UNDERSTANDING PERSONALITY STYLES OF WOMEN IN PHASE II AND III RHEUMATOID ARTHRITIS CLINICAL TRIALS

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INTRODUCTION

Before any medication can be distributed, it must first undergo a series of four extensive clinical trials on human subjects to ensure the safety and efficacy of the drug, as outlined by the Food and Drug Administration (CFR, Section 21). These trials range from small studies conducted on seemingly healthy, asymptomatic volunteers called Phase I trials, to smaller trials testing safety and efficacy in symptomatic participants known as Phase II and III trials, to mass post-market studies conducted on thousands of symptomatic participants, or Phase IV trials ("An Introduction to Clinical Trials," 2006). There is a large body of research looking at why people choose to participate in Phase I trials where healthy volunteers are used to assess safety of the drug by introducing the drug to the human body (Lowton, 2005; Meyer, 2001; Harth, Johnstone, Thong, 1992). Identified factors influencing participation include financial compensation, altruism, promotion of science, and personality traits such as extroversion, low anxiety, independence, and openness to new experiences (Lowton, 2005, Weinfurt, K.P., et al, 2003; Crumbo, C.L., Rybeczyk, G.K., Wagner, L.J., 1997). However, there is limited research on how these factors influence volunteer participation in latter phases of clinical research when the drug is tested on symptomatic participants, or patients who possess the medical condition the drug is intended to treat.

Given the research collected on phase I participants, one may guess that factors such as financial incentives and free healthcare play a role in one's decision to participate in a Phase II or III clinical trial as well (Lowton, 2005). One may also guess that

personality is an influencing factor for participation as it is in phase I. However, personality traits identified in phase I participants such as openness to new experiences, low anxiety, independence, and extroversion are not commonly seen in people with long term chronic illnesses such as rheumatoid arthritis, cystic fibrosis, and heart disease (Lowton, 2005, Came, J. et al., 1989; Moos and Solomon, 1965). Numerous studies have repeatedly found depression, high anxiety, introversion, and hopelessness associated with chronic illness (Bauer, H., and Duijsens, I.J., 1998; Ashutosh, et al., 1997). Given the obvious discrepancy of the identified personality characteristics typically seen in clinical trial volunteers and those reportedly seen in chronically ill patients, there appears to be a need to identify if there are personality characteristics specific to chronically ill patients who choose to participate in clinical trials. This study will focus specifically on patients with Rheumatoid Arthritis (RA) and if personality characteristics seen in phase I volunteers are also found in phase II and III pharmaceutical trials as well.

Nearly 40 million Americans have been diagnosed with some form of arthritis, making it the leading cause of disability in the Unites States, with prevalence and incidence rates two to three times higher in females than in males (Mayo Clinic, 2002). Rheumatoid arthritis was chosen for this study not only because of the high prevalence rates and attention it has received in the pharmaceutical world, but also because of the significant amount of research that has been dedicated to the study of personality styles of those who have been diagnosed with the illness. There have been many well-established links between personality and the onset and course of rheumatoid arthritis (Moos and Solomon, 1965). An early study comparing arthritic women to non-arthritic siblings found that overall the arthritic participants showed more subservience, nervousness,

restlessness, depression, conservatism, and hypersensitivity to anger, which later research was able to link to a positive or negative course of illness (Moos and Solomon, 1963; Moos, et al, 1963, 1965). However, it is not clear if personality traits associated with the illness were present before the illness, or if they are the result of a very painful and disabling chronic illness.

Research also suggests that personality is linked to level of functioning; participants who exhibit poorer functioning display greater introversion, depression, social isolation, anxiety, anger, fear, and insufficient coping skills, while higher functioning individuals displayed more extroversion, greater coping skills, etc. And while there is some disagreement about the exact role personality and psychosocial factors play in disease development, most agree that it can have an impact on the efficacy of treatment, including one's response to medication (Meyer, 2001). This fact necessitates the need for the pharmaceutical companies to understand the type of person participating in clinical studies, as personality may impact the efficacy results and generalizability of new medications.

As previously stated, research conducted on phase I participants reveals an openness to new experiences, low anxiety, sociability, and independence (Lowton, 2005, Weinfurt, K.P., et al, 2003; Crumbo, C.L., Rybeczyk, G.K., Wagner, L.J., 1997). The present study looked to determine whether rheumatic clinical trial participants possessed similar personality styles to phase I participants, or if they displayed styles consistent with those of the rheumatic population. The hypothesis was that participants in the phase II and III trials displayed personality styles more consistent with those of phase I volunteers versus those of the chronically ill. Specifically, the researcher expected the

clinical trial participants to display higher levels of extroversion, independence, willingness to take risks, and lower anxiety than patients with Rheumatoid Arthritis that are not in trials. This study attempted to answer that question by comparing the results of a personality assessment taken by arthritic patients who are currently or have previously been enrolled in a pharmaceutical drug trial and arthritic patients who have not.

METHOD

Participants

Data were collected from two groups of participants. Both the experimental and the control groups consisted of female participants between the ages of 23-83 who were diagnosed as "definite" or "classical" Rheumatoid Arthritis, as defined by the ARA Diagnostic Criteria for rheumatoid arthritis (Arnett, Et al., 1988). To meet criteria for definite RA, participants must experience four to five of the following symptoms: morning stiffness, arthritis of three or more joint areas, arthritis of hand joints, symmetrical soft tissue joint swelling, subcutaneous rheumatoid nodules, radiographic changes, or a positive serum rheumatoid factor. For a classical diagnosis participants must meet six to seven of these criteria. The participants fit within classes II and III of the global functioning status as defined by the American College of Rheumatology (Hochberg, et al., 1992). Those classes are broken into four divisions: class 1- no functional impairment in daily living tasks; class 2- able to adequately function in normal life with minor impairment; class 3- limited function, but still able to engage in daily living tasks; class 4- unable to function independently.

Women only were selected for this current study due to the higher prevalence of rheumatoid arthritis in women versus men. Limiting the study to women only also helped control for personality differences that may be better attributed to gender differences. The experimental group or Clinical Trial Participant group (referred to as "CT-Participant" from this point forward) consisted of forty-four female participants who

were enrolled in a Phase II or Phase III Rheumatoid Arthritis pharmaceutical drug trial at the time of the study. The number of participants was limited by the size of the pharmaceutical research facility. Participants were recruited through an independent pharmaceutical research facility in the Midwest. The control group, or Non-Clinical Trial Participant group (referred to as "NCT-Participants" from this point forward) consisted of thirty-eight females who had never participated in a clinical trial for rheumatoid arthritis or any other illness/condition. These patients were recruited through physicians' offices that specialize in the treatment of RA. Approval was obtained from the Institutional Review Board at Oklahoma State University.

Procedure

Prior to the beginning of the study, packets were distributed to the participating physician's office and research facility, which then gave them to consenting participants. Included in these packets were an informed consent (see Appendix C), a demographic questionnaire (Appendix B), and the Millon Inventory of Personality Styles Revised (MIPS-R), a paper and pencil personality inventory. The packets were prepared with a counter-balance of presentation of the demographic survey and assessment to protect internal validity. Once the information was filled out, participants sealed their envelopes and return them to the physician's staff. The researcher collected the packets from each facility on a weekly basis until data collection was complete. To protect confidentiality, each participant's identifying information was collected separately from the assessment materials. Specifically, participant consent forms were collected in a single envelope that remained separate from each sealed envelope containing the completed demographic questionnaire and MIPS assessment. Participants had the opportunity to enter their name

separately for one of four twenty-five dollar drawings. A separate form was available in the assessment packet, which allowed participants to enter their name and phone number/email address. These forms were also stored in a separate envelope from the demographic questionnaire and MIPS so as to protect participant confidentiality.

All participants were asked to complete a demographic questionnaire that assessed variables including age, income, education, ethnicity, access to health insurance, access to Medicaid/Medicare, and motivation for their participation in the current or previous clinical trial if applicable (see Appendix B). Specified motives for participation assessed in previous research included the following: financial incentives (including compensation, free healthcare, and free medication), dedication to the advancement of science, physician recommendation, and altruism (Lowton, 2005, Weinfurt, K.P., et al, 2003; Crumbo, C.L., Rybeczyk, G.K., Wagner, L.J., 1997). Information was obtained on socioeconomic status and level of education as these variables have been linked to the onset and progression of rheumatoid arthritis as well as motivation for participating in clinical research (Harth, et al., 1992).

Instrument

Each participant completed the Millon Personality Style Index-Revised (MIPS-R), a non-clinical one hundred and eighty-item true/false assessment of general personality traits. Developed by Theodore Millon (2004), the MIPS-R measures twenty-four personality styles or traits through twelve pairs of bipolar content scales. These include six Motivating Styles (pleasure-enhancing vs. pain-avoiding, actively modifying vs. passively accommodating, and self-indulging vs. other-nurturing), eight Thinking Styles (externally focused vs. internally focused, realistic/sensing vs. imaginative/

intuiting, thought-guided vs. feeling-guided, and conservation-seeking vs. innovation-seeking), and ten Behaving Styles (asocial/withdrawing vs. gregarious/ outgoing, anxious/hesitating vs. confident/asserting, unconventional/dissenting vs. dutiful/conforming, submissive/yielding vs. dominant/controlling, and dissatisfied/ complaining vs. cooperative/agreeing). There are three validity indices: positive impression, negative impression, and consistency. The assessment was designed at an eighth grade reading level and can be administered through paper and pencil or online. It takes an estimated twenty to thirty minutes to complete. Because prior research and related literature identifies personality traits such as extroversion, anxiety, independence, and risk taking as prevalent among phase I participants, this study focused on four sets of polar scales for a total of eight scales in the MIPS-R that reflect those styles. Specific scales that identify personality issues of extroversion, anxiety, independence, and risk taking are the externally focused vs. internally focused scales, conservation-seeking vs. innovation-seeking scales, anxious/hesitating vs. confident/asserting scales, and the submissive/yielding vs. dominant/controlling scales. Breaking each scale down further, the elevated scores on the externally focused scale suggests a pattern of turning to others for stimulation and support. It suggests a dependence on others for guidance and feelings of self-worth. Elevated scores on the internally focused scale suggest drawing from her own feelings for inspiration, at times resulting in a distancing from others. An elevated score on the Conservation-Seeking scale suggests a trend towards orderliness, traditionalism, and conservative behavior and beliefs. This scale is counterbalanced by the Innovation-Seeking scale, suggesting a tendency towards risk-taking and creativity. The Anxious/Hesitating scale measures tendencies towards shyness, timidity, and

anxiety, while the Confident/Asserting scale measures outspokenness, ambitiousness, and self-assuredness. An elevated score on the Submissive/Yielding scale indicates a tendency towards suffering and domination, possibly giving up opportunities to help themselves while waiting for others to help. The Dominant/Controlling scale suggests domineering behavior, fearlessness, and aggression.

The MIPS-R utilizes prevalence scores ranging from zero to one hundred instead of standard T-scores, with a reference score of fifty indicating possession of that personality style. Scores were standardized on four samples: adult men and women and college-age men and women. Separate gender norms are used when determining the prevalence scores. Median reliability coefficients for the adult male and female samples are .76 and .78 respectively, with a median split-half reliability of .80 for both males and females (Millon, 2004). Given the participant sample in the current study, only statistical data for the female adult population was used. For the scales used in the current study coefficient alpha ranged from .71 (Innovation-Seeking) to .85 (Anxious/ Hesitating). Test-retest data showed a .85 median correlation coefficient in a study of fifty adults who took the test twice in a range of 20-82 days. Test retest reliabilities for the scales used in the current study range from .83 (Conservation-Seeking) to .90 (Externally Focused, Internally Focused, Innovation-Seeking, and Submissive/Yielding). Strong patterns of scale inter-correlations and scale-item overlap also suggest moderately strong internal validity.

The MIPS-R correlates positively with several established personality assessments including the Myers Briggs Type Indicator (MBTI), 16PF, California Psychological Inventory, NEO Personality Inventory, and the Minnesota Multiphasic

Personality Inventory-2 (MMPI-2) (Millon, 2004), indicating strong external validity. For example, the Externally Focused scale of the MIPS-R correlates inversely with the Enthusiastic (r =. 61) and the Bold (r = .72) traits measured by the 16PF. The Bold trait also correlated with the Confident/Asserting scale (r = .70) and the Anxious/Hesitating scale (r = -.72). The Extraversion factor measured in the 16PF correlates with the Externally Focused (r = .75) and the Anxious/Hesitating (r = -.62) scales. The Anxiety Factor of the 16PF correlates with the Anxious/Hesitating scale (r =.50). The Independence factor of the 16PF moderately correlates with the Confident/Asserting scale (r =.54). The Externally Focused scale correlates most strongly with the Extraversion and Introversion scales of the MBTI (r =.67 and -.71 respectively), as does the Internally Focused scale (r =-.63 and r =.64 respectively). The Anxious/Hesitating (r =-.55 and r =.60) and Confident/Asserting (r =.46 and r =-.52) scales also correlate most strongly with the Extroversion and Introversion scales of the MBTI. The Conservation-Seeking scale correlates with the Judging and Perceiving scales of the MBTI (r =.59 and -.60 respectively). The Innovation-Seeking scale also correlates most strongly with the MBTI Judging and Perceiving scales (r =-.51 and .55 respectively).

The MIPS-R was selected for several reasons, the most important being its ability to provide a solid yet broad assessment of personality traits found in a normal population sample. The specific content scales allowed for the measurement of identified factors including anxiety and dependence previously identified as traits found in arthritic patients, while scales such as innovation-seeking would suggest the openness to new experiences commonly seen in clinical trial participants. While other assessments such as the 16PF and NEO-PI would provide similar information, this particular assessment is

shorter in length and simplified in its True/False answering style, which may have been easier for patients to complete given the possibility of joint pain and physical discomfort often seen in arthritic patients.

RESULTS

Given the hypothesis that there would be significant differences between the CT-Participant and the NCT- Participant groups on scales reflecting extroversion (scales 4A-Externally Focused and 4B-Internally Focused), openness to new experiences (scales 7A-Conservation-Seeking and 7B-Innovation-Seeking), independence (scales 11A-Submissive/Yielding and 11B-Dominant/Controlling), and anxiety (scales 9A-Anxious/Hesitating and 9B—Confident/Asserting), the best approach was to conduct a series of four MANOVAs with follow-up ANOVAs if the MANOVA was significant. This allowed for the greatest measurement of difference between groups, while providing protection against Type I error.

The data analyses also included comparisons between the participant and non-participant groups on demographic variables including Age, Level of Education, Household Income, Access to Health Insurance, and Access to Medicaid/Medicaid, through the use of multiple one-way ANOVAs and chi-square analyses.

Demographic Comparison of Groups

Data were collected from eighty-two female participants over the course of two months (n=44 for CT-Participants; n=38 for NCT-Participants). The ages ranged from 23 years to 83 years old, with a mean age of 56.68 years (mean = 54.55, SD 10.877 for CT-Participants; mean = 59.16, SD 14.181 for NCT-Participants). See Table 1 for complete frequency response information on demographic variables.

Table 1: Frequency Chart of Demographic Variables Between Groups

		CT-Participants	NCT-Participants
Household Income	No Answer	1	6
	Under $15000	6	2
	$15000-$30000	10	5
	$30000-$45000	9	4
	$45000-$60000	8	7
	$60000 +	10	14
Level of Education	Did not complete H.S	7	3
	High School/GED	10	12
	Some College/Technical	8	8
	College/Technical Degree	13	11
	Graduate School	6	4
Race/Ethnicity	Caucasian	35	32
	African American	1	1
	Hispanic/Latino	1	0
	Native American	7	7
Heath Insurance	Yes	36	37
	No	8	1
Currently Employed	Yes	23	15
	No	21	23
Receiving Medicaid/Medicare	Yes	17	14
	No	27	24
Participant in Previous Trial	Yes	3	0
	No	41	38

Several one-way ANOVAs were conducted on demographic variables including age, income, and level of education. At alpha$\leq$ .05, no significant differences were found between groups on any of these variables (Age-$F(1,81)=2.770$, p=.100; Household Income-$F(1,81)=.151$, p=.699; Level of Education-$F(1,81)=.000$, p=.990). No inferential statistics were conducted for the demographic variable, ethnicity. It can be seen, however, from a visual inspection of the data that the grand majority of the participants in the both groups were Caucasian. Of significant note is that there were seven Native Americans in both the CT-Participant group and NCT-Participant group. Chi-square analyses were conducted on variables that yielded a Yes/No response including current employment, previous participation in a clinical trial and access to health insurance and Medicaid/Medicare. A significant difference was found in access to health insurance

(Pearson Chi-Square with one degree of freedom=5.05, p=.025). No significant differences were found in current employment (Pearson Chi-Square with one degree of freedom=1.343, p=.246), Medicaid/Medicare (Pearson Chi-Square with one degree of freedom= .028, p=.867), and previous enrollment in a clinical trial (Pearson Chi-Square with one degree of freedom=2.689, p=.101).

The mean scores of reasons to participate in clinical trials were also calculated from data collected from the CT-Participant group, including Free Healthcare/ Medication, To Help Others, To Improve Science, Financial Compensation, Doctor Recommendation, and Previous Treatment Was Not Effective. Only CT-Participants were asked to rank on a scale of one (strongly disagree) to five (strongly agree) the influence these factors had on the decision to participate in a clinical trial. The results were as follows: To Help Others (mean=3.39; SD=1.833), To Improve Science (mean=3.34; SD= 1.855), Free Healthcare (mean=2.93; SD=1.676), Financial Compensation (mean=1.82; SD=1.317), Doctor Recommendation (mean=3.50; SD=2.029), and Previously Ineffective Treatment (Mean=3.09; SD=1.939).

Analyses of Personality Differences

Because the MIPS-R uses prevalence scores instead of T-scores or stanines, the results did not provide normative data so all analyses were conducted using the raw scores (See Figure 1 for a graphic representation of the means for each group).

Fig 1. Summary of mean raw scores on MIPS-R scales between CT-Participant and NCT- Participant groups.

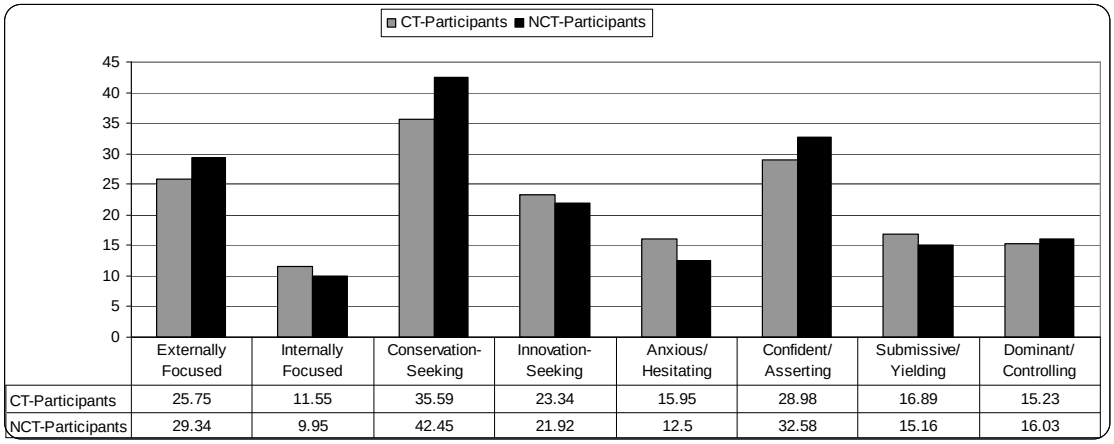


Table 2: MIPS-R Raw Score Means and Standard Deviations

Group	External Focused	Internal Focused	Conser. Seeking	Innov. Seeking	Anxious Hesitate	Confident Asserting	Submis. Yielding	Dominant Control.
CT-Part.								
Mean	25.75	11.55	35.59	23.34	15.95	28.98	16.89	15.23
Std. Deviation	9.224	7.822	9.968	9.899	11.475	10.832	6.085	7.291
NCT-Part.								
Mean	29.34	9.95	42.45	21.92	12.50	32.58	15.16	16.03
Std. Deviation	10.278	8.504	10.428	8.152	12.390	12.185	8.096	7.038

Four separate MANOVAs were conducted comparing the results of the eight MIPS-R scales between the CT-Participant and NCT-Participant groups (see Tables 2-4). Each MANOVA compared two polar scales; for example the first MANOVA compared scores on the Introversion scale and scores on the Extroversion scale between groups. If any significant differences were found at the $p<.05$ level, univariate follow-up ANOVAs were performed to confirm a significant difference on that scale.

Specifically the first MANOVA analyzed the results of the Introversion and Extroversion scales between the two groups (see Table 3). No significant results were

found (F (2,79)= 1.986; p=.144). The second MANOVA compared the Conservation-Seeking and Innovation-Seeking subscales. A significant difference was found at the p<.05 level (F (2,79)=4.571; p=.013). Follow-up ANOVAs confirmed a significant difference (F(1,80) = 4.612, p=.013) on the Conservation-Seeking scale, but no difference on the Innovation Seeking Scale (F(1,80)=.493, p=.485). The third MANOVA compared scores on the Anxious/Hesitating and Confident/Asserting scales. No significant differences were found at the p<.05 level (F (2,79)=1.058; p=.352) The final MANOVA compared the Submissive/Yielding and the Dominant/Controlling scores between groups. No significant differences were found at the p<.05 level (F (2,79)=.607; p=.548).

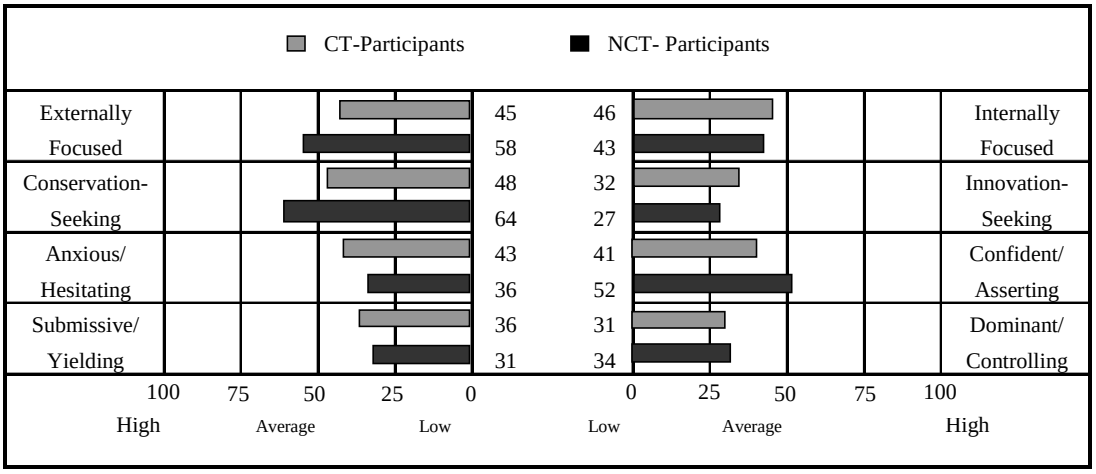
Table 3: MANOVA Results

GROUP	Wilkes Lambda Value	F	Hypothesis df	Error df	Sig
MANOVA 1 Externally Focused/ Internally Focused	.952	1.986	2.000	79.000	.144
MANOVA 2 Conservation-Seeking/ Innovation-Seeking	.896	4.571	2.000	79.000	.013
MANOVA 3 Anxious/ Hesitating Confident/Asserting	.974	1.058	2.000	79.000	.352
MANOVA 4 Submissive/Yielding Dominant/ Controlling	.985	.607	2.000	79.000	.548

The mean raw scores for each scale were then computed into a mean prevalence score in order to provide insight into the response patterns of each group (see Figure 2). The prevalence scores fell on a scale of zero to one hundred, with zero being low and one hundred being high. Any score higher than fifty recognizes a presence of that personality style. Results from the CT-Participant group ranged from 31 on the Dominant-

Controlling scale to 48 on the Conservation-Seeking group. Though the CT-Participant group scored significantly lower on the Conservation Seeking scale, the score still fell within the average range (prevalence score=48). The NCT-Participant group's prevalence scores ranged from 27 on the Innovation-Seeking scale to 64 on the Conservation-Seeking scale. They had three scores above 50: the Externally Focused, Conservation-Seeking, and the Confident/Asserting, indicating a presence of those personality styles.

Figure II: Prevalence score determined by mean raw score for both NCT-Participant and CT-Participant Groups on 8 MIPS-R Scales



DISCUSSION

It was hypothesized that Clinical Trial Participants would possess personality characteristics reportedly seen in Phase I clinical trial volunteers, such as openness to new experiences, low anxiety, independence, and extroversion (Lowton, 2005, Weinfurt, K.P., et al, 2003; Crumbo, C.L., Rybeczyk, G.K., Wagner, L.J., 1997). These traits differ significantly from those seen in personality research in rheumatic patients, which includes higher levels of dependence, anxiety, and introversion (Lowton, 2005; Cami, J. et al.; 1989; Moos and Solomon, 1965). These apparent differences in personality styles in populations that overlap in the clinical research field, and the lack of documented research on those differences, are what led to the current study. This study sought to determine if there are underlying personality characteristics that differentiate people with rheumatoid arthritis who participate in clinical trials, from those who do not. This knowledge could possibly lead to a greater understanding of what the clinical trial participant looks like in Phase II and III studies, thus aiding in the efficacy and generalizability of pharmaceutical research as well as recruitment and retention for pharmaceutical trials.

To test the hypothesis that there are personality differences between RA patients who participate in clinical trials versus those who do not, eighty-two women diagnosed with RA were given a demographic questionnaire and general personality assessment, the Millon Index of Personality Styles- Revised (MIPS-R) (Clinical Trial Participants N=44; Non-Clinical Trial Participants N=38). Comparisons on demographic data including age,

household income, level of education, current employment, and access to health insurance and Medicaid/Medicare revealed no significant differences between groups with the exception of access to health insurance; fewer CT-Participants had health insurance. Multiple MANOVAs performed on the MIPS-R scores revealed no significant differences on seven of the eight personality scales, including Introversion, Extroversion, Innovation-Seeking, Anxious/ Hesitating, Confident/Asserting, Submissive/Yielding, and Dominant/Controlling. There were significant differences on only one scale: the Conservation-Seeking scale. This indicates that people with Rheumatoid Arthritis who do not participate in clinical trials display a higher degree of conservatism and traditionalism and thus may not be willing to step outside of traditionally accepted medical interventions. When comparing the Innovation-Seeking mean prevalence scores, neither the CT-Participants nor the NCT-Participant group approached an average score. Thus indicating, that while CT-Participants may exhibit less conservative and traditional views, it does not necessarily translate to more innovative and forward thinking when compared to the general population.

Overall, scores for both the CT-Participant and the NCT-Participant groups fell near average on all scales, challenging previous findings that people with Rheumatoid Arthritis experienced higher than average rates of anxiety, introversion, and dependence. In fact, the NCT-Participant sample scored higher than the CT-participant group on the Extroverted and Confident/ Asserting scales. This leads to questions of the validity of past research on the personality styles of people with RA.

Given the small sample size for each group it is difficult to say with certainty that the personality styles identified in this study can be generalized to the entire rheumatic

population, and the population that participates in clinical drug trials. Results may be further limited given the lack of a true control sample used in this study, such as a healthy control sample (although using prevalence scores that were normed on a healthy female population may provide somewhat for the comparison). Ideally data would be gathered from a larger sample, possibly from multiple research sites that would provide for greater diversity. The study is also limited in the generalizability of a universal personality profile for participants in latter phases of clinical trials, as this study only looked at rheumatoid arthritis. Though there were limited significant differences noted in this single study, it would still be beneficial to conduct studies across multiple illnesses and indications to further rule out any underlying personality traits that lead one to participate in a clinical drug trial.

Also important to note, research has recently focused on the lack of diversity in pharmaceutical trials, usually linked to distrust and a history of mistreatment (Sung, et al., 2003; Anderson, D., 2004). Surprisingly, this study had seven out of forty-four women in the CT-Participant group who identified themselves as Native American, which represents a significant percentage of the total group. The higher percentage of Native Americans may be attributed to study taking place in Oklahoma. Looking at response data, five of the seven participants reported having access to health insurance and none reported receiving Medicaid/Medicare benefits. And though information was not gathered on the extensiveness of health insurance coverage, these results suggest participation was not based on lack of medical care. Therefore further research may be beneficial in understanding motivation for volunteering in typically under-represented populations.

Unfortunately the current study did not provide much insight into the motivating factors behind participating in a pharmaceutical research study. As personality may be ruled out as one of those factors, that turns the need to explore other options. For example the highest ranked motivating factor for participation in a clinical trial according to the demographic survey was Doctor Recommended (mean=3.50, on a scale of 1 to 5). What are the ethical concerns for physicians recruiting their own patients as participants in clinical trials where the physicians benefit financially? On another note, ranked nearly as high in motivating factors, was Desire to Help Others (mean=3.39) and Desire to Improve Science (mean=3.34), suggesting a need to further explore altruism, chronic illness, and clinical trials.

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APPENDICES

APPENDIX A

REVIEW OF THE LITERATURE

CLINICAL TRIALS

What is a Clinical Trial?

Before any medication can be put on the market, it must undergo a series of four intense trials to assess both safety and efficacy of the drug, as regulated by the Food and Drug Administration (FDA, 2004). These four phases of clinical trials are appropriately referred to as Phase I, Phase II, Phase III and Phase IV, and each serves a specific purpose in the process of obtaining drug approval and providing data for drug marketing and distribution. During Phase I research, the drug is typically introduced to a "healthy" human participant. This means that the participant has no known chronic or debilitating illness that could negatively interact with the medication. Each phase, including phase I is usually designed as a randomized control trial (RCT) in which participant and researcher are blinded to dosage level of the trial drug or whether they are put on placebo. Researchers use this phase to assess how the drug metabolizes in the system, pharmacological actions, any side effects, safe dosage ranges, and early signs of efficacy (www.clinicaltrials.gov, 2006). This initial stage is more focused on safety rather than on how well the drug works as it is introduced in the systems of otherwise healthy individuals, not symptomatic patients. Phase I studies usually last a few days, and are often conducted in hospital settings where researchers can closely monitor the participants in case of any medical emergencies. Phase I studies are conducted on a small sample of people, usually twenty to eighty participants scattered around the world (www.clinicaltrials.gov, 2006). Once the new drug has been deemed safe for human

consumption, it moves onto the next phase of testing.

Phase II clinical trials are controlled studies where the emphasis of testing moves from safety evaluations towards the efficacy of the new drug. This research is conducted on "symptomatic" participants who display the specific indications associated with conditions and illnesses the medication is designed to treat. During this phase researchers continue to closely assess the safety and short-term side effects of the medication even though it has passed the Phase I testing. This research is usually conducted through hospitals, physician's offices, and independent research centers in the United States as well as numerous countries worldwide. The number of participants enrolled in this research is still relatively small, usually one hundred to three hundred participants per drug trial. The number is kept small because the general safety is still being assessed in addition to efficacy, however the research is conducted using a longer timetable than was used in Phase I testing with ranges from days to years. Assuming a drug is shown to be safe and relatively effective, it moves into Phase III testing.

Phase III is similar to phase II with the intent of assessing overall efficacy and safety, but is conducted on a larger scale including more participants, usually between one thousand and three thousand. Again, studies can be conducted in hospital settings, physician's offices or through independent research facilities. Phase IV trials are conducted once the drug has been approved by the FDA and is available to the general public, and are aimed at improving general knowledge of the risk-benefit ratio of drug usage. During this time researchers continue to closely monitor drug efficacy and safety for the originally specified indications as well as for other indications.

Who are the Volunteers?

According to Lemonick and Goldstein (2002) in 2001 there were 80,000 clinical trials conducted world wide, involving over twenty million participants. In the United States most participants are Caucasian and between the ages of eighteen and sixty-five, though the research community has made significant efforts aimed at increasing the recruitment of racial and ethnic minorities (Anderson, D., 2004). Researchers suggest the lack of data on ethnic minorities may be based in part on an overall mistrust of the researchers' intentions (Sung, et al., 2003). There has also been limited information on children and elderly, as parents may be less willing to enroll their children in trials and elderly may be less willing to take health risks, but data suggests the trend is changing for the elderly. This may be linked to the increase in research on age-related illnesses as well as the rising healthcare costs for the elderly. The typical participant has a lower socio-economic status, earning on average 19% lower income and having less education than the average American. It is assumed the prospect of free medication and free healthcare may attract lower SES participants (Anderson, 2004).

A "healthy" volunteer participating in a Phase I study is typically characterized by age, sex, body weight, and body size. They are considered to be in good health with no identifiable medical conditions, which allows researchers to observe how the study medication reacts in the human body. However, some research suggests that in reality there is no "healthy" volunteer, that instead many who participate may have some undiagnosed physical condition, personality disorder, or psychopathology (Lasagna, L. and von Felsinger, J.M., 1954). For example Lasagna and von Felsinger (1954) reported that after completing a personality assessment and clinical interview, some "healthy

volunteers" appeared to experience severe psychosis, though authors did not expand on specific psychiatric illnesses the volunteers may have been experiencing. Follow-up data revealed that of the fifty-five participating subjects, at least two had been previously hospitalized for psychiatric reasons. Given the limited knowledge of the exact psychological diagnoses and the use of the poorly reliable Rorschach and psychological interview as the assessment tools, the findings from this study are limited in their generalizability. In 1993 in a study completed by Butler et al, eighty-one "normal" participants, who would typically qualify for participation in clinical trials, were given a series of psychological assessments including the MMPI-II, the Scale for the Assessment of Negative Symptoms, the Scale for the Assessment of Positive Symptoms, the Brief Psychiatric Rating Scales, the Hamilton Depression Rating Scale, SCL-90, Magical Ideation Scale, the Modified Michigan Alcoholism Screening Test, and a structured clinical interview to assess for psychosis and substance abuse. Results indicated that fifteen participants were substance abuse likely, nineteen were psychosis prone, and eight were psychosis prone and substance abuse likely. This data represents knowledge that pharmaceutical researchers would not have on their participants, as it is not standard practice to assess for mental illness or substance abuse. Interestingly, as in the Lasagna study, no specific mental illness such as depression, anxiety, etc was assessed, but rather an overall "psychosis" rating was given. Regardless, it is evident that there may be factors pharmaceutical companies are not taking into account in their drug research.

In addition to psychopathology, researchers have also examined personality traits found in phase I volunteers such as emotional control and stability, assertiveness, sociability, flexibility, self-reliance, initiative, and impulsivity (Garcia, et al., 1998). This

may be of critical importance to assess, as some pharmokenetic parameters have shown to be impacted by personality traits and emotional states, which will be discussed in greater detail further on (Claridge, G.S., Donald, J., and Birchall, P.M., 1981). Thus given the possibility of biologically influencing personality traits, researchers argue in addition to extensive medical tests, extensive psychological testing should be conducted on Phase I participants, and arguably, all phases of clinical trial participants including symptomatic volunteers.

A "symptomatic" volunteer possesses some medical condition that fits within the inclusion/exclusion criteria established in each individual trial. For example a person enrolled in a Phase II study for rheumatoid arthritis would have to meet criteria for a diagnosis for rheumatoid arthritis. And there are numerous studies testing rheumatoid arthritis medication, but each study may vary on criterion for inclusion/ exclusion such as disease severity, symptoms, smoking/alcohol use, etc. As implied above, there is not the same call for assessing the mental health and personality profiles of symptomatic participants in later phases of research, so researchers have little knowledge of the type of person participating in phase II, III, and IV trials outside of demographic and disease information. And though no explanation is given for this, one may assume there is still the potential for personality to impact the trial results, perhaps even more so that in phase I trials. As research has shown, personality may impact one's response to medication. If there are symptomatic patients testing new drugs, they may represent a subset of those with chronic illness, and thus may limit the generalizability of drug efficacy.

Potential Risks and Benefits

There is no denying the potential risk of participating in a clinical drug trial.

Given the fact that most trials are set up as RCTs, participants in latter phases may be placed on too low a dose to be medically effective or they may be placed on a placebo. This potential is an obvious source of concern for those experiencing an illness (Chen, et al., 2003). Being placed on a low dose or placebo could have a detrimental impact not only on one's initial and continued participation in a trial, but also their morale considering that research has identified hope and desperation as influencing factors in phase II and III volunteering (Lowton, K., 2005). It seems many participants expect they will receive new and "better" treatment than what has been offered in the past (Cami, J., et al., 1988). Ethical consideration has also been given to the notion of exploitation, as many trial participants have no health insurance and come from lower socio-economic backgrounds (Harth, et al., 1992, National Bioethics Advisory Board, 2001). There is also concern about physicians incorporating research into their private practices and the possibility of patient exploitation for their own financial gain (Lowton K., 2005).

It seems researchers will constantly be forced to confront these challenges due to regulations established by the FDA. Ways that researchers circumvent the perceived risks and ethical concerns include providing extensive informed consents on potential risks, opportunities to withdraw consent at any time, and safety measures for clients whose condition may deteriorate during the trial. For example, if a volunteer in an osteoporosis study continues to experience decreased bone density during the study, they would be pulled from the study and given medication that is already an approved treatment.

There are also benefits to participation worth mentioning. In a 2005 an article by N. Herbert-Croteau et al., reported breast cancer participants enrolled in clinical drug

trials showed significantly lower mortality rates than those treated by standard methods, though the exact reasoning for this was not explored. To researchers, this strengthens the belief that participating in trials may benefit people by providing the most up to date treatment methods. It also calls attention to the power of belief, as improvements are sometimes seen in volunteers placed on placebo. Buchi, S., et al. (1997) suggests that a willingness to participate in a clinical trial demonstrated an ability to better adjust and cope with chronic illness. This data came from a study looking at COPD patients who entered a trial rehabilitation program and displayed greater improvements in breathing and overall functioning than those receiving traditional treatment. While some criticize the use of low-income volunteers who do not have medication, the reality is that clinical trials provide the opportunity for people to receive medical attention and cutting edge treatments they may otherwise have been unable to afford. There are also the obvious incentives such as financial compensation and free healthcare for the duration of the study and often follow-up visits. But as will be shown, there is much more to one's decision to volunteer than free medication and healthcare.

Why Volunteer?

There have been many studies conducted over the last several years looking at the motivating factors for enrolling in a pharmaceutical trial when physical safety and health is potentially at risk (Garcia, et al., 1998, Ball, et al., 1993, Meyer, 2001, Chen, et al., 2003). Given the potential risks involved with volunteering it may not be surprising that most research as focused around why someone chooses to enroll in a Phase I trial, when healthy participants are asked to introduce a drug into their system that could cause at the minimum some form of physical discomfort or side effect, and at its worst potentially

lethality. The most commonly cited motivations for participation include financial incentives, free healthcare and medication, altruism, scientific interest/advancement of science, and personality characteristics such as attraction to risky activities (Cami, J., et al., 1988). Crumbo et al. (1997) cites personal and political reasons for participation in phase I HIV vaccine trials, with 73% of participants knowing someone who had AIDS or HIV. Unfortunately research on motivating factors behind participation in phase II and phase III testing, particularly personality factors, just isn't available.

In fact Karen Lowton (2005) points out there is no real understanding of how people from different diagnostic patient groups respond to requests for research participation, which participation is obviously necessary for all phase II, III, and IV trials. She attempted to begin answering those questions by looking at motivating factors of participants with cystic fibrosis, though results were limited at best. Thirty-one patients receiving treatment at a cystic fibrosis center and one hundred and eighty three other clinic patients were interviewed on topics such as health, quality of life, and beliefs about clinical trial participation. The data was then coded and analyzed. Her results showed volunteers were strongly influenced to participate by their current state of health, trial characteristics, and the social context. Given this was a qualitative study, it may be beneficial to quantitatively assess motivations, as well as patient characteristics to aid in increasing researcher knowledge of phase II and III participants.

So while many studies address participation in Phase I studies, researchers must start almost from the beginning when looking at the later phases. One may almost assume factors such as free medication and healthcare continue to be motivating factors in participation in later phases, but what about the other identified factors, specifically

personality? For the purposes of the current study, the research will focus on the influence of personality on participation in phase II and phase III clinical trials.

Personality and Clinical Trials

When examining data collected on Phase I volunteers, there is consensus that several factors influence one's decision to participate, including personality (Meyer, 2001). Personality traits identified in phase I participants typically include emotional control and stability, assertiveness, sociability, flexibility, self-reliance, initiative, and impulsivity (Garcia, et al., 1998, Ball, et al., 1993, Cami, et al., 1988). Cami, et al (1988), found elevated scores of extroversion and psychoticism as assessed by the Eysenck Personality Questionnaire (EPQ) in sixty-two male phase I volunteers. Results were compared to a control sample of ninety-six male college students who had similar sociocultural characteristics. Researchers infer the elevated psychoticism and extroversion suggests greater impulsivity and sociability, which could be used as predicting factors of clinical research participation. In contrast, Ball, C.J., et al (1993) assessed the personality structure of sixty-five phase I volunteers using the Eysenck Personality Questionnaire, in which results showed a pattern of increased extroversion, and decreased neuroticism and psychoticism. Ball, et al suggests the significantly low neuroticism and high extroversion may cause a higher threshold for thrill sensation, which may influence participation in clinical research and other potentially dangerous behaviors. These results were also present in a study by Eysenck and Eysenck (1975) in which healthy volunteers also demonstrated high extroversion and low neuroticism and psychoticism when given the EPQ. While the EPQ is a valid and reliable assessment, the research may be lacking given the limited information available, suggesting a more

comprehensive assessment such as the MIPS, 16PF and MMPI could be useful as researchers continue to expand their knowledge of clinical volunteers.

Again, the research is unavailable for participants in Phase II and III studies, with no discussion on why researchers see this to be of little importance. Only one study was located where research looked for presence of psychopathology and personality disorders in Phase II and III trials, but not overall personality traits (Barrett, J., 1981). In this case participants were found to have higher degrees of psychological issues including depression and anxiety than was accounted for in the clinical trial descriptions. For example instead of diagnosing depression, a participant was described as having some depressive symptoms, which did not give a clear picture of what those were. Authors argue diagnoses should be clear and explicit to aid in the generalizability of drug efficacy information.

Why would this information be important for researchers to know, especially those conducting clinical trials on new medications? One reason is that personality has repeatedly been shown to impact the absorption, biotransformation, and other pharmokenetic parameters of several medications (Tishler et al., 2003, Meyer, F.P., 2001). These include but are not limited to diazepam, caffeine, paracetamol, and theophylline (Meyer, F.P., 2001). Psychological and personality factors that have been shown to influence drug absorption include but are not limited to introversion/extroversion, levels of anxiety, and success/failure motivation. For example, extroversion and neuroticism are associated with high barbiturate threshold, and neuroticism is linked to high diazepam absorption (Claridge, G.S., Donald, J., and Birchall, P.M., 1981). However, Garcia et al. (1998) suggests the influence of

personality may not be as powerful as once believed, following a study analyzing emotional reactivity, performance, and vigilance in anxious and non-anxious volunteers. Researchers saw an increase in emotional reactivity, but no difference in performance and vigilance following emotional induction. The researchers inferred that personality might not be necessary to assess prior to research involvement, as it may not influence medication efficacy results. While researchers acknowledge this is a big conclusion to reach, it seems more research is needed in the area of personality/psychopathology and drug interaction.

Researchers also suggest that personality characteristics influence the reporting styles of the participants, not just the pharmokenetic parameters (Ball, C.J., McLaren, P.M., and Morrison, P.J., 1993). They suggest that personality traits may impact the frequency of reported side effects. Meyer (2001) reported that participants who scored high on anxiety scales had more complaints of side effects due to study medication, whereas participants who expressed less nervousness, emotional stability, and high motivation had fewer complaints. These reasons have influenced researchers to categorize more based on personality characteristics, motivation, and emotional state, but only in Phase I studies. It seems that researchers should especially be interested in obtaining personality information from phase II, III, and IV participants, given that personality has long been associated with the onset and progression of chronic illness.

The Future of Clinical Research

There is no denying the plethora of information available on Phase I research and participants, but there is an obvious lack of data on Phase II-IV participants. Possible explanations may be an assumption that the medication and healthcare are the obvious

motivators behind participation. Researchers may also ignore latter phases of clinical trials because they do not appear to carry the same risk potential as participation in a phase I study. However, safety is continually assessed with every phase, with the latter phases having the added goal of testing efficacy. There appears to be growing awareness that there are inconsistencies between personality characteristics found in research participants, and those found in people with chronic illness, i.e. Lowton's study on cystic fibrosis (1995). If one looks to research on specific illnesses, the need to assessment becomes even more apparent. For example people with Rheumatoid Arthritis and other chronic illnesses are often reported as being depressed, anxious, and dependent, a far cry from the extroverted low-neurotic profile of a phase I volunteer. Meyers (2001) calls attention to the fact that drugs will be used on people with complete opposite characteristics than phase I participants as reason to assess personality on phase I participants, yet fails to connect this to a need to assess personality in phase II studies. I argue that personality and other motivating factors influencing participation in Phase II and III are just as important as they are in Phase I, if not more so, as companies should gather data on the exact population they are trying to find cures for. Especially when considering the data that suggests personality influences drug action, pharmaceutical companies should look at all volunteers to improve drug knowledge, external validity, as well as recruitment strategies.

This may seem a challenging and daunting task, as it would involve researchers gathering personality information on every patient group, so this study will start with one: Rheumatoid Arthritis. Specifically this study will examine the personality characteristics of rheumatoid arthritic patients in phase II and phase III clinical trials, and the role

personality may play in one's decision to participate.

RHEUMATOID ARTHRITIS

What is Rheumatoid Arthritis?

Rheumatoid Arthritis (RA) is disease that causes inflammation of the joints that is not associated with injury or wear, as is osteoarthritis. Studies show that RA is the number one cause of disability in the United States, with nearly forty million people experiencing some form or symptom of arthritis (Mayo Clinic on Arthritis, 2002). These numbers have made finding a cure a priority for research institutions and pharmaceutical companies, which has proven very challenging, as there is currently no known cause or cure-all for rheumatoid arthritis.

Though the exact cause of the disease is unknown, it has been shown to have a genetic link and may be connected to an abnormal immune system. RA is thought to be an autoimmune disease in which the body starts attacking itself; specifically, antibodies attack the lining of the joints. The American Rheumatism Association established seven diagnostic criteria for rheumatoid arthritis, of which one must satisfy at least four or five for a definite diagnosis, and six to seven for a classical diagnosis (Arnett, F., et al, 1988). Those criteria include: morning stiffness, arthritis of three or more joint areas, arthritis of hand joints, symmetrical soft tissue joint swelling, subcutaneous rheumatoid nodules, radiographic changes to bones or joints, or a positive serum rheumatoid factor. Symptoms can also include pain and swelling in the joints of the hands, feet, wrists and ankles; aches and stiffness of joints and muscles; decreased mobility in diseased joints; deformity of affected joints; fatigue; nodules on hands, feet, elbows, knees and the scalp. The symptoms are generally chronic, but can come and go and vary in intensity over the

course of the disease. RA typically begins between the ages of 20-50, though can be present in children (referred to as juvenile arthritis). Diagnosticians classify patients according to stages, or disease progression, and classes, which describes the level of functional incapacity. Those classes are broken into four divisions: class 1- no functional impairment in daily living tasks; class 2- able to adequately function in normal life with minor impairment; class 3- limited function, but still able to engage in daily living tasks; class 4- unable to function independently.

There are many identified factors that influence the onset and progression of the disease including the environment, viruses, bacteria, fungi, gender, an imbalance of enzymes, stress/emotional trauma, and the focus of the current study, personality factors (Mayo Clinic, 2002). Cobb, B. et al., (1969) concluded that people with certain psychological characteristics, when exposed to the right environmental factors, will display physiologic responses associated with certain illnesses, i.e. rheumatoid arthritis. Oberai and Kirwan (1988) agree that pre-morbid personality may play a role in the development of RA, as unconscious or habitual patterns of coping may reflect a tendency to deny emotions and thus those individuals are more prone to somatic complaints. Some researchers argue there is no concrete way to determine if there are personality traits present before the onset of the illness, and therefore causality data should be considered inconclusive (Moos and Solomon, 1965; Anderson, et al, 1985). This considered, there is much agreement that personality plays a role in the course of illness and treatment efficacy.

Personality and Rheumatoid Arthritis

Research is lacking in the area of causality or whether there is a "rheumatoid

personality" that predisposes someone to the illness. The question still remains if these personality traits were present prior to the onset of rheumatoid arthritis or if they are a result of a painful and often disabling disease. Therefore research conducted looking at personality profiles of arthritics should be used with caution. Data may also be flawed based on sampling errors, assessment selection, etc (Nalven, F.B and O'Brien, J.F., 1968, Moos and Solomon, 1966, Anderson et al, 1985). Much of the data on personality and arthritis is dated backing the fifties, with research conducted from several theoretical approaches ranging from psychoanalytic to behaviorally focused, but mostly relying on heavily psychoanalytical assessment. For example several researchers relied on assessments such as the Rorschach or psychoanalysis, in which results may have been influenced by subjective interpretations. Others have taken fully validated and reputable assessments such as the MMPI and created their own assessment tools, which decreased validity, reliability, and generalizability. Many studies also used instruments such as the MMPI, which are better suited to assess psychopathology, not normal personality characteristics. In fact there is little differentiation within the literature between state/trait personality factors, and psychopathology.

Studies in the past have had difficulty determining control variables to represent the closest match to the experimental sample in studies of psychosomatic illnesses such as rheumatoid arthritis and hypertension (Hardyck and Moos, 1966). They suggest that even with control groups, researchers will find widely differing personality characteristics. Rarely are rheumatic participants compared to other chronic illness groups or other rheumatic groups, and the use of otherwise healthy people as control groups may influence finding significant results. Researchers suggest that there is no

specific match that can truly account for familial, socioeconomic, age, gender, educational, and other environmental differences that have been identified as influential in the course of illness in arthritic patients, though unfortunately that is a flaw common in most research. Therefore research studies designed to establish personality profiles specifically in psychosomatic patient samples are potentially obsolete. Some researchers have chosen to compare family members, as they share the closest match in psychological and sociological factors that have been linked to the onset and progression of rheumatoid arthritis. Others have attempted to match on disease severity and course of illness, which is what is proposed for the current study, as control and experimental group will match on disease severity and functional mobility. Research complications aside, there is a plethora of important research on personality and rheumatoid arthritis of which the following details:

Dating back to 1909, the relationship between personality and rheumatoid arthritis has been well researched, though the exact nature of this relationship still is not clear (Moos, H.D., and Solomon, G.F., 1964; Robinson, et al., 1972; Hardyck, C., and Moos, H.D., 1966; Moos, H.D., and Solomon, G.F., 1965). For example, many have tried to establish a "rheumatoid personality" that may suggest a predisposition to the illness. Those personality traits linked with rheumatoid arthritis have included subservience, nervousness, restlessness, depression, conservatism, and hypersensitivity to anger (Moos and Solomon, 1964). There is significant debate about whether or not personality traits associated with rheumatoid arthritis were present prior to or after disease onset, which unfortunately may never be known, as it would be near impossible to predict who will later develop the disease and thus provide opportunities to assess personality prior and

following disease onset. There is also significant debate about what those personality traits found in people with rheumatoid arthritis are, and how those results were determined. For example much of the research out there dates back to before 1970, and assessments relied heavily on projective measurements and investigator inferences. In an article reviewing rheumatoid arthritis/personality research written by Rudolph Moos (1964) it was stated that much of the research conducted before 1963 did not include the use of control subjects, as well as utilized a very strong psychoanalytic approach to study design and interpretation. Overall common results included a tendency to over-somaticize and reflect personality traits such as rigidity and conformity. Though researchers all had similar findings, results can only be generalized so far without proper control and design. Others still argue that there is in fact no "rheumatoid personality," but rather a "chronic illness personality" that develops following the onset of any illness. Anderson et al (1985) describes the chronic illness personality as depressed and neurotic. In a 1988 study by Antonio Puente comparing MMPI scores of chronic arthritics to chronic pain patients similar in SES, educational level and sex, no significant differences in personality profiles were detected. This study is limited by the low number of participants (twenty-two in each control and experimental group). It is also limited by the use of the MMPI that, while widely used as a personality assessment, emphasizes more psychopathology and less personality description. These obvious discrepancies necessitate further exploration into the research to explore critical errors that may compromise earlier findings and conclusions regarding the nature of the relationship between personality and rheumatoid arthritis.

Moos and Solomon conducted several studies in the 1960's as part of a

longitudinal study looking at rheumatoid arthritis and personality factors. One such study compared personalities of sixteen arthritic patients to their closest-aged, same-sexed, healthy, non-arthritic siblings (1965). The researchers saw this as an opportunity to control for influential background factors including age, sex, and parent's occupational status. Moos and Solomon assessed specific personality traits including dependency, physical activity, masochism, nervousness, and depression through the use of the Minnesota Multiphasic Personality Inventory (MMPI), a semi-structured interview, and a specially constructed personality test the incorporated results from previous research in the field of personality and rheumatoid arthritis. Results from the MMPI and the devised assessment showed significant differences on the compliance/subservient, nervous/restless, depression, conservatism/security, and sensitivity to anger scales. Contradicting previous research, Moos and Solomon did not find significant differences in dependency, interest in physical activity, or duty-orientation and conscientiousness. There were no significant findings supported by all three assessments.

Looking at this study from a critical standpoint, several factors appear to impact the validity of this study. First, scales were rationally derived from the MMPI, which may negatively impact the validity, reliability, and generalizability of the results. As the researchers themselves pointed out, there were no statistical analyses conducted between assessments, which may have strengthened or weakened their findings. A glaring limitation to this study is the lack of subjects, with only 16 sibling pairs providing data, all of who were women. Interestingly, results from medical exams required for participation revealed several of the "healthy" siblings had characteristics associated with latent rheumatoid arthritis, which was not included as a control factor. It appears that

researchers did not see this as a necessary control variable as they did not present with somatic complaints as the rheumatic siblings did. However, this may be an important variable to consider, as part of the underlying research goal of their longitudinal research is to determine the exact relationship between personality and rheumatoid arthritis (i.e. causality, onset, impact on disease progression).

Taking the results from this study, Moos and Solomon (1964) attempted to generalize their findings to a larger experimental group. In this study forty-nine female rheumatic patients and fifty-three of their "healthy" female family members completed the MMPI. As in the previous study, eleven scales were rationally derived from specific questions on the MMPI. In this study however, the nine clinical scales and three validation scales were also used. Results showed the rheumatic siblings were elevated on the hypochondriasis, depression, and hysteria scales. These results appear to match data collected on chronic illness suffers, suggesting rheumatoid arthritics share similar experiences such as over-somatization, self-sacrifice, masochism, rigidity, conformance, and perfectionism (Cohen, 1949). Moos and Solomon infer that emotional suppression, especially suppression of anger, may lead to muscle tension and thus increased joint pressure, pain, and joint damage, linking personality with the onset and progression of the disease. While this study increased the number of participants, it is still hampered, as in the previous study, by the presence of latent rheumatic symptoms in the "healthy" volunteers. The results are also limited by the use of only female participants as well as the questionable validity of the derived MMPI scales. This study does, however, present with solid quantifiable results from a valid assessment that reflects a difference in personality traits between rheumatic patients and a healthy control sample. Moos

previously critiqued researchers' failure to assess and incorporate socio-economic status information into research. While parent's occupational status and age were assessed, no statistical analyses were conducted to explore the impact these factors may have on results. And while these two articles represent data obtained from long-term studies, no chronological data was collected from participant groups over a long period of time. Some may argue that this may not be necessary as personality traits are inherent and therefore consistent across time, but there is no research that supports this throughout the course of this chronic and often debilitating illness.

Personality and the Course of Illness

Though the exact mechanisms are unclear, it is accepted that personality factors in addition to biomedical factors have long-term effects on the course of illness. Robinson, et al (1972) sought to clarify the relationship between personality and disease progression in a study comparing forty-one chronically ill patients with rheumatoid arthritis, osteoarthritis, and other non-arthritic chronic pain illnesses. Robinson and colleagues questioned the role of personality and disease progression in rheumatoid arthritis compared to other non-arthritic chronic pain illnesses to determine if personality characteristics such as anxiety and depression evolve over time as illnesses progress. The chronically ill participants were identified as new arthritis (NRA), old arthritis (ORA), and new pain or old pain patients. The goal of the study was to identify personality factors associated with various stages of arthritis, and whether these factors are associated only with arthritis and therefore contribute to disease onset and progression, or whether results represent personality patterns seen in the onset of other chronic pain illnesses and therefore represent a generic chronic illness pattern of personality responses. Personality

traits were assessed using Cattell's 16PF, as well as the Eysenck Personality Inventory (EPI). Results showed near statistical significance on overall differences between NRA and ORA. This contradicted the author's hypothesis, which was that NRA and ORA scores would be highly similar. NRA and other pain groups exhibited greater anxiety scores. The authors suggest this does not reflect a consistent personality profile for RA patients, but rather a pattern of variability on single scales (for example overly suppressing anger or overly expressing anger). Statistically the results are not strong given the lack of participants, with an average of ten participants per group. However this study does suggest the need to further explore the relationship of rheumatoid arthritis to other chronic illnesses, particularly in the popular field of personality research.

In much of their research, Moos et al., (1963, 1964,1965) also sought to establish the relationship between personality factors and the course of illness. When controlling for stage of illness, researchers saw differences in functional capacity, which they attribute to personality differences (Moos, R.H. and Solomon, G.F., 1964). Participants who displayed poor functioning displayed greater introversion, depression, social isolation, anxiety, anger, fear, and insufficient coping skills, while higher functioning individuals displayed more extroversion, greater coping skills, etc. Moos and Solomon also hypothesized that "negative" personality traits could be potentially harmful, as they may intensify the crippling effects of rheumatoid arthritis. They determined that anxiety and neuroticism might increase risk of arthritic flares or increase joint pain and stiffness, fatigue, and swelling (Moos, 1964). In one study forty-nine arthritic women were classified by stage of disease progression (one through four with one being early stage and four being late stage RA), and class of functional incapacity (with one being little

incapacitation to four being very incapacitated) (Moos, R.H. and Solomon, G.F., 1964). From this group two subgroups were picked for study participation. These groups consisted of women whose degree of functional incapacity was higher than disease progression (n=11) and a second group of participants who presented with greater disease progression than functional incapacitation (n=18). The researchers attempted to match for disease progression and duration of illness, but were not successful given the limited number of participants. Each group was then given a demographic questionnaire and the MMPI. The demographic questionnaire allowed researchers to control for age, education, marital status, number of children and occupational class. The MMPI analyses included rationally derived scales used in their previous research (Moos and Solomon, 1964; Moos et al 1963). Using T-tests to compare results of the two groups responses showed 32.9% significance at the 0.01 level, indicating a there were significantly different response patterns between the two groups. Results showed that participants who were functioning below their disease stage would exhibit acute distress and an inability to cope. Results also suggest they experience greater shyness, introversion, alienation, and decreased social participation. The group that functioned equal to or better than their disease stage would suggest exhibited less depression and apathy, and greater motivation.

From this study researchers hypothesized that successful rehabilitation could be determined by psychological characteristics prior to the beginning of rehabilitation. Therefore successful rehabilitation may also require psychological interventions to help overcome the personality traits that may interfere. According to Moos and Solomon, these findings may also suggest rheumatoid arthritics are not a homogeneous group, and

therefore may not present with a solid personality profile from which to make comparisons of the group as a whole. They also suggest the importance of controlling for stage, class, and duration of illness when conducting personality studies. Critically this study is discredited some by the size of the sample groups (n=11, n=18). The statistical analysis is questionable considering the use of rationally derived scales instead of the validated MMPI scales. While the researchers assessed age, education, etc., no analyses represented these differences. However, this article adds credence the question of whether people with chronic illnesses participate in clinical trials out of desperation or whether they represent a subgroup within RA of people who are better able to function as they are willing to look outside the box of traditional and established treatment.

Langley, et al (1983) conducted a study examining the effects of placebo therapy in rheumatoid arthritis and found that rheumatic patients experiencing anxiety are more prone to pain, yet respond more positively to placebo. In this study pain was assessed daily for twenty-five days in twenty-three participants with rheumatoid arthritis. All participants were given a placebo the last nine days, with the first sixteen days serving as a baseline pain provider. The Eysenck Personality Inventory was completed prior the beginning of the study. Results show that introverted participants showed no change in pain response (i.e. did not report improvements or decline in pain). Neuroticism was higher in participants who reported side effects. The study is obviously limited by the low number of participants (final n=18), but findings still pose an interesting question about the role of anxiety in medical treatment. In this study, high neuroticism scores were reflected in those who reported negative side effects, and those who reported improvement. This has several implications for the medical field in addition to the

pharmaceutical research field, as personality may influence drug response data.

Personality also impacts the course of illness in such a way that if a person experiences high anxiety and fear, they may be less likely to engage in physical activity for fear of pain or permanent damage. The lack of physical activity actually leads to greater impaired functioning. Brooks and McFarlane (1983) also found that psychological factors predicted more variance in disability than disease activity. And while the personality traits do not directly cause functional decline, evidence suggests they may impact one's response to medication. McLaughlin, et al (1953) states that personality differences in arthritic patients impacted patients' responses to a number of different medications, but particularly ACTH. In an exploratory study looking at men and women diagnosed with RA, stress and anxiety were found to negate any positive reaction to treatment. Limitations to this study include the limitations in assessment and diagnosis of personality/psychological traits, suggesting the study should be replicated using modern assessment and treatment interventions.

Latman and Walls (1996) established a relationship between stress and the onset of rheumatoid arthritis. In this study 128 participants diagnosed with classical or definite arthritis and 79 participants diagnosed with osteoarthritis were asked to complete Cattell's 16PF and the Social Readjustment Scale of Holmes and Rahe which assesses any stressful life events at the age of disease onset. Examples of stressful events include loss of a family member or spouse, marital discord, problems at work, financial troubles, pregnancy, illness, and interpersonal conflicts (Booth, 1937). Results showed that RA patients experienced greater stress at the time of disease onset. And though a causal relationship was not established, participants with rheumatoid arthritis experienced

stressful events at the time of disease onset tended to display greater disease and symptom severity as opposed to participants with osteoarthritis. There was no statistical difference between personality scores between RA and OA, however RA participants tended to exhibit greater anxiety and seriousness. This may reflect the relationship between anxiety/neurosis and disease progression, as one may be more susceptible to anxiety during difficult life events. This study may have erred by not using a healthy control group, as OA can be pain and debilitating just as RA. However, it is possible that type of data may lend credit to the chronic illness personality hypothesis versus the rheumatoid personality.

Lowman, E.W., et al (1954) showed that personality factors leading to successful RA rehabilitation included independence, a realistic outlook, emotional control, and pleasure seeking behaviors. This suggests that treatment and rehabilitation success could be predicted by personality traits, and has led to an increase in research studying the impact of psychotherapy in treatment, which has shown great success (Bradley, et al., 1987). In a study looking at 53 patients with RA, pain, anxiety, and disease activity were reduced when treatment included psychotherapy.

CLINICAL TRIALS AND RHEUMATOID ARTHRITIS

As the research suggests, there is debate about whether or not a rheumatoid personality exists. There is substantial evidence, however, that suggests the personality styles play a role in disease onset and progression. Given the role personality plays in disease progression, it is not a stretch to question whether there are there similar personality characteristics at work that influence one to seek alternative treatments such as participating in clinical trials. So the presenting question is: how do personality styles

in participants in rheumatoid arthritis clinical trials compare against personality features in those who do not participate in clinical trials? Are personality styles of participants reflective of the extroverted, independent Phase I volunteer, or do the styles match those commonly seen in chronically ill arthritic patients? Participating in a trial may be seen as a willingness to explore alternative options, an openness to new experiences, which is in line with the research conducted on stage I participants that suggests an openness to new experiences, low anxiety, and independence. However coping with a chronic illness has been shown to negatively impact personality and psychopathology. The personality of a rheumatic clinical trial participant could skew the drug efficacy data, as higher anxiety and introversion are linked to greater somatic complaints as well as biomedical drug interactions.

It is also important to consider the impact of SES, as Koster, et al. (2004) associated low SES and low education with functional mobility decline and physical disabilities in the chronically ill, including rheumatoid arthritis. Data reports that participants in clinical trials typically come from lower SES. The pharmaceutical companies do not appear to control for SES when running trials, just as they do not control for personality traits. To answer these and other questions there appears to be no doubt of the importance for researchers to assess personality in all phases of clinical trials, not just phase I. Therefore it is the purpose of the present study to examine personality characteristics of rheumatoid arthritic participants in phase II and phase III clinical trials. In addition, the present study will account for variables including socio-economic status, education, motivation for participation in the clinical trial, gender, and race. Despite the lack of information in this area, it is hypothesized that personality

profiles of rheumatoid arthritics who participate in later phase clinical trials will more closely resemble those of phase I participants than that of a typical arthritic. Specifically it is hypothesized clinical trial participants will display greater extroversion, openness to new experiences, independence, and less anxiety. If this hypothesis is accurate, the implications for pharmaceutical research could be tremendous, as it research has already shown personality may impact how drugs react in the body. If there is a specific personality type that engages in pharmaceutical research, all medical data may be skewed or inaccurate, as the results would not reflect how medication reacts in the general population.

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APPENDIX B

Demographic Questionnaire

Please circle the answer that best fits you:

1. Age :_____

2. Annual Household Income: **A**. Under $15,000 **B**. $15,000-30,000 **C**. $30,000-45,000 **D.** $45,000-60,000 **E.** $60,000+

3. Highest Level of Education:

   A. Did not complete high school **B.** High school/GED **C.** Some college/technical

   D. College/Technical Degree **E.** Graduate School

4. Race/Ethnicity:

   A. Caucasian **B.** African American **C.** Hispanic/Latino **D.** Asian/Pacific Islander

   E. Native American **F.** Other: _____

5. Do you have health insurance? **A.** Yes **B**. No

6. Are you currently employed? **A.** Yes **B**. No

7. Do you receive Medicaid/Medicare? **A.** Yes **B**. No

8. Have you ever participated in a pharmaceutical trial not related to Rheumatoid Arthritis?
   Yes **No** If yes, please describe what for: _____

9. If you answered yes to #8 or if you are currently enrolled in a clinical trial for rheumatoid arthritis, please answer the following question. Provided below are commonly reported reasons for participating in clinical trials. Please rank on a scale from 1 to 5 how these factors influenced your decision to participate in a clinical trial.

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
A. Free healthcare/medication	1	2	3	4	5
B. To help others	1	2	3	4	5
C. To improve science	1	2	3	4	5
D. Financial compensation	1	2	3	4	5
E. My doctor recommended it	1	2	3	4	5
F. Previous treatment was not effective	1	2	3	4	5

APPENDIX C

Understanding Personality Styles of Participants in Phase II and III Rheumatoid Arthritis Clinical Trials

INFORMED CONSENT

In this study the researcher, Elisabeth Riccardi, is looking at personality characteristics of people with Rheumatoid Arthritis who choose to participate in Phase II and Phase III clinical drug trials. Elisabeth, a doctoral student in the counseling psychology program, is conducting the project through Oklahoma State University. Participants will be asked to fill out two documents. One is a demographic questionnaire; the other is the Millon Inventory of Personality Styles Revised (MIPS), a general personality inventory. This should take no more than 45 minutes to complete. No identifying information will be requested, so confidentiality of responses will be protected.

The records of this study will be kept confidential. Research records will be stored securely here onsite, and only researchers and individuals responsible for research oversight will have access to the records. It is possible that the consent process and data collection will be observed by research oversight staff responsible for safeguarding the rights and well-being of people who participate in research. Once all surveys are completed, the researcher will collect the records. At that time the records will continue to be kept in a locked cabinet under the researcher's care while the data is recorded and analyzed. Once analysis in complete, all records will be shredded and disposed of properly so as to continue to protect confidentiality. Any written results will discuss group findings and will not include information that will identify you.

There are no foreseeable discomforts that will arise from participating in the study, however if this occurs, it is recommended that you seek the help of a mental health professional. There is no obligation to participate in this study, but if you choose to participate, you have the opportunity to enter a drawing for one of four $25 dollar gift certificates. If you choose to enter your name for the drawing, the name will be kept separate from the responses, thus still maintaining confidentiality.

If you have any questions regarding your participation in this study, please contact Elisabeth Riccardi at Elisabeth.Riccardi@gmail.com, or her advisor, Don Boswell, PhD., at don.boswell@okstate.edu. If you have questions about the research and your rights as a research volunteer, you may also contact Dr. Shelia Kennison, IRB Chair, 219 Cordell North, Stillwater, OK 74078, 405-744-1676 or irb@okstate.edu.

I have read and fully understand the consent form. I sign it freely and voluntarily. A copy of this form has been given to me.

_____ _____

Signature of Participant Date

I certify that I have personally explained this document before requesting that the participant sign it.

_____ _____

Project Director or authorized representative Date

APPENDIX D

Solicitation Script

Hello. A counseling student from Oklahoma State University, Elisabeth Riccardi, is conducting a study here at our office as part of her doctoral training. She is studying personality styles in patients with rheumatoid arthritis and patients who participate in clinical drug trials, and is looking for participants to complete a one-time only survey study. Participation is completely voluntary, and if you would like to participate, you will be asked to read and sign an informed consent and then complete a brief demographic survey and personality survey. All information will be kept confidential, and the entire process should take no more than 30-45 minutes to complete. If you choose to participate you also may enter your name into a drawing for one of four $25 gift certificates, which will be drawn once all data in collected, probably in July or August. Again, you are not required to participate; this is completely voluntary. Would you be interested in filling out the surveys today?

APPENDIX E

Oklahoma State University Institutional Review Board

Date:	Thursday, May 22, 2008
IRB Application No	ED0865
Proposal Title:	Understanding Personality Styles of Participants in Phase II and III Rheumatoid Arthritis Clinical Trials
Reviewed and Processed as:	Expedited

Status Recommended by Reviewer(s): Approved Protocol Expires: 5/21/2009

Principal Investigator(s):

Elisabeth Riccardi
11433 Heritage Green Dr.
Cornelius, NC 28031

Donald Boswell
406 Willard
Stillwater, OK 74078

The IRB application referenced above has been approved. It is the judgment of the reviewers that the rights and welfare of individuals who may be asked to participate in this study will be respected, and that the research will be conducted in a manner consistent with the IRB requirements as outlined in section 45 CFR 46.

☒ The final versions of any printed recruitment, consent and assent documents bearing the IRB approval stamp are attached to this letter. These are the versions that must be used during the study.

As Principal Investigator, it is your responsibility to do the following:

1. Conduct this study exactly as it has been approved. Any modifications to the research protocol must be submitted with the appropriate signatures for IRB approval.
2. Submit a request for continuation if the study extends beyond the approval period of one calendar year. This continuation must receive IRB review and approval before the research can continue.
3. Report any adverse events to the IRB Chair promptly. Adverse events are those which are unanticipated and impact the subjects during the course of this research; and
4. Notify the IRB office in writing when your research project is complete.

Please note that approved protocols are subject to monitoring by the IRB and that the IRB office has the authority to inspect research records associated with this protocol at any time. If you have questions about the IRB procedures or need any assistance from the Board, please contact Beth McTernan in 219 Cordell North (phone: 405-744-5700, beth.mcternan@okstate.edu).

Sincerely,

Shelia Kennison, Chair
Institutional Review Board

VITA

Elisabeth Ann Riccardi

Candidate for the Degree of

Doctor of Philosophy

Thesis: UNDERSTANDING PERSONALITY STYLES OF WOMEN IN PHASE II AND III RHEUMATOID ARTHRITIS CLINICAL TRIALS

Major Field: Counseling Psychology

Biographical:

Personal Data: Born in Columbus, Mississippi on September 2, 1980; the daughter of Ralph and Janet Riccardi

Education: Bachelor of Arts degree in Psychology, Magna Cum Laude, from The University of Oklahoma, Norman, Oklahoma in May of 2002. Completed the requirements for the Doctor of Philosophy degree with a major in Counseling Psychology at Oklahoma State University, Stillwater, Oklahoma in December 2008.

Experience: Experience in Community Mental Health, University Counseling Services, and Adolescent Psychology. Completed APA accredited internship at the University Counseling and Psychological Services Center, Appalachian State University, Boone, North Carolina.

Professional Memberships: American Psychological Association, North Carolina Psychological Association

Name: Elisabeth Ann Riccardi Date of Degree: December, 2008

Institution: Oklahoma State University Location: Stillwater, Oklahoma

Title of Study: UNDERSTANDING PERSONALITY STYLES OF WOMEN IN PHASE II AND III RHEUMATOID ARTHRITIS CLINICAL TRIALS

Pages in Study: 65 Candidate for the Degree of Doctor of Philosophy

Major Field: Counseling Psychology

Scope and Method of Study: The purpose of the current study was to explore personality styles that may influence someone with a chronic illness to participate in a Phase II or III clinical drug trial related to that specific illness. Forty-four female patients diagnosed with Rheumatoid Arthritis who were enrolled in a pharmaceutical drug trial (CT-Participants) and thirty-eight female patients diagnosed with Rheumatoid Arthritis who were not enrolled in a drug trial (NCT-Participants) were asked to complete a demographic questionnaire and the Millon Index of Personality Styles-Revised (MIPS-R). The MIPS-R was used to measure the presence of personality traits identified as contributing factors to participation in Phase I trials including: openness to new experiences, low anxiety, extroversion, and independence. The demographic questionnaire assessed age, race/ethnicity, annual household income, level of education, and access to healthcare, Medicaid, and Medicare.

Findings and Conclusions: Demographically the two groups were statistically matched on age, level of education, annual household income, and access to Medicaid/Medicare. The two groups differed significantly on access to health insurance. There was a significant difference between the two groups on the Conservation-Seeking scale indicating a tendency for the NCT-Participant group to exhibit more traditional and conservative behaviors, and thus less open to new experiences. The CT-Participants and NCT-Participants matched on all other scales including Introversion/Extroversion, Submissive/Yielding, Innovation-Seeking, and Anxious/Hesitating, Confident/Asserting, and Dominant/Controlling scales, indicating those who participate in clinical drug trials share personality traits commonly associated with Rheumatoid Arthritis.

Advisor's Approval Dr. Don Boswell