olson and Ms. Kenney described that at least one significant advantage of a clinical study is that a patient is seen more frequently, for longer visits, and can therefore be more closely monitored. They described that medication compliance is very important and with more frequent monitoring, compliance is better. He said there is a 5x greater rate of re-hospitalization for patients who do not take their anti-psychotics.

I asked what might be prescribed to DRM or any other subject had they not been in this study. Dr. Olson said he believes each of the drugs in this study is equally efficacious and so prescribing is based more on negative symptoms, e.g. if a patient already has a problem with weight he may not prescribe Olanzapine; if patient has trouble sleeping he may prescribe Seroquel; if patient has a blood relative with success on one drug he may prefer to try that first; etc.

In summary, DRMs commitment was stayed under terms and agreement that he would participate in treatment acceptable to his social worker. This study was presented as a choice to DRM, he was evaluated as able to provide consent, and he did voluntarily enroll. No evidence was found that DRMs social worker/case manager disagreed with this plan or that he or DRM wished to change it at any time

3) DRM was not in a state to have been able to give voluntary, informed consent.

As noted, DRM was admitted to FUMC-R on 11/12/03 upon transfer from Regions Hospital where he had been brought in by police in handcuffs and placed on a 72-hour hold. By 11/13/03 he started taking Risperdal voluntarily while inpatient on Station 12. A petition for commitment was prepared and filed in court 11/17/03. On 11/20/03 the court issued a stay of commitment. The terms of the stay and conditions of discharge were arrived at by DRMs treatment team. At no time was DRM under a Jarvis Order.

On 11/21/03 DRM was evaluated as able to give consent by Ms. Kenney and witnessed by Ms. Lemke. He subsequently signed the study consent form with Ms. Kenney and Dr. Olson. Both the evaluation and consent documents are attached as Exhibit #14 and 15. Note that the evaluation of subjects' ability to consent is an additional step performed at this study site - it is neither required nor mentioned in the study protocol.

By the time DRM consented on 11/21/03 he had undergone an internal medicine evaluation (11/13/03), had an MRI and thyroid studies (11/17/03), a neuropsychological evaluation (11/18/03), a chemical dependency evaluation (11/21/03), and had been observed on a daily basis by numerous medical and mental health care staff on Station 12. There was nothing different about this subject than others enrolled to indicate he couldn't provide voluntary, informed consent per review of his medical records or the approved study protocol which allows for enrollment of inpatient subjects.

4) DRM was kept on study despite deterioration.

DRM consented to this study 11/21/03 and began taking study medication 12/5/03. The symptom he consistently scored on the PANSS as mild to moderately severe is G12, "Lack of judgment and insight: Impaired awareness or understanding of one's own psychiatric condition and life situation.***" Portions of his PANSS and CGIs evaluations – scoring on any question of "3", Mild or higher scores, are attached for reference as Exhibit #21. Below is a summary of DRMs PANSS G12 score and CGI scores over time.

(PANSS severity scale: 1 = Absent, 2 = Minimal, 3 = Mild, 4 = Moderate, 5 = Moderately Severe, 6 = Severe, 7 = Extreme. CGI severity scale: 1 = Normal, Not ill, 2 = Minimally ill, 3 = Mildly ill, 4 = Moderately ill, 5 = Markedly ill, 6 = Severely ill, and 7 = Very severely ill.)

	SC	BL	V1 12/11	V2 12/19	V3 12/24	V4 12/31	V5 1/8	V6 1/16	V7 1/30	V8 2/13	V9 3/2	V10 3/31*	V11 4/28*
G12	**	4	5	5		5		3	3	4	3	5	5
CGI	5		3	3	2	3	2	2	2	2	2	4	3

**Abbreviated PANSS at screening

*rater up to Visit #9 was Jean Kenney, V10 and V11 rater was Julie Pearson

The SAE report for DRMs death (Exhibit #12) states in part "Over the last few months, DRMs ADLs have deteriorated, often with a disheveled appearance and wearing the same clothes as previous visits." I asked Ms. Kenney about "ADLs" and she described that it is terminology, not an actual list or scale that is documented and tracked. There is also a reference to declining ADLs in a progress note (Exhibit #17, page 18). Otherwise, review of DRMs records – attached and described further below, does not appear to indicate a significant decline or deterioration.

At the same time, records show that DRMs mother had serious concerns. Excerpts from study visit notes and correspondence are highlighted here for reference.

12/11/03	[study] Visit #1, "Schizophrenia"
12/19/03	Visit #2, "Schizophrenia". Ms. Kenney notes that mother is very concerned – DRM is getting messages from the TV, still has belief in the cult, and she is convinced he is covering symptoms.
1/16/04	Visit #6, note that DRM has started Day Treatment program [1/14/04]
1/30/04	Visit #7, notes group home has questioned DRMs medication compliance and started more closely monitoring
2/26/04	notes DRM due for Visit #9 – he called to say he'd forgotten appointment
2/27/04	notes were to have a family meeting today, mother did not show
3/2/04	Visit #9, "Schizophrenia"
3/25/04	Ms. Kenney notes conversation with mother and her friend regarding DRM canceling therapy appointments, not talking in therapy, and unrealistic plans to move
3/31/04	Visit #10, DRM completed Workbook Sheet #5 which asks "Recovery: Look at the following timeline of recovery and mark where you think you are in the recovery process." DRM rated himself at the top of the curve, "Full recovery with no symptoms and functioning well in life." [Exhibit #21, page 50]
4/15/04	several notes regarding meeting held at request of Case Manager Dave Pettit on DRMs readiness for independent living. Mother notes concerns. Dr. Olson discusses extending stay of commitment. Ms. Kenney notes calls from DRMs mother's friend and mother stating: his meds are not working, he's out of control, "Do we have to wait until he kills himself or someone else before anyone does anything."

4/28/04 Visit #11, Calgary Depression Rating Scale is performed looking at 9 items and DRM is rated 1 – Absent for each indicator of depression.

PANSS comments: "DRM presents disheveled today, hair unkempt, wearing jacket on hot day."

Besides this study, DRM was participating and being observed in his group home – **Theodore I**; the **Day Treatment** program at FUMC-R three times per week; individual therapy at the **Eagan Counseling Clinic**; and regularly meeting with his Dakota County **Case Manager** who is the responsible liaison between the court and physician for a committed person. No deterioration appears to have been noted in these arenas.

When DRM was discharged from the FUMC-R on 12/8/03 he went directly to **Theodore I**, a "Rule 36" residential facility for adults with mental illness. Dr. Olson described that DRM would have been discharged sooner but they were waiting for bed to become available at Theodore I. "Medication exchange records" were carried by DRM between Theodore I with staff notes on one side and MD/Dr. Olson notes on the other. No problems were noted in exchange records except on 1/30/04. That note states home staff began more rigorous medication check with DRM - having him observed during and after dosing, to assure he was swallowing meds. [It was suspected that he might be palming medication because of one occasion when it was thought he brought his hand down from his mouth too quickly – see Memo of Telecon with Eric Anderson, Attachment #8]. No other concerns were suggested by the notes which are attached as Exhibit #17 page 20 - 27.

DRM was admitted to the FUMC-R outpatient **Day Treatment Program** on 1/14/04. In this program he received 2 hours of group therapy and 1 hour of occupational therapy 3 times per week. Various assessments were made at each session regarding observable behavior; appearance; mood; affect; thought content and form; psychomotor behavior; what type of intervention is needed, including regarding safety; and, a continued plan. Notes indicate some progress being made and he "graduated" from Day Treatment/was discharged on 5/5/04. Day Treatment records are attached as Exhibit #20.

DRM was additionally receiving outpatient therapy from the **Eagan Counseling Clinic** about once per month. No deterioration was noted in that setting either per discussion with DRMs counselor and his review of notes – see memo of telecon, Attachment #4.

As noted, Dave Pettit, **Dakota County Case Manager** was the responsible liaison between the court and Dr. Olson. I attempted to contact Mr. Pettit during this inspection but was told through his department director he would not be allowed to speak about this or any case without a signed release from a living relative. A release was not pursued per discussion with the CDER assignment contact. Mr. Pettit reportedly had fairly frequent contact with DRM and was described by more than one

person interviewed as a very good, involved, experienced case manager. There was no indication in records, discussion, or interviews during this inspection of disagreement with DRMs enrolling or continuing in this study.

Overall, there is no evidence of suggestion or request to change DRMs treatment plan, change medications, or re-hospitalize him from any of the 4 non-study arenas noted.

At the same time, Dr. Olson described that no one was in favor of dropping DRMs commitment when his 6-month stay was nearing expiration. He said DRM did not object to this. He said their intention was to keep him in the area, to stabilize and continue treatment whether on or off study instead of rushing on his ultimate goal which was to return to California. Dr. Olson's recommendation to extend his stay of commitment is attached as Exhibit #19 page 18.

Both Dr. Olson and Ms. Kenney said DRMs main presentation was not fully grasping, having insight into the severity of his disease. He did not present any depression, suicidal thoughts, satanic or religious thoughts [as had been present at admit]. He appeared to be compliant with medications. He was thought to have improved somewhat in the Day Treatment program such that close to discharge from that program he was looking for an apartment with his case manager, and had started at a drop in center/community program. They were aware that DRMs mother did **not** think he was doing well. It is documented that they encouraged DRM to get a 2nd opinion if for no other reason than his mother being very concerned about his treatment and belief that he was not doing well. He declined to get a 2nd opinion.

Ms. Kenney expressed that she was impressed that DRM chose to take a more active route in his outpatient care and told him so. She said he could have easily done less. She said he could have chosen to accept standard treatment and wouldn't have had to come in for the numerous, lengthy visits and evaluations.

In talking to Dr. Olson, Ms. Kenney, Mr. Peterson from Theodore I, and Dr. Andersen, each said they were shocked to hear of DRMs suicide. He did not show evidence of that kind of deterioration. Dr. Olson said there was no increase in delusional thinking and that when patients start becoming grossly psychotic they usually talk about – as DRM did at admit. He said that if a patient is not taking medication there is normally a change in behavior. In the case of DRM there was not evidence to support an additional 72-hour hold or take him off study medication/change medication. When asked if there are any clues in retrospect, Dr. Olson said only that his method of suicide showed intent to complete it and somehow being removed enough to be able to persist through it.

5) **The CIs are guilty of misconduct and the University of MN is possibly shielding their staff.**

I did not find any evidence of misconduct, significant violation of the protocol or regulations governing clinical investigators or IRBs in this inspection, data audit, or interviews.

Other investigations of DRMs death: (1) The UMN IRB performed a routine, full-board review of DRMs death/SAE. No irregularities were noted or further follow-up performed per records (Exhibit #17 page 35) and per contact with the IRB (memo of telecon with Moira Keane, Attachment #7).

(2) A post-mortem/morbidity and mortality conference on the DRM case was conducted on 1/5/05. No reports, summaries, notes, or formal recommendations were or are made reportedly. It is a hospital-driven internal peer-review used for improvement and teaching per Keith Dunder, UMN attorney (reference memo of telecom, Attachment #5).

(3) The MN Department of Human Services performed an investigation in response to a complaint that staff at the Theodore I group home neglected DRM, a "vulnerable adult" prior to his death at that facility. No indication of maltreatment/neglect of supervision was found and no further follow-up recommended. The report was provided through MN DHS and is attached to a memo of telecom with Investigator Norm Isaacson – Attachment #6.

(4) DRMs death is also being investigated by the MN Office of the Ombudsman for Mental Health & Mental Retardation. That investigation is still in-process. Results will be available publicly. See memo of telecom with Jo Zillhardt of that office – Attachment #10.

Dr. Olson said [and records show] that in addition to the above he and Ms. Kenney have been contacted by letter or visits from the following offices requesting records, which have provided:

- Patricia M. Siebert, Attorney, Disability Law Center, Minneapolis, MN - an advocacy organization;
- MN Attorney General Mike Hatch regarding providing records to DRMs mother – Dr. Olson isn't sure if this in conjunction with other offices;
- DRMs mother directly and also through Keith Dunder, Attorney, Academic Health Center Counsel, UMN, Minneapolis, MN; and,
- Robins, Kaplan, Miller and Ciresi, LLP, Minneapolis, MN – a law firm, on behalf of DRMs mother.

INSPECTION

Protocol: The protocol sent with this assignment - Attachment #3, is the same as that on site and so no additional copy was collected. Deviations from the protocol were documented and a log is attached for reference as Exhibit #22. No un-reported deviations were found in this inspection.

Subjects' records: Subject records consist of a **clinical chart/binder** containing signed consent forms, lab reports, study visit notes, etc.; and, a **binder of source data forms** for mainly the various evaluation scales, e.g. SCID, PANSS, CGI. These are maintained in a locked room in the ARC. Subjects additionally have an **inpatient medical chart** if hospitalized and **outpatient medical chart** if s/he participated in for example the Day Treatment program, which are maintained in the medical records department at FUMC-R. Subject records are adequate to account for all subjects through their stated participation in this study. There are examples of subject records for DRM attached as Exhibit #17, 21, 13, and 20, respectively.

Consent of human subjects: A consent form is on file for each subject, signed prior to screening, per review of subject source records. Additionally, an Evaluation to Sign Consent Form was performed, witnessed, and documented for subjects prior to obtaining informed consent. This evaluation to sign consent form was initiated by this site, i.e. it was not required or suggested by the protocol or sponsor. An example signed consent form and evaluation are attached for reference as Exhibit #14 and 15. The consent form was revised on 5/2/02, 7/1/02, 10/23/02, 3/25/03, and 3/24/04 and approved by the IRB.

Informed consent was performed by study staff and by the clinical investigator. The study was explained by both parties. Study staff – almost always Jean Kenney, sometimes Elizabeth Lemke performed the evaluation to consent and obtained consent form signatures.

Subjects were recruited from the physicians/FUMC-Riverside patient population and referrals from other physicians and community groups. Dr. Olson and Ms. Kenney received IRB approval and did make some presentations at local mental health centers on this and at least one other study to increase awareness and provide a contact for referral.

Institutional Review Board: The UMN Institutional Review Board (IRB), Minneapolis, MN 55455 (FEI 2127205) provided initial and continuing review and approval of this study. The original application for review to the IRB is dated 2/11/02. Final approval was received in a letter dated 4/22/02, and continuing approval via letters 2/3/03 and 2/2/04. Portions of the application for review, progress reports, and IRB Submission Log are attached as Exhibit #23.

To date, reports and change requests appear to have been appropriate and submitted timely with one exception – see verbal observation #2 under **Discussion with Management** regarding a consent form update on risks of diabetes and hyperglycemia. Also, the original application to the IRB stated this study wasn't associated with an IND – verbal observation #1.

Adverse events: Adverse events to date appear to have been appropriately captured and reported per review of subject records. Two serious AEs occurred and were reported to the sponsor and IRB:

- Subject #13/DRM death/suicide on 5/8/04 – Exhibit #12.
- Subject #20/CLW pregnancy/fetal miscarriage on 5/6/04 – Exhibit #24.

Sponsor/monitor: Quintiles is the contract monitor on this study. A Senior Clinical Research Associate from Cincinatti, OH was assigned to this site first followed by another senior CRA located in Waukesha, WI. The first monitor visit was on 1/7/03 and additional visits have been made about quarterly including during this inspection, the week of 1/10/05. A copy of the Site Visit Log and post-visit letters/reports are attached for reference as Exhibit #25.

Test article accountability: Test articles were ordered for individual subjects via an Interactive Voice Response System (IVRS) phone system operated by Quintiles (Triangle Park, NC). Test articles were delivered to the attention of Ms. Kenney at the ARC. Subject compliance was checked at each visit. No deficiencies were noted in accounting for test articles received, dispensed, or returned. Records appear adequate to track all TAs received and dispensed.

Electronic records and signatures: Data was entered into an electronic system from source documents such as data forms provided by the sponsor/monitor, lab reports, etc. versus direct entry. None of the electronic case report forms are copied or kept here and I did not request any for review.

DATA AUDIT

This study started here with the signing of the first subject consent on 11/19/02. Final subject visits should be completed during 3/05. Twenty subjects were screened for this study. Of the 20:

- 17 were randomized (#14 was a screen failure, #16 decided against participating before randomization, and #17 could not be reached after screening)
- Subject #13 died/committed suicide
- Subject #1 moved out of state
- Subject #20 quit, would not come in for scheduled visits after V9
- 2 were lost to follow-up (#2 and #5)
- 3 were discontinued due to inadequate therapeutic effect (#6, #7, and #9)
- 6 completed the study (#3, #4, #8, #10, #11, and #12)
- 3 remain on study as of 1/05 (#15, #18, and #19).

Records reviewed in this inspection and data audit that are not elsewhere noted include:

- all correspondence with the sponsor, monitor, and IRB
- 1572's – copies are attached as Exhibit #26
- 12 sets of subject records in depth, including subject #13/DRM
- all subject records regarding consent, eligibility, adverse events, concomitant medications, current status, etc.
- financial disclosure information
- drug accountability records.

DISCUSSION WITH MANAGEMENT

No FD 483 List of Observations was issued. At the close of the inspection I held an exit meeting with Dr. Olson. Also present at that time were Ms. Kenney, Ms. Lemke, and Erica Carlson, Community Program Assistant. We discussed several items verbally including the following.

1. In the original application for IRB review (Exhibit #23) Appendix E is checked off to indicate the drugs used in this study are approved and an IND is not applicable, which was not the case. The IRB questioned that and Dr. Olson reasserted that an IND wasn't associated with or required for this study (Exhibit #23, page 5). Eventually this was resolved. Dr. Olson said he didn't know an IND was involved initially. I stated this is important information to provide to an IRB, why, and that any time he signs a 1572 that's an indicator that he's working on an IND study. He said he is more aware of this now and will be attentive to it.

2. Study sites were apprised of new risks of diabetes and hyperglycemia by the sponsor on 3/15/04. This site added new risk language to the consent forms on 3/24/04 but did not submit these changes to the IRB until 5/10/04 (Exhibit #23, page 10). The revised consent forms were approved in an IRB meeting 5/26/04 per letter from the IRB dated 6/1/04. We discussed that the risks should have been updated more timely. Dr. Olson explained the background of the warnings, and that subjects were observed and samples analyzed for these risks from the beginning. He and Ms. Kenney acknowledged this observation.

3. Regarding subject records we discussed more clearly documenting: why one subject was continued on study after early decline (Subject #6); discussion with one subject regarding choice to remain on study (Subject #18); and, dating corrections (Subject #2). These observations were acknowledged by both Dr. Olson and Ms. Kenney.

We briefly discussed review of records concerning the complaint. We discussed the post-inspection process and that concluded discussion of this inspection.

ATTACHMENTS

1. Assignment from CDER/HFD-46, dated 12/14/04
2. Complaint, and log of communications since the complaint
3. Protocol, dated 3/1/03

Memos of Telecons:

4. Bill Andersen, PhD, LP, Eagan Counseling Clinic, Eagan, MN
5. Keith Dunder, Attorney, Office of the General Counsel, AHC, UMN including copies of letters he's sent to DRMs mother and requested to forward here
6. Norm Isaacson, Investigator, MN Dept. of Human Services and including faxed copy of Investigation Memorandum, issued 10/29/04
7. Moira Keane, Director, Research Subjects' Protection Programs, UMN
8. Eric Peterson, Administrator, Boston Health Care/Theodore I group home
9. S. Charles Schulz, MD, Co-investigator and Head, Dept. of Psychiatry, UMN including copies of letters between himself and DRMs mother, dated 3/15/04 and 4/28/04
10. Jo Zillhardt, Medical Review Coordinator, MN Office of the Ombudsman for Mental Health & Mental Retardation, including copy of a letter from DRMs mother to that office, 11/2/04

EXHIBITS

CVs:

1. Stephen C. Olson, MD
2. S. Charles Schulz, MD
3. John P. Vuchetich, MD, PhD
4. Jean M. Kenney
5. Elizabeth Lemke
6. Julie Pearson
7. Tanya K. Adelman
8. Angela M. Holmes Guimaraes
9. Christa R. Surerus-Johnson
10. Death Certificate for DRM/Subject #13, issued 7/9/04 (and e-mail from L. Thomas, MD, Coroner to CAFÉ medical director, dated 6/8/04 requesting a blind break)
11. Autopsy Report for DRM/Subject #13, 5/8/04 and 6/17/04
12. SAE Report, 5/11/04 re: DRM suicide on 5/8/04.

13. DRM inpatient medical records:
    - Admission Note, 11/12/03
    - Internal medicine consult, 11/13/03 (pg 3)
    - Discharge Summary, 12/8/03 (pg 4)
    - Regions Hospital Emergency Center records (admit prior to transfer here)
        - 72 Hour Hold, 11/12/03 (pg 7)
        - Crisis Program Psychiatric Assessment, 11/12/03
        - Emergency Physician's Record
        - Emergency Nursing Record
    - Progress notes, 11/12 – 12/8/03 (pg 12) including Attending Notes on:
        - 11/13/03 (pg 15)
        - 11/17/03 (pg 25)
        - 11/19/03 (pg 29)
        - 11/21/03 (pg 35)
        - 11/25/03 (pg 40)
        - 12/1/03 (pg 46)
        - 12/2/03 (pg 48)
        - 12/3/03 (pg 51)
        - 12/5/03 (pg 56)
        - 12/8/03 (pg 58)
    - Orders for treatment (pg 60)
    - Medication Administration Records (pg 71)
    - Neuropsychological Evaluation, 11/18/03 (pg 78)
    - Chemical Dependency Evaluation, 11/21/03 (pg 82)
    - Adult CD Assessment, 11/28/03 (pg 83)
    - Treatment Plan Review on 11/21/03, 12/1/03, and 12/8/03 (pg 84)
    - Adult Sr Assessment of Suicide Risk for Discharge, 12/8/03 (pg 87)
    - Discharge agreement, signed 12/8/03 (pg 88)
    - Interagency Assessment & Transfer Form, MD and Nursing Orders (pg 89)
    - Miscellaneous correspondence:
        - Request for records from MN Disability Determination Services
        - Authorization to Disclose Information to Social Security Admin.
        - Authorization to Release information to Eagan Counseling Clinic
14. DRM Evaluation to Sign Consent Form, 11/21/03
15. DRM Study Consent Form, 11/21/03 (and HIPAA Authorization, signed 11/24/03)
16. DRM SCID, performed 11/24/03

17. DRM clinical binder records:
    - screening source data forms
    - study progress notes (pg 11)
    - Boston Health Care/Theodore I medication exchange records (pg 20):
        - 12/11/03
        - 12/19/03
        - 1/8/04
        - 1/16/04
        - 1/30/04
        - [no date]
        - 2/13/04
        - 3/31/04
    - Authorization to Release information to David Pettit & Dakota Cty, 11/26/03 (pg 28)
    - Authorization to Release information to Theo I residence, 12/4/03
    - Medication Instructions, dated 12/11/03 and 12/19/03 (pg 30)
    - Payment Grid (pg 32)
    - Phone Call Information note re: call from mother, 2/18/04 (pg 33)
    - Newspaper notice of death, 5/11/04 (pg 34)
    - Correspondence with IRB re: SAE-death:
        - Coverletter for SAE report for DRM faxed to IRB 5/12/04 (pg 35)
        - IRB questions re: DRM SAE/death, 5/13/04 (pg 36)
        - IRB Official Notification to FDA re: DRM SAE/death, 5/13/04 (pg 37)
        - Response to IRB from Dr. Olson, 5/17/04 re: DRM SAE/death (pg 38)
        - Letter from IRB 6/1/04 (pg 40)
        - Letter from IRB 6/25/04 stating review of DRM SAE is concluded (pg 41)
    - Correspondence with monitor/Quintiles re: SAE-death, 5/11&12/04 (pg 42)
    - Letter from MN Office of the OMHMR to Jean Kenney, 6/21/04 (pg 45)
    - Letter to MN Office of the OMHMR from Dr. Olson, 7/6/04 (pg 46)
    - Letter from MN Disability Law Center to MN Atty General M. Hatch, 7/30/04 (pg 47)
18. Correspondence to and from DRMs mother:
    - to Whom It May Concern from MW [no date]
    - copies of e-mail between DRM and MW in 9/19-23/03 provided to Dr. Olson
    - to Dr. Olson from MW, 11/24/03 (pg 8)
    - to Dr. Schulz from MW, 4/26/04 (pg 10)
    - to MW from Dr. Schulz, 4/28/04 (pg 11)
    - draft of letter to MW from Dr. Schulz with notes from Dr. Olson, 4/28/04 (pg 13)
    - Fax Cover Sheet for fax of 4/04 letters to UMP Risk Mgmt from Dr. Olson

19. DRM court and court related records:
    - Petition for Judicial Commitment, 11/14/03 filed 11/17/03
    - Examiner's Statement in Support of Petition for Commitment, 11/14/03 (pg 3)
    - Pre-Petition Screening Program Report, 11/17/03 (pg 5)
    - Order to Confine, to Transport for Examination, Hearing, Appointment of Attorney, Examiner and Notice, 11/17/03 (pg 9)
    - Order to Release Medical Records, 11/17/03 (pg 11)
    - Court Medication Summary, 11/20/03 (pg 12)
    - Findings of Fact, Conclusions of Law and Order for Stayed Commitment, 11/20/03 (pg 13)
    - Court Medication Summary, 11/26/03 (pg 17)
    - Letter to Dakota County Social Services from Dr. Olson, 4/27/04 re: recommendation to extend stay of commitment to disallow leaving the state. (pg 18)
    - Addendum to 4/27/04 letter from Jean Kenney, 5/3/04 re: diagnosis info. – 295.30 Schizophrenia, paranoid type (pg 20)
20. DRM outpatient chart records:
    - Discharge Summary, 5/5/04
    - Adult Day Treatment Progress Notes, 1/14 – 5/5/04 (pg 4)
    - Intake assessment, 1/14/04 (pg 39)
    - Phone Contacts log (pg 45)
    - Miscellaneous correspondence
21. Source Document data forms, portions of PANSS and CGI with any score of 3 or higher, screening to Visit #11
22. Protocol Deviations Log
23. IRB records:
    - Portion of application for IRB review, 2/11/02
    - Response to IRB from Dr. Olson, 4/3/02, including re: status of test articles (pg 5)
    - Progress report to IRB, 12/24/03 (pg 7)
    - Request for review of CF change to add risk of diabetes, 5/10/04 (pg 10)
    - Progress report to IRB, 12/17/04 (pg 11)
    - IRB Submission Log (pg 16)
24. SAE report for subject #20/CLW, pregnancy/fetal miscarriage, 5/6/04
25. Monitoring records:
    - Site Visit Log
    - 1/8/03 for visit on 1/7/03
    - [notes dated 4/28/03] for visit 4/28/03
    - 9/24/03 for visit on 9/11-12/03
    - 1/21/04 for visit on 1/13-14/04
    - 5/17/04 for visit on 4/26-27/04
    - 8/9/04 for visit on 7/26-27/04

26. 1572s, dated:

- 4/2/02
- 6/13/02
- 11/25/02
- 10/21/03
- 12/22/03
- 1/7/04
- 7/9/04
- 12/17/04

Sharon L. Matson

Sharon L. Matson, Investigator