

Reproductive Medicine Network

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Males, Antioxidants, and Infertility (MOXI) Trial

Protocol Leader: Anne Z. Steiner, MD, MPH

Data and Coordination Leader: Heping Zhang, PhD

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Prepared by:

The RMN Data Coordination Center

Collaborative Center for Statistics in Science

Yale University School of Public Health

300 George Street, Suite 523

New Haven, CT 06511

(203) 785-5185

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Protocol Subcommittee

Group email address: rmn.moxi@mailman.yale.edu

Name	E-mail
Anne Z. Steiner, MD, MPH	anne_steiner@med.unc.edu
Matt Coward, MD	mccoward@med.unc.edu
Esther Eisenberg, MD, MPH	eisenbes@mail.nih.gov
Stephen A. Krawetz, PhD	steve@compbio.med.wayne.edu
Puneet Masson, MD	Puneet.Masson@uphs.upenn.edu
Nanette Santoro, MD	nanette.santoro@ucdenver.edu
Jim Smith, MD, MS	SmithJF@urology.ucsf.edu
Peter Snyder, MD	pjs@mail.med.upenn.edu
J. C. Trussell, MD	jctrussell1@verizon.net
Heping Zhang, PhD	heping.zhang@yale.edu

Table of Contents

1	ACRONYMS	6
2	STUDY SYNOPSIS.....	8
2.1	OBJECTIVES	8
2.2	PATIENT POPULATION	8
2.3	STUDY DESIGN	8
2.4	TREATMENT	8
2.5	PRIMARY OUTCOME	9
2.6	SECONDARY OUTCOME	9
2.7	INTERNAL PILOT	9
2.8	STATISTICAL ANALYSIS	9
2.9	REGULATORY COMPLIANCE.....	10
3	BACKGROUND AND SIGNIFICANCE.....	11
3.1	BACKGROUND.....	11
3.2	SIGNIFICANCE	13
3.3	INNOVATION	14
4	OBJECTIVES.....	15
4.1	PRIMARY AIM	15
4.2	SECONDARY AIM	15
4.3	TERTIARY AIMS	15
4.4	INTERNAL PILOT	15
5	STUDY DESIGN	17
5.1	OVERVIEW AND SCHEMA	17
5.2	STUDY POPULATION	18
5.2.1	<i>Inclusion Criteria</i>	<i>18</i>
5.2.2	<i>Exclusion Criteria</i>	<i>18</i>
5.2.3	<i>Study Termination Criteria.....</i>	<i>19</i>
5.2.4	<i>Rationale for Criteria</i>	<i>19</i>
5.3	RECRUITMENT.....	20
5.4	SCREENING	21
5.5	INFORMED CONSENT.....	21
5.6	TREATMENT PROTOCOLS	22
5.6.1	<i>Antioxidant formulation.....</i>	<i>22</i>
5.6.2	<i>Placebo.....</i>	<i>24</i>
5.6.3	<i>Manufacturing of ConceptionXR and Quality Control.....</i>	<i>24</i>
5.6.4	<i>Distribution</i>	<i>24</i>
5.7	STUDY FLOW:	25
5.7.1	<i>Screening:.....</i>	<i>25</i>
5.7.2	<i>Study treatment visit 1 (males only):</i>	<i>26</i>
5.7.3	<i>Study treatment visit 2 (males only):</i>	<i>27</i>
5.7.4	<i>Study treatment visit 3 (males only):</i>	<i>27</i>
5.7.5	<i>Clomid and IUI cycles (couple):.....</i>	<i>28</i>
5.7.6	<i>Study visit 4 (males only):</i>	<i>31</i>
5.7.7	<i>Pregnancy ultrasound(s):</i>	<i>31</i>
5.7.8	<i>20-week contact:.....</i>	<i>31</i>
5.7.9	<i>Pregnancy outcome:.....</i>	<i>31</i>
6	DATA COLLECTION.....	32

6.1 SPECIMEN COLLECTION, PROCESSING, AND SHIPMENT32

 6.1.1 Semen Collection32

 6.1.2 Semen analysis.....33

 6.1.3 DNA integrity testing.....33

 6.1.4 SCSA.....33

 6.1.5 TUNEL.....33

 6.1.6 COMET34

6.2 COMPLIANCE34

 6.2.1 Measurement of vitamin levels34

6.3 DIETARY ASSESSMENT34

6.4 MALE URINARY TESTING FOR ENVIRONMENTAL CONTAMINANTS35

6.5 STRESS BIOMARKER TESTING35

6.6 MALE LABORATORY TESTING (CENTRAL CORE LABORATORY).....35

6.7 MALE SUNSCREEN USAGE36

6.8 QUALITY OF LIFE (QOL) MEASURES36

6.9 EARLY PREGNANCY ULTRASOUND36

6.10 ASCERTAINMENT OF PREGNANCY OUTCOMES37

6.11 PREGNANCY REGISTRY37

6.12 BIOLOGIC REPOSITORY37

6.13 CENTRAL CORE LABORATORY37

7 DATA ANALYSIS38

7.1 INTERNAL PILOT38

7.2 PRIMARY AND SECONDARY OUTCOMES.....39

7.3 SAMPLE SIZE AND STATISTICAL POWER39

8 TECHNICAL ASPECTS.....42

8.1 REPORTING ADVERSE EVENTS42

8.2 DATA COLLECTION AND MANAGEMENT (INCLUDING QUALITY ASSURANCE/COMPLIANCE MEASURES).....45

 8.2.1 Data Entry and Forms.....45

 8.2.2 Features of Data Management System45

 8.2.3 Data Security.....45

 8.2.4 Data Quality Control.....45

8.3 STUDY MONITORING.....46

8.4 DATA AND SAFETY MONITORING BOARD47

8.5 REPORTING48

8.6 OBLIGATION OF THE INVESTIGATOR48

 8.6.1 IRB Review48

 8.6.2 Maintenance/Retention of site records48

8.7 REGULATORY REQUIREMENTS.....49

8.8 PROTOCOL AMENDMENTS.....49

8.9 TIMELINE50

9 RMN PUBLICATIONS POLICY.....51

9.1 MAIN STUDY51

 9.1.1 Major Publications.....51

 9.1.2 Minor Publications.....54

9.2 ANCILLARY STUDY55

 9.2.1 Publication Policy on Ancillary Papers55

9.3 PILOT STUDY56

9.4 RELATED PUBLICATIONS.....57

9.5 OUTSIDE STUDIES57

9.6 PRESENTATIONS.....57

9.7 TIMELINES58

9.8 NICHD CLEARANCE.....58

10 REFERENCES59

11 INFORMED CONSENT65

11.1 INFORMED CONSENT TEMPLATE – MALE PARTNERS65

11.2 INFORMED CONSENT TEMPLATE – FEMALE PARTNERS.....83

12 APPENDIX A: MALE MEDICAL HISTORY QUESTIONNAIRE.....101

13 APPENDIX B: FEMALE MEDICAL HISTORY QUESTIONNAIRE116

14 APPENDIX C: LIST OF PROHIBITED CONCOMITANT MEDICATIONS131

15 APPENDIX D: REVIEW OF ANTIOXIDANT FORMULATIONS134

15.1 COMMERCIALY AVAILABLE FORMULATIONS134

15.2 RESEARCH FORMULATIONS135

16 APPENDIX E: RISK FACTORS FOR GENETIC DISORDERS.....138

17 APPENDIX F: FEMALE SEXUAL FUNCTION INDEX (FSFI)140

18 APPENDIX G: SF-12V2 HEALTH SURVEY145

19 APPENDIX H: PATIENT HEALTH QUESTIONNAIRE (PHQ-9).....148

20 APPENDIX I: FERTIQOL150

21 APPENDIX J: EPWORTH SLEEPINESS SCALE.....151

22 APPENDIX K: STOP BANG QUESTIONNAIRE152

23 APPENDIX L: FEMALE SEXUAL DISTRESS SCALE (FSDS- REVISED 2005).....153

24 APPENDIX M: INTERNATIONAL INDEX OF ERECTILE FUNCTION (IIEF)154

25 APPENDIX N: DIET HISTORY QUESTIONNAIRE II157

26 APPENDIX O: AUTOMATED SELF-ADMINISTERED 24-HOUR RECALL (ASA24).....197

27 APPENDIX P: QADAM QUESTIONNAIRE208

28 APPENDIX Q: PSYCHOSEXUAL DAILY QUESTIONNAIRE.....209

29 APPENDIX R: SUN EXPOSURE AND BEHAVIOUR INVENTORY (SEBI V2).....210

30 APPENDIX S: INVESTIGATOR SIGNATURE OF AGREEMENT214

31 APPENDIX T: DATA AND SAFETY MONITORING PLAN.....215

Figure 1: Schema for the Participation Timeline..... 17

Figure 2: SAE flowchart 44

Table 1: Overview of Timing and Content of Data Collection for Primary Cohort..... 32

Table 2: Sample size estimates under a variety of assumptions 40

Table 3: Power for subgroup analyses 40

Table 4: Types of Serious Adverse Events and Their Reporting Requirements 43

Table 5: Timeline for MOXI..... 50

Table 6: RMN Publication Authorship 53

Table 7: Authorship Order of the RMUs and Outside Sites 53

1 Acronyms

Assisted Reproductive Technologies	ART	Intrauterine Insemination	IUI
Advisory Board	AB	Investigational New Drug	IND
American Congress of Obstetricians and Gynecologists	ACOG	National Institute of Child Health and Human Development	NICHHD
Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation	AMIGOS	Ovarian Hyperstimulation Syndrome	OHSS
Clinical Report Form	CRF	Principal Investigator	PI
Clomiphene Citrate	CC	Progesterone	P4
Code of Federal Regulations	CFR	Protected Health Information	PHI
Data and Safety Monitoring Board	DSMB	Quality Control	QC
Data Coordination Center	DCC	Randomized Controlled Trial	RCT
Deoxyribonucleic Acid	DNA	Reactive oxygen species	ROS
DNA fragmentation index	DFI	Reproductive Medicine Network	RMN
Ectopic Pregnancy	EP	Reproductive Medicine Unit	RMU
Follicle Stimulating Hormones	FSH	Serious Adverse Event	SAE
Food and Drug Administration	FDA	Single cell gel electrophoresis	Comet
Health Insurance Portability and Accountability Act	HIPAA	Sperm Chromatin Structure Analysis	SCSA
Human Chorionic Gonadotropin	hCG	Terminal Deoxynucleotide Transferase-mediated dUTP Nick-end Labeling	TUNEL

Human Investigation Committee	HIC	Time to Conceive	TTC
Identification	ID	Total and Free Testosterone	T, FT
<i>In Vitro</i> Fertilization	IVF	Ultrasound	U/S
Institutional Review Board	IRB	University of North Carolina	UNC
Intracytoplasmic sperm injection	ICSI		

2 Study Synopsis

2.1 Objectives

The objective of the Males, Antioxidants, and Infertility (MOXI) Trial is to examine whether treatment of infertile males with an antioxidant formulation improves male fertility. The central hypothesis is that treatment of infertile males with antioxidants will improve sperm structure and function, resulting in higher fertilization rates and improved embryo development, leading to higher pregnancy and live birth rates. Findings from this research will be significant in that they will likely lead to an effective, non-hormonal treatment modality for male infertility. An effective treatment for men would also reduce the treatment burden on the female partner, lower costs, and provide effective alternatives to couples with religious or ethical contraindications to ART. If antioxidants do not improve pregnancy rates, but do improve sperm motility and DNA integrity, they could allow for couples with male factor infertility to use less intensive therapies such as intrauterine insemination. Male fertility specialists currently prescribe antioxidants based on the limited data supporting their use. A negative finding, lack of any benefit, would also alter current treatment of infertile males.

2.2 Patient population

The population will consist of 790 heterosexual couples, who have been attempting to conceive for ≥ 12 months, recruited from the Reproductive Medicine Network (RMN) clinical sites and their surrounding communities over a two-year period.

2.3 Study design

This will be a multi-center, randomized, placebo-controlled trial of antioxidant formulation, ConceptionXR Motility Support Formulation by Theralogix ("ConceptionXR") for the male partner. The randomization scheme will be stratified by participating site. The study will contain an internal pilot study.

2.4 Treatment

790 male subjects will be equally randomized via computer-generated randomization to receive: A) ConceptionXR Motility Support Formulation (Theralogix) containing an antioxidant combination including Vitamin C, Vitamin E, folic acid, selenium, zinc, and L-carnitine by oral ingestion twice daily or B) a placebo by oral ingestion twice daily in a double-blinded fashion. Treatment assignments will be randomized within each site by varying block size design. Treatment will occur for a minimum of 3 months and a maximum of 6 months. Couples will attempt to conceive naturally during the first 3 months and with clomiphene citrate with intrauterine insemination in months 4 through 6.

2.5 Primary outcome

The primary outcome will be live birth rate following up to 6 months of treatment with antioxidants as compared to placebo.

2.6 Secondary outcome

The secondary outcomes will be pregnancy rate, miscarriage rate, time to pregnancy, and semen parameters and DNA fragmentation at 3 months of treatment with an antioxidant as compared to placebo.

2.7 Internal Pilot

We will be conducting an internal pilot study with a three-fold objective. The objective of the internal pilot is 1) to determine the distribution of the semen abnormalities in the study population, 2) to examine the effect of our antioxidant formulation on male semen parameters and DNA integrity at 3 months of treatment compared to controls, and 3) to determine the feasibility of the proposed recruitment paradigm. The first 120 men enrolled in the MOXI trial will be included in the internal pilot. Assuming we fail to reject the null hypothesis that motility and DNA fragmentation percentage do not differ between the two treatment groups (antioxidant and placebo) at 3 months, the MOXI trial will stop enrolling subjects. Assuming we reject the null hypothesis that motility and DNA fragmentation percentage do not differ between the two treatment groups (antioxidant and placebo) at 3 months, the MOXI trial will continue. As the primary outcome will not be analyzed for the pilot, adjustments in significance levels will not be required for the primary analyses. Feasibility will be assessed by recruitment pace. We anticipate that the pilot enrollment will be completed by 6 months. If we fail to meet this pace, the recruitment strategies may need to be altered or the study stopped at the conclusion of the pilot.

2.8 Statistical Analysis

The primary outcome is a live birth resulting from a pregnancy that is conceived within the 6 months from initiation of treatment. Live birth is defined as a delivery of a live infant after 20-weeks gestation. Secondary outcomes include pregnancy, defined by a positive home pregnancy test within the 6 months of treatment. We will conduct an intent-to-treat analysis. Cumulative incidence of live birth and pregnancy will be compared between those couples randomized to antioxidants and those couples randomized to placebo. In addition, discrete-time hazard models will be used to compare time-to-pregnancy between the two treatment groups. Subsequent subgroup analyses will be conducted to assess for effect modification by type of baseline sperm abnormality (asthenospermia, high DNA fragmentation, oligospermia).

After transformations, if needed, semen parameter measures will be analyzed using a generalized linear mixed model (including random effects for site if necessary) or generalized linear model (if fixed effects for site are used). Interaction terms will be used to determine the

extent to which the change in semen parameter measures differs by type of baseline sperm abnormality (asthenospermia, high DNA fragmentation, oligospermia). If there is evidence of effect modification, change estimates will be determined for each type of baseline sperm abnormality.

For the power analysis, we assume live birth rates of 35% in the antioxidant group and 25% in the control group, and 17% drop-out. Under these assumptions, the power by using a two-sided chi square test at $\alpha=0.05$ would be 0.80.

2.9 Regulatory Compliance

The DCC is working with the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) to ensure that clinical study data and regulatory requirements are met regarding the Food and Drug Administration (FDA) code for federal regulations and Investigational New Drug (IND) submissions.

This trial is registered on <http://www.clinicaltrials.gov> (NCT # 02421887), and has been issued IND # 125753.

3 Background and Significance

3.1 Background

A variety of pathologic conditions including infection (1), varicocele (2), and cancer (3), along with environmental exposures including organic chemicals (4), pharmaceuticals, smoking (5), and radiation appear to increase oxidative stress, measured as reactive oxygen species (ROS), in semen. The sperm plasma membrane and nuclear genomes are highly susceptible to damage due to ROS due to high levels of polyunsaturated fatty acids, deficiencies in intracellular antioxidant enzymes, and limited capacity for DNA repair in sperm (6). ROS cause lipid peroxidation and thereby structural modifications to the membrane, which have been shown to interfere with sperm motility, the acrosome reactions, and sperm-oocyte fusion (7). ROS damage the nuclear and mitochondrial genome by causing single and double DNA breaks, chemical modifications of bases, DNA crosslinks, and DNA protein crosslinks (8). Damaged DNA may be repaired by endogenous repair mechanisms; however, if these are overwhelmed, the damaged DNA will be integrated into the embryo. It has been proposed that this damaged DNA will impair embryonic development, lead to pregnancy loss, or result in birth defects or morbidity in the offspring.

Given that ROS negatively affect the sperm plasma membrane, which is important for fertilization, and sperm DNA, which is important for normal embryonic and fetal development, it is logical that ROS will diminish a sperm's capacity to fertilize or lead to impaired embryo development. Clinically this would be observed as reduced fertility and greater pregnancy loss in female partners of men with elevated levels of ROS. While ROS are not commonly measured in semen, ROS damage to sperm, as measured by loss of motility and DNA fragmentation, can be quantified. Sperm motility can be measured using a standard semen analysis. DNA integrity is measured using a number of assays including Terminal Deoxynucleotide Transferase-mediated dUTP Nick-end Labeling (TUNEL), Sperm Chromatin Structure Analysis (SCSA), and single cell gel electrophoresis (Comet).

In fact, previous studies have shown that low sperm motility and high DNA fragmentation, as measured by the SCSA, are associated with a longer time-to-pregnancy among couples trying to conceive (9). Sperm motility lower than 32% is associated with 2.5 times the odds of infertility (10). Evenson et al. found that couples that did not conceive had 30% more DNA fragmentation compared to couples that conceived within 3 months of attempt (9). DNA fragmentation was also greater among those couples that did not conceive with intrauterine insemination and intracervical insemination compared to those that did conceive (11-13). DNA fragmentation levels have not consistently been associated with live birth rates following ART. Some studies have shown that fertilization and pregnancy rates are lower with high DNA fragmentation (14-20), while others have not shown an association (11, 17, 21, 22). These discrepancies may be

due to the variety of assays used to measure DNA fragmentation, the use of ICSI (ROS plasma membrane damage may be mitigated with intracytoplasmic sperm injection) (13-15, 23-25), and the variety of cut-off values used to define high DNA fragmentation. In addition, sperm preparation techniques may decrease the percentage of sperm with fragmented DNA in the aliquots of sperm used for *in vitro fertilization* (26).

Vitamin C, E, and other naturally occurring antioxidants are low molecular mass ROS scavengers found in semen (27). Low levels of seminal vitamin C are associated with poor semen quality (27). Seminal concentrations of antioxidants are lower in men with infertility compared to fertile men (28-30). As antioxidants appear to lower ROS and ROS appear to negatively affect fertility, antioxidants have been proposed as a treatment for male factor infertility.

The limited data suggest that antioxidants improve sperm motility and reduce DNA fragmentation. A previous observational study showed that a health conscious diet is associated with a decrease in sperm DNA fragmentation, suggesting that natural antioxidants are beneficial to sperm (31). However, another observational study using food frequency questionnaires failed to find an association between any antioxidant measure and DNA fragmentation, perhaps because the cohort was comprised of healthy volunteers (32). Studies of supplements have tended to show an improvement in semen parameters with the use of antioxidants. Benefits of Vitamin C (33), selenium (34), N-acetylcysteine (35), L-carnitine (36), and Zinc (37) on sperm motility have been seen after 3 months of treatment. Unfortunately, most of these studies have been small and heterogeneous. While most studies included only infertile men, some included those with normal baseline semen parameters and some with abnormal baseline semen parameters. Only one clinical trial has compared DNA integrity between men treated with antioxidants (Vitamin C and Vitamin E) and a control group (38). This study of 64 men found that after 2 months of treatment, men who received antioxidants had on average 14% (10.1-17.5%) less fragmented sperm. DNA integrity needs to be assessed in addition to traditional semen parameters as a significant number of men will have high levels of DNA fragmentation despite a normal semen analysis (39-41).

The paternal genome is thought to be activated between cleavage stage and blastocyst stage during embryonic development. It has been suggested that sperm DNA fragmentation will alter embryonic development in these later stages (42). Aberrant embryo development could lead to miscarriage or subsequent congenital abnormalities. Meta-analyses of previous studies examining the association between DNA fragmentation and miscarriage suggest that high DNA damage as measured by TUNEL assay is associated with an increase in the risk of miscarriage (Mantel-Hansel Risk ratio (random effects model) 3.94 (95% CI 2.54, 6.32)(43). The association was not as strong when the SCSA was used as the measure of DNA fragmentation (RR 1.47, 95% CI 1.04, 2.09). Only one underpowered study examined the relationship between miscarriage and DNA fragmentation among couples conceiving naturally (9). It is impossible to determine

the amount of DNA fragmentation in the fertilizing sperm *in vivo* and *in vitro* as assays to assess sperm DNA integrity preclude their use. Thus it is assumed that the overall percentage of sperm with DNA damage in a given ejaculate reflects the probability that the DNA from the sperm that fertilized the egg was damaged. It is possible that the probability of an embryologist selecting a sperm with DNA fragmentation to fertilize an oocyte *in vitro* would differ from the probability that a sperm with DNA fragmentation would fertilize an oocyte *in vivo*.

Clinical studies of the use of antioxidants in the treatment of male infertility have been encouraging. A recent meta-analysis found that use of antioxidants by males with infertility was associated with 4.85 times the odds (95% CI 1.92-12.24) of live birth following ART compared to men who did not use antioxidants (44). While these findings are encouraging, they fail to provide a definitive answer as to whether antioxidants improve male fertility. The meta-analysis included 3 studies for a total of 214 participants and the quality of the evidence was graded as low. These studies examined the antioxidants vitamin E (45, 46) and zinc (47), while studies using pregnancy as an outcome have shown L-carnitine to be promising (36, 48). Finally, these studies all used antioxidants in combination with ART; it is certainly possible that the response to antioxidants will differ with *in vivo* fertilization.

3.2 Significance

Although clinical trials suggest that antioxidants have a positive effect on sperm motility, DNA integrity, and pregnancy rates in couples undergoing assisted reproductive technologies, there are significant gaps in our knowledge of their impact on fertility (44). Gaps exist due to limitations in existing literature. 1) A variety of antioxidants at varying doses and duration have been used, precluding a strong conclusion as to whether a specific regimen is beneficial. 2) Most studies have had small sample sizes, usually less than 50 subjects. 3) Studies have utilized heterogeneous populations, limiting ability to combine results of multiple studies. 4) Most studies have used changes in semen parameters or DNA integrity as the endpoint, rather than clinical outcomes. 5) Studies have used antioxidants in conjunction with *in vitro* fertilization with intracytoplasmic sperm injection (ICSI) when measuring effectiveness. This has precluded the possibility of studying antioxidant effects on *in vivo* fertilization, which relies on normal sperm function. Our proposed study will improve generalizability, but still allow for sufficient power to determine benefit among subgroups, and will look at reproductive endpoints including pregnancy, miscarriage, and live birth.

Findings from this research will be significant in that they will likely lead to an effective, natural treatment modality for men with abnormal sperm. An effective, inexpensive, non-invasive treatment for male subfertility would be of significant benefit, as no such treatment has been clinically validated. An effective treatment for men would also reduce the treatment burden on the female partner, lower costs, and provide effective alternatives to couples with religious or ethical contraindications to ART. Even if antioxidants are found not to be of benefit to any

subgroup, this research will help us better understand the reproductive impact of sperm DNA integrity, leading to treatments that could improve fertility, pregnancy outcomes, and offspring health.

Another important possible benefit of antioxidant use in males is their potential to reduce offspring morbidity. Increasing evidence highlights a link between paternal age and offspring morbidities including autism (49), schizophrenia (50), and sporadic autosomal dominant disorders (51). It is possible that these disorders may be attributable to DNA fragmentation due to increased ROS in aging males (15, 52). While the proposed study will not directly address the therapeutic benefits of antioxidants in the prevention of these morbidities, it will address a potential mechanism and possibly suggest a preventative therapy by providing information about relationships between chronological age, DNA fragmentation, and relative effectiveness of antioxidant therapy in treating DNA fragmentation.

3.3 Innovation

This proposal is innovative in that it 1) focuses on male infertility, 2) examines both primary clinical outcomes such as live birth, and intermediate outcomes, such as semen parameters, 3) seeks to discover a cure for male infertility that does not require ART, and 4) will use the highest quality study design, an adequately powered, randomized controlled trial. While biologic evidence supports the hypothesis that antioxidants would improve male fertility, our unique study design will allow the RMN to ultimately determine if antioxidants improve male fertility without the use of ART.

4 Objectives

4.1 Primary Aim

Our primary aim is to compare live birth rates in infertile couples (≥ 12 months of infertility) following up to 6 months of male treatment with antioxidants, as compared to placebo. This is a randomized, multi-center trial in which couples receive clomiphene citrate and IUI in the second half of treatment. The primary outcome measure will be cumulative incidence of live birth of pregnancies conceived following up to 6 months of male treatment with the antioxidant formulation or placebo.

4.2 Secondary Aim

We will assess secondary outcomes including cumulative pregnancy rates with pregnancy defined as a positive pregnancy test, clinical pregnancy rates defined as presence of a fetus with cardiac activity, miscarriage rate, defined as the loss of a pregnancy prior to 20-weeks gestation, and time to pregnancy. In addition, we will examine changes in semen parameters and DNA fragmentation at 3 months of treatment.

4.3 Tertiary Aims

Subsequent subgroup analyses will be conducted to assess for effect modification by type of baseline sperm abnormality (oligospermia, asthenospermia, high DNA fragmentation). Additional questions that can be addressed with this cohort could include:

1. Do high levels of DNA fragmentation increase the risk of miscarriage?
2. Does DNA fragmentation increase with paternal age?
3. Does DNA fragmentation increase time to pregnancy (and decrease fecundability)?
4. How do SCSA and TUNEL assays for DNA fragmentation compare?

4.4 Internal Pilot

While there are a number of small randomized controlled trials showing that antioxidants improve semen parameters and a few that show that they increase pregnancy rates following ART, the studies vary tremendously in their choice of antioxidant and formulation. There are a number of commercial products marketed to improve male fertility. No trials have been published in peer-reviewed journals using any of these formulations. We have chosen a commercial antioxidant formulation, which includes the antioxidants that appear to improve semen parameters based on the existing literature. For this reason, we will be conducting an internal pilot study.

The objective of the internal pilot is to examine the effect of our antioxidant formulation, ConceptionXR, on male semen parameters and DNA integrity at 3 months of treatment compared to controls. We hypothesize that motility will be significantly higher and DNA fragmentation

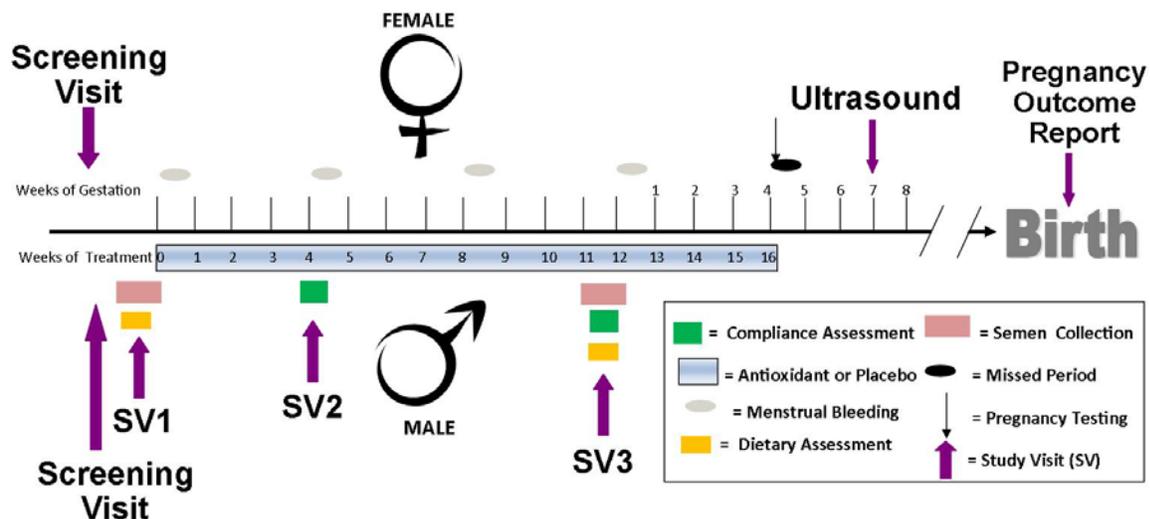
significantly lower among those men treated with antioxidants compared to placebo. A secondary objective of the internal pilot is to determine the feasibility of recruitment into a male fertility study. A tertiary objective, which will only be assessed if we fail to meet the primary and secondary objectives of the internal pilot, would be to compare live birth rates and pregnancy rates.

5 Study Design

5.1 Overview and Schema

To achieve our objective, we will conduct the Males, Antioxidants, and Infertility (MOXI) Trial, a randomized controlled trial of the effect of antioxidants on semen parameters and male fertility. Couples will be recruited from the clinics and will undergo a screening visit. At the female screening visit, she will provide consent, complete a questionnaire and any necessary screening tests, provide a blood sample, and complete a food frequency questionnaire. At the male screening visit, he will provide consent, complete a questionnaire, provide a semen sample, if no semen analysis within the past 6 months is available, and complete a food frequency questionnaire. A total of 790 couples will be enrolled. At the first study visit the male partner will provide a semen sample and complete a dietary assessment. The male will be randomized to the placebo or antioxidant arm. Treatment will follow for 3 months. If the couple has not conceived, treatment will continue for up to an additional 3 months and the female will receive up to 3 cycles of clomid and IUI. Throughout the *pre-conception* window, women will use ovulation predictor kits and check a home pregnancy test with missed menses. Men will provide a semen sample after 3 months of treatment. Compliance will be assessed at 1, 3, and 6 months. An ultrasound will be performed between 7 and 9 weeks gestation and pregnancy outcomes determined.

Figure 1: Schema for the Participation Timeline



5.2 Study Population

5.2.1 Inclusion Criteria

Couple

- 12 or more months of infertility (primary or secondary) for couples with female partner under 35. 6 or more months of infertility (primary or secondary) for couples with female partner 35 years of age or older.
- Heterosexual
- Cohabiting and able to have regular intercourse

Male:

- ≥ 18 years of age
- At least one abnormal semen parameter on a semen analysis within the past 6 months:
 - Sperm concentration ≤ 15 Million/ml
 - Total motility $\leq 40\%$
 - Normal morphology (Kruger) $\leq 4\%$
 - DNA fragmentation (SCSA, DNA fragmentation index) $>25\%$

Female:

- ≥ 18 years of age and ≤ 40 years of age
- For women ≥ 35 years of age, evidence of normal ovarian reserve as assessed by menstrual cycle day 3 (+/-2 days) FSH ≤ 10 IU/L with estradiol ≤ 70 pg/mL, AMH ≥ 1.0 ng/mL, OR antral follicle count >10 within one year prior to study initiation.
- Evidence of at least one patent fallopian tube as determined by an HSG or laparoscopy showing at least one patent fallopian tube or a saline infusion sonogram showing spillage of contrast material. OR An uncomplicated intrauterine non-IVF pregnancy and uncomplicated delivery and postpartum course resulting in live birth within the last three years will also serve as sufficient evidence of a patent tube and normal uterine cavity as long as the subject did not have, during the pregnancy or subsequently, risk factors for Asherman's syndrome or tubal disease or other disorder leading to an increased suspicion for intrauterine abnormality or tubal occlusion.
- Regular cycles defined as ≥ 25 days and ≤ 35 days in duration
- Evidence of ovulation including biphasic basal body temperatures, positive ovulation predictor kits, or progesterone level ≥ 3 ng/ml.

5.2.2 Exclusion Criteria

Couple:

- Previous sterilization procedures (vasectomy, tubal ligation). The prior procedure may affect study outcomes.
- Planning *in vitro* fertilization in the next 6 months

Male:

- Sperm concentration < 5 million/mL on screening semen analysis
- Current use of a medication or drug that would affect reproductive function or metabolism (see Appendix C for list)
- Current multivitamin or herb use (requires 1-month wash-out)
- Current serious medical illnesses, such as cancer, heart disease, or cirrhosis
- Seizure disorder
- Current use of anticoagulants
- Untreated hypothyroidism
- Uncontrolled diabetes mellitus

Female:

- History of radiologic or surgically confirmed moderate to severe endometriosis
- Body mass index >35 kg/m²
- Currently pregnant
- History of polycystic ovarian syndrome
- Current serious medical illnesses, such as cancer, heart disease, or cirrhosis
- History of systemic chemotherapy or pelvic radiation
- Current use of a medication or drug that would affect reproductive function or metabolism (see Appendix C for list)

5.2.3 *Study Termination Criteria*

1. Development or suspicion of an allergic or serious adverse reaction to any of the medications in the study
2. Non-compliance with study medications and/or protocol
3. Cessation of attempts to conceive
4. Assisted reproductive technology, outside of study related procedures

5.2.4 *Rationale for Criteria*

Only couples with no known female fertility problems will be eligible (*no known endometriosis or polycystic ovarian syndrome) as this is a study of male infertility. Women must be ovulatory as this study aims to focus on male fertility. Men on anticoagulants will be excluded, as vitamin E is thought to interact with anticoagulants increasing the risk of bleeding.

We are restricting the study to couples that have been trying to conceive for at least 12 months and men with abnormal semen parameter(s) as this is a study of couples with male infertility. Abnormal semen parameters were defined by the 5th percentile lower reference limit for semen parameters from fertile men whose partners had a time-to-pregnancy of 12 months or less based on the WHO population study (53) and the SCSA time-to-pregnancy study (9). We are restricting to female partners less than 35 years of age, or between 35 and 38 years of age with normal measures of ovarian reserve, to minimize the likelihood of reduced fertility due to reproductive aging.

Our exclusion criteria include a lower limit for sperm count. Men with very low sperm counts are more likely to have hypogonadism or obstruction and would be unlikely to benefit from antioxidants. Approximately 32% of males between the ages of 31 and 50 take a daily multivitamin (54). Multivitamin use is more frequent among those with more education, higher incomes, healthier lifestyles and diets, and lower body-mass indexes (55). For this reason, exclusion of men on vitamins 1) could possibly lead to selection bias and 2) might not be feasible. Thus the inclusion criteria call for a 1-month washout period for those men taking vitamins.

5.3 Recruitment

A total of 790 men will be recruited over a 2-year period (approximately 30 men per month). We will recruit subjects using methods previously proven effective in AMIGOS, which enrolled a similar study population.

Hospital/Local Health Care Referrals

Subjects will be recruited at each site from individual practice(s) as well as faculty/resident clinics. Ongoing contact with practice and faculty members as well as with residents will be made by the investigators and coordinators, reminding them of the inclusion criteria, importance of the study, etc. In addition, the investigators will describe the study to members of other departments in the hospital, primarily family practice, medical endocrinology, urology, and gynecology who also see and treat these patients. Contact with local physicians will be made and/or grand rounds will be given to disseminate information about the study.

Local Publicity Office

Investigators will meet with their local Public Relations offices and plan a news release about the study. They will also make themselves available for any newspaper, radio, or TV stories that may increase public awareness of the study. The full gamut of local media sources should be utilized. Often there is greater yield with more extensive coverage in smaller local outlets as opposed to brief mentions in outlets with larger circulation. News release will mention the uniqueness of the study, which may improve male fertility treatment.

Local Advertisements

Advertisements will be placed in local newspapers and will be continued on a regular basis if response is good.

Contact with infertility support groups

Contact will be made with both national and local support groups to spread information about the study through informational brochures and/or participation in local meetings. The American Infertility Association also may be helpful in promoting awareness of this study.

National Professional Organizations

Contact will be made with the publicity office of The American Society for Reproductive Medicine, and other potentially helpful organizations to solicit their support and potential informational releases.

Web sites

The study will be prominently displayed on the RMN web site. Additionally, each RMN center should have a web page devoted to this study with general as well as contact information. Information should also be available at the NICHD web site with links to each RMN center. An ad should also be placed at “Center Watch” on the web.

National Advertising

We would consider placing a trial ad in the health section of a select or a series of selected national publications with all of our local numbers/contacts.

IRB Approval

It is expressly acknowledged that all informational material that could be construed to be advertising will be approved by the appropriate IRB prior to dissemination.

5.4 Screening

Couples will be screened through a 3-part process. The first step will be a review of medical records to assess for potential eligibility, when recruiting from the clinic.

Both the female and the male partner will need a screening visit; however, these can be scheduled at the same time. The screening visit will be conducted by the study coordinator and will include questionnaires and laboratory testing. The screening visit will not require physician participation, unless a physical exam is needed. Eligibility will be determined by review of responses to the questionnaire and results of the laboratory testing, and review of medical records.

5.5 Informed Consent

We will obtain a limited waiver of HIPAA authorization to allow us to access and use protected health information to review eligibility criteria and contact potential subjects. Female written consent including HIPAA is obtained at the screening visit for the female visit prior to any blood draws or questionnaires. A medical records release form will be obtained at the pregnancy ultrasound. Male written consent and HIPAA will be obtained at the male screening visit prior to the semen analysis and completion of questionnaires. Both males and females will be asked to sign an optional consent form for storage of de-identified residual samples (semen, blood, and data).

Randomization, Allocation, Masking: A total of 790 men will be randomized to one of two treatment groups. The randomization scheme will be generated using a computer generated random number sequence in randomly varying blocks of 4 and 6. The allocation assignments will

be managed by the data coordinating center allowing for concealment. Allocation will be 1:1 stratified by site and female age (<35 years and ≥35 years of age).

The site investigator will be provided a password protected account for a web-based secured randomization service. At the first study visit the investigator or designee will login in order to randomize a patient into the trial. The system will query the site for patient eligibility information. If the patient is eligible, the site will be provided with a patient identifier and a study kit number. The Study Coordinator at each site will be responsible for storing, dispensing, and performing pill/vial counts on the study medications.

5.6 Treatment Protocols

ConceptionXR and placebo will be provided in similar packages. Package will state the study name but will not reveal the allocation assignment. The packages will be stored at room temperature (58-80° F). Each participant will be assigned 3 packages. Package 1 will contain a 30-day supply of treatment; package 2, a 60-day supply, and package 3, a 90-day supply.

5.6.1 *Antioxidant formulation*

The antioxidant formulation, ConceptionXR Motility Support Formula includes a combination of antioxidants: Vitamin C, Vitamin E, folic acid, selenium, L-carnitine, zinc, and lycopene, a carotenoid with antioxidant properties. The formulation also includes just one other “active” ingredient, Vitamin D. Men will take 2 pills (one in tablet form, one in capsule form) by mouth twice a day. Each antioxidant selected has been previously studied in a randomized controlled trial and found to positively impact sperm structure or function and/or pregnancy rates following assisted reproductive technology. This commercial formulation was selected based on its antioxidant formulation. Our review of the medical literature found that the above listed antioxidants have data to support their use.

Vitamin C: The total daily dosage of Vitamin C will be 500 mg. Commercial products include Vitamin C in the form of ascorbic acid at doses of 60 to 5000 mg. Randomized controlled trials (all with combination formulations) have included dosages ranging from 10 to 1000 mg (33, 34, 37, 38, 56-58). In general, Vitamin C is not used alone but in combination with vitamin E, as it appears to enhance the anti-oxidant properties of Vitamin E. The tolerable upper intake level for vitamin C is 2000 mg per day.

Vitamin E: The total daily dosage of Vitamin E in the form of d-alpha tocopheryl succinate will be 400 IU. Vitamin E has been shown to improve pregnancy rates following IVF in small randomized controlled trials (45, 46). Vitamin E also has been shown to reduce DNA fragmentation (38) and increase sperm motility at 6 months (46). Commercial formulations include a daily dosage of 150 IU to 400 IU. Randomized trials include doses ranging from 22.5 IU to 1500 IU (34, 37, 38, 45, 46, 56, 58-60). The lower doses were found in combination pills.

In general, the RCTs of Vitamin E and male fertility have tended to use higher doses than we propose. However, Vitamin E will be just one of multiple antioxidants. Second, an RCT of almost 15,000 healthy men over 50 years of age showed that 400 IU of synthetic vitamin E use was associated with a significant increased risk of hemorrhagic stroke over 8 years of treatment (61). It should be noted that the men in the MOXI trial will be, on average, younger and will take the vitamin for a short interval (at most 6 months). In another trial, the SELECT trial, of men over age 50, synthetic vitamin E at 400 IU/day for 5.5 years was found to increase the risk of prostate cancer 1.5 years after cessation of therapy. No differences in prostate cancer rates were seen during the 5.5 years of treatment (62). In addition, a meta-analysis found an increased risk of death at doses of 400 IU/day (43). Vitamin E can interact with anticoagulants increasing the risk of bleeding. Therefore, men on anticoagulants will be excluded from participation. Adverse effects of Vitamin E include fatigue, weakness, headache, nausea, diarrhea, flatulence and abdominal pain at high doses (over 1000 mg/day). However, at lower doses as prescribed in this trial, Vitamin E is generally well tolerated.

Selenium: The total daily dosage of selenium in the organic form of L-selenomethionine will be 0.20mg. Commercial products include selenium at doses between 0.05 mg and 0.133 mg. Randomized trials included doses ranging from 0.026 to 0.225mg, which the most common dose being 0.20mg (34, 56, 59, 60, 63). These trials have shown that selenium increases sperm motility at 3 and 6 months (34, 63). The tolerable upper limit intake level for selenium (from supplements and food) is 0.4 mg. Levels above this are associated with hair and nail brittleness and loss.

L-carnitine: The total daily dosage of L-carnitine in the form of L-carnitine-L-tartrate and L-carnitine fumarate will be 1000 mg. Commercial products include L-carnitine at doses between 50 and 1000 mg. Randomized controlled trials included doses ranging from 2000 to 3000 mg (48, 58, 64, 65). Common L-carnitine adverse effects include diarrhea, nausea, stomach cramps, and vomiting. Uncommon serious adverse effects include seizures. L-carnitine has been shown to increase pregnancy rates following IVF in small, randomized, placebo-controlled trials (36, 48).

Zinc: The total daily dosage of zinc will be 20 mg. Commercial products include zinc in the form of zinc amino acid chelate at doses of 10 to 70 mg. Randomized controlled trials have included dosages ranging from 25 to 500 mg (37, 47, 56). These small trials have shown that zinc increased pregnancy rates following ART and improved sperm motility at 3 months. The tolerable upper intake level for zinc is 40 mg per day.

Folic acid: The total daily dosage of folic acid will be 1000 mcg. Commercial products include folic acid at doses of 60 to 5000 mcg. Randomized controlled trials (including combination formulations and isolated) have included dosages ranging from 500 to 5000 mcg (56, 66, 67). These small trials have suggested that folic acid improves sperm concentration. The tolerable upper intake level for folic acid is 1000 mcg per day.

Lycopene: The total daily dosage of lycopene will be 10 mg. Commercial products include lycopene at doses of 10-100 mg. A randomized controlled trial (of an antioxidant combination) included lycopene at a dosage of 6 mg (56). Dietary lycopene intake is positively correlated with sperm morphology (68). Daily supplements containing 30mg of lycopene have been used safely.

Combination formulations: A number of small studies have examined the effect of a combination of antioxidants on pregnancy following IVF and/or semen parameters (34, 37, 38, 56-60, 63, 65, 69-73). The antioxidant formulations vary from study to study. Menevit (Lycopene, Vitamin E, Vitamin C, Zinc, Selenium, folic acid, and garlic) treatment of the male partner for 3 months prior to IVF was shown to increase subsequent pregnancy rates following IVF with ICSI compared to placebo (38.5% versus 16%) in a randomized controlled trial including 60 couples (56). This formulation is similar to ConceptionXR except that Menevit does not include Vitamin D or L-Carnitine and ConceptionXR does not include garlic. Menevit is not available in the US. Side effects in the combination anti-oxidant group occurred in 8% of males and were mild (gastroesophageal reflux and constipation).

Vitamin D: Vitamin D is included in ConceptionXR in the form of cholecalciferol at a dose of 2000IU. Cross-sectional studies suggest a positive association between serum 25-hydroxyvitamin D level and sperm motility in both fertile and infertile men (74, 75). Vitamin D supplementation has not been assessed in a clinical trial on male fertility. The tolerable upper limit of Vitamin D is 4000IU per day.

5.6.2 *Placebo*

The placebo will weigh, smell, and look the same as the antioxidant supplement, ConceptionXR, using an inert substance. The placebo will be compounded by Theralogix.

5.6.3 *Manufacturing of ConceptionXR and Quality Control*

ConceptionXR Motility Support Formula is manufactured by Theralogix. All active components and doses along with inert components are publically available (www.theralogix.com). All Theralogix supplements are manufactured in an NSF GMP-registered facility. ConceptionXR is independently tested and certified by NSF International for content accuracy, purity, and freedom from contaminants. The average expiration date for most dry powder dietary supplements is 2 years.

5.6.4 *Distribution*

The ConceptionXR and placebo bottle will be shipped to an investigative drug service (IDS, Almac or comparable) in 3 batches. The IDS will label kits with unique blinded identifiers (randomly allocated to supplement and placebo) and distribute in a blinded fashion to the study sites.

5.7 Study Flow:

5.7.1 Screening:

Female Screening Visit:

1. Obtain informed, signed consent
2. Complete medical history and physical exam of female study participant
 - a. Complete RMN Medical History case reporting form
 - b. Obtain Vital signs, height, weight, neck circumference
 - c. Pap smear, if necessary, per current ACOG time-frame guidelines
 - d. Standard physical exam conducted by clinician (if not done within past 12 months)
 - e. Pelvic ultrasound (or sonohysterogram) with documentation of uterine size, presence of fibroids, and ovarian dimensions within past 12 months.
3. Pre-conception counseling
4. Sonohysterogram or hysterosalpingogram to verify patency in at least one tube, and normal uterine cavity (or documentation within past 3 years). An uncomplicated intrauterine non-IVF pregnancy and uncomplicated delivery and postpartum course resulting in live birth within the last three years will also serve as sufficient evidence of a patent tube and normal uterine cavity as long as the subject did not have, during the pregnancy or subsequently, risk factors for Asherman's syndrome or tubal disease or other disorder leading to an increased suspicion for intrauterine abnormality or tubal occlusion.
5. Collect blood for tests to determine eligibility (if not already obtained).
6. Offer optional blood test for Rubella, Varicella, HIV, and genetic tests for cystic fibrosis, SMA, sickle cell, and thalassemia (based on ethnicity). The costs for these blood tests are not included in determining the patient care budget for this protocol. Patients need to be made aware that they will be responsible for paying for these tests if their insurance company does not cover the costs.

Determine eligibility. If eligible:

1. Have the participant complete the following RMN questionnaires:
 - Genetic Risk Factors questionnaire
 - Female Sexual Function Index (FSFI)
 - SF-12
 - PHQ-9
 - FertiQoL
 - Epworth Sleepiness
 - Stop-Bang (Sleep apnea)

- Female Sexual Distress Scale (FSDS)
 - Diet History Questionnaire II (DHQ-II)
2. Obtain height and weight
 3. Obtain blood and urine sample for RMN Biorepository, if consent obtained
 4. Provide salivary collection kit and instructions, if consent obtained
 5. Explain how to use ovulation predictor test and pregnancy tests
 6. Advise the participant to contact us with a positive pregnancy test to schedule pregnancy ultrasound

Male Screening Visit:

1. Obtain informed, signed consent
2. Obtain a semen sample if semen analysis has not been performed within the past 6 months.

Determine eligibility. If eligible:

3. Complete the following RMN questionnaires:
 - a. Partner Genetic Risk Factors Questionnaire
 - b. SF-12
 - c. PHQ-9
 - d. FertiQoL
 - e. Epworth Sleepiness
 - f. Stop-Bang (Sleep apnea)
 - g. International Index of Erectile Function (IIEF)
 - h. Psychosexual daily questionnaire (PDQ)
 - i. Androgen Decline in the Aging Male quantitative questionnaire (qADAM)
 - j. Diet History Questionnaire II
 - k. Sun Exposure and Behaviour Inventory (SEBI)
4. Provide instructions for future semen collections.
5. Provide salivary collection kit and instructions, if consent obtained
6. Obtain semen sample for RMN Biorepository, if consent obtained

5.7.2 Study treatment visit 1 (males only):

1. Participant completes the ASA24.
2. Obtain height and weight and neck, waist and hip circumferences.
3. Obtain a semen sample following appropriate abstinence and evaluate by semen analysis as suggested by WHO 5 standards.
 - a. Samples will be evaluated for volume, sperm concentration, percent sperm motility, forward progressive motility, at the local site laboratory.

- b. Prepare semen slides. Incidence of normal sperm morphology will be determined using WHO 5 morphological assessment by a single technician at a central laboratory.
 - c. Three aliquots of raw semen will be frozen and stored at -20° C, then shipped in batches to a central site for TUNEL analysis, SCSA, and COMET assay.
 - d. If consent obtained, a fourth aliquot of raw semen will be obtained for the RMN Biorepository.
4. Collect blood sample
 - a. Collect serum for UVA central laboratory for measurement of total testosterone, FSH, LH, vitamin D 25-OH.
 - b. Collect and store serum. Randomly selected samples will be shipped to a central laboratory for analysis of antioxidant levels.
 - c. If consent obtained, collect blood sample for RMN Biorepository.
 5. Collect urine sample to be sent to a central laboratory for testing for environmental contaminants.
 6. Randomization and assignment of study drug kit
 7. Dispense assigned study pill kit. Instruct participant to take one capsule and one tablet twice a day. Provide 1-month supply (Package 1). Instruct participant to bring pill bottles with any remaining pills with him on day of next visit.
 8. Dispense patient journal.
 9. Schedule study visit 2 for ≤ 30 days.
 10. Provide male with 7 ovulation strips with instructions and 2 pregnancy tests with instructions.

5.7.3 *Study treatment visit 2 (males only):*

1. Count remaining pills.
2. Assess for side effects from treatment.
3. Collect blood sample
 - a. Collect and store serum. Randomly selected samples will be shipped to a central laboratory for analysis of antioxidant levels.
4. Dispense assigned study pill kits. Instruct participant to take one capsule and one tablet twice a day. Provide 2-month supply (Package 2). Instruct participant to bring pill bottles with any remaining pills with him on day of next visit.
5. Dispense patient journal.
6. Schedule study visit 3 for ≤ 60 days. Provide semen collection instructions for next visit.
7. Provide male with 14 ovulation strips and 4 pregnancy tests.

5.7.4 *Study treatment visit 3 (males only):*

1. Participant completes the ASA24 online.

2. Count remaining pills.
3. Assess for side effects from treatment.
4. Collect blood sample
 - a. Collect serum for UVA central laboratory for measurement of vitamin D 25-OH.
 - b. Collect and store serum. Randomly selected samples will be shipped to a central laboratory for analysis of antioxidant levels.
5. Obtain a semen sample following appropriate abstinence and evaluate by semen analysis as suggested by WHO 5 standards.
 - a. Samples will be evaluated for volume, sperm concentration, percent sperm motility, forward progressive motility at the local site laboratory.
 - b. Prepare semen slides. Incidence of normal sperm morphology will be determined using Kruger Strict morphological assessment by a single technician at a central laboratory.
 - c. Three aliquots of raw semen will be frozen, stored at -20° C, and then shipped in batches to a central site for TUNEL, SCSA, and COMET assay.
6. Dispense assigned study pill kit. Instruct participant to take one capsule and one tablet twice a day. Provide 3-month supply (Package 3). Instruct male to have female partner call with menses to schedule baseline ultrasound for clomiphene citrate/IUI cycle.
7. Dispense patient journal.
8. Schedule study visit 4 for ≤ 120 days. Instruct participant to bring pill bottles with any remaining pills with him on day of next visit.

5.7.5 *Clomid and IUI cycles (couple):*

Baseline Ultrasound Visit

1. Females will call with menses and come in Day 1-5 (Preferably day 3 for baseline monitoring) for first cycle only.
2. Perform comprehensive baseline ultrasound.
3. Dispense Infertility Treatment Medications: 10 tablets of clomiphene citrate and 10,000 IU hCG. Patient is to take clomiphene citrate 100 mg for 5 days starting on cycle days 1,2,3,4 or 5.
4. Dispense patient journal

Monitoring Visit number 1: Within 3 days after completing 5-day drug cycle (Cycle Day 8-12)

1. Transvaginal ultrasound for endometrial and follicular monitoring
2. Adverse effects and concomitant medications query

Monitoring Visit number 2 and beyond:

Visits for subjects will be conducted on an individualized basis until hCG administration. When a decision has been made to give hCG on the next day, a follow up monitoring visit on that day is unnecessary.

- Transvaginal ultrasound examination for endometrial and follicular monitoring
- Adverse effects and concomitant medications query

hCG administration day:

1. 10,000 IU in 1 cc diluent delivered IM
2. Transvaginal ultrasound examination for endometrial and follicular monitoring is not necessary if one has been performed within 2 days.

Criteria for hCG administration:

- First occurrence of lead follicle reaching 20 mm (in average diameter in two dimensions), or
 - First occurrence of two lead follicles greater than 18 mm diameter (in average diameter in two dimensions), or
- The day after the lead follicle reaching 18 mm (in average diameter in two dimensions), or the day of detection of presumptive ovulation by ultrasound

Criteria for withholding hCG:

- If a leading follicle does not reach a mean diameter of 18 mm after 18 days of treatment, or
- Endogenous LH surge happens [which can lead to premature luteinization], or
- Increased risk for OHSS and/or high-order multiple gestational pregnancy exists when more than 4 growing follicles develop (mean diameter >18 mm), or

**Protocol medication adjustment:*

1. If no ovulation or development of at least one follicle ≥ 18 mm in average diameter, then increase dosage in the subsequent cycle.
2. If only one follicle ≥ 18 mm in average diameter, the dosage increase for subsequent cycles will be left to physician's discretion.
3. If more than four follicles are ≥ 18 mm in average diameter, dosage will be reduced in the subsequent cycle.

**Cancellation criteria:* Cycles will be cancelled if significant adverse reactions develop in response to administered medications, if criteria for withholding hCG administration are encountered, or per patient's request.

Insemination day visit:

1. Each site will perform its standard sperm processing and intrauterine insemination procedure.
2. Record parameters of semen analysis before and after sperm preparation.
3. Record time of insemination.
4. Instruct patient to check urine pregnancy test 2 weeks after insemination and call with results.
5. Provide clomiphene citrate for next cycle. Counsel not to take it until instructed to do so.

Pregnancy test: Patient is to do a home pregnancy test 2 weeks after insemination using the urine home pregnancy tests provided.

Four possible outcomes:

- A. No pregnancy on urine pregnancy test
- B. Positive urine pregnancy test- serum β hcg level returns <5 mIU/ml- no pregnancy
- C. Positive urine pregnancy test- serum β hcg level returns >5 mIU/ml, retest for rising level in 2 days- no pregnancy
- D. Positive urine pregnancy test- serum β hcg level returns >5 mIU/ml, retest for rising level in 2 days- pregnancy

A. Negative Urine Pregnancy Test/No pregnancy: *Repeat cycles until pregnancy occurs or male completes a total of 6 months of treatment.*

Criteria to initiate Cycles 2 or 3 (Day 3 +/- 2 days):

1. Negative urine pregnancy test,
2. Male still on treatment.

Cycle 2 and 3 will be identical to Cycle 1, except that there will be no Baseline Ultrasound visit. When the subject contacts the site with the results of her urine pregnancy test or start of menses, she will be instructed by the site to start her clomiphene citrate. She will then return to the site for Monitoring Visit 1 (see above).

In women who report a positive urine pregnancy test, obtain serum β hcg level.

B & C. Positive Urine Pregnancy Test (no pregnancy)

Patient will have a serum β hcg level checked. If >5 mIU/ml, return in 2 days to check for a rising level in serum β hCG; if the first level is <5 mIU/ml or if there is not a rising level, patient will initiate Cycles 2 or 3.

D. Positive Urine Pregnancy Test (pregnancy): *Biochemical pregnancy will be defined as β hCG >5 units/ml 2 weeks after insemination followed by a rising level two days later*

- Patient will have a serum β hcg level checked. If >5 mIU/ml, patient will return in 2 days to check a rising level in serum β hCG.
- If rising β hcg level, schedule Pregnancy Ultrasound Visit. Instruct male to come to pregnancy ultrasound visit to complete study visit 4. Remind him to bring his pill bottle.

5.7.6 *Study visit 4 (males only):*

1. Count remaining pills.
2. Confirm pregnancy status (pregnant or not pregnant) of female partner.
3. Assess for side effects from treatment.
4. Obtain blood sample from those males whose female partner did not conceive.
 - a. Collect and store serum. Randomly selected samples will be shipped to a central laboratory for analysis of antioxidant levels.

5.7.7 *Pregnancy ultrasound(s):*

To be done between 6 and 9 weeks gestation. Clinical pregnancy rate will be defined as the identification of intrauterine sac(s) with positive fetal cardiac activity in at least one sac.

1. A transvaginal ultrasound will be performed between 6 and 9 weeks gestation to assess advancement of the pregnancy by locating the gestational sac(s) and to determine fetal viability by detection of fetal heart motion.
2. Remind participant to contact the study coordinator within 2 weeks of the end of pregnancy.
3. Determine where she will be obtaining prenatal care and delivering. Obtain permission to access maternal and neonatal medical records to abstract data related to the birth of the infant.
4. Participation in the intervention phase of the study will end for couples that experience a pregnancy loss.
5. Obtain a separate consent form to enter the patient into the Pregnancy Registry.

5.7.8 *20-week contact:*

Women who do not report an end of pregnancy prior to 20-weeks gestation, will be contacted to confirm pregnancy status and update information on site of prenatal care and planned delivery.

5.7.9 *Pregnancy outcome:*

Subjects will be contacted to obtain pregnancy outcome information including outcome (miscarriage, ectopic, abortion, live birth) and answer follow-up questions specific to that outcome (for miscarriage: date miscarriage identified, for live birth: date of delivery, gestational number, birth weight, gender, and obstetrical complications). Medical records will also be obtained from the prenatal site, pediatrician, and hospital as needed to confirm obstetrical and neonatal outcomes.

6 Data Collection

Table 1: Overview of Timing and Content of Data Collection for Primary Cohort

Data Collection (multiple checks within column indicates that data acquisition is distributed over contacts and/or updates)	Semen Analysis	DNA Fragmentation (TUNEL and/or SCSA)	Dietary Assessment	Compliance	Fetal development, estimated date of delivery, Clinical pregnancy	Pregnancy Outcomes
Female screening visit			✓			
Male screening visit	✓	---	✓	---	---	---
Study visit 1	✓	✓	✓	✓	---	---
Study visit 2	---			✓	---	---
Study visit 3	✓	✓	✓	✓		
Study visit 4				✓		
Pregnancy Ultrasound (6 wks gestation)	---	---		---	✓	---
Pregnancy Status Update (20 to 24 wks)	---	----		---	---	✓
Pregnancy Outcome Reporting and Medical Record Review	----	----		---	---	✓

6.1 Specimen collection, processing, and shipment

6.1.1 Semen Collection

Semen samples will be obtained at the screening visit (as needed), visit 1, and visit 3. Semen assessment at the screening visit and visit 1 will occur prior to treatment. Samples will be assessed using a standard semen analysis, including assessment of morphology using strict criteria, the SCSA, COMET, and TUNEL. These analyses will allow us to assess sperm motility and

DNA structure, two components frequently affected by ROS. Couples will not be informed of results until the end of the study, as this information could lead to behavior changes. Men will be asked to abstain from ejaculation 2-5 days prior to collection. Samples will be collected by masturbation at the clinical site. Samples will be allowed to liquefy for 30 minutes at 37° C prior to analyses.

6.1.2 *Semen analysis*

Subsequently the initial physical characteristics (e.g. volume, pH) will be recorded. Count and motility will be measured using 5µl of semen loaded on a sperm counting chamber (Microcell, Conception Technologies, San Diego, CA) (76). Semen smears will be made for each sample, stained by the Papanicolaou method, and shipped to a central laboratory for assessment of sperm morphology by a single technician, using strict criteria defined by WHO 5 (77). Semen analyses will be conducted at the screening visit, study visit 1 (prior to treatment), and study visit 3 (at 3 months of treatment).

6.1.3 *DNA integrity testing*

DNA integrity needs to be assessed in addition to traditional semen parameters as a significant number of men will have high levels of DNA fragmentation despite a normal semen analysis (39-41). There are three common assays of sperm DNA integrity: two of which measure actual DNA strand breaks (neutral COMET and TUNEL) and one of which measures the potential for strand breaks (SCSA) (78, 79). The SCSA assay is proposed as it is the only DNA integrity testing method that is standardized in a commercial laboratory. It is the only test in wide clinical use.

6.1.4 *SCSA*

An aliquot of raw semen will be sent to a central laboratory. SCSA will be performed as previously described (80), generating a DNA fragmentation index (DFI) on 5000 sperm per sample. The assay is based on the color of fluorescence of acridine orange stained sperm, where red fluorescence reflects damaged DNA (single-stranded) and green fluorescence reflects native (single-stranded) DNA. The DFI is calculated as the ratio of damaged DNA (red)/total DNA (red + green). Previous studies have shown that males with sperm with a DFI greater than 25% have a longer time to natural pregnancy (9). SCSA has been shown to be highly precise and reproducible (CV 1-3%) (80). Results will be faxed to the RMN data coordinating center. SCSA will be conducted on the study visit 1 sample (prior to treatment) and study visit 3 sample.

6.1.5 *TUNEL*

One aliquot of raw semen will be sent to a central laboratory. The TUNEL assay will be performed on fixed, permeabilized sperm as described (81, 82). End labeling of breaks will be performed using fluorescent dUTP and terminal transferase and will employ a commercial, widely used kit (TUNEL in situ cell death detection kit, Roche). All TUNEL assays will be performed at a single site will be analyzed in batches of 10–20 samples, and a minimum of 10,000 sperm will be assessed per assay. Previous ROC analysis suggests that a 20% fragmentation cutoff would yield a 96.5% sensitivity and 89.4% specificity to detect infertile males (82). TUNEL assay will be conducted on samples from study visit 1 (prior to treatment) and study visit 3 (after 3 months of treatment).

6.1.6 COMET

One aliquot of raw semen will be sent to a central laboratory for the COMET assay. The comet assay is one of the simplest methods to measure sperm DNA damage by quantifying the single and double strand breaks. The principle of the assay is that the sperm nuclear DNA is separated in an electric field based on charge and size, which is viewed with a fluorescent DNA-specific dye. The resulting images, which resemble comets with an intact head and tail, determine the extent of DNA damage based on the intensity of staining and morphology of the comet. The COMET assay will be conducted on the study visit 1 sample (prior to treatment) and study visit 3 sample.

6.2 Compliance

Compliance and cross-over will be assessed via two mechanisms: 1) pill counts and 2) measurement of Vitamin E (alpha-tocopherol), L-carnitine, and zinc (and, if possible, Vitamin C and selenium) in blood. Compliance and cross-over will be assessed by these 2 mechanisms at study visits 2, 3, and 4 (corresponding to months 1, 3, and 6 of treatment). At study visit 1 (month 0 of treatment), a baseline measurement will be established.

6.2.1 Measurement of vitamin levels

A random sample of 10% of blood samples (as done in the SU.VI.MAX study (83)) obtained at study visits 2, 3, and 4 will be shipped to a laboratory such as the Clinical Pharmacology Analytical Services Laboratory (CPAS) in the Department of Experimental and Clinical Pharmacology in the College of Pharmacy at the University of Minnesota (<http://www.pharmacy.umn.edu/cpas/services/index.htm>). All three vitamins will be measured using a LC-MS/MS method. Internal standards are commercially available. These samples will allow us to assess for compliance. As placebos will also be samples, we will also be able to assess for cross-over.

6.3 Dietary assessment

A previous observational study showed that a health-conscious diet is associated with a decrease in sperm DNA fragmentation, suggesting that natural antioxidants are beneficial to sperm (31). However, another observational study using food frequency questionnaires failed to find an association between any antioxidant measure and DNA fragmentation, perhaps because the cohort was comprised of healthy volunteers (32). Therefore, to assess for possible effect modification by baseline dietary composition and vitamin intake, we will assess these through a 24-hour recall during the 1st study visit and a food frequency questionnaire at baseline. Secondary analysis could be conducted to examine the relationship between baseline dietary composition and vitamin intake and semen parameters and couple fecundability and fertility over the study period. A second 24-hour recall will be obtained at the 3-month study visit to determine if there were differential changes in dietary composition among treatment groups.

To measure food intake, we will use the validated, self-administered, web-based, 24-hour recall questionnaire, ASA24 and Diet History Questionnaire II. The method allows for collection of detailed intake and portion sizes. It does not affect what an individual chooses to eat on a given day, due to its retrospective data collection. It is administered in close proximity to the intake

6.1.6 COMET

One aliquot of raw semen will be sent to a central laboratory for the COMET assay. The comet assay is one of the simplest methods to measure sperm DNA damage by quantifying the single and double strand breaks. The principle of the assay is that the sperm nuclear DNA is separated in an electric field based on charge and size, which is viewed with a fluorescent DNA-specific dye. The resulting images, which resemble comets with an intact head and tail, determine the extent of DNA damage based on the intensity of staining and morphology of the comet. The COMET assay will be conducted on the study visit 1 sample (prior to treatment) and study visit 3 sample.

6.2 Compliance

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day minimizing recall issues. The ASA24 format and design is based on a modified version of the interviewer-administered Automated Multiple Pass Method (AMPM) developed by the US Department of Agriculture. The ASA24 consists of a respondent web site (<https://asa24.westat.com/>) and a researcher website (<https://asa24.westat.com/researchersite.html>). The respondent website guides the participant through the completion of a 24-hour recall for the previous day from midnight to midnight using a dynamic user interface. Information and instructions on the ASA24 can be found at https://asa24.westat.com/assets-r/docs/ResearcherSite_Instructions.pdf and a demonstration at <http://asa24demo.westat.com/>. The male participants will complete the ASA24 on the day of study visit 1 and study visit 3.

The Diet History Questionnaire II (DHQ II) is a food frequency questionnaire (FFQ) developed at the Risk Factor Monitoring Branch. The DHQ II consists of a respondent website and a researcher website. The respondent website guides the participant through the completion of a questionnaire regarding portion size, usual intake, and dietary supplements over the past year. Information and instructions on the DHQ II can be found at <http://appliedresearch.cancer.gov/dhq2/> and a demonstration at <https://appliedresearch.cancer.gov/cgi-bin/dhq2.pl?module=2&method=1>. In summary, the DHQ has been validated as a measure of frequency and nutrient assessment. The full and extensive list of the 176 nutrients, dietary constituents, and food groups assessed with the DHQ is available on the website. Both male and female participants will complete the DHQ II at screening.

6.4 Male urinary testing for environmental contaminants

Urine samples will be obtained from male participants at the visit 1 for future assessment for common environmental contaminants such as Bisphenol-A (BPA). Samples will be collected into BPA-free collection containers at the clinical site and transferred to BPA-free cryovials by study staff. Samples will be stored frozen until shipped in batches to a central laboratory for analysis.

6.5 Stress biomarker testing

A first morning (basal) salivary sample will be obtained from male and female participants using a salivary collection device. Participants will be told to collect the sample immediately upon awakening before eating, drinking, smoking or brushing their teeth. Samples from males will be collected around the time of study visit one and returned at the time of study visit one or by prepaid overnight shipping. Females will collect their sample shortly after their screening visit and return the sample via prepaid overnight shipping. Samples will be stored at -20°C until analysis. Samples will be analyzed for stress biomarkers such as amylase and cortisol. Participation in this part of the study will be optional.

6.6 Male laboratory testing (central core laboratory)

The core lab will analyze the blood samples from the males at study visit 1 (prior to treatment) for total testosterone, LH, FSH and Vitamin D25-OH. They will also analyze the blood samples from the males at study visit 3 for Vitamin D25-OH.

6.7 Male sunscreen usage

There is increasing concern that benzophenone (BP)-type ultraviolet filters, used in sunscreens, are absorbed by the skin and act as endocrine disruptors (84). Sunscreen ingredients have been demonstrated in vivo² and in vitro³ to act as endocrine disruptors: either affecting estrogen (those containing PB-2 [tetrahydroxybenzophenone] and BP-8 [3,4-dihydroxy-4-methoxybenzophenone]) (85,87) while other UV filters (13 of 29 filters), disrupted progesterone's effect on sperm calcium ion channels (86). While not all UV filters have been associated with a reduction in male fertility, the SEBI (Sun Exposure and Behaviour Inventory) (88) questionnaire will be used to evaluate whether or not men using more sunscreen will experience less fecundity. Future analysis of repository blood or urine samples may be used to more accurately specify which UV filters are responsible for less fecundity.

Sunscreens with PABA block the specific sunlight spectrum responsible for cutaneous synthesis of vitamin D (89). Since the MOXI preparation contains vitamin D, the frequency and amount of both sun exposure and sunscreen usage should be documented.

6.8 Quality of Life (QOL) Measures

Mood, quality of life, and sexual function will be assessed at baseline in both males and females. Quality of life will be assessed by the Medical Outcomes Survey (PHQ-9) and Short Form 12 (SF-12). Female sexual function will be assessed by the Female Sexual Function Inventory (FSFI) along with the Female Sexual Distress Scale (FSDS). This measure is considered the "gold standard" paper and pencil assessment of sexual function and has excellent psychometric properties. Male sexual response will be assessed by the International Index of Erectile Function (IIEF), a multidimensional scale for assessment of erectile dysfunction. The measure addresses the relevant domains of male sexual function (erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction). We will assess hypogonadal symptoms with the Androgen Deficiency and the Aging Male quantitative (qADAM) questionnaire and psychosexual function with the Psychosexual Daily Questionnaire (PDQ). We will assess quality of life relating to infertility and treatment with the FertiQoL survey. There may also be some impact on fertility and we will investigate this in our study. We will use two simple scales to evaluate sleep, the STOP BANG questionnaire for sleep apnea, and the Epworth Sleepiness Scale. (See Appendices)

6.9 Early Pregnancy Ultrasound

A transvaginal ultrasound (standard for first trimester imaging), will be scheduled, ideally between 6 2/7 and 7 2/7 weeks of gestation; no later than 9 6/7 weeks. This ultrasound confirms estimated date of delivery, and in the case of loss, documents likely developmental stage at the time of the loss (e.g. empty gestational sac, fetal pole not heart rate, normal fetal pole). Presence and size of gestational sac, presence and size of yolk sac, presence of fetal pole and crown-rump length, and presence of cardiac motion and heart rate will be recorded. With minimal costs, ultrasounds achieve 2 study goals. They serve as an incentive to subjects for participation and compliance with study protocols and they provide estimates of miscarriage and clinical pregnancy rates.

6.10 Ascertainment of Pregnancy Outcomes

Participants will be encouraged to report outcome (miscarriage, ectopic, abortion, live birth) and answer follow-up questions specific to that outcome (for miscarriage: date miscarriage identified and for live birth: date of delivery, gestational number, birth weight, gender, and obstetrical complications).

6.11 Pregnancy Registry

All subjects who deliver will be encouraged to participate in our Pregnancy Registry which currently provides infant follow up till age 3. This is currently a separate protocol and we will also obtain separate informed consent for participation in this protocol.

6.12 Biologic Repository

We will use the RMN biorepository as a biological specimen's bank at baseline prior to randomization in both females and males. This Biorepository will serve a two-fold purpose. First, it can serve as a repository to run additional serum assays for novel markers of infertility or treatment success that are discovered while the study is ongoing. Second, it will serve as a source of samples for further studies including proteomics, metabolomics, etc. We will collect whole blood, serum, and urine from female and male participants, if consented. We will also collect semen from male partners, if consented. Subjects will be able to opt in or opt out of these studies via separate signature on the consent form. We will also store leftover serum samples for additional post hoc studies. Study subjects will be separately consented to store and use their leftover serum samples from the study and will similarly be able to opt out. Further details of specimen processing can be found in the Manual of Operations and Procedures.

6.13 Central Core Laboratory

Screening labs to determine eligibility will be run in the local RMN site labs. Given the variability of assays between labs, assays will be performed in a central lab at the Ligand Assay Core lab at the University of Virginia.

7 Data Analysis

7.1 Internal Pilot

We will be conducting an internal pilot study with a three-fold objective. The objective of the internal pilot is 1) to determine the distribution of various types of semen abnormalities in the study population, 2) to examine the effect of our antioxidant formulation on male semen parameters and DNA integrity at 3 months of treatment compared to controls, and 3) to determine the feasibility of the proposed recruitment paradigm.

The first 120 men enrolled in the MOXI trial will be included in the internal pilot. The 120 men will complete the entire MOXI protocol. Once the first 120 men enrolled in MOXI have completed study visit 3, the DCC will complete the data analysis for the internal pilot. After data cleaning and transformations, if needed, semen parameter measures will be analyzed using a generalized linear mixed model (including random effects for site if necessary) or generalized linear model (if fixed effects for site are used). Interaction terms will be used to determine the extent to which the change in semen parameter measures differs by type of baseline semen abnormality (oligospermia, asthenospermia, high DNA fragmentation), if there is evidence of effect modification, change estimates will be determined for type.

If we assume that 50% of the males will have low motility (<40%) after taking into account potential dropouts and that the drop-outs will be randomly distributed, we should have 30 men in each group. Based on Fedder et al. we can assume that the percentage of sperm motility at the end of treatment in antioxidant group can be increased by 32% (SD20%) from basement and that in the placebo group it will be increased by 20 % (SD12%)(83). Furthermore, Khadem et al. (38) reported that DNA fragmentation decreased from 22.1±7.7% to 9.1±7.2% in antioxidant group (38). Under these assumptions, or pilot phase will have 80% power to detect the differences suggested in the literature with $\alpha=0.05$.

Feasibility will be assessed by recruitment pace. We anticipate that the pilot enrollment will be completed by 6 months starting from when all the sites have been initiated to start the trial. Thus 120 couples will be recruited over the 6 months. The pilot goal assumes that recruitment pace will increase over the course of the entire study period.

Assuming we fail to reject the null hypothesis that motility and DNA fragmentation percentage do not differ between the two treatment groups (antioxidant and placebo), the MOXI trial will stop enrolling subjects. Enrolled couples will complete the study protocol. Data analyses will be conducted for the primary and secondary outcomes for the primary study. These results could be used to power a future study should point estimates suggest that male partner treatment with antioxidants increases live birth or pregnancy rates.

Assuming 1) we reject the null hypothesis that motility and DNA fragmentation percentage do not differ between the two treatment groups (antioxidant and placebo) and 2) we determine that the study is feasible, the MOXI trial will continue until a total of 790 couples have been enrolled. Since the primary outcome will not be analyzed for the pilot, it is not thought that adjustments in significance levels will be required for these analyses.

7.2 Primary and Secondary Outcomes

The primary outcome is a live birth resulting from a pregnancy occurring within the 6 months of treatment. Live birth is defined as a delivery of a live infant after 20-weeks gestation. Secondary outcomes include pregnancy, defined by a positive home pregnancy test within the 6 months of treatment. We will conduct an intent-to-treat analysis. Cumulative incidence of live birth and pregnancy will be compared between those couples randomized to antioxidants and those couples randomized to placebo. In addition, discrete-time hazard models will be used to compare time-to-pregnancy between groups. Subsequent subgroup analyses will be conducted to assess for effect modification by type of baseline sperm abnormality. All analyses will include fixed or random effect terms as needed to account for potential site effects.

7.3 Sample Size and Statistical Power

For the power analysis, we assume live birth rates of 35% in the antioxidant group and 25% in the control group, and 17% drop-out (based on drop-out rate in prior RMN trials). A 25% live birth rate was estimated, assuming 5% live birth rate in the first 3 months of timed intercourse and a 20% live birth rate in the 3 clomid/IUI cycles. The 20% live birth rate is the live birth rate in AMIGOS participants receiving up to 3 cycles of clomid/IUI and female partner under the age of 35. Under these assumptions, a sample size of 395 per group will yield 80% power using a two-sided chi square test at $\alpha=0.05$ (Table 2).

Table 2: Sample size estimates under a variety of assumptions

Proportion (%) of live birth in placebo group	Proportion (%) of live birth in antioxidant group	Power (%)	Number of patients per arm with 0% dropout	Total number of patients with 0% dropout	Total number of patients with 17% dropout
20	30	80	294	588	708
20	30	90	392	784	944
25	35	80	328	656	790
25	35	90	440	880	1060
30	40	80	356	712	858
30	40	90	477	954	1150
20	35	80	138	276	332
20	35	90	185	370	446
25	40	80	152	304	366
25	40	90	203	406	490

For subgroup analyses, power is dependent on the distribution of the sperm abnormalities, the control live birth rate and the treatment effect difference (see Table 3).

Table 3: Power for subgroup analyses

Proportion affected (%)	Total N for subgroup	Control Group Pregnancy Proportion (%)	Treatment Effect Difference (%)	Alpha	Power (%)
70	552	20	10	0.05	78
60	474	20	10	0.05	71
50	394	20	10	0.05	63
40	316	20	10	0.05	54
30	236	20	10	0.05	43
70	553	20	15	0.05	98
60	474	20	15	0.05	96
50	395	20	15	0.05	92
40	316	20	15	0.05	85
30	237	20	15	0.05	74
70	553	25	15	0.05	97

60	474	25	15	0.05	94
50	395	25	15	0.05	89
40	316	25	15	0.05	82
30	237	25	15	0.05	69

8 Technical Aspects

8.1 Reporting Adverse Events

All serious adverse events (SAEs) that occur from the start of study drug through thirty days after the last dose of study medication must be reported or if the patient is pregnant, 6 weeks following delivery. A serious adverse event is defined as: fatal or immediately life-threatening; severely or permanently disabling; requiring or prolonging inpatient hospitalization; overdose (intentional or accidental); congenital anomaly; pregnancy loss after 20-weeks gestation; neonatal death up to 6 weeks after delivery; or, any event adversely affecting the study's risk/benefit ratio. Additionally, any event that, based on appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above is considered an SAE.

If an SAE occurs and is thought to be related to the study medication, the study medication will be discontinued. Twenty-four hour unblinding will be available through the web-based randomization system to break the randomization code for the individual patient if this is required by the PI for proper treatment of the patient.

The site PI will report the SAE by completing and signing the Serious Adverse Event Report Form [available in the "Study Forms" section of the RMN members-only website], and then emailing the document in PDF format to rmn.dcc@mailman.yale.edu. Subjects will be identified by study number only. No other identifying information will be included on the form. The site PI must determine and record on the SAE form whether the SAE is unanticipated or anticipated, and if it is related, possibly related, or unrelated to participation in the research.

DCC staff will enter the SAE information in the central database. The Safety Surveillance team, consisting of the DCC, NICHD research scientist and lead PI of the protocol, will analyze the SAE to determine if it meets the criteria listed in the OHRP 45CFR46 and/or FDA 21CFR312.32 & 3.14.80.

These determinations will dictate timeframes for sites' submission to the DCC, and the DCC's submission to the DSMB:

Upon receiving notification of an SAE, the DSMB will review it via a closed-session email or conference-call discussion arranged by the NICHD RMN Committee Coordinator (RMN CC). The DSMB will send a report to the RMN CC within two weeks; reports for life-threatening SAEs will be submitted in one week. The DSMB report will include: statement indicating what related information the DSMB reviewed; the review date; the DSMB's assessment of the information reviewed; and the DSMB's recommendation, if any, for the DCC.

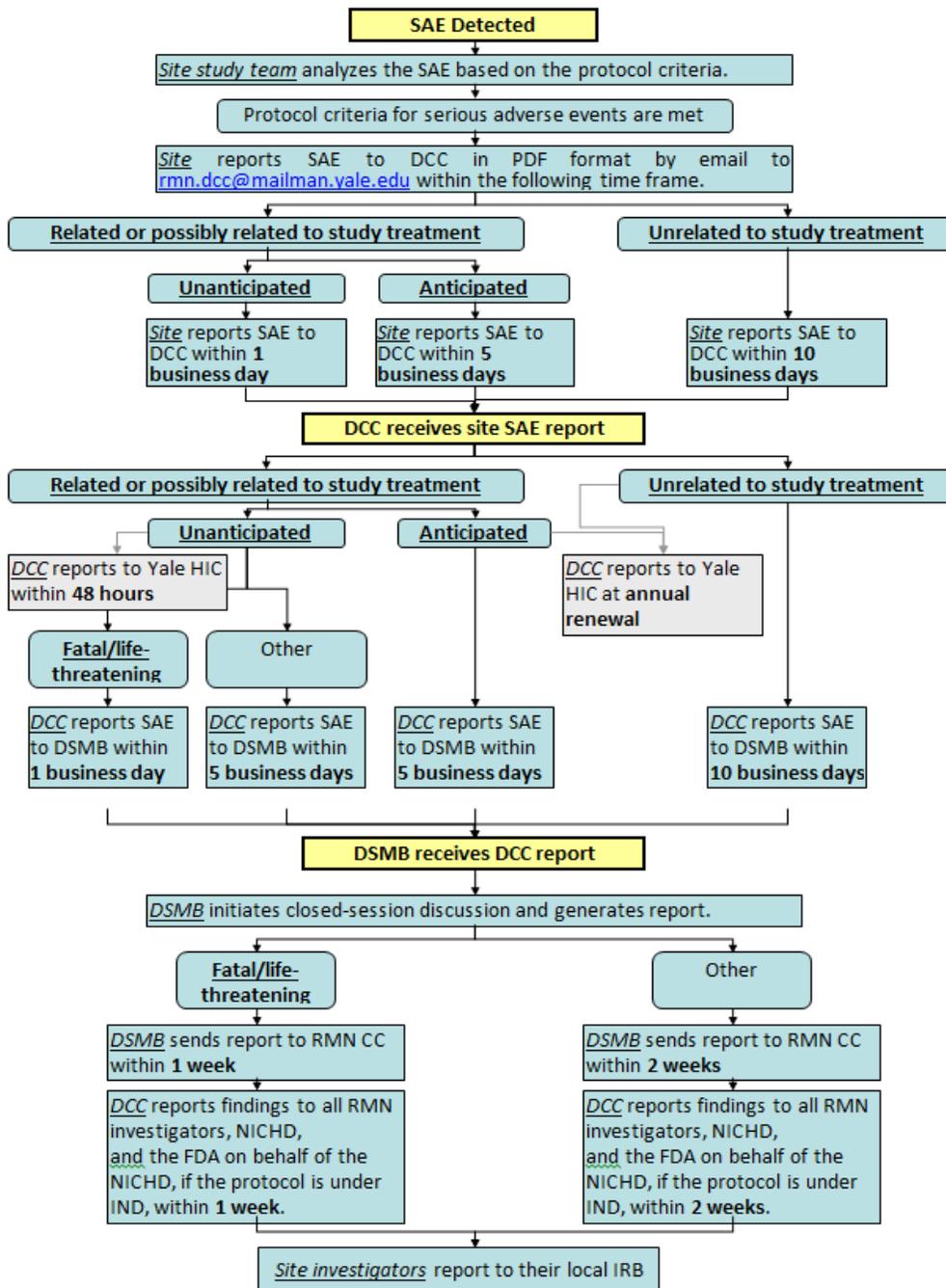
Table 4: Types of Serious Adverse Events and Their Reporting Requirements

TYPE	SITE	DCC
Unanticipated and related/possibly related SAE, fatal or life-threatening	Report to DCC within 1 business day of discovery	Notify DSMB by end of next business day of receiving site report
Other unanticipated and related/possibly related SAE	Report to DCC within 1 business day of discovery	Notify DSMB 5 business days of receiving site report
Anticipated and related/possibly related SAE	Report to DCC within 5 business days of discovery	Notify DSMB 5 business days of receiving site report
Unrelated SAE (anticipated or unanticipated)	Report to DCC within 10 business days (no more than 3 weeks) of discovery	Notify DSMB within 10 business days (no more than 3 weeks) of receiving site report

The RMN CC will then forward the DSMB report to the DCC for the record and appropriate distribution. The DCC will forward reportable events to all RMN investigators, NICHD, and the FDA on behalf of the NICHD if the protocol is under IND. The NICHD Project Scientist will review, sign, and return the IND safety report to the DCC within 2 business days, and will follow up with the site PI and DCC on the SAE until it is resolved. The Protocol PI will evaluate the frequency and severity of the SAEs and determine if modifications to the protocol and consent form are required. Site PIs will report the SAE to their site IRB according to local IRB requirements. For more information, please see the RMN/DSMB Communication Procedure.

Adverse events deemed non-serious will also be recorded throughout study participation from the start of study drug through one week after the last dose of study medication, and reported to the DCC. If an anticipated serious adverse event occurs at a frequency greater than expected, the DCC will notify the DSMB by the end of the next business day of discovery and follow the procedures for reporting serious and unanticipated and related adverse events. The DCC will forward relevant safety information to the DSMB. If an adverse event not initially determined to be reportable to the FDA under 21CFR312.32 is so reportable, the DCC will report the adverse event to the FDA within 15 calendar days after the determination is made. A flow chart for SAEs follows:

Figure 2: SAE flowchart



CFR= Code of Federal Regulations

8.2 Data Collection and Management (including quality assurance/compliance measures)

8.2.1 *Data Entry and Forms*

Case Report Forms (CRFs) will be developed as the protocol is developed. They will also be implemented in a Web-based Oracle data management system. The Web data entry forms will be similar to the paper forms with the same questions. However, the Web forms usually have more flexibility than the paper forms, such as pull-down menus.

8.2.2 *Features of Data Management System*

Features of the data management system include study definition; different types of data entry (including double entries and complete audit trail); forms control; query capture, reporting, and resolution; dictionary coding of Adverse Events (AEs) and medical terms; and clinical data review Tools; and prepares data and CRF images to FDA e-Submission Standards. The end-user/reporting/ad hoc query front-end uses a standard Web browser, so that data entry and browsing can be done from any machine with Internet access, without purchase of special software. Login to this system will be through a secured Web server with the security under the protection of Yale Center for Clinical Investigations.

8.2.3 *Data Security*

A data server and Web server will be used. The data server will be managed by YNHH IT center and the website two servers will be separated and managed by Forte Research Systems. The web server will be accessible through a secured login, but the data server can only be accessed through the web server. For security purposes, no login to the data server will be permitted, and access to the back end is limited to authorized individuals. PHI, including patient names and addresses, will be locked and secured at the participating sites, and data will be linked through a unique identification number, which will be assigned after a patient is screened or enrolled. Access will be limited to authorized individuals (21 CFR 11.10(d)). Each user of the system will have an individual account. The user will log into the account at the beginning of a data entry session, input information (include changes) on the electronic record, and log out at the completion of the data entry session. The system will be designed to limit the number of log-in attempts and record unauthorized access log-in attempts. Individuals will work only under their own access key, and not share these with others. The system will not allow an individual to log onto the system to provide another person access to the system. Access key Users will be asked to change their passwords at established intervals commensurate with a documented risk assessment. This plan has been adapted from the guidelines for computerized systems used in clinical investigations established by the U.S. Department of Health and Human Services Food and Drug Administration.

8.2.4 *Data Quality Control*

Competency to perform procedure/tests in the protocol

The site PI will be responsible for ensuring that study related tests are performed by competent personnel. The criteria for determination of competency may vary between sites in the study.

Attempts will be made to standardize operating procedures whenever possible to minimize inter-site variation.

Quality Control Steps

Quality control of data will be handled on three different levels. The first level is the real-time logical and range checking built into the web-based data entry system. The research coordinators and data entry clerks at the participating sites are required to ensure the data accuracy as the first defense. The second is the remote data monitoring and validation that is the primary responsibility of the data manager and programmer at the DCC. The data manager will conduct monthly comprehensive data checks (SAS programs run on a regular basis as a systematic search for common errors and omissions), as well as regular manual checks (within the database system). Manual checks will identify more complicated and less common errors. The data manager will query sites until each irregularity is resolved. The third level of quality control will be the site visits, where data in our database will be compared against source documents. Identified errors will be resolved between our center and clinical sites. The visits will assure data quality and patient protection.

An audit trail will be added as another security measure. This will ensure that only authorized additions, deletions, or alterations of information in the electronic record have occurred and allows a means to reconstruct significant details about study conduct and source data collection necessary to verify the quality and integrity of data. Computer generated, time-stamped audit trails will be implemented for tracking changes to electronic source documentation.

Controls will be established to ensure that the system's date and time are correct. This is a multi-center clinical trial and will be located in different time zones. System documentation will explain time zone references as well as zone acronyms. Dates and times will include the year, month, day, hour, and minute to the date provided by international standard-setting agencies (e.g. US National Institute of Standards and Technology). The ability to change the date or time will be limited to authorized personnel, and such personnel will be notified if a system date or time discrepancy is detected.

In addition to internal safeguards built into the computerized system, external safeguards will be implemented. Data will be stored at the Data Coordination Center. Records will be regularly backed up, and record logs maintained to prevent a catastrophic loss and ensure the quality and integrity of the data. This plan has been adapted from the guidelines for computerized systems used in clinical investigations established by the U.S Department of Health and Human Services Food and Drug Administration.

8.3 Study Monitoring

A monitoring plan that satisfies ICH/GCP guidelines for monitoring clinical trials will be used. A Project Manager from the DCC will lead this effort, and report findings to the DCC PI. The Project Manager will have full knowledge of the study protocol, Manuals of Procedures, and is familiar with the database system and is trained to review patient charts. The Project Manager will be responsible for training and supervising other personnel.

Once personnel at participating site are trained to recruit patients, the Project Manager will be sent to the site to help initiate the study according to the study protocol, and to ensure that the clinical site meets the scientific, clinical, and regulatory requirements. For example, the Project Manager will review all signed and dated forms required by the FDA (such as financial disclosure forms), the curriculum vitae and certifications of the investigators and personnel, CRF training, and the written IRB approval of the protocol and consent form.

The on-site monitor will return to the clinical site after a defined number of patients are recruited (can be as early as the recruitment of the 2nd patient) or a certain time period has passed, depending on the duration of the protocol execution. The schedule of visits will be discussed and agreed in the Steering Committee and we anticipate that the Project Manager will visit each participating site at least once.

During the site visit, the clinical sites should provide to the monitor a space and access to all relevant records including medical records and regulatory binders, and there would be immediate verbal feedback provided to the site after original source documents are compared to entries in the CRF. The clinical sites must agree to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved. The on-site monitor will conduct an audit of a random sample of entered information against the source documents, a review of all regulatory documents, a review of all informed consents, and a review of all pharmacy logs. The clinical site PI and coordinator should be available to meet the monitor during the visit. The monitor will review electronic data from all sites, providing a method for identifying systematic errors or problems.

To assure Good Clinical/Laboratory Practice, the monitor will control adherence to the protocol at the clinical sites and evaluate the competence of the personnel at the clinical sites including the ability to obtain written informed consents and record data correctly. The monitor will inform the DCC PI, the Steering Committee, and NICHD regarding problems relating to facilities, technical equipment, or medical staff. A thorough written report will follow each site-visit and will include a detailed itemization of discrepancies and items requiring follow-up or reconciliation. This report will also be forwarded to the NICHD Research Scientist for review. The monitor will be responsible for maintaining regular contacts between the investigators in the clinical sites and the RMN. When the study ends, the monitor will also visit the clinical site to provide assistance for close-out.

8.4 Data and Safety Monitoring Board

The NICHD has established an independent DSMB to review and interpret data generated from RMN studies and to review protocols prior to their implementation. Its primary objectives are to ensure the safety of study subjects, the integrity of the research data and to provide NICHD with advice on the ethical and safe progression of studies conducted in the RMN. The DSMB advises on research design issues, data quality and analysis, and research participant protections for each prospective and on-going study. A copy of the DSMB Charter can be found in the appendix.

The DSMB members are appointed by the Director of NICHD in accordance with established NIH and NICHD policies. DSMB members are experts in and represent the following fields:

biostatistics, epidemiology, infertility, gynecology, andrology and ethics. The NICHD Committee Coordinator is responsible for scheduling regular committee meetings, recording all meeting minutes and summarizing the committee recommendations for the Steering Committee and NICHD. Steering Committee members are prohibited from attending closed sessions of the DSMB. Open sessions may be attended by Steering Committee members or Chairperson when requested by NICHD and the DSMB.

The DSMB has quarterly teleconferences to review Network randomized trial protocols with respect to ethical and safety standards, monitors the safety of on-going clinical trials, monitors the integrity of the data with respect to original study design, and provides advice on study conduct. The DSMB periodically monitors data quality, including protocol adherence and adverse events. As outlined in the protocols, the DSMB will conduct interim evaluations of the data. It may recommend protocol modifications based on concern for subject welfare and scientific integrity.

8.5 Reporting

Administrative Reports will be prepared by the DCC - which include monthly and quarterly reports on accrual, data quality and study compliance - and presented to the Steering Committee and DSMB. Statistical reports include reports to the SC, DSMB and AB from the data analysis, and special reports for scientific manuscripts.

Statistical Reports will be generated in SAS. Reports are provided for DSMB reviews, and for final analysis of study results in preparation for scientific publications. The content of the interim reports will be very complete, and will serve as the template for the final report of each study, which in turn will form the basis of the publication of the results. Our proposed reports to the DSMB would include the following: a protocol description and history; accrual rates; site performance in terms of accrual; eligibility; protocol violations; data accuracy and minority representation; patient characteristics by treatment and site; and the rate of adverse experiences.

8.6 Obligation of the Investigator

8.6.1 IRB Review

The site PI is responsible for submitting the approved protocol and consent form to the IRB for review. The IRB must approve all aspects of the study as detailed in the protocol, including the patient informed consent form. It is anticipated that there will be minor site-specific changes in the consent form. The IRB must periodically review the status of the study at appropriate intervals not exceeding one year. The site PI will also be responsible for submitting revisions to the protocol to the IRB, as directed by the DCC, and promptly communicating serious adverse events that result during the study, to both the local IRB and the DCC. After the approval, the informed consent and IRB approval (or amendment) letters must be forwarded to the DCC.

8.6.2 Maintenance/Retention of site records

In order to comply with Good Clinical Practice (GCP) requirements, the investigators must maintain the master patient log that identifies all patients entered into the study for a period of

two years after the study ends so that the subjects can be identified by audit. The PI must maintain adequate records pertaining to subjects' files and other source data for a minimum of 5 years after completion of the study.

8.7 Regulatory Requirements

The DCC will work with NICHHD staff by providing them with clinical study data, reports, and other support as required for AE Reporting and IND submissions. The Project Managers will work with NICHHD colleagues in meeting all regulatory requirements including compliance with ICH and HIPAA requirements, FDA code for federal regulations (Title 21), and IND applications. For example, the DCC Project Managers will register this clinical trial in a timely manner with ClinicalTrials.gov via a web based data entry system called the Protocol Registration System (PRS).

8.8 Protocol Amendments

Once the protocol is approved by the Steering Committee, it is then reviewed by an Advisory Board and a DSMB. After all approvals, the DCC will finalize the protocol document that serves as the agreement among all members of the Network. In the meantime, because the DCC administers all patient care costs for the RMN, the DCC will promptly issue subcontracts to the participating sites based on the cost agreements made by the Steering Committee and NICHHD.

After the protocols are approved by the RMN and the Steering Committee decides that changes are necessary for scientific or clinical reasons, the DCC will facilitate the procedure in a timely and diligent fashion. The RMN investigators and key personnel will participate in teleconferences and meetings, discuss, vote, and document circumstance and rationales for the changes as well as the implementation procedure for the changes. These include revising study hypotheses, designs, sample sizes, data entry forms, and appropriate statistical analyses. Once the amendments are finalized and agreed to by the RMN, they will be submitted to the IRB and DSMB for review and approval.

8.9 Timeline

Table 5: Timeline for MOXI

Study Activities	Year 1				Year 2				Year 3				Year 4				Year 5			
	J-M	A-J	J-S	0-D																
IND exemption	█																			
Formulate, test, package antioxidant and placebo	█	█																		
Finalize protocol, IRB revisions, interview modifications	█	█																		
Active enrollment of participants			█		█	█	█	█	█	█										
Treatment of participants			█		█	█	█	█	█	█										
Pregnancy Ultrasound				█	█	█	█	█	█	█	█									
Determination of Pregnancy Outcome					█	█	█	█	█	█	█	█								
Medical Record Abstraction				█	█	█	█	█	█	█	█	█	█							
Clean and compile data				█	█	█	█	█	█	█	█	█	█	█						
Analyze data (begin with clinical fecundability)																			█	█
Prepare and disseminate results																				█

9 RMN Publications Policy

The publications policy proposes guidelines for publications that originate from our collaborative Reproductive Medicine Network. Decisions concerning publications shall be determined by consensus (majority vote) of the collaborating Principal Investigators (or designees) noted below as the "Network." This policy is designed to promote prompt, exact, quality publications and presentations of Network studies with appropriate academic recognition of those with significant contributions. Protocols are classified into three types: 'Main Study' (which may include major and minor publications), "Ancillary Study", and 'Pilot Study'. Additionally, there may be publications from concepts or ideas generated by the RMN ("Related Publications") or from other groups utilizing RMN data and/or specimens, known as "Outside Studies" (those utilizing data and/or specimens from the RMN studies). Abstract submissions to national meetings will also follow the publications policy below. The progress of publications (including presentations) will be a standing agenda note on all teleconferences and meetings. The Steering Committee will make the final decision regarding disputes with respect to analysis request approval, prioritization, presentation, authorship and/or manuscript submission.

9.1 Main Study

A Main Study is a Network study designed prospectively by an investigator independent of other studies. Generally, that investigator becomes Lead Investigator of the protocol and Chair of the Protocol Subcommittee. At the end of each Main Study, a primary analysis resulting in the primary manuscript and a number of secondary analyses is produced based on the research questions stated in the protocol. The Protocol Subcommittee Chair is the primary author of the primary analysis. A Main Study can generate major (related to the major hypotheses) and minor publications (relating to secondary hypotheses).

9.1.1 Major Publications

A major publication is defined as one reporting results of the major hypotheses tested. (For example: Does hMG/IVF increase cyclic fecundity in couples with unexplained or male factor infertility?)

a. Authorship

Publications will include the names of investigators from each RMU and the DCC rather than merely identify the "Reproductive Medicine Network". Each RMU and the DCC will have up to two authors per publication, ordinarily the PI and the Co-PI, but this may at times involve another investigator who has contributed to the study at his/her site, in lieu of the PI or Co-PI. The Principal Investigator at each RMU will be responsible for submitting the names of the two authors from that unit and designating them as either the primary and secondary authors of the unit. No more than 2 authors may represent a RMN site. An ancillary site (such as a SCCPIR) may only have 1 investigator. The Steering Committee Chair and NICHD Project Scientist will be authors. Occasionally, additional authors, both within and outside the RMN

may be appropriate. In these cases, the final decision will be by Network consensus (majority vote of the Steering Committee required).

For the purpose of authorship, only one person from each site owns the primary PI status. This “PI” status is determined by the duration of the time from the start to end date of the site award. It is determined by whoever has served longer. There is NO automatic authorship for other PIs (new or old). They will be treated as any other RMN investigators, and their authorship would be resolved on a case-by-case basis per the current policy (i.e. based on the contribution to specific manuscripts and recommended by the first author and/or writing group). The general order of the authorship is as follows: Group A (the protocol lead PI and site PIs), Group B (important and long term contributors such as some additional site PIs, CREST PIs, DCC second author, core lab author, some co-Investigators), Group C (nominated ad hoc co-authors such as some additional site PIs, DCC third author, and others), Group D (SC Chair, NICHD Project Scientist, and DCC PI), and finally the RMN.

b. First Author

The lead investigator initiating the protocol, chairing the Protocol Subcommittee will be the first author. The first author will always be expected to prepare the initial draft of the manuscript, after receiving approval from the Network to proceed. The author will prepare the first draft of the manuscript in a timely fashion after receiving all the relevant data analyses from the DCC. The primary author will circulate the final draft to all authors prior to submission, with a timely turnaround of comments from other authors expected. Final decision of the manuscript content will be determined by the Protocol Subcommittee. In the event that the initiating protocol investigator declines first authorship or fails to meet the timeline determined by the Steering Committee (as determined by majority vote) and monitored monthly, the next RMU investigator in the rank order of authors (described below) will be the first author.

c. Authorship Order

All authorships are expected to meet reasonable criteria as set forth by the International Committee of Medical Journal Editors. (Uniform requirements for manuscripts submitted to biomedical journals: <http://www.icmje.org>. Updated February 2006. Accessed April 4, 2007.) The overall authorship order will be 1) the primary author, 2) RMU investigators, additional outside investigators with a limit of one author per site (e.g. SCCPIR investigators if applicable), followed by the Steering Committee Chair, NIH Project Scientist, and then the authors of the DCC.

Table 6: RMN Publication Authorship

Authorship Order Category	Description
1	Lead Investigator of the Protocol (N = 1)
2	Primary RMN Investigators of the Protocol (N = 6); DCC Investigator (N = 1)
3	Outside Investigators (i.e. Primary Investigator of SCCPIR sites) (N = to be determined)
4	Additional Investigators (by Steering Committee vote) (N = to be determined)
5	Secondary RMN Investigators (N = 7)
6	Steering Committee Chair (N = 1)
7	NIH Project Scientist (N = 1)
8	DCC PI (N = 1)
9	“for the NICHD Reproductive Medicine Network”

Table 7: Authorship Order of the RMUs and Outside Sites

Investigative Sites	# Subjects Rank	Accuracy Rank	Total Rank	Authorship Order
A	1	4	5	3
B	2	7	9	6
C	3	1	4	2
D	4	2	6	4
E	5	3	8	5
F	6	5	11	7

It is anticipated that there will be up to 18-25 authors per major manuscript. The authorship order of the RMUs and outside sites will be based upon subject recruitment, data accuracy and promptness of data report according to the chart below:

Data accuracy will be ranked according to the rate of missing or false data entries/randomized subjects at each site. Inquiries that show data was accurately entered will not count against this rate of data inaccuracy. Each site's PI will be responsible for documenting the contributions to the study of that site's authors. In the event the journal editor requires fewer authors even after written documentation of the authors' contribution has been provided, the Steering Committee will vote on the authorship order which will include at a minimum the Lead Investigator and PI of the DCC (or his/her designee) in the positions listed above with the authorship order ending with the footnoted statement "for the Reproductive Medicine Network". The other authors will be referenced in the footnote and listed in the title page.

d. Acknowledgement Section

The acknowledgement section will include other investigators and study personnel who contributed substantially to the study by site, as well as members of the Advisory Board and the Data and Safety Monitoring Board. The designation will list the initials of the individuals followed by their highest degree (e.g. C. L. Gnatuk, J.A. Ober, R.N., etc.).

Significant contributions include but are not limited to protocol review, initiation and participation at each site, subject recruitment and enrollment, study conduct, data analysis, and preparation of the manuscript.

9.1.2 Minor Publications

Minor studies are defined as those in which the hypotheses would not be the main elements of Network studies, but in which the study data base would be utilized to test secondary hypotheses. (One example would be testing whether metformin use spares the dose of clomiphene resulting in lower dose needs.) Ideas for "minor studies" will, in general, be proposed by a single individual, who would direct all efforts leading to publication and representation. The results from minor studies would be handled similarly to those from major studies. The "Protocol" is defined as the Concept Protocol/study design of the hypothesis resulting in the publication.

Authorship will follow the Major Publications guidelines above with the exception that the individual leading the minor study would be the first author, followed by the ranked primary RMN investigators involved in developing the Concept Protocol. The Lead Investigator of the minor publication can propose additional investigators who contributed to the study, whose inclusion in the authorship will be voted on by the Steering Committee (majority vote of SC required for inclusion in authorship). Centers may wish to withdraw inclusion from authorship of publications

of minor studies in which only data are contributed, and this will be the decision of the individual site (RMU) PI.

9.2 Ancillary Study

An Ancillary Study is an observational study, conducted as a supplement to a Main Study. By definition, an Ancillary Study involves all or a subset of patients enrolled in a Main Study. An Ancillary Study does not involve any additional participants. To be defined as an Ancillary Study, there must be a need for collection of additional data not already collected in the Main Study. An Ancillary Study may also be designed by another Network investigator, who would serve as the lead investigator and primary author of the paper. Ancillary Studies may be a “single-center” or “multi-center”.

A “single-center” Ancillary Study is a study in which all data are collected, stored and analyzed at a single center. The center bears the additional cost of such a study. The study requires approval of the Main Study Protocol Subcommittee and the Steering Committee. The center conducting the study is responsible for the analysis and reporting of the results. Abstracts and manuscripts resulting from data from the single-center Ancillary Study are not subject to the RMN Publications Policies.

A “multi-center” Ancillary Study is defined as one for which data or material (such as specimens) are collected at more than one center, or additional funds for conduct of the study are provided by the NICHD RMN and the DCC provides data analysis. Multi-center Ancillary Studies require the approval of the Main Study Protocol Subcommittee and the Steering Committee.

Authorship will be as per Major Publications above with the exception that the individual leading the Ancillary Study and writing the paper would be the first author, followed by ranked RMN primary investigators, etc. A center not participating in the Ancillary Study would not receive authorship unless by majority vote of the Steering Committee.

9.2.1 *Publication Policy on Ancillary Papers*

Authorship

1. RMN will be included as the group author and the acknowledgement will define the entire RMN roster as provided by all PIs.
2. The SC Chair, the NICHD Project Scientist, and all PIs will be co-authors upfront. The order will be recommended by the lead author(s).
3. Based on the ICJME statement for authorship (http://www.icmje.org/ethical_1author.html), anyone who makes additional contributions that are documented and substantive will be co-authors. Correcting typos and making grammar suggestions may be below the threshold.
4. The responsibilities of the lead authors and the DCC:

- a) If the first and corresponding authorships are offered to a fellow and the PI at a site, this team will recommend the order of the others. The DCC prepares the data for a specific manuscript with a note from the SC that the data should not be used for 'mining' other than answering the predefined questions. The site PI is responsible for the appropriate conduct of the analysis.
- b) The lead author or shared lead authors (at most two) from an RMN or CREST site is given the first choice of one authorship position and the DCC PI makes the second choice. These authors recommend the order of the others. The DCC will assist in the concepts, data preparation, data analysis, and manuscript section writing. If the lead author is not a site PI, the PI plays an administrative and logistic role to ensure that the lead author, whether within the institution, an affiliated CREST site or any other collaborating center, meets the timelines and expectations expressed below, and in return will be offered the second author, or the one preceding the DCC senior author position.

Timeline and expectations

1. The DCC prepares the data set within one month upon receiving the proper specification of the variables and cohort(s), assuming that the data exist in the database.
2. Time from receipt of primary data to first draft is not expected to exceed 3 months. Time from first draft to submitted manuscript is not expected to exceed 3 months.
3. Co-authors are expected to return comments and edits on manuscript drafts within two weeks of the request unless otherwise stated. Failure to respond within this time frame will lead to the assumption that the co-author fully approves the draft and has no comments or corrections.
4. The lead author(s) will be responsible for updating the progress of manuscripts at his/her site (and any CREST sites affiliated with that RMN site) on the Publication Subcommittee conference calls (which will replace Recruitment Subcommittee conference calls) to ensure that reasonable progress is occurring. The Publication Subcommittee can vote to change the authorship if the progress remains slow (e.g., exceeding the timeline expressed above) after two warnings.

9.3 Pilot Study

A Pilot Study is a preliminary study that generates data to help in the design of a Main Study and is the responsibility of the Main Study Protocol Subcommittee. The DCC collaborates with the Protocol Committee to complete the analysis, which may or may not generate an abstract for presentation and/or a manuscript for publication. The DCC writes a Final Report if there is sufficient data to justify one. It is not expected that there will be any secondary analyses resulting from a Pilot Study.

9.4 Related Publications

A related publication is one that has had significant input from members of the RMN Steering Committee at formal meetings in terms of study significance and design. It is distinct from an ancillary publication in that a related publication reports on a study, concept or new methodology that has not been subjected to formal DSMB review and approval. Generally, “Related Publications” will arise from ideas and studies discussed with the Steering Committee, but not voted upon to become formal protocols.

The investigator who initiates, conducts and writes the study, and those whom he/she names will be the sole authors. The authors should acknowledge the contribution of the NICHD Reproductive Medicine Network in the author line of the publication according to the format of the journal.

9.5 Outside Studies

Outside studies will result from the sharing of intellectual property, data and/or specimens with investigators whose protocols have been approved by the Steering Committee, and who comply with all components of those policies. All publications will acknowledge the assistance of the NICHD, the RMN, and the Protocol Subcommittee in making the database available on behalf of the project. In addition, however, a disclaimer will need to be included stating, “The contents of this report represent the views of the authors and do not represent the views of the NICHD Reproductive Medicine Network.” The authors will be requested to cc the submitted manuscript to the NICHD program official to ensure compliance. These policies apply to both Network centers and outside centers.

9.6 Presentations

Network data should be presented before national organizations by the Lead Investigators of Main Studies, Ancillary, and Pilot studies. Organizations that might be appropriate include the American Fertility Society, the Society for Gynecologic Investigation, the American College of Obstetricians and Gynecologists, the American Urology Society and other urology or andrology societies. All presentations will be approved by the Publications and Presentations Committee. Once data are published in at least abstract form, all members of the Network can cite them publicly in lectures.

However, investigators should avoid citing specific numbers in review articles and chapters, for this could jeopardize peer review publication. Authorship, First Author, and Author Order are as described for Major Publications, and if there is an authorship limit to the abstract, we will follow the plan above under Major Publications. Oral and poster presentations, including those resulting from secondary analyses at professional societies, must list all authors and participating institutions. In addition, they must include both the NICHD RMN logo and NIH Department of Health and Human Services logos that can be found on the Network web site.

9.7 Timelines

After conclusion of each protocol, the initiating investigator, designated as first author, will consult with the DCC for data analysis and conclusions. The investigator will draft an abstract for distribution to the Network and discussion at the next teleconference or Steering Committee meeting. This should be completed within two months of study completion. Presentation of such abstract may be discussed at this time.

The first author will prepare a draft manuscript within 3 months of data analysis for Network distribution. After incorporating network comments, discussion at the next Steering Committee meeting should allow preparation for publication to ensue in the following 3 months, such that submission will be possible 6 months after data analysis is complete.

9.8 NICHD Clearance

Prior to submitting an abstract for presentation or publication for journal review, the document should be sent to the Project Scientist for submission for NICHD Clearance.

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11 Informed Consent

11.1 Informed Consent Template – Male Partners

University of North Carolina Research Subject Combined Informed Consent and HIPAA Authorization Form

Protocol Title: Males, Antioxidants, and Infertility (MOXI) Trial

Principal Investigator: Anne Steiner, MD, MPH
4007 Old Clinic Bldg, CB 7570
Chapel Hill, NC 27599
919-966-5283

Emergency Contact: 919-966-5283 Monday to Friday, 9AM to 5PM
919-966-4131 During non-business hours (Ask for the Reproductive Endocrinologist on call)

Why am I being asked to volunteer?

You are being invited to participate in a research study. Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the study doctor and/or the research team about this form. If you decide to participate, you will be asked to sign this form.

What is the purpose of this research study?

The purpose of this research study is to learn if taking antioxidants can improve male fertility. After 1 year of trying, some couples will not become pregnant. This is called infertility. Male infertility can be caused by DNA damage in sperm. The DNA damage affects the sperm's ability to move or fuse with the egg. Earlier studies have shown that taking antioxidants such as vitamin C, vitamin E, selenium, N-acetylcysteine, L-carnitine, and Zinc might improve this DNA damage. While we know that taking antioxidants might improve DNA damage, we don't know if taking antioxidants can help couples get pregnant. This study will try to determine if taking antioxidants can help infertile couples achieve pregnancy.

You are being invited to participate in this research study because you are an adult male and you and your partner are currently experiencing infertility. To participate in this study you must be trying to get pregnant and living with your female partner.

How many people will take part in this study?

A total of approximately 790 couples at six institutions will take part in this study, including approximately 50 people from this institution.

How long will I be in the study?

You will be enrolled in the study for a minimum of 3 months or a maximum of 6 months.

What am I being asked to do?

If you decide to take part in this study, you and your partner will be asked to complete a brief eligibility questionnaire by phone or in person. If you and your partner qualify to take part in research, you and your partner will be scheduled to come into one of the study centers for a screening visit. This consent form will be reviewed by you and the study coordinator. The purpose of the study, all procedures involved, the risks, and the time commitment related to this study will be discussed. Once all questions have been answered, you will sign this consent form. A copy of this signed consent form will be given to you for your records. Your partner will also sign a separate consent form for participation in this study.

Your screening visit will include the following tests and assessments:

- Complete a questionnaire about your medical history, current medications, infertility history, demographic information, and family history.

- You will be asked to provide a semen sample if you have not had a semen analysis within the past 6 months, which will be used to determine if you are eligible for the study. If you have previously had a semen analysis test done within the past 6 months, we will ask you to sign a medical release form so we can obtain those results.

If you are considered eligible, you will be given 8 questionnaires to complete. A Medical Outcomes Survey (PHQ-9) and the Short Form 12 (SF 12) will assess your daily activities. A Risk Factor for Genetic Disorders questionnaire is completed to determine if you have an increased risk of fathering a child with a genetic disorder. FertiQOL will assess how your infertility affects your thoughts and feelings. The Stop Bang Questionnaire and Epworth Sleepiness Scale (ESS) will assess your sleep habits. The Diet History Questionnaire will be completed to assess your food choices over the past year. The International Index of Erectile Function Survey (IIEF), Psychosexual Daily Questionnaire (PDQ) and qADAM questionnaire will assess your sexual function. The Sun Exposure and Behaviour Inventory (SEBI) will assess your sunscreen usage. You will be free to skip any questions that you would prefer not to answer.

If both you and your partner are considered eligible for the study, you will return to the study center to begin study treatment. You will be randomized by a computer system to receive either an antioxidant formulation or placebo. A placebo is a pill that looks just like the antioxidant tablets but does not contain any active medication.

Neither you nor your study team will know which treatment you will receive. Half of participants are expected to receive placebo. You will take the study drug for at least three and up to six months. You will be asked to provide a semen sample at study visit 1 and 90 days later, at study visit 3. We will also obtain approximately 15mL of blood (2 teaspoons) from your vein at study visits 1, 2, 3 and 4. If you and your partner have not become pregnant by the end of three months of study treatment, your partner will receive up to three cycles of infertility treatment in the form of clomiphene citrate and intrauterine insemination (IUI). You will be given an additional 3 months of study medication to take during this time.

This study will include the following tests and assessments:

Questionnaires

You will be required to complete the questionnaires described above at your screening visit. In addition, you will also complete the ASA24, which asks you questions about the food you have eaten over the past 24 hours. You will be asked to complete the ASA24 twice throughout this study, at study visit 1 and study visit 3.

Blood Draws

We will collect approximately 15mL of blood (2 teaspoons) from your vein at four different times throughout the study. These blood draws will be used to look at certain reproductive hormones and vitamin levels in your blood. You will not be given these results.

Urine sample

You will provide a urine sample at the first study visit. The urine sample will be used to test for common environmental pollutants. You will not be given these results.

Semen Collection

You will be asked to provide a semen sample at screening (if necessary), study visit 1, study visit 3, and for each insemination cycle up to 3 cycles. For this semen analysis test, it is important to not have sex or masturbate for 48 hours prior to collecting your samples.

The following are the instructions you will follow to collect your sample. There is a private room near the lab where specimens can be collected.

1. Wash your hands and genitals in the normal way and dry thoroughly.
2. Use the cup provided by the study coordinator or the lab. Do not open the container until you are ready to produce the sample.
3. Collect the sample by masturbation, putting the entire specimen directly into the cup.
4. Do not use lubricants or condoms, as these are harmful to sperm.
5. Seal the cup immediately with the lid.

Once you have completed your collection, a semen analysis will be performed to determine the concentration of sperm, motility (moving) and morphology (appearance). You will be given your results.

Repository Semen and Blood Specimen Collection

If you consent to the optional part of the study, an additional 2 tablespoons of blood will be drawn for future testing. A portion of your semen will also be collected and stored as part of the repository. These will only be collected if you have consented to the optional part of the study.

Study Timeline

Study visit 1

- Complete a food intake questionnaire (ASA24) online

- Height / Weight
- Measurement of neck, waist and hip circumference
- Provide a semen sample
- Provide a urine sample
- Provide a blood sample
- Randomization
- Pick up one month's supply of study medication

Study visit 2 (approximately 30 days after visit 1)

- Provide a blood sample
- Give old study pill packages, including any leftover pills to study staff
- Pick up 2 month's supply of study medication
- Pick up ovulation strips and pregnancy tests
- Schedule next study visit

Study visit 3 (approximately 60 days after visit 2)

- Complete a food intake questionnaire (ASA24) online
- Give old study pill packages, including any leftover pills to study staff
- Provide a semen sample
- Provide a blood sample
- Pick up 3 month's supply of study medication

If you and your partner have not become pregnant:

Clomiphene Citrate + Intrauterine Insemination Cycles (up to 3)

- Assist your partner with the injection of hCG trigger medication
- Provide semen for IUI

Study visit 4 (approximately 90 days following visit 3)

- Provide a blood sample
- Give old study pill packages to study staff, including any leftover pills

The following study procedures will be performed once you and your partner have become pregnant:

- Pregnancy Ultrasound (between 6 to 9 weeks gestation)

- **Pregnancy Status Update:** Women will be contacted by study staff (usually between 20 and 22 weeks gestation) to get an update on where she is receiving prenatal care and where she expects to deliver her baby.
- **Pregnancy Outcome:** Study staff will contact you or your partner after the planned delivery date to obtain pregnancy outcome information such as birth weight, date of delivery, or delivery complications.

What will happen to the blood sample that I donate to the study?

The sample of blood you donate to the study will not have your name on it and will be stored in a freezer with other samples. The samples will be stored until they are used by the investigators at The University of North Carolina, or their collaborators. The blood will be tested for certain reproductive hormones and vitamin levels in your blood. You will not be able to remove your sample once it is donated.

What are the possible risks or discomforts?

You may experience minimal discomfort, bruising, and a low risk of infection with the blood draw. We understand that you may not want others to know that you and your partner are trying to get pregnant. We will do our best to protect your confidentiality. In addition, there may be uncommon or previously unknown risks related to the study medication or study procedures. You should report any problems to the researcher. The doses of antioxidants in the supplement have been shown to be safe. Do not take any vitamins in addition to the supplement you are provided as you may then exceed the safe dosage of each vitamin.

Risks of Genetic Testing:

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information.

This law generally will protect you in the following ways:

Health insurance companies and group health plans may not request your genetic information that we get from this research.

Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this Federal law does not protect you or your family against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Also, GINA does not prohibit discrimination of individuals with a genetic disorder that has been diagnosed. However, in order to do everything possible to keep this from happening, the results of this test will NOT be given to anyone outside the study staff. This means that it will not be made available to you, your family members, your private physician, your employer, your insurance company or any other party as allowed by law.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

You will not benefit personally from being in this research study. Research is designed to benefit society by gaining new knowledge.

What other choices do I have if I do not participate?

You do not have to participate in this study to receive treatment for your infertility. Choosing not to participate will not have any effect on your clinical care.

Will I be paid for being in this study?

You will not be paid to be in the study but you will receive study medications (antioxidant pills or placebo) free of charge. You and your partner will receive six free pregnancy tests and 21 ovulation strips while participating in this study. If you and your partner do not become pregnant following 3 months of study treatment, your partner will receive infertility treatment in the form of clomiphene citrate and intrauterine insemination. If your partner becomes pregnant during the study, you will receive an ultrasound of your baby. You will not have to pay for the antioxidant, placebo, clomiphene citrate, the IUI procedures, or the pregnancy ultrasound.

Will I have to pay for anything?

For costs of tests and procedures that are only being done for the research study:

- The semen analysis will be provided by the Reproductive Medicine Network at no cost to you.
- You and/or your insurance company will not be charged for the cost of any tests or procedures that are required as part of the research.
- The research-related tests and procedures that will be provided at no cost to you include: semen analysis and research-related blood work and urine collection.

For costs of medical services for care you would receive even if you were not in this research study:

- You and/or your insurance company will be responsible for the cost of routine medications, tests and procedures that you would receive even if you were not in this research.
- You and/or your insurance company will be billed for the costs of these routine tests and procedures in the usual manner.
- You will be responsible for any co-payments, co-insurance and deductibles that are standard for your insurance coverage.
- You will be responsible for any charges not reimbursed by your insurance company.
- Some insurance companies will not pay for routine costs for people taking part in research studies. Before deciding to be in this research you should check with your insurance company to find out what they will pay for.

If you have any questions about costs and insurance, ask the research study doctor or a member of the research team about putting you in touch with a financial counselor to determine exactly what the deductible and co-pay will be for you; this is highly variable depending on your type of insurance.”

What happens if I am injured from being in the study?

All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury from being in this study.

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate,

for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of North Carolina to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed in the consent form.

When is the Study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped at any time by your physician, the study Sponsor, or the Food and Drug Administration (FDA) without your consent because:

- The Primary Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The Sponsor, the study Principal Investigator, or the Food and Drug Administration (FDA) has decided to stop the study.

If you decide to participate, you are free to leave the study at any time. Withdrawal will not interfere with your future care.

What information about me may be collected, used or shared with others?

The following information may be used or disclosed for this research project:

- Name, address, telephone number, email address, date of birth
- Medical record number
- Information from your medical records pertaining to your medical history, pregnancy outcome, and information related to all assessments and treatments for this pregnancy

Why is my information being used?

Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- do the research

- oversee the research
- see if the research was done right.

Who may use and share information about me?

The following individuals may use or share your information for this research study:

Representatives of the following people/groups within The University of North Carolina may use your health information and share it with other specific groups in connection with this research study.

- The principal investigator, Anne Steiner, MD, MPH
- The University of North Carolina-Chapel Hill Institutional Review Board
- The University of North Carolina-Chapel Hill Human Subjects Protection Office
- The members of the research team working with Anne Steiner
- Other authorized personnel at The University of North Carolina who may have access to your information to perform their daily duties (laboratory personnel, financial personnel, etc.).

Who, outside of the School of Medicine, might receive my information?

The above people/groups may share your health information with the following people/groups outside The University of North Carolina for their use in connection with this research study. These groups, while monitoring the research study, may also review and/or copy your original The University of North Carolina records.

- The Office of Human Research Protections in the U.S. Department of Health and Human Services
- Food and Drug Administration
- Data Coordination Center at Yale University
- Reproductive Medicine Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development
- National Institute of Health
- The University of Pennsylvania Institutional Review Board
- The University of Pennsylvania Human Subjects Protection Office

Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to The University of North Carolina procedures developed to protect your privacy.

How long may the School of Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- The University of North Carolina's Institutional Review Board grants permission
- As permitted by law
- As permitted by law

Who is sponsoring this study?

This research is funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

Who can see or use my information? How will my personal information be protected?

The investigators and the research team will be able to see your medical records as authorized by you. Results of laboratory tests and clinical procedures done for the monitoring or treatment of your infertility will be placed in your medical record and will be accessible to employees of the health system that are not part of the research team. This information may also be viewed by your insurance company during routine audits.

Privacy and confidentiality measures:

Your records that are used in the research at The University of North Carolina will include your study identification number, your initials, and visit date and will be kept in a secured area in a locked file cabinet. Your samples collected for research purposes will be labeled with your study identification number, initials, and visit date and will be stored in a -80 degree freezer.

For research records sent to the Data Coordination Center at Yale University, you will be identified by your study identification number and study visit date. Your blood specimens will not identify you and you cannot be linked to your specimen. The list that matches your name with your code number will be kept in a secured area in a locked file cabinet or in a password-protected electronic document at University of North Carolina.

To help protect your privacy, a Certificate of Confidentiality will be obtained from the federal government. This Certificate means that the researchers cannot be forced (for example by court subpoena) to share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the U.S. government that is used for checking or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

The Certificate, however, does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information. This means that you and your family should actively protect your own privacy.

The Certificate of Confidentiality does not prevent researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under the following circumstances: child abuse, intent to harm yourself or others, or if you have reportable communicable disease that state or federal law requires us to report such as Tuberculosis, HIV infection, or Syphilis.

In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared. Your de-identified information may be used in the future for other research. Your de-identified data will be shared with the National Institute of Child Health and Human Development on the Data and Specimen Hub which is a resource for investigators to share de-identified research data from studies.

A copy of this consent form will go in to your medical record. This will allow the doctors caring for you to know what study medications or tests you may be receiving as a part of the study and know how to take care of you if you have other health problems or needs during the study.

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. If this study is being overseen by the Food and Drug Administration (FDA), they may review your research records.

If you test positive for reportable infectious diseases, by law we have to report the infection to the City of Philadelphia Health Department/PA Department of Health. We would report your name, gender, racial/ethnic background, and the month and year you were born.

Electronic Medical Records and Research Results

What is an Electronic Medical Record?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

If you are receiving care or have received care within the University of North Carolina Health System (outpatient or inpatient) and are participating in a University of North Carolina research study, results of research-related procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UNC.

If you have never received care within UPHS and are participating in a University of North Carolina research study that uses UNC services, an EMR will be created for you for the purpose of maintaining any results of procedures performed as part of this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a

hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). Results of research procedures performed as part of your participation in the study (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in this EMR.

Once placed in your EMR, these results are accessible to appropriate UNC workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UNC to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc.).

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Institutional Review Board with any question, concerns or complaints at the University of North Carolina by calling 919-966-3113 or by email to IRB_subjects@unc.edu.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of North Carolina to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of North Carolina to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you.

Name of Subject (Please Print)	Signature of Subject	Date

Name of Person Obtaining Consent (Please Print)	Signature	Date

Optional part(s) of the study

In addition to the main part of the research study, there is another part of the research. You can be in the main part of the research without agreeing to be in this optional part.

Optional Collection of Saliva for Biomarkers of Stress

As part of an optional part of the study, you will provide us with a sample of saliva. This saliva sample will be tested for biomarkers of stress such as amylase and cortisol. You will be asked to collect the sample upon waking using a kit provided to you. There are no risks or pain associated with the collection. The sample can be returned in person or via prepaid overnight shipping. Neither you nor your doctor will receive the

results of these tests. There is no cost to you to participate in this optional portion of the study.

You should initial below to indicate your preference for the collection of your saliva for testing:

_____ I give my permission for my saliva to be collected and tested for stress biomarkers.

_____ I decline my permission for my saliva to be collected and tested for stress biomarkers.

Optional Storage of Blood for RMN Biologic Repository

As part of an optional study, we are obtaining a sample of your blood to be stored in a Biologic Repository by the Reproductive Medicine Network for future use. If you agree, approximately 2 tablespoons of your blood will be collected at the randomization visit and shipped to the RMN Biologic Repository (a central location) and stored for a minimum of 5 years, and perhaps into the future. Your sample will be tested for DNA and to measure other substances in your blood. If you agree to allow us to collect and store a blood sample from you for future use in the repository, your sample will be labeled with a bar code label and unique identifier. These samples will be stored in a locked laboratory at The University of North Carolina, until shipment to the repository. If you consent to the collection of your blood for the repository, it will be kept indefinitely or until the sample is exhausted by the Reproductive Medicine Network. Once your blood has left The University of North Carolina, there is no way to have it returned or withdrawn for testing. You will not be able to withdraw your permission for the use of your blood sample for future use at this time.

We are also collecting blood and urine as a part of this study. If you agree, we would like to retain any leftovers after their use in the study for future use, including measuring other substances from your blood and urine. If you agree to let us retain these samples they will be stored in a locked laboratory at The University of North Carolina, until shipment to the repository. If you consent to the retention of these samples blood and urine for the repository, they will be kept indefinitely or until the sample is exhausted by the Reproductive Medicine Network. Once your blood and urine has left the University of North Carolina, there is no way to have it returned or withdrawn for testing. You will not be able to withdraw your permission for the use of your blood and urine sample for future use at this time.

- These future studies may be helpful in understanding male infertility and the vitamins used in this trial.

- It is unlikely that these studies will have a direct benefit to you.
- The results of these tests will not have an effect on your care.
- Neither your doctor nor you will receive results of these future research tests, nor will the results be put in your health record.
- It is possible that your blood might be used to develop products or tests that could be patented and licensed. There are no plans to provide financial compensation to you should this occur. If you have any questions, you should contact a member of the research team.

You should ***initial*** below to indicate your preference for the collection of your blood and urine for the repository:

_____ I **give my permission** for my blood sample to be collected and sent to the repository for future testing.

_____ I **decline my permission** for my blood sample to be collected and sent to the repository for future testing.

You should ***initial*** below to indicate your preference for your leftover blood and urine to be retained and sent to the repository:

_____ I **give my permission** for my leftover blood and urine sample(s) to be retained and sent to the repository for future testing.

_____ I **decline my permission** my leftover blood and urine sample(s) to be retained and sent to the repository for future testing.

Optional Storage of Semen for Future Use in Research

As part of an optional study, we want to obtain a sample of your semen to be stored by the RMN for future testing in the RMN Biologic Repository. If you agree, your semen sample will be collected at the screening visit after informed consent. We are also collecting semen as a part of this study. If you agree, we would like to retain any leftover semen not used for the primary study for future research.

Your sample will be stored for a minimum of 5 years, and perhaps further into the future. Your sample will be tested for the chemicals that make up all of your genes and contain your genetic information. These samples can be used for other research in the future

after this study is over. Your sample will not be labeled with any of your personal information, such as your name or a code number. The sample for the repository is labeled with a bar code and cannot be directly linked back to you. They will be available for use in future research studies indefinitely and cannot be removed due to the inability to identify them.

- These future studies may be helpful in understanding male fertility and the vitamins used in this trial.
- It is unlikely that these studies will have a direct benefit to you.
- The results of these tests will not have an effect on your care.
- Neither your doctor nor you will receive results of these future research tests, nor will the results be put in your health record.
- It is possible that your semen sample might be used to develop products or tests that could be patented and licensed. There are no plans to provide financial compensation to you should this occur. If you have any questions, you should contact a member of the research team.

You should ***initial*** below to indicate your preference for the collection of your semen sample for the repository:

_____ I **give my permission** for a portion of my semen sample to be collected and sent to the repository for future testing.

_____ I **decline my permission** for a portion of my semen sample to be collected and sent to the repository for future testing.

11.2 Informed Consent Template – Female Partners

**University of North Carolina
Research Subject
Combined Informed Consent and HIPAA Authorization Form**

Protocol Title: Males, Antioxidants, and Infertility (MOXI) Trial

Principal Investigator: Anne Steiner, MD, MPH
4007 Old Clinic Bldg, CB 7570
Chapel Hill, NC 27599
919-966-5283

Emergency Contact: 919-966-5283 Monday to Friday, 9AM to 5PM
919-966-4131 During non-business hours (Ask for the Reproductive Endocrinologist on call)

Why am I being asked to volunteer?

You are being invited to participate in a research study. Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the study doctor and/or the research team about this form. If you decide to participate, you will be asked to sign this form.

What is the purpose of this research study?

The purpose of this research study is to learn if taking antioxidants can improve male fertility. After 1 year of trying, some couples will not become pregnant. This is called infertility. Male infertility can be caused by DNA damage in sperm. The DNA damage affects the sperm's ability to move or fuse with the egg. Earlier studies have shown that taking antioxidants such as vitamin C, vitamin E, selenium, N-acetylcysteine, L-carnitine, and Zinc might improve this DNA damage. While we know that taking antioxidants might improve DNA damage, we don't know if taking antioxidants can help couples get pregnant. This study will try to determine if taking antioxidants can help infertile couples achieve pregnancy.

You are being invited to participate in this research study because you are an adult female and you and your partner are currently experiencing infertility. To participate in this study, you must be trying to get pregnant and living with your male partner.

How many people will take part in this study?

A total of approximately 790 couples at six institutions will take part in this study, including approximately 50 people from this institution.

How long will I be in the study?

If you achieve pregnancy during this study, you will be enrolled in this study from the time you sign this consent form until you have your early pregnancy ultrasound. Study staff will contact you to obtain information about your pregnancy outcome. If you and your partner do not become pregnant, you will be enrolled in this study from the time you sign this consent form to the time your partner has completed six months of study treatment.

What am I being asked to do?

If you decide to take part in this study, you and your partner will be asked to complete a brief eligibility questionnaire by phone or in person. If you and your partner qualify to take part in research, you and your partner will be scheduled to come into one of the study centers for a screening visit. This consent form will be reviewed by you and the study coordinator. The purpose of the study, all procedures involved, the risks, and the time commitment related to this study will be discussed. Once all questions have been answered, you will sign this consent form. A copy of this signed consent form will be given to you for your records. Your partner will also sign a separate consent form for participation in this study.

Your screening visit will include the following tests and assessments:

- Your past medical and menstrual history will be recorded. This form will ask a series of questions about your medical health, family health history, reproductive and gynecological history, pregnancy history, and current use of medications.
- Your height, weight, vital signs (blood pressure and pulse) and neck circumference will be collected and your body mass index (BMI) will be calculated.
- You will be given 9 questionnaires to complete. A Risk Factor for Genetic Disorders questionnaire is completed to determine if you have an increased risk of having a baby with a genetic disorder. Any potential problems that may lead to complications during pregnancy will be addressed at this time and we may refer you to a genetics counselor prior to starting the study. The Female Sexual Function Index (FSFI) and Female Sexual Distress Scale (FSDS) will assess your sexual function. A Medical Outcomes Survey (PHQ-9) and the Short Form 12 (SF 12) will assess your daily activities. FertiQOL will assess how your infertility affects your thoughts and feelings. The Stop Bang Questionnaire and Epworth Sleepiness Scale (ESS) will assess your sleep habits. The Dietary History Questionnaire II will be completed to assess your current dietary intake. You will be free to skip any questions that you would prefer not to answer.
- The following tests will be done if you have not had them done previously. If you have had them done, you will need to sign a medical record release so that we may obtain these results.
 - Blood work may be drawn to determine your eligibility for the study. Tests that may be drawn are a progesterone level, FSH, estradiol, or AMH level.
 - If you have had not had a test within the past 3 years to determine that your fallopian tubes are open, a sonohysterogram (SHG) or hysterosalpingogram (HSG) will be completed. During the SHG, sterile saline fluid is injected through an intrauterine catheter that contains a balloon. The balloon is inflated and the shape of your uterus can be seen and the fluid that accumulates in the back area of your uterus determines that at least one fallopian tube is open. If it can't be determined by the SHG, it will be necessary for a different procedure to be performed. An HSG procedure is done in the radiology department using radio-opaque contrast dye that is injected into the uterus and is visualized flowing through the fallopian tube. If you have been pregnant within the last three years and your pregnancy and delivery were uncomplicated, the SHG or HSG may not be necessary.
 - A physical exam will be performed by the physician if not done within the past 12 months.
 - A pap smear will be collected if you are 21 or older and have not had one within the time period specified by current guidelines.

If you consent to the optional part of the study, an additional 2 tablespoons of blood will be drawn and a urine sample collected for the biological repository.

If you and your partner are considered eligible for the study, your partner will return to the study center to begin study treatment. Your partner will be randomized by a computer system to receive either an antioxidant formulation or placebo. A placebo is a pill that looks just like the antioxidant tablets but does not contain any active medication.

Neither you, your partner, nor your study team will know which treatment he will receive. Half of participants are expected to receive placebo. He will take the study drug for at least three and up to six months. If you are not pregnant by the end of the third month of study treatment, you will receive up to three cycles of infertility treatment in form of clomiphene citrate and intrauterine insemination (IUI) while he is on treatment.

The following procedures will be performed if you and your partner have **not** become pregnant following the third study visit (after 3 months of study treatment):

Baseline Visit – Infertility Treatment (clomiphene citrate + IUI)

You will call on the first day of your next menstrual period following your partner's third study visit to schedule your baseline visit for infertility treatment between menstrual cycle day 1-5. At this visit the following procedures will occur:

- Transvaginal Ultrasound. This involves inserting an ultrasound probe into your vagina to visualize your ovaries and uterus. Measurements and ultrasound pictures will be recorded of your ovaries and uterus.
- Your medications will be given to you at this time. You will receive clomiphene citrate. You will be instructed to begin your medications if your urine pregnancy test is negative and your ultrasound results are within a normal range. You will also receive hCG injection medication to be used when directed by your physician prior to your insemination. You and your partner will be taught the technique for administering an intramuscular injection.

Monitor Visits (cycle day 8 to 12 and then beyond as required)

You will be required to return to the clinic within 3 days after completing your 5 day treatment of clomiphene citrate. A transvaginal ultrasound will be performed. You may be required to return to the clinic regularly for additional monitoring visits until you have met the criteria for hCG administration. These visits will be individualized and based on your physician's discretion.

When your main follicle (cyst which contains an egg) gets to a certain size, you will be instructed to self or partner-administer an injection of hCG at a dose of 10,000 IU. A cycle may be cancelled if the lead follicles become too large or too small after 18 days of monitoring.

Intrauterine Insemination Visit

You must return to the clinic within 44 hours of the hCG shot. Your partner will provide a semen sample. This sample will be washed and prepared for the insemination. A speculum will be placed in your vagina and a thin flexible catheter will be placed into your cervix. The sperm will be injected through the catheter and into your uterus.

Urine Pregnancy Test

Two weeks after insemination you will do a urine pregnancy test at home and call the study coordinator with your results.

If you have a positive urine pregnancy test, you will be required to return to the clinic for a blood pregnancy test (quantitative bhCG). If your bhCG is positive you will return 2 days later for repeat bhCG to check for a rising level. If the level is not rising, you will begin the next cycle of treatment with the start of your menstrual cycle. If the bhCG level has risen, you will be schedule for an ultrasound approximately 14-21 days after the positive result.

Follow up Initiation of Cycle 2 & 3

If your urine pregnancy test is negative after a cycle, you may start another cycle of treatment. You may participate for a maximum of 3 cycles. A cycle may be cancelled if any significant adverse reactions develop in response to the medications, if you are unable to have the hCG injection, or if you request the cycle to be cancelled. The study coordinator will provide you with instructions to start your medication on cycle day 3 (+ or – 2 days). The study physician may change the start dose of your Clomiphene Citrate. You will be scheduled for a return monitoring visit during menstrual cycle day 8-12.

The following study procedures will be performed once you and your partner **have** become pregnant:

- Pregnancy Ultrasound (between 6 to 9 weeks gestation)
- Pregnancy Status Update: Women will be contacted by study staff (usually between 20 and 22 weeks gestation) to get an update on where she is receiving prenatal care and where she expects to deliver her baby.

- **Pregnancy Outcome:** Study staff will contact you or your partner after the planned delivery date to obtain pregnancy outcome information such as birth weight, date of delivery, or delivery complications.

Pregnancy Ultrasound:

This transvaginal ultrasound will determine the location of your pregnancy, number of gestational sacs and to assess fetal heartbeat.

Pregnancy Care:

You may need additional ultrasounds done to evaluate the progress of the pregnancy if necessary. Pregnancy care is not part of this study. You will be scheduled with your obstetrician for follow up prenatal care. If you do not have a doctor who delivers babies, you will be referred to one. Before being released from the study, you will be asked to sign a medical release form so the study coordinator can obtain your pregnancy and delivery information. You will be contacted between 12 and 22 weeks to see how your pregnancy is progressing.

What will happen to the blood sample that I donate to the study?

The sample of blood you donate to the study will not have your name on it and will be stored in a freezer with other samples. The samples will be stored until they are used by the investigators at The University of North Carolina, or their collaborators. The blood will be tested for certain reproductive hormones and vitamin levels in your blood. You will not be able to remove your sample once it is donated.

What are the possible risks or discomforts?

You may experience minimal discomfort, bruising, and a low risk of infection with the blood draw. You may experience abdominal or pelvic discomfort due to the transvaginal ultrasound used in this study.

Risks associated with the sonohystogram/hysterosalpingogram include pain, bleeding, damage to the uterus, pelvic infection, interrupting an unrecognized pregnancy, small amount of radiation exposure, allergic reaction to the radio-opaque dye.

Risks associated with clomiphene citrate: visual changes (such as blurring of vision, double vision, light sensitivity), abdominal pain, nausea, vomiting, constipation, mood changes, depression, headache, hot flashes, respiratory difficulty, fatigue, abnormal endometrial thickening, multiple pregnancies, formation of ovarian cyst causing ovarian hyperstimulation syndrome, ovarian enlargement, breast discomfort, abnormal uterine

bleeding, bloating, hair loss, arrhythmias, chest pain, allergic reaction, palpitations, and stroke or pulmonary embolism.

Risks associated with intrauterine insemination include Vasovagal response (feeling lightheaded, dizzy, sweating); possible infection.

We understand that you may not want others to know that you and your partner are trying to get pregnant. We will do our best to protect your confidentiality. In addition, there may be uncommon or previously unknown risks related to the study medication or study procedures. You should report any problems to the researcher.

Risks of Genetic Testing:

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information.

This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this Federal law does not protect you or your family against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Also, GINA does not prohibit discrimination of individuals with a genetic disorder that has been diagnosed. However, in order to do everything possible to keep this from happening, the results of this test will NOT be given to anyone outside the study staff. This means that it will not be made available to you, your family members, your private physician, your employer, your insurance company or any other party as allowed by law.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

You will not benefit personally from being in this research study. Research is designed to benefit society by gaining new knowledge.

What other choices do I have if I do not participate?

You do not have to participate in this study to receive treatment for your infertility. Choosing not to participate will not have any effect on your clinical care.

Will I be paid for being in this study?

You will not be paid to be in this study. You and your partner will receive 6 free pregnancy tests and 21 ovulation strips while participating in this study. If you and your partner do not become pregnant following 3 months of study treatment, you will receive infertility treatment in the form of clomiphene citrate, human chorionic gonadotropin, and intrauterine insemination. If you become pregnant during the study, you will receive an ultrasound of your baby. You will not have to pay for the clomiphene citrate, human chorionic gonadotropin, the IUI procedures, or the pregnancy ultrasound.

Will I have to pay for anything?

For costs of tests and procedures that are only being done for the research study:

- The Clomiphene Citrate and hCG injection will be provided by RMN at no cost to you.
- You and/or your insurance company will not be charged for the cost of any tests or procedures that are required as part of the research.
- The research-related tests and procedures that will be provided at no cost to you include:
 - All study required blood tests
 - Physical exam
 - Transvaginal ultrasound (s)
 - Tests ordered for the study to determine tubal patency such as a sonohystogram
 - Intrauterine inseminations
 - Ovulation predictor kits
 - Urine pregnancy tests
 - Supplies for injection medication such as; syringes, alcohol swabs, gauze, and band-aids

- 1 Pregnancy Ultrasound

For costs of medical services for care you would receive even if you were not in this research study:

- You and/or your insurance company will be responsible for the cost of routine medications, tests and procedures that you would receive even if you were not in this research.
- You and/or your insurance company will be billed for the costs of these routine tests and procedures in the usual manner.
- You will be responsible for any co-payments, co-insurance and deductibles that are standard for your insurance coverage.
- You will be responsible for any charges not reimbursed by your insurance company.
- Some insurance companies will not pay for routine costs for people taking part in research studies. Before deciding to be in this research you should check with your insurance company to find out what they will pay for.

The following is a list of the non-covered services related to this study:

- Prior testing
- Rubella, Varicella, & HIV testing
- Pap Smear
- Carrier screening for genetic diseases
- Doxycycline prescription for after the HSG procedure, if necessary
- Remaining obstetrical ultrasounds after the first one
- Pregnancy care and delivery costs

If you have any questions about costs and insurance, ask the research study doctor or a member of the research team about putting you in touch with a financial counselor to determine exactly what the deductible and co-pay will be for you; this is highly variable depending on your type of insurance.

What happens if I am injured from being in the study?

All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury from being in this study.

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of North Carolina to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed in the consent form.

When is the Study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped at any time by your physician, the study Sponsor, or the Food and Drug Administration (FDA) without your consent because:

- The Primary Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The Sponsor, the study Principal Investigator, or the Food and Drug Administration (FDA) has decided to stop the study.

If you decide to participate, you are free to leave the study at anytime. Withdrawal will not interfere with your future care.

What information about me may be collected, used or shared with others?

The following information may be used or disclosed for this research project:

- Name, address, telephone number, email address, date of birth
- Medical record number
- Information from your medical records pertaining to your medical history, pregnancy outcome, and information related to all assessments and treatments for this pregnancy

Why is my information being used?

Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- do the research
- oversee the research
- see if the research was done right.

Who may use and share information about me?

The following individuals may use or share your information for this research study:

Representatives of the following people/groups within The University of North Carolina may use your health information and share it with other specific groups in connection with this research study.

- The principal investigator, Anne Steiner, MD, MPH
- The University of North Carolina Institutional Review Board
- The University of North Carolina Human Subjects Protection Office
- The members of the research team working with Anne Steiner
- Other authorized personnel at The University of North Carolina who may have access to your information to perform their daily duties (laboratory personnel, financial personnel, etc.)

Who, outside of the School of Medicine, might receive my information?

The above people/groups may share your health information with the following people/groups outside The University of North Carolina for their use in connection with this research study. These groups, while monitoring the research study, may also review and/or copy your original The University of North Carolina records.

- The Office of Human Research Protections in the U.S. Department of Health and Human Services
- Food and Drug Administration
- Data Coordination Center at Yale University
- Institutional Review board at The University of Pennsylvania
- Reproductive Medicine Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development
- National Institute of Health
- City of Chapel Hill Health Department/NC Department of Health

Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to The University of North Carolina procedures developed to protect your privacy.

How long may the School of Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- The University of North Carolina's Institutional Review Board grants permission
- As permitted by law
- As permitted by law

Who is sponsoring this study?

This research is funded by the National Institute of Child Health and Human Development. This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

Who can see or use my information? How will my personal information be protected?

The investigators and the research team will be able to see your medical records as authorized by you. Results of laboratory tests and clinical procedures done for the

monitoring or treatment of your infertility will be placed in your medical record and will be accessible to employees of the health system that are not part of the research team. This information may also be viewed by your insurance company during routine audits.

Privacy and confidentiality measures:

Your records that are used in the research at The University of North Carolina will include your study identification number, your initials, and visit date and will be kept in a secured area in a locked file cabinet. Your samples collected for research purposes will be labeled with your study identification number, initials, and visit date and will be stored in a -80 degree freezer.

For research records sent to the Data Coordination Center at Yale University, you will be identified by your study identification number and study visit date. Your blood specimens will not identify you and you cannot be linked to your specimen. The list that matches your name with your code number will be kept in a secured area in a locked file cabinet or in a password-protected electronic document at University of North Carolina

To help protect your privacy, a Certificate of Confidentiality will be obtained from the federal government. This Certificate means that the researchers cannot be forced (for example by court subpoena) to share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the U.S. government that is used for checking or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

The Certificate, however, does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information. This means that you and your family should actively protect your own privacy.

The Certificate of Confidentiality does not prevent researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in

the research project under the following circumstances: child abuse, intent to harm yourself or others, or if you have reportable communicable disease that state or federal law requires us to report such as Tuberculosis, HIV infection, or Syphilis.

In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared. Your de-identified information may be used in the future for other research. Your de-identified data will be shared with the National Institute of Child Health and Human Development on the Data and Specimen Hub which is a resource for investigators to share de-identified research data from studies.

A copy of this consent form will go in to your medical record. This will allow the doctors caring for you to know what study medications or tests you may be receiving as a part of the study and know how to take care of you if you have other health problems or needs during the study.

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. If this study is being overseen by the Food and Drug Administration (FDA), they may review your research records.

If you test positive for reportable infectious diseases, by law we have to report the infection to the City of Chapel Hill Health Department/NC Department of Health. We would report your name, gender, racial/ethnic background, and the month and year you were born.

This is to keep track of how many people in the U.S. have HIV infection. It is also to make sure that states get enough money from the federal government to support the medical care of people living with HIV. The Health Department does not share the names of HIV infected people with anyone else. It removes all personal identifiers, such as your name, before giving information on the number of HIV infections to the federal government.

Electronic Medical Records and Research Results

What is an Electronic Medical Record?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

If you are receiving care or have received care within the University of North Carolina (outpatient or inpatient) and are participating in a University of North Carolina research study, results of research-related procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UNC Healthcare.

If you have never received care within UNC and are participating in a University of North Carolina research study that uses UNC services, an EMR will be created for you for the purpose of maintaining any results of procedures performed as part of this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). Results of research procedures performed as part of your participation in the study (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in this EMR.

Once placed in your EMR, these results are accessible to appropriate UNC workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UNC to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc.).

Optional part(s) of the study

In addition to the main part of the research study, there is another part of the research. You can be in the main part of the research without agreeing to be in this optional part.

Optional Collection of Saliva for Biomarkers of Stress

As part of an optional part of the study, you will provide us with a sample of saliva. This saliva sample will be tested for biomarkers of stress such as amylase and cortisol. You will be asked to collect the sample upon waking using a kit provided to you. There are no risks or pain associated with the collection. The sample can be returned in person or via prepaid overnight shipping. Neither you nor your doctor will receive the results of these tests. There is no cost to you to participate in this optional portion of the study.

You should initial below to indicate your preference for the collection of your saliva for testing:

_____ I give my permission for my saliva to be collected and tested for stress biomarkers.

_____ I decline my permission for my saliva to be collected and tested for stress biomarkers.

Optional Storage of Blood and Urine for RMN Biologic Repository

As part of an optional study, we are obtaining a sample of your blood and urine to be stored in a Biologic Repository by the Reproductive Medicine Network for future use. If you agree, approximately 2 tablespoons of your blood will be collected at the randomization visit and shipped to the RMN Biologic Repository (a central location) and stored for a minimum of 5 years, and perhaps into the future. Your sample will be tested for DNA and to measure other substances in your blood and urine. If you agree to allow us to collect and store a blood and urine sample from you for future use in the repository, your sample will be labeled with a bar code label and unique identifier. These samples will be stored in a locked laboratory at The University of North Carolina, until shipment to the repository. If you consent to the collection of your blood and urine for the repository, it will be kept indefinitely or until the sample is exhausted by the Reproductive Medicine Network. Once your blood and urine has left University of North Carolina, there is no way to have it returned or withdrawn for testing. You will not be able to withdraw your permission for the use of your blood and urine sample for future use at this time.

- These future studies may be helpful in understanding male infertility and the vitamins used in this trial.
- It is unlikely that these studies will have a direct benefit to you.
- The results of these tests will not have an effect on your care.
- Neither your doctor nor you will receive results of these future research tests, nor will the results be put in your health record.
- It is possible that your blood might be used to develop products or tests that could be patented and licensed. There are no plans to provide financial compensation to you should this occur. If you have any questions, you should contact a member of the research team.

You should ***initial*** below to indicate your preference for the collection of your blood and urine for the repository:

_____ I **give my permission** for my blood and urine sample to be collected and sent to the repository for future testing.

_____ I **decline my permission** for my blood and urine sample to be collected and sent to the repository for future testing.

Who can I call with questions, complaints or if I’m concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Institutional Review Board with any question, concerns or complaints at the University of North Carolina by calling 919-966-3113 or by email to IRB_subjects@unc.edu.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of North Carolina to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of North Carolina to disclose that personal health information to outside organizations or people involved with the operations of this study.

By signing below, you also indicate that you have read the information written above and have indicated your choices for the optional part(s) of the research study.

A copy of this consent form will be given to you.

Name of Subject (Please Print) Signature of Subject Date

Your signature below means that you have explained the optional part(s) to the research to the subject or subject representative and have answered any questions he/she has about the research.

Name of Person Obtaining
Consent (Please Print)

Signature

Date

12 Appendix A: Male Medical History Questionnaire



Male Medical History

Source Document

Reproductive Medicine Network

Males, Antioxidants, and Infertility (MOXI) Trial

MEDICAL HISTORY

Do you have a history of any of the following medical conditions or problems?

Body System	Response (If NO, skip to next question)	Condition/Problem	Currently Symptomatic	Requires Medication
1. Problems with your head, ears, eyes, nose or throat?	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Hearing loss <input type="checkbox"/> Blindness <input type="checkbox"/> Sinus <input type="checkbox"/> Surgery (specify): _____ <input type="checkbox"/> Other (specify): _____	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
2. Problems with your brain, nervous system or any psychiatric conditions?	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Stroke <input type="checkbox"/> Migraines <input type="checkbox"/> Seizures <input type="checkbox"/> CVA/TIA <input type="checkbox"/> Depression <input type="checkbox"/> Anxiety <input type="checkbox"/> Bipolar disorder <input type="checkbox"/> Schizophrenia/Psychosis <input type="checkbox"/> Obsessive-Compulsive Disorder <input type="checkbox"/> ADD/ADHD <input type="checkbox"/> Eating Disorder (anorexia, bulimia)	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>

		<input type="checkbox"/> Post-Traumatic Stress <input type="checkbox"/> Acute Stress Disorder <input type="checkbox"/> Substance/Alcohol Abuse <input type="checkbox"/> Phobia/Agoraphobia <input type="checkbox"/> Surgery (specify): _____ <input type="checkbox"/> Other (specify): _____	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
3. Problems with your respiratory system?	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Asthma <input type="checkbox"/> Pneumonia <input type="checkbox"/> COPD <input type="checkbox"/> Emphysema <input type="checkbox"/> TB <input type="checkbox"/> Surgery (specify): _____ <input type="checkbox"/> Other (specify): _____	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
4. Problems with your heart or cardiovascular system?	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Previous heart attack <input type="checkbox"/> Congenital heart defect <input type="checkbox"/> Palpitations <input type="checkbox"/> Arrhythmias <input type="checkbox"/> Valve disease <input type="checkbox"/> Angina <input type="checkbox"/> CHF <input type="checkbox"/> Hypertension <input type="checkbox"/> Syncope <input type="checkbox"/> Blood clot in leg, lung, brain <input type="checkbox"/> Surgery (specify): _____ <input type="checkbox"/> Other (specify): _____	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/>

<p>5. Problems with your muscles, joints, bones or musculoskeletal system?</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Arthritis <input type="checkbox"/> Lupus <input type="checkbox"/> Osteoporosis <input type="checkbox"/> Gout <input type="checkbox"/> Disc disease <input type="checkbox"/> Surgery (specify): _____ <input type="checkbox"/> Other (specify): _____	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
<p>6. Problems with your gastrointestinal system?</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Irritable bowel <input type="checkbox"/> GI cancer <input type="checkbox"/> Liver disease <input type="checkbox"/> Peptic ulcer <input type="checkbox"/> GERD <input type="checkbox"/> Hepatitis <input type="checkbox"/> Pancreatitis <input type="checkbox"/> Surgery (specify): _____ <input type="checkbox"/> Other (specify): _____	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
<p>7. Problems with your blood and metabolic system?</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Clotting <input type="checkbox"/> Anemia <input type="checkbox"/> Hyperlipidemia <input type="checkbox"/> Diabetes <input type="checkbox"/> Hyper/hypothyroidism <input type="checkbox"/> Surgery (specify): _____ <input type="checkbox"/> Other (specify): _____	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
<p>8. Problems with the whole body?</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Cancer <input type="checkbox"/> Alcoholism <input type="checkbox"/> Drug abuse	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/>

		<input type="checkbox"/> Allergies <input type="checkbox"/> Fatigue <input type="checkbox"/> Weakness <input type="checkbox"/> Surgery (specify): _____ <input type="checkbox"/> Other (specify): _____	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
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9. Have you ever been treated for cancer?

Yes No → Skip to Question #10

9a. If yes, specify type of cancer:

- Testicular
- Hodgkin's
- Lymphoma
- Leukemia
- Bladder
- Prostate
- Other

(specify): _____

9b. Was surgery used for treatment?

Yes No

9c. Was chemotherapy used for treatment?

Yes No → Skip to Question #9d

9c1. If yes, specify type: (check all that apply)

- Cisplatinum chemotherapy (Platinol)
- Cyclophosphamide (Cytoxan)
- Busulfan (Myleran)
- Nitrosoureas (Carmustine, Lomustine)
- L-phenylalanine mustard (Alkeran)
- Bleomycin (Blenoxane, Bleomycin)
- Chlorambucil (Leukeran)
- Procarbazine (Natulan, Matulane)
- Nitrogen mustard (Mustargen)
- Other

(specify): _____

Unknown

9d. Was radiation used for treatment?
#10

Yes No → Skip to Question

9d1. If yes, specify location:

Pelvic

Brain

Total body irradiation

Other

(specify): _____

10. Have you had a high fever (≥ 103 °F) in the last six months? Yes No

11. Have you ever been diagnosed with a sexually transmitted infection/disease?

Yes No → Skip to Question #12

11a. Type of STD/STI: (check all that apply)

Gonorrhea

Chlamydia

Syphilis

Herpes Simplex Virus (HSV)

Human Papillomavirus (HPV)

Trichomoniasis (Trich)

Other

(specify): _____

11b. Did you receive treatment?

Yes No

12. Have you ever had a urinary tract infection (bladder infection)?

Yes No → Skip to Question #13

12a. Indicate number of times:

— —

13. Have you ever had epididymitis?

Yes No → Skip to Question #14

13a. Indicate number of times:

— —

14. Have you ever had prostatitis?

Yes No → Skip to Question #15

14a. Indicate number of times:

— —

18e. How many of times have you tried to quit smoking
(ever)? _____ times

18f. How long ago did you quit smoking?

<1 year 11-15 years
 1-5 years >15 years
 6-10 years NA- currently smoking

18g. Do/did you use any other forms of tobacco? Yes No → *Skip to Question #19*

18g1. If yes, please indicate other tobacco products:

Cigars Pipes
 Snus/snuff/dip Chew
 Electric Cigarettes
 Dissolvables
 Hookah/water pipe
 Other (specify): _____

19. On a scale of 1 thru 7, are you around smokers much of the time?

1- Not at all true of me
 2
 3
 4
 5
 6
 7- Extremely true of me

20. How many people who live in your household use tobacco? (Do not count yourself) _____ people

21. Does your spouse or partner currently use tobacco? Yes No

22. Have you used any recreational drugs or non-prescribed prescription medicines in the last 3 months? Yes No → Skip to Question #23

22a. If yes, indicate what type:

- Marijuana
- Cocaine
- Methadone / Narcotics
- Other (specify): _____

23. During the last 12 months, how often did you usually have any kind of drink containing alcohol? Choose only one. (By a drink we mean half an ounce of absolute alcohol (e.g. a 12 ounce can or glass of beer or cooler, a 5 ounce glass of wine, or a drink containing one shot of liquor))

- Everyday
- 5 to 6 times a week
- 3 to 4 times a week
- twice a week
- once a week
- 2 to 3 times a month
- once a month
- 3 to 11 times in the past year
- 1 or 2 times in the past year

→If any of the responses are checked above, proceed to Question #24.←

I did not drink any alcohol in the past year, but I did drink in the past

→ Skip to Question #23a.

I never drank any alcohol in my life

→ Skip to Question #23b.

23a. During your **lifetime**, what is the maximum number of drinks containing alcohol that you drank within a 24-hour period?

- 36 drinks or more
- 24 to 35 drinks
- 18 to 23 drinks
- 12 to 17 drinks
- 8 to 11 drinks
- 5 to 7 drinks
- 4 drinks
- 3 drinks
- 2 drinks
- 1 drink

→STOP HERE, and proceed to Question #26.←

23b. So you have never had a drink containing alcohol in your entire life?

- Yes, I never drank →Skip to Question #26
- No, I did drink. →Return to Question #23

24. During the last 12 months, how **many** alcoholic drinks did you have on a typical day when you drank alcohol? Choose only one.

- 25 or more drinks
- 19 to 24 drinks
- 16 to 18 drinks
- 12 to 15 drinks
- 9 to 11 drinks
- 7 to 8 drinks

- 5 to 6 drinks
- 3 to 4 drinks
- 2 drinks
- 1 drink

25. During the last 12 months, how often did you have 4 or more drinks containing any kind of alcohol within a two-hour period? Choose only one. (That would be equivalent of a least 4 12-ounce cans or bottles of beer, 4 five ounce glasses of wine, 4 drinks each containing one shot of liquor or spirits.)

- Everyday
- 5 to 6 days a week
- 3 to 4 days a week
- 2 days a week
- one day a week
- 2 to 3 days a month
- one day a month
- 3 to 11 days in the past year
- 1 or 2 days in the past year
- 0 days in the past year

26. Are you exposed to pesticides on a regular basis? Yes No

27. Have you been exposed to toxic chemicals? Yes No → Skip to Question #28

27a. If yes, what types:

28. Are you exposed to radiation (x-rays) regularly? Yes No

29. Are you exposed to prolonged heat regularly?

(e.g. hot tubs, saunas)?

Yes No

30. Have you ever taken testosterone or anabolic steroids? Yes No → Skip to Question #31

30a. Are you currently using steroids?

Yes No → Skip to Question #31

30b. Please list:

PATERNITY/FERTILITY HISTORY

31. Have you ever created a pregnancy with anyone?

Yes No

32. Have you ever had any infertility treatment and/or surgery in the past?

Yes No → Skip to Question #33

32a. What type of treatment/surgery did you have?

(check all that apply)

- Varicocele Repair
- Vasectomy Reversal
- In Vitro Fertilization
- In Vitro Fertilization with
Intracytoplasmic
Sperm Injection (IVF
with ICSI)
- Viagra/Cialis/Levitra
- Intrauterine Insemination
(IUI)
- Intrauterine Insemination
with ICSI (IUI with ICSI)
- Inguinal hernia repair
- Prostate Surgery
- Other

(specify): _____

33. During the time you have been trying to conceive, have you ever had a male genital examination? Yes No → Skip to Question #34

33a. If yes, were you told that you have dilated scrotal veins? (e.g. varicoceles) Yes No

34. How long have you and your partner been trying to get pregnant?
 — — — — months OR Unknown

35. Have you achieved pregnancy with your current partner? Yes No → Skip to Question #36

35a. If yes, complete the table below:

Pregnancy	Date
<input type="checkbox"/> #1	___/___/_____ Month Day Year
<input type="checkbox"/> #2	___/___/_____ Month Day Year
<input type="checkbox"/> #3	___/___/_____ Month Day Year
<input type="checkbox"/> #4	___/___/_____ Month Day Year
<input type="checkbox"/> #5	___/___/_____ Month Day Year

36. Currently, what is your average frequency of intercourse with your partner?

- <1 per month
- 1-2 times per month
- 1 time per week
- 2-3 times per week
- Daily

37. Do you know how to time intercourse to your partner’s menstrual cycle?
 Yes No

38. Do you use any lubrication during intercourse? Yes No

MEDICATION INFORMATION

39. Are you currently taking any medications? Yes No

(include prescription medications and over the counter medications, do not include supplements here)

→If Yes, please list all medications on the Concomitant Medications CRF←

40. Are you taking any vitamins, multivitamins, or herbal supplements?
 Yes No

→If Yes, please speak with the study staff immediately←

41. Have you taken any vitamins, multivitamins, or herbal supplements over the past six months?
 Yes No

DEMOGRAPHICS

42. What is your age? _____ years old

43. What is your marital status? (check only one)

- Single
- Married
- Divorced
- Separated
- Widowed

44. What is your highest level of education?

- 8th grade or less
- Some high school
- High school graduate
- Some college
- College graduate
- Graduate degree

45. What is your occupation? (check only one)

- Management, Business & Financial Occupations
- Computer, Engineering & Science Occupations
- Education, Legal, Community Service, Arts, & Media Occupations
- Healthcare Practitioners and Technical Occupations
- Service Occupations
- Sales and Related Occupations
- Office & Administrative Support Occupations
- Farming, Fishing, & Forestry Occupations
- Construction & Extraction Occupations
- Installation, Maintenance, & Repair Occupations
- Production Occupations
- Transportation & Material Moving Occupations
- Military Specific Occupations
- Student

- Retired
- Unemployed
- Disabled

46. What is your annual Household Income?

(check only one)

- <\$25,000
- \$25,000 to \$49,999
- \$50,000 to \$74,999
- \$75,000 to \$100,000
- >\$100,000
- Wish to not answer

47. What type(s) of Insurance coverage do you have? (check all that apply)

- Managed Care Plan or HMO
- Other Private Insurance
- Medicaid
- Medicare
- Self-pay/Uninsured

48. Are you currently participating in any other clinical trial?

- Yes No

SIGNATURE

Patient completed form Study coordinator performed an interview of this questionnaire

I have reviewed the data captured on this form and to the best of my knowledge it is correct.

Signature: _____

Date: ___/___/___

Month Day Year

13 Appendix B: Female Medical History Questionnaire



Medical History-Female Partner

Source Document

Reproductive Medicine Network

Males, Antioxidants, and Infertility (MOXI) Trial

MEDICAL HISTORY

Do you have a history of any of the following medical conditions or problems?

Body System	Response (If NO, skip to next question)	Condition/Problem	Currently Symptomatic	Requires Medication
1. Problems with your head, ears, eyes, nose or throat?	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Hearing loss <input type="checkbox"/> Blindness <input type="checkbox"/> Sinus <input type="checkbox"/> Surgery (specify): _____ <input type="checkbox"/> Other (specify): _____	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
2. Problems with your brain, nervous system or any psychiatric conditions?	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Stroke <input type="checkbox"/> Migraines <input type="checkbox"/> Seizures <input type="checkbox"/> CVA/TIA <input type="checkbox"/> Depression <input type="checkbox"/> Anxiety <input type="checkbox"/> Bipolar disorder <input type="checkbox"/> Schizophrenia/Psychosis	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>

		<input type="checkbox"/> Obsessive-Compulsive Disorder <input type="checkbox"/> ADD/ADHD <input type="checkbox"/> Eating Disorder (anorexia, bulimia) <input type="checkbox"/> Post-Traumatic Stress <input type="checkbox"/> Acute Stress Disorder <input type="checkbox"/> Substance/Alcohol Abuse <input type="checkbox"/> PMS/PMDD <input type="checkbox"/> Phobia/Agoraphobia <input type="checkbox"/> Surgery (specify): _____ <input type="checkbox"/> Other (specify): _____	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
<p>3. Problems with your respiratory system?</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Asthma <input type="checkbox"/> Pneumonia <input type="checkbox"/> COPD <input type="checkbox"/> Emphysema <input type="checkbox"/> TB <input type="checkbox"/> Surgery (specify): _____ <input type="checkbox"/> Other (specify): _____	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>

<p>4. Problems with your heart or cardiovascular system?</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Previous heart attack <input type="checkbox"/> Congenital heart defect <input type="checkbox"/> Palpitations <input type="checkbox"/> Arrhythmias <input type="checkbox"/> Valve disease <input type="checkbox"/> Angina <input type="checkbox"/> CHF <input type="checkbox"/> Hypertension <input type="checkbox"/> Syncope <input type="checkbox"/> Blood clot in leg, lung, brain <input type="checkbox"/> Surgery (specify): _____ <input type="checkbox"/> Other (specify): _____	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
<p>5. Problems with your muscles, joints, bones or musculoskeletal system?</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Arthritis <input type="checkbox"/> Lupus <input type="checkbox"/> Osteoporosis <input type="checkbox"/> Gout <input type="checkbox"/> Disc disease <input type="checkbox"/> Surgery (specify): _____ <input type="checkbox"/> Other (specify): _____	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
<p>6. Problems with your gastrointestinal system?</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Irritable bowel <input type="checkbox"/> GI cancer <input type="checkbox"/> Liver disease <input type="checkbox"/> Peptic ulcer <input type="checkbox"/> GERD <input type="checkbox"/> Hepatitis <input type="checkbox"/> Pancreatitis	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>

		<input type="checkbox"/> Surgery (specify): _____ <input type="checkbox"/> Other (specify): _____	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>
7. Problems with your blood and metabolic system?	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Clotting <input type="checkbox"/> Anemia <input type="checkbox"/> Hyperlipidemia <input type="checkbox"/> Diabetes <input type="checkbox"/> Hyper/hypothyroidism <input type="checkbox"/> Surgery (specify): _____ <input type="checkbox"/> Other (specify): _____	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>

8. Problems with the whole body?	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Cancer (specify): _____ <input type="checkbox"/> Alcoholism <input type="checkbox"/> Drug abuse <input type="checkbox"/> Allergies <input type="checkbox"/> Fatigue <input type="checkbox"/> Weakness <input type="checkbox"/> Adrenal or Ovarian androgen secreting tumor <input type="checkbox"/> Cushing's Syndrome <input type="checkbox"/> Surgery (specify): _____ <input type="checkbox"/> Other (specify): _____	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
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→If any of these conditions require medication treatment, record medications on the concomitant medication log←

ENVIRONMENTAL EXPOSURES

9. Have you ever used cigarettes? Never → *Skip to Question #10*
 Current
 Former

→Current or former users, proceed to questions 9a through 9g←

- 9a. Are you currently smoking? Yes No

- 9b. On average, how many cigarettes do/did you smoke per day?
 1-10 21-40
 11-20 >40

- 9c. On days that you can/could smoke cigarettes freely, how soon after you wake do you smoke your first cigarette of the day? minutes hours

- 9d. How many years have/had you smoked? <1 year 6-10 years
 1-5 years >15 years

- 9e. How many times have you tried to quit smoking (ever)? _____ times

- 9f. How long ago did you quit smoking? <1 year 11-15 years
 1-5 years >15 years
 6-10 years
 NA- currently smoking

9g. Do/did you use any other forms of tobacco? Yes No → Skip to Question #10

- 9g1. If yes, please indicate other tobacco products:
- Cigars
 - Pipes
 - Snus/snuff/dip
 - Electric Cigarettes
 - Dissolvables
 - Hookah/water pipe
 - Other
- (specify): _____

10. On a scale of 1 thru 7, are you around smokers much of the time?

- 1- Not at all true of me
- 2
- 3
- 4
- 5
- 6
- 7- Extremely true of me

11. How many people who live in your household use tobacco? (Do not count yourself)

— — people

12. Does your spouse or partner currently use tobacco? Yes No

13. Have you used any recreational drugs or non-prescribed prescription medicines in the last 3 months? Yes No → Skip to Question #14

13a. If yes, indicate what type(s): (check all that apply) Marijuana

- Cocaine
- Methadone/Narcotics
- Other
(specify): _____

14. During the last 12 months, how often did you usually have any kind of drink containing alcohol? Choose only one. (By a drink we mean half an ounce of absolute alcohol (e.g. a 12 ounce can or glass of beer or cooler, a 5 ounce glass of wine, or a drink containing one shot of liquor).

- Everyday
- 5 to 6 times a week
- 3 to 4 times a week
- twice a week
- once a week
- 2 to 3 times a month
- once a month
- 3 to 11 times in the past year
- 1 or 2 times in the past year

→If any of the responses are checked above, proceed to Question #15.←

I did not drink any alcohol in the past year, but I did drink in the past

→ Skip to Question #14a.

I never drank any alcohol in my life

→ Skip to Question #14b.

14a. During your lifetime, what is the maximum number of drinks containing alcohol that you drank within a 24-hour period?

- 36 drinks or more
- 24 to 35 drinks
- 18 to 23 drinks

- 12 to 17 drinks
- 8 to 11 drinks
- 5 to 7 drinks
- 4 drinks
- 3 drinks
- 2 drinks
- 1 drink

→STOP HERE, and proceed to Menstrual History Section.←

14b. So you have never had a drink containing alcohol in your entire life?

- Yes, I never drank →*Skip to next section*
- No, I did drink. →*Return to Question #14*

15. During the last 12 months, how many alcoholic drinks did you have on a typical day when you drank alcohol? Choose only one.

- 25 or more drinks
- 19 to 24 drinks
- 16 to 18 drinks
- 12 to 15 drinks
- 9 to 11 drinks
- 7 to 8 drinks
- 5 to 6 drinks
- 3 to 4 drinks
- 2 drinks
- 1 drink

16. During the last 12 months, how often did you have 4 or more drinks containing any kind of alcohol within a two-hour period? Choose only one. (That would be equivalent of a least 4 12-

Check if used	Medication	Duration (months)
<input type="checkbox"/>	21a. Birth control pills	____ <input type="checkbox"/> Unknown
<input type="checkbox"/>	21b. Progesterone (e.g. Provera)	____ <input type="checkbox"/> Unknown
<input type="checkbox"/>	21c. Letrozole	____ <input type="checkbox"/> Unknown
<input type="checkbox"/>	21d. Anastrozole	____ <input type="checkbox"/> Unknown
<input type="checkbox"/>	21e. Cabergoline (Dostinex)	____ <input type="checkbox"/> Unknown
<input type="checkbox"/>	21f. GnRH agonist (e.g. any form- Lupron, Synarel)	____ <input type="checkbox"/> Unknown
<input type="checkbox"/>	21g. Metformin (Glucophage)	____ <input type="checkbox"/> Unknown
<input type="checkbox"/>	21h. Rosiglitazone (Avandia)	____ <input type="checkbox"/> Unknown
<input type="checkbox"/>	21i. Other (specify): _____	____ <input type="checkbox"/> Unknown
<input type="checkbox"/>	21j. Other (specify): _____	____ <input type="checkbox"/> Unknown
<input type="checkbox"/>	21k. Other (specify): _____	____ <input type="checkbox"/> Unknown
<input type="checkbox"/>	21l. Other (specify): _____	____ <input type="checkbox"/> Unknown

22. Have you ever had a pap smear? Yes No → Skip to

Question #23

22a. Date of last pap smear: ____ / ____ / _____

22b. Was the result of this pap smear abnormal? Yes No

23. Have you ever been diagnosed with a sexually transmitted disease/infection? Yes No → Skip to

Question #24

23a. Type of STD/STI: (check all that apply)

- Gonorrhea
- Chlamydia
- Syphilis

- Herpes Simplex Virus (HSV)
- Human Papillomavirus (HPV)
- Trichomoniasis (Trich)
- Other

(specify): _____

23b. Did you receive treatment? Yes No

24. Have you been diagnosed with Pelvic Inflammatory disease?

Yes No → Skip to Question #25

24a. Did you receive treatment? Yes No

25. Have you ever been diagnosed with Fibroids? Yes No → Skip to Question #26

25a. Did you receive treatment? Yes No

26. Have you ever been diagnosed with Endometriosis? Yes No → Skip to Question #27

26a. Did you receive treatment? Yes No

27. Have you ever had any gynecological procedures or surgeries done with the past?

Yes No → Skip to Question #28

If yes, check below types of procedures or surgeries done: (check all that apply)

Check if ever had	Type of Procedure or Surgery	Date (MM/YYYY)
<input type="checkbox"/>	27a. Ultrasound (transvaginal or abdominal)	___/___/___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27b. Hysterosalpingogram (HSG)	___/___/___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27c. Sonohysterogram (SHG)	___/___/___ <input type="checkbox"/> Unknown

<input type="checkbox"/>	27d. Hysteroscopy	___/___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27e. Colposcopy	___/___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27f. Salpingo-oophorectomy	___/___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27g. Tubal ligation	___/___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27h. Endometrial ablation	___/___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27i. Polypectomy	___/___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27j. Oophorectomy	___/___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27k. Uterine dilation & curettage	___/___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27l. Salpingectomy	___/___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27m. Ovarian surgery	___/___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27n. Hysterectomy with or without oophorectomy	___/___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27o. Unilateral or bilateral oophorectomy	___/___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27p. Ovarian cyst removal	___/___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27q. Endometriosis	___/___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27r. Lysis of adhesions	___/___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27s. Myomectomy	___/___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27t. UAE (uterine artery embolization)	___/___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27u. Diagnostic laparoscopy	___/___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27v. IUD removal	___/___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27w. Caesarean section	___/___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27x. LEEP	___/___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27y. Other (specify): _____	___/___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	27z. Other (specify): _____	___/___ ___ <input type="checkbox"/> Unknown

INFERTILITY HISTORY

28. How long have you been trying to get pregnant? ___ months OR Unknown

29. Have you ever received a diagnosis from a physician for why you have trouble getting pregnant? Yes No → *Skip to Question #30*

- 29a. What was your diagnosis? (Check all that apply)
- Ovulatory dysfunction (e.g. PCOS)
 - Tubal factor (e.g. blocked tubes)
 - Endometriosis
 - Uterine factor (e.g. fibroids)
 - Male factor infertility
 - Unexplained
 - Intra-abdominal adhesions
 - Cervical factor

30. Have you ever received therapy for infertility? Yes No → *Skip to Question #31*

If yes, check below types of therapies previously used: (check all that apply)

Check if ever used	Name of Therapy	Number of times received (enter "99" if unknown)	Date (MM/YYYY)
<input type="checkbox"/>	30a. Clomiphene Citrate (Clomid)	___	___ / ___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	30b. Clomid and Intrauterine Insemination (IUI)	___	___ / ___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	30c. Letrozole (Femara)	___	___ / ___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	30d. Letrozole and Intrauterine Insemination (IUI)	___	___ / ___ ___ <input type="checkbox"/> Unknown
<input type="checkbox"/>	30e. Intrauterine Insemination with no medication	___	___ / ___ ___ <input type="checkbox"/> Unknown

<input type="checkbox"/>	30f. Clomid/gonadatropins/IUI	---	___ / ___	<input type="checkbox"/> Unknown
<input type="checkbox"/>	30g. Gonadatropins (infertility shots)	---	___ / ___	<input type="checkbox"/> Unknown
<input type="checkbox"/>	30h. Gonadatropins with IUI	---	___ / ___	<input type="checkbox"/> Unknown
<input type="checkbox"/>	30i. Lupron/gonadotropins/IUI	---	___ / ___	<input type="checkbox"/> Unknown
<input type="checkbox"/>	30j. In Vitro Fertilization (IVF)	---	___ / ___	<input type="checkbox"/> Unknown
<input type="checkbox"/>	30k. IVF with Intracytoplasmic Sperm Injection (ICSI)	---	___ / ___	<input type="checkbox"/> Unknown
<input type="checkbox"/>	30l. Frozen Transfer	---	___ / ___	<input type="checkbox"/> Unknown
<input type="checkbox"/>	30m. Donor sperm	---	___ / ___	<input type="checkbox"/> Unknown
<input type="checkbox"/>	30n. Donor egg	---	___ / ___	<input type="checkbox"/> Unknown
<input type="checkbox"/>	30o. Donor embryo	---	___ / ___	<input type="checkbox"/> Unknown
<input type="checkbox"/>	30p. Other (specify): _____	---	___ / ___	<input type="checkbox"/> Unknown
<input type="checkbox"/>	30q. Other (specify): _____	---	___ / ___	<input type="checkbox"/> Unknown

CONCOMITANT MEDICATIONS

31. Are you allergic to any medications? Yes No → Skip to Question #32

Please list these medications:

32. Are you currently taking any medications on a daily basis? Yes No

33. Are you currently taking any vitamins or supplements on a daily basis?

Yes No

→If YES to Question #32 & #33, complete Concomitant Medication CRF←

SIGNATURE

- Patient completed form
- Study coordinator performed an interview of this questionnaire

To the best of your knowledge the above information is correct.

Signature of Patient: _____ Date: ____/____/_____
Month Day Year

The above information has been verified with the patient and is complete.

Signature: _____ Date: ____/____/_____
Month Day Year

14 Appendix C: List of Prohibited Concomitant Medications

Female

Progestins (Oral or Cyclic)

medroxyprogesterone acetate (Provera, Cycrin, Amen, Curretab)

megestrol (Megase) norethindrone (Aygestin)

progesterone gel (Crinone)

Micronized progesterone (Prometrium)

GnRH Agonists/Antagonists Leuprolide (Lupron)

nafarelin (Synarel)

buserelin gosarelin (Zoladex)

ganarelix (Antagon) cetrotorelix

(Cetrotide) Gonadotropins

Pergonal

Repronex

Follistim

Gonal-F

Fertinex

Metrodin

Injectable Contraceptives

medroxyprogesterone acetate (Depo Provera)

Oral Contraceptives Any Brand

Continuous Progestins (Not including cyclic)

Any Brand

Contraceptive Implants

Norplant (levonorgestrel implants)

Implanon

Clomiphene

Letrozole (femara)

Tamoxifen

Male

Inflammatory bowel disease medications - Need 3 month washout

Sulfasalazine

Azulfidine

Azulfidine EN

Azathioprine

Infliximab

Antihypertensives - Need 3 month washout

Calcium channel blockers

Nifedipine

Adalat

Afeditab

Nifediac

Nifedical

Procardia

Spironolactone

5 alpha reductase medications

Finasteride (Propecia, Proscar)

Alfatradiol (Eli-Cranell Alpha, Pantostin)

Dutasteride (Avodart)

Flutamide

Cimetidine (Tagamet) - Need 3 month washout

Immunosuppressive agents within the past 1 year

Chemotherapeutic agents within the past 1 year

Androgens - Need 6 month washout

DHEA or DHEAS, androstenedione

OTC "testosterone boosting" herbals and supplements

OTC workout enhancing supplements

Synthetic testosterone or anabolic steroids - Need 6 month washout

Testred

Android

Axiron

Androgel 1%

Androgel 1.62%

Tesetim

Fortesta

Vogelxo

Striant

Androderm

Natesto

Aveed

Testosterone cypionate

Testosterone enanthate

Testopel

Testosterone modulating medications - Need 3 month washout

Clomid

Anastrozole

HCG

Profasi

Ovidrel

Lupron

Zoladex

Cannabis (**Marijuana**) - Need 3-month washout

15 Appendix D: Review of Antioxidant Formulations

15.1 Commercially Available Formulations

Ingredient	Coast 4 Caps	Countboost 2 Caps	ProCreation 2 Caps	Fertilaid 3 Caps	Fertilsan 3 Caps	MotilityBoost 2 Caps	Proceptin 4 Caps	Proxeed 1 packet	Popmen 3 Caps	Conception XR 4 caps	Blend 2 caps
Acetyl-L-Carnitine							x	500 mg			
Calcium (as amino acid chelate)			50 mg								
Chromium (as polynicotinate)			.12 mg	.12 mg					.12 mg		
Coenzyme Q10 (Ubiquinone)		x		x	15 mg	x	x	20 mg			
Copper (as gluconate)			2 mg						2 mg		
Folate (as folic acid)	1 mg		400 mcg	500 mcg	.8 mg		533 mg	.2 mg	.5 mg	1mg	0.4mg
Glutathione											
Iodine				150 mcg					.15 mg		
Iron (as amino acid chelate)			5 mg								
L-Arginine (free from amino acid)			100 mg		500 mg	x	x				
L-Carnitine (as L-carnitine-L-tartrate)			50 mg	x	500 mg	x	x	1000 mg		1000mg	
L-Glutathione		x					x				
L-Methionine	25 mg						x				
L-taurine			50 mg								
Lycopene	100 mg						x			10mg	
Manganese (as amino acid chelate)			5 mg	120 mg					2 mg		
N-acetyl-L-cystine					80 mg	x					
Niacin (as Inositol Hexanicotinate)		25 mg	20 mg	20 mg					20 mg		
Pantothenic Acid (as calcium pantothenate)			10 mg	10 mg					10 mg		
Relora® (U.S. Patent 6,582,735)	250 mg										
Selenium (as L-selenomethionine)	0.25 mg		.1 mg	0.1mg	.06 mg		.133 mg	.05 mg	.1 mg	0.2mg	0.07mg
Thiamin (as thiamine HCl) (vitamin B1)			20 mg	1.5 mg					1.5 mg		
Turmeric (curcuma longa rhizome)			50 mg								
Vitamin A (as beta carotene)	5000 IU		5000 IU	5000IU			200 IU		5000 IU		
Vitamin B12 (as cyanocobalamin)	0.015 mg	0.5 mg	.02 mg	.025 mg		.5 mg	1 mg	1.5 mcg	25 mcg		0.006mg
Vitamin B2 (as Riboflavin)		15 mg	20 mg	1.7 mg					1.7 mg		
Vitamin B6 (as pyridoxine HCl)			20 mg	2mg	25 mg		1.3 mg		2 mg		2mg
Vitamin C (as ascorbic acid)	200 mg	500 mg	60 mg	250 mg	200 mg		167 mg	90 mg	250 mg	500mg	120mg
Vitamin D3 (cholcalciferol)			400 IU	400 IU	.01 mg		267 IU		400 IU	2000IU	
Vitamin E (as d-alpha tocopheryl acid succinate)	400IU		150 IU	150 IU	120 mg		267 IU		150 IU	400IU	150IU
Vitamin K2 (as menatetrenone)			.1 mg	.08 mg					.08 mg		
Zinc (as zinc amino acid chelate)	70 mg		25 mg	30 mg	40 mg		27mg	10 mg	30 mg	20mg	15mg

15.2 Research Formulations

Ingredient	Akiyama 1999	Balercia 2005	Balercia 2009	Biagotti 2003	Cavallini 2004	Ciftci 2009	Conquer 2000	Dawson 1990	Galatioto 2008	Greco 2005	Keskes-Ammar 2003
Acetyl-L-Carnitine		3g (1)		1g	1g						
Calcium (as amino acid chelate)									x		
Chromium (as polynicotinate)											
Coenzyme Q10 (Ubiquinone)			200 mg								
Copper (as gluconate)											
Folate (as folic acid)											
Glutathione											
Iodine											
Iron (as amino acid chelate)											
L-Arginine (free from amino acid)											
L-Carnitine (as L-carnitine-L-tartrate)		3g (2)		2g	2g						
L-Glutathione											
L-Methionine											
L-taurine											
Lycopene											
Manganese (as amino acid chelate)											
N-acetyl-l-cystine						600mg			600mg		
Niacin (as Inositol Hexanicotinate)											
Pantothenic Acid (as calcium pantothenate)											
Relora® (U.S. Patent 6,582,735)											
Selenium (as L-selenomethionine)											0.225mg
Thiamin (as thiamine HCl) (vitamin B1)									x		x
Turmeric (curcuma longa rhizome)											
Vitamin A (as beta carotene)									x		
Vitamin B12 (as cyanocobalamin)											x
Vitamin B2 (as Riboflavin)											
Vitamin B6 (as pyridoxine HCl)											x
Vitamin C (as ascorbic acid)								1000mg	x	1000mg	
Vitamin D3 (cholcalciferol)											
Vitamin E (as d-alpha tocopheryl acid succinate)	600mg								x	1000mg	400mg
Vitamin K2 (as menatetrenone)											
Zinc (as zinc amino acid chelate)											
Zinc (as zinc sulfate)											
Cinnoxizam				?	30mg q4day						
Docosahexaenoic acid (DHA)							800mg				

16 Appendix E: Risk Factors for Genetic Disorders

The following questions are designed to determine if you have an increased risk of having a baby with a genetic disorder. Sometimes genetic disorders occur even when there is no history of problems in your family. The following questions are related to you and your immediate family including mother, father, sister, brother, child, or grandparent. If you answer “yes” to any of the following questions and would like more information, please discuss this with your physician.

Questions	Yes	No	Unknown	N/A
1. If you conceive during this study, will you be 35 or older when your baby is due?				
2. If you are of Mediterranean or Asian descent, does anyone in your family have thalassemia? (a blood disorder that causes anemia)				
3. Is there a family history of neural tube defects?				
4. Have you had a child with a neural tube defect?				
5. Does anyone in your family have a history of congenital heart defects? (heart problems when they were born)				
6. Does anyone in your family have Down Syndrome?				
7. Have you ever had a child with Down Syndrome?				
8. If you are of Eastern European Jewish or French Canadian descent, does anyone in your family have a history of Tay-Sachs disease? (a disorder of the central nervous system)				
9. If you are of Eastern European Jewish descent, does anyone in your family have a history of Canavan disease? (a disorder of the central nervous system that leads to blindness and muscle weakness)				
10. If you are of African American descent, is there any history of sickle cell trait? (a type of anemia)				

11. If you are of African American descent, is there any history of sickle cell disease? (a type of anemia)				
12. Do you or anyone in your family have a history of hemophilia? (a disorder that causes bleeding)				
13. Do you or anyone in your family have a history of muscular dystrophy? (a neuromuscular disorder)				
14. Do you or anyone in your family have a history of cystic fibrosis? (a disorder that causes thick mucous in the lungs and other organs)				
15. Do you or anyone in your family have a history of Huntington's disease? (a degenerative brain disease)				
16. Do you or anyone in your family have a history of alpha-1 antitrypsin deficiency? (lack of a liver protein)				
17. Do you or anyone in your family have a history of mental retardation?				
17a. If yes to Question #17, was the person ever tested for fragile-x syndrome? (a condition which can cause mild to severe mental retardation)				
18. Do you or anyone in your family have a history of any other genetic disease, chromosomal disorder or birth defect?				
19. Do you have any metabolic disorders such as diabetes or phenylketonuria (PKU)? (a disorder which prevents the normal use of protein foods)				
20. Have you ever had 3 or more miscarriages in a row?				
21. Have you ever had a baby that was stillborn?				

17 Appendix F: Female Sexual Function Index (FSFI)

Female Sexual Function Index (FSFI) ©

Subject Identifier _____

Date _____

INSTRUCTIONS: These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation and vaginal intercourse.

Sexual intercourse is defined as penile penetration (entry) of the vagina.

Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CHECK ONLY ONE BOX PER QUESTION.

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how **often** did you feel sexual desire or interest?

- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

2. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?

- Very high
- High
- Moderate
- Low
- Very low or none at all

Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how **often** did you feel sexually aroused ("turned on") during sexual activity or intercourse?

- No sexual activity
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

4. Over the past 4 weeks, how would you rate your **level** of sexual arousal ("turn on") during sexual activity or intercourse?

- No sexual activity
- Very high
- High
- Moderate
- Low
- Very low or none at all

5. Over the past 4 weeks, how **confident** were you about becoming sexually aroused during sexual activity or intercourse?

- No sexual activity
- Very high confidence
- High confidence
- Moderate confidence
- Low confidence
- Very low or no confidence

6. Over the past 4 weeks, how **often** have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

- No sexual activity
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

7. Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse?

- No sexual activity
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

8. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse?

- No sexual activity
- Extremely difficult or impossible
- Very difficult
- Difficult
- Slightly difficult
- Not difficult

9. Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse?

- No sexual activity
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

10. Over the past 4 weeks, how **difficult** was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

- No sexual activity
- Extremely difficult or impossible
- Very difficult
- Difficult
- Slightly difficult
- Not difficult

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **often** did you reach orgasm (climax)?

- No sexual activity
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **difficult** was it for you to reach orgasm (climax)?

- No sexual activity
- Extremely difficult or impossible
- Very difficult
- Difficult
- Slightly difficult
- Not difficult

13. Over the past 4 weeks, how **satisfied** were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

- No sexual activity
- Very satisfied
- Moderately satisfied
- About equally satisfied and dissatisfied
- Moderately dissatisfied
- Very dissatisfied

14. Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner?

- No sexual activity
- Very satisfied
- Moderately satisfied
- About equally satisfied and dissatisfied
- Moderately dissatisfied
- Very dissatisfied

15. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner?

- Very satisfied
- Moderately satisfied
- About equally satisfied and dissatisfied
- Moderately dissatisfied
- Very dissatisfied

16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life?

- Very satisfied
- Moderately satisfied
- About equally satisfied and dissatisfied
- Moderately dissatisfied
- Very dissatisfied

17. Over the past 4 weeks, how **often** did you experience discomfort or pain during vaginal penetration?

- Did not attempt intercourse
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

18. Over the past 4 weeks, how **often** did you experience discomfort or pain following vaginal penetration?

- Did not attempt intercourse
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

19. Over the past 4 weeks, how would you rate your **level** (degree) of discomfort or pain during or following vaginal penetration?

- Did not attempt intercourse
- Very high
- High
- Moderate
- Low
- Very low or none at all

Thank you for completing this questionnaire

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
	▼	▼	▼
a. <u>Moderate activities</u> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.....	<input type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input type="checkbox"/> 3
b. Climbing <u>several</u> flights of stairs	<input type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input type="checkbox"/> 3

3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

- a. Accomplished less than you would like 1 2 3 4 5
- b. Were limited in the kind of work or other activities 1 2 3 4 5

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

- a. Accomplished less than you would like 1 2 3 4 5
- b. Did work or other activities less carefully than usual 1 2 3 4 5

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

- a. Have you felt calm and peaceful?..... 1..... 2..... 3..... 4..... 5
- b. Did you have a lot of energy?..... 1..... 2..... 3..... 4..... 5
- c. Have you felt downhearted and depressed?..... 1..... 2..... 3..... 4..... 5

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

Thank you for completing these questions!

19 Appendix H: Patient Health Questionnaire (PHQ-9)

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME: _____ DATE: _____

Over the last 2 weeks, how often have you been bothered by any of the following problems?

(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3

add columns + +

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card). TOTAL:

10. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all	_____
	Somewhat difficult	_____
	Very difficult	_____
	Extremely difficult	_____

PHQ-9 Patient Depression Questionnaire

For initial diagnosis:

1. Patient completes PHQ-9 Quick Depression Assessment.
2. If there are at least 4 ✓s in the shaded section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.

Consider Major Depressive Disorder

- if there are at least 5 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Consider Other Depressive Disorder

- if there are 2-4 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician, and a definitive diagnosis is made on clinical grounds taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient.

Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #10) and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (eg, every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.
2. Add up ✓s by column. For every ✓: Several days = 1 More than half the days = 2 Nearly every day = 3
3. Add together column scores to get a TOTAL score.
4. Refer to the accompanying **PHQ-9 Scoring Box** to interpret the TOTAL score.
5. Results may be included in patient files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

Scoring: add up all checked boxes on PHQ-9

For every ✓ Not at all = 0; Several days = 1;
More than half the days = 2; Nearly every day = 3

Interpretation of Total Score

Total Score	Depression Severity
1-4	Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

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A2662B 10-04-2005

20 Appendix I: FertiQoL

FertiQoL International

Fertility Quality of Life Questionnaire (2008)

For each question, kindly check (tick the box) for the response that most closely reflects how you think and feel. Relate your answers to your current thoughts and feelings. Some questions may relate to your private life, but they are necessary to adequately measure all aspects of your life.

Please complete the items marked with an asterisk (*) only if you have a partner.

For each question, check the response that is closest to your current thoughts and feelings		Very Poor	Poor	Nor good nor poor	Good	Very Good
A	How would you rate your health?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
For each question, check the response that is closest to your current thoughts and feelings		Very Dissatisfied	Dissatisfied	Neither Satisfied Nor Dissatisfied	Satisfied	Very Satisfied
B	Are you satisfied with your quality of life?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
For each question, check the response that is closest to your current thoughts and feelings		Completely	A Great Deal	Moderately	Not Much	Not At All
Q1	Are your attention and concentration impaired by thoughts of infertility?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Q2	Do you think you cannot move ahead with other life goals and plans because of fertility problems?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Q3	Do you feel drained or worn out because of fertility problems?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Q4	Do you feel able to cope with your fertility problems?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
For each question, check the response that is closest to your current thoughts and feelings		Very Dissatisfied	Dissatisfied	Neither Satisfied Nor Dissatisfied	Satisfied	Very Satisfied
Q5	Are you satisfied with the support you receive from friends with regard to your fertility problems?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
*Q6	Are you satisfied with your sexual relationship even though you have fertility problems?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
For each question, check the response that is closest to your current thoughts and feelings		Always	Very Often	Quite Often	Seldom	Never
Q7	Do your fertility problems cause feelings of jealousy and resentment?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Q8	Do you experience grief and/or feelings of loss about not being able to have a child (or more children)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Q9	Do you fluctuate between hope and despair because of fertility problems?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Q10	Are you socially isolated because of fertility problems?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
*Q11	Are you and your partner affectionate with each other even though you have fertility problems?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Q12	Do your fertility problems interfere with your day-to-day work or obligations?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Q13	Do you feel uncomfortable attending social situations like holidays and celebrations because of your fertility problems?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Q14	Do you feel your family can understand what you are going through?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
For each question, check the response that is closest to your current thoughts and feelings		An Extreme Amount	Very Much	A Moderate Amount	A Little	Not At All
*Q15	Have fertility problems strengthened your commitment to your partner?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Q16	Do you feel sad and depressed about your fertility problems?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Q17	Do your fertility problems make you inferior to people with children?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Q18	Are you bothered by fatigue because of fertility problems?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
*Q19	Have fertility problems had a negative impact on your relationship with your partner?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
*Q20	Do you find it difficult to talk to your partner about your feelings related to infertility?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
*Q21	Are you content with your relationship even though you have fertility problems?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Q22	Do you feel social pressure on you to have (or have more) children?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Q23	Do your fertility problems make you angry?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Q24	Do you feel pain and physical discomfort because of your fertility problems?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

22 Appendix K: Stop Bang Questionnaire

STOP BANG Questionnaire

Height _____ inches/cm Weight _____ lb/kg

Age _____

Male/Female

BMI _____

Collar size of shirt: S, M, L, XL, or _____ inches/cm

Neck circumference* _____ cm

1. Snoring

Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?

Yes No

2. Tired

Do you often feel tired, fatigued, or sleepy during daytime?

Yes No

3. Observed

Has anyone observed you stop breathing during your sleep?

Yes No

4. Blood pressure

Do you have or are you being treated for high blood pressure?

Yes No

5. BMI

BMI more than 35 kg/m²?

Yes No

6. Age

Age over 50 yr old?

Yes No

7. Neck circumference

Neck circumference greater than 40 cm?

Yes No

8. Gender

Gender male?

Yes No

* Neck circumference is measured by staff

High risk of OSA: answering yes to three or more items

Low risk of OSA: answering yes to less than three items

Adapted from:

STOP Questionnaire

A Tool to Screen Patients for Obstructive Sleep Apnea

Frances Chung, F.R.C.P.C.,* Balaji Yegneswaran, M.B.B.S.,† Pu Liao, M.D.,‡ Sharon A. Chung, Ph.D.,§
Santhira Vairavanathan, M.B.B.S.,_ Sazzadul Islam, M.Sc.,_ Ali Khajehdehi, M.D.,† Colin M. Shapiro, F.R.C.P.C.#
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23 Appendix L: Female Sexual Distress Scale (FSDS- Revised 2005)

INSTRUCTIONS

Below is a list of feelings and problems that women sometimes have concerning their sexuality. Please read each item carefully, and circle the number that best describes HOW OFTEN THAT PROBLEM HAS BOTHERED YOU OR CAUSED YOU DISTRESS DURING THE PAST 7 DAYS INCLUDING TODAY. Circle only one number for each item, and take care not to skip any items. If you change your mind, erase your first circle carefully. Read the example before beginning, and if you have any questions please ask about them.

Example: How often did you feel: **Personal responsibility for your sexual problems.**

NEVER	RARELY	OCCASIONALLY	FREQUENTLY	ALWAYS
0	1	2	3	4

HOW OFTEN DID YOU FEEL:

1. Distressed about your sex life	0	1	2	3	4
2. Unhappy about your sexual relationship	0	1	2	3	4
3. Guilty about sexual difficulties	0	1	2	3	4
4. Frustrated by your sexual problems	0	1	2	3	4
5. Stressed about sex	0	1	2	3	4
6. Inferior because of sexual problems	0	1	2	3	4
7. Worried about sex	0	1	2	3	4
8. Sexually inadequate	0	1	2	3	4
9. Regrets about your sexuality	0	1	2	3	4
10. Embarrassed about sexual problems	0	1	2	3	4
11. Dissatisfied with your sex life	0	1	2	3	4
12. Angry about your sex life	0	1	2	3	4
13. Bothered by low sexual desire	0	1	2	3	4

24 Appendix M: International Index of Erectile Function (IIEF)

(Write the number that best describes your erectile function for the past 4 weeks in the spaces provided.)

Over the past four weeks:

1. How often were you able to get an erection during sexual activity? _____

- 0 = No sexual activity
- 1 = Almost never/never
- 2 = A few times (much less than half the time)
- 3 = Sometimes (about half the time)
- 4 = Most times (much more than half the time)
- 5 = Almost always/always

2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration? _____

- 0 = No sexual activity
- 1 = Almost never/never
- 2 = A few times (much less than half the time)
- 3 = Sometimes (about half the time)
- 4 = Most times (much more than half the time)
- 5 = Almost always/always

3. When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner? _____

- 0 = Did not attempt intercourse
- 1 = Almost never/never
- 2 = A few times (much less than half the time)
- 3 = Sometimes (about half the time)
- 4 = Most times (much more than half the time)
- 5 = Almost always/always

4. During intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner? _____

- 0 = Did not attempt intercourse
- 1 = Almost never/never
- 2 = A few times (much less than half the time)
- 3 = Sometimes (about half the time)
- 4 = Most times (much more than half the time)
- 5 = Almost always/always

5. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse? _____

- 0 = Did not attempt intercourse
- 1 = Extremely difficult
- 2 = Very difficult
- 3 = Difficult
- 4 = Slightly difficult
- 5 = Not difficult

6. How many times have you attempted sexual intercourse? _____

- 0 = No attempts
- 1 = One to two attempts
- 2 = Three to four attempts

- 3 = Five to six attempts
- 4 = Seven to ten attempts
- 5 = Eleven or more attempts

7. When you attempted sexual intercourse, how often was it satisfactory for you? _____

- 0 = Did not attempt intercourse
- 1 = Almost never/never
- 2 = A few times (much less than half the time)
- 3 = Sometimes (about half the time)
- 4 = Most times (much more than half the time)
- 5 = Almost always/always

8. How much have you enjoyed sexual intercourse? _____

- 0 = No intercourse
- 1 = No enjoyment
- 2 = Not very enjoyable
- 3 = Fairly enjoyable
- 4 = Highly enjoyable
- 5 = Very highly enjoyable

9. When you had sexual stimulation or intercourse, how often did you ejaculate? _____

- 0 = No sexual stimulation/intercourse
- 1 = Almost never/never
- 2 = A few times (much less than half the time)
- 3 = Sometimes (about half the time)
- 4 = Most times (much more than half the time)
- 5 = Almost always/always

10. When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax? _____

- 0 = No sexual stimulation/intercourse
- 1 = Almost never/never
- 2 = A few times (much less than half the time)
- 3 = Sometimes (about half the time)
- 4 = Most times (much more than half the time)
- 5 = Almost always/always

11. How often have you felt sexual desire? _____

- 1 = Almost never/never
- 2 = A few times (much less than half the time)
- 3 = Sometimes (about half the time)
- 4 = Most times (much more than half the time)
- 5 = Almost always/always

12. How would you rate your sexual desire? _____

- 1 = Very low/none at all
- 2 = Low
- 3 = Moderate

4 = High
5 = Very high

13. How satisfied have you been with your overall sex life? _____

1 = Very dissatisfied
2 = Moderately dissatisfied
3 = About equally satisfied and dissatisfied
4 = Moderately satisfied
5 = Very satisfied

14. How satisfied have you been with your sexual relationship with your partner? _____

1 = Very dissatisfied
2 = Moderately dissatisfied
3 = About equally satisfied and dissatisfied
4 = Moderately satisfied
5 = Very satisfied

15. How would you rate your confidence that you could get and keep an erection? _____

1 = Very low
2 = Low
3 = Moderate
4 = High
5 = Very high

*RC Rosen, A Riley, G Wagner et al. The international index of erectile dysfunction (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997 49: 822-30.

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This is a sample form. Do not use for scanning.

1. Over the past 12 months, how often did you drink **carrot juice**?
- NEVER (GO TO QUESTION 2)
- | | |
|---|--|
| <input type="checkbox"/> 1 time per month or less | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 2-3 times per day |
| <input type="checkbox"/> 1-2 times per week | <input type="checkbox"/> 4-5 times per day |
| <input type="checkbox"/> 3-4 times per week | <input type="checkbox"/> 6 or more times per day |
| <input type="checkbox"/> 5-6 times per week | |
- 1a. Each time you drank **carrot juice**, how much did you usually drink?
- Less than 1/2 cup (4 ounces)
 1/2 to 1 1/4 cups (4 to 10 ounces)
 More than 1 1/4 cups (10 ounces)
2. Over the past 12 months, how often did you drink **tomato juice** or **other vegetable juice**?
(Please do not include carrot juice.)
- NEVER (GO TO QUESTION 3)
- | | |
|---|--|
| <input type="checkbox"/> 1 time per month or less | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 2-3 times per day |
| <input type="checkbox"/> 1-2 times per week | <input type="checkbox"/> 4-5 times per day |
| <input type="checkbox"/> 3-4 times per week | <input type="checkbox"/> 6 or more times per day |
| <input type="checkbox"/> 5-6 times per week | |
- 2a. Each time you drank **tomato juice** or **other vegetable juice**, how much did you usually drink?
- Less than 3/4 cup (6 ounces)
 3/4 to 1 1/4 cups (6 to 10 ounces)
 More than 1 1/4 cups (10 ounces)
3. Over the past 12 months, how often did you drink **orange juice** or **grapefruit juice**?
- NEVER (GO TO QUESTION 4)
- | | |
|---|--|
| <input type="checkbox"/> 1 time per month or less | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 2-3 times per day |
| <input type="checkbox"/> 1-2 times per week | <input type="checkbox"/> 4-5 times per day |
| <input type="checkbox"/> 3-4 times per week | <input type="checkbox"/> 6 or more times per day |
| <input type="checkbox"/> 5-6 times per week | |
- 3a. Each time you drank **orange juice** or **grapefruit juice**, how much did you usually drink?
- Less than 3/4 cup (6 ounces)
 3/4 to 1 1/4 cups (6 to 10 ounces)
 More than 1 1/4 cups (10 ounces)

Question 4 appears in the next column

- 3b. How often was the orange juice or grapefruit juice you drank **calcium-fortified**?
- Almost never or never
 About 1/4 of the time
 About 1/2 of the time
 About 3/4 of the time
 Almost always or always
4. Over the past 12 months, how often did you drink **other 100% fruit juice** or **100% fruit juice mixtures** (such as apple, grape, pineapple, or others)?
- NEVER (GO TO QUESTION 5)
- | | |
|---|--|
| <input type="checkbox"/> 1 time per month or less | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 2-3 times per day |
| <input type="checkbox"/> 1-2 times per week | <input type="checkbox"/> 4-5 times per day |
| <input type="checkbox"/> 3-4 times per week | <input type="checkbox"/> 6 or more times per day |
| <input type="checkbox"/> 5-6 times per week | |
- 4a. Each time you drank **other 100% fruit juice** or **100% fruit juice mixtures**, how much did you usually drink?
- Less than 3/4 cup (6 ounces)
 3/4 to 1 1/2 cups (6 to 12 ounces)
 More than 1 1/2 cups (12 ounces)
- 4b. How often were the other 100% fruit juice or 100% fruit juice mixtures you drank **calcium-fortified**?
- Almost never or never
 About 1/4 of the time
 About 1/2 of the time
 About 3/4 of the time
 Almost always or always
5. How often did you drink **other fruit drinks** (such as cranberry cocktail, Hi-C, lemonade, or Kool-Aid, diet or regular)?
- NEVER (GO TO QUESTION 6)
- | | |
|---|--|
| <input type="checkbox"/> 1 time per month or less | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 2-3 times per day |
| <input type="checkbox"/> 1-2 times per week | <input type="checkbox"/> 4-5 times per day |
| <input type="checkbox"/> 3-4 times per week | <input type="checkbox"/> 6 or more times per day |
| <input type="checkbox"/> 5-6 times per week | |

Question 6 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

5a. Each time you drank **fruit drinks**, how much did you usually drink?

- Less than 1 cup (8 ounces)
- 1 to 2 cups (8 to 16 ounces)
- More than 2 cups (16 ounces)

5b. How often were your fruit drinks **diet or sugar-free**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

6. How often did you drink **milk as a beverage** (NOT in coffee, NOT in cereal)? *(Please do not include chocolate milk and hot chocolate.)*

- NEVER (GO TO QUESTION 7)
- 1 time per month or less
- 2-3 times per month
- 1-2 times per week
- 3-4 times per week
- 5-6 times per week
- 1 time per day
- 2-3 times per day
- 4-5 times per day
- 6 or more times per day

6a. Each time you drank **milk as a beverage**, how much did you usually drink?

- Less than 1 cup (8 ounces)
- 1 to 1½ cups (8 to 12 ounces)
- More than 1½ cups (12 ounces)

6b. What kind of **milk** did you usually drink?

- Whole milk
- 2% fat milk
- 1 % fat milk
- Skim, nonfat, or ½% fat milk
- Soy milk
- Rice milk
- Other

7. How often did you drink **chocolate milk** (including hot chocolate)?

- NEVER (GO TO QUESTION 8)
- 1 time per month or less
- 2-3 times per month
- 1-2 times per week
- 3-4 times per week
- 5-6 times per week
- 1 time per day
- 2-3 times per day
- 4-5 times per day
- 6 or more times per day

Question 8 appears in the next column

7a. Each time you drank **chocolate milk**, how much did you usually drink?

- Less than 1 cup (8 ounces)
- 1 to 1½ cups (8 to 12 ounces)
- More than 1½ cups (12 ounces)

7b. How often was the chocolate milk **reduced-fat or fat-free**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

8. How often did you drink **meal replacement or high-protein beverages** (such as Instant Breakfast, Ensure, Slimfast, Sustacal or others)?

- NEVER (GO TO QUESTION 9)
- 1 time per month or less
- 2-3 times per month
- 1-2 times per week
- 3-4 times per week
- 5-6 times per week
- 1 time per day
- 2-3 times per day
- 4-5 times per day
- 6 or more times per day

8a. Each time you drank **meal replacement or high-protein beverages**, how much did you usually drink?

- Less than 1 cup (8 ounces)
- 1 to 1½ cups (8 to 12 ounces)
- More than 1½ cups (12 ounces)

9. Over the past 12 months, did you drink **soda or pop**?

- NO (GO TO QUESTION 10)
- YES

9a. How often did you drink **soda or pop IN THE SUMMER**?

- NEVER
- 1 time per month or less
- 2-3 times per month
- 1-2 times per week
- 3-4 times per week
- 5-6 times per week
- 1 time per day
- 2-3 times per day
- 4-5 times per day
- 6 or more times per day

Question 10 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

9b. How often did you drink **soda** or **pop** **DURING THE REST OF THE YEAR?**

- NEVER
- 1 time per month or less 1 time per day
- 2-3 times per month 2-3 times per day
- 1-2 times per week 4-5 times per day
- 3-4 times per week 6 or more times per day
- 5-6 times per week

9c. Each time you drank **soda** or **pop**, how much did you usually drink?

- Less than 12 ounces or less than 1 can or bottle
- 12 to 16 ounces or 1 can or bottle
- More than 16 ounces or more than 1 can or bottle

9d. How often were these sodas or pop **diet** or **sugar-free**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

9e. How often were these sodas or pop **caffeine-free**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

10. Over the past 12 months, did you drink **sports drinks** (such as Propel, PowerAde, or Gatorade)?

NO (GO TO QUESTION 11)

YES

10a. How often did you drink **sports drinks** **IN THE SUMMER?**

- NEVER
- 1 time per month or less 1 time per day
- 2-3 times per month 2-3 times per day
- 1-2 times per week 4-5 times per day
- 3-4 times per week 6 or more times per day
- 5-6 times per week

Question 11 appears in the next column

10b. How often did you drink **sports drinks** **DURING THE REST OF THE YEAR?**

- NEVER
- 1 time per month or less 1 time per day
- 2-3 times per month 2-3 times per day
- 1-2 times per week 4-5 times per day
- 3-4 times per week 6 or more times per day
- 5-6 times per week

10c. Each time you drank **sports drinks**, how much did you usually drink?

- Less than 12 ounces or less than 1 bottle
- 12 to 24 ounces or 1 to 2 bottles
- More than 24 ounces or more than 2 bottles

11. Over the past 12 months, did you drink **energy drinks** (such as Red Bull or Jolt)?

NO (GO TO QUESTION 12)

YES

11a. How often did you drink **energy drinks** **IN THE SUMMER?**

- NEVER
- 1 time per month or less 1 time per day
- 2-3 times per month 2-3 times per day
- 1-2 times per week 4-5 times per day
- 3-4 times per week 6 or more times per day
- 5-6 times per week

11b. How often did you drink **energy drinks** **DURING THE REST OF THE YEAR?**

- NEVER
- 1 time per month or less 1 time per day
- 2-3 times per month 2-3 times per day
- 1-2 times per week 4-5 times per day
- 3-4 times per week 6 or more times per day
- 5-6 times per week

11c. Each time you drank **energy drinks**, how much did you usually drink?

- Less than 8 ounces or less than 1 cup
- 8 to 16 ounces or 1 to 2 cups
- More than 16 ounces or more than 2 cups

Question 12 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

12. Over the past 12 months, did you drink **beer**?

NO (GO TO QUESTION 13)

YES

12a. How often did you drink **beer** **IN THE SUMMER**?

NEVER

- | | |
|---|--|
| <input type="checkbox"/> 1 time per month or less | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 2-3 times per day |
| <input type="checkbox"/> 1-2 times per week | <input type="checkbox"/> 4-5 times per day |
| <input type="checkbox"/> 3-4 times per week | <input type="checkbox"/> 6 or more times per day |
| <input type="checkbox"/> 5-6 times per week | |

12b. How often did you drink **beer** **DURING THE REST OF THE YEAR**?

NEVER

- | | |
|---|--|
| <input type="checkbox"/> 1 time per month or less | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 2-3 times per day |
| <input type="checkbox"/> 1-2 times per week | <input type="checkbox"/> 4-5 times per day |
| <input type="checkbox"/> 3-4 times per week | <input type="checkbox"/> 6 or more times per day |
| <input type="checkbox"/> 5-6 times per week | |

12c. Each time you drank **beer**, how much did you usually drink?

- Less than a 12-ounce can or bottle
 1 to 3 12-ounce cans or bottles
 More than 3 12-ounce cans or bottles



13. Over the past 12 months, did you drink **water** (including tap, bottled, and carbonated water)?

NO (GO TO QUESTION 14)

YES

13a. How often did you drink **water** (including tap, bottled, and carbonated water) **IN THE SUMMER**?

NEVER

- | | |
|---|--|
| <input type="checkbox"/> 1 time per month or less | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 2-3 times per day |
| <input type="checkbox"/> 1-2 times per week | <input type="checkbox"/> 4-5 times per day |
| <input type="checkbox"/> 3-4 times per week | <input type="checkbox"/> 6 or more times per day |
| <input type="checkbox"/> 5-6 times per week | |

Question 14 appears in the next column

13b. How often did you drink **water** (including tap, bottled, and carbonated water) **DURING THE REST OF THE YEAR**?

NEVER

- | | |
|---|--|
| <input type="checkbox"/> 1 time per month or less | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 2-3 times per day |
| <input type="checkbox"/> 1-2 times per week | <input type="checkbox"/> 4-5 times per day |
| <input type="checkbox"/> 3-4 times per week | <input type="checkbox"/> 6 or more times per day |
| <input type="checkbox"/> 5-6 times per week | |

13c. Each time you drank **water**, how much did you usually drink?

- Less than 12 ounces or less than 1 bottle
 12 to 24 ounces or 1 to 2 bottles
 More than 24 ounces or more than 2 bottles

13d. How often was the water you drank **tap water**?

- Almost never or never
 About 1/4 of the time
 About 1/2 of the time
 About 3/4 of the time
 Almost always or always

13e. How often was the water you drank **bottled, sweetened water** (with low or no-calorie sweetener, including carbonated water)?

- Almost never or never
 About 1/4 of the time
 About 1/2 of the time
 About 3/4 of the time
 Almost always or always

13f. How often was the water you drank **bottled, unsweetened water** (including carbonated water)?

- Almost never or never
 About 1/4 of the time
 About 1/2 of the time
 About 3/4 of the time
 Almost always or always

14. How often did you drink **wine** or **wine coolers**?

NEVER (GO TO QUESTION 15)

- | | |
|---|--|
| <input type="checkbox"/> 1 time per month or less | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 2-3 times per day |
| <input type="checkbox"/> 1-2 times per week | <input type="checkbox"/> 4-5 times per day |
| <input type="checkbox"/> 3-4 times per week | <input type="checkbox"/> 6 or more times per day |
| <input type="checkbox"/> 5-6 times per week | |

Question 15 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

14a. Each time you drank **wine** or **wine coolers**, how much did you usually drink?

- Less than 5 ounces or less than 1 glass
- 5 to 12 ounces or 1 to 2 glasses
- More than 12 ounces or more than 2 glasses

15. How often did you drink **liquor** or **mixed drinks**?

- NEVER (GO TO QUESTION 16)
- 1 time per month or less
- 2-3 times per month
- 1-2 times per week
- 3-4 times per week
- 5-6 times per week
- 1 time per day
- 2-3 times per day
- 4-5 times per day
- 6 or more times per day

15a. Each time you drank **liquor** or **mixed drinks**, how much did you usually drink?

- Less than 1 shot of liquor
- 1 to 3 shots of liquor
- More than 3 shots of liquor

16. Over the past 12 months, did you eat **oatmeal**, **grits**, or **other cooked cereal**?

- NO (GO TO QUESTION 17)
- YES

16a. How often did you eat **oatmeal**, **grits**, or **other cooked cereal IN THE WINTER**?

- NEVER
- 1-6 times per winter
- 7-11 times per winter
- 1 time per month
- 2-3 times per month
- 1 time per week
- 2 times per week
- 3-4 times per week
- 5-6 times per week
- 1 time per day
- 2 or more times per day

16b. How often did you eat **oatmeal**, **grits**, or **other cooked cereal DURING THE REST OF THE YEAR**?

- NEVER
- 1-6 times per year
- 7-11 times per year
- 1 time per month
- 2-3 times per month
- 1 time per week
- 2 times per week
- 3-4 times per week
- 5-6 times per week
- 1 time per day
- 2 or more times per day

16c. Each time you ate **oatmeal**, **grits**, or **other cooked cereal**, how much did you usually eat?

- Less than ¼ cup
- ¼ to 1¼ cups
- More than 1¼ cups

16d. How often was **butter** or **margarine** added to your oatmeal, grits or other cooked cereal?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

17. How often did you eat **cold cereal**?

- NEVER (GO TO QUESTION 18)
- 1-6 times per year
- 7-11 times per year
- 1 time per month
- 2-3 times per month
- 1 time per week
- 2 times per week
- 3-4 times per week
- 5-6 times per week
- 1 time per day
- 2 or more times per day

17a. Each time you ate **cold cereal**, how much did you usually eat?

- Less than 1 cup
- 1 to 2½ cups
- More than 2½ cups

17b. How often was the cold cereal you ate **Total Raisin Bran**, **Total Cereal**, or **Product 19**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

17c. How often was the cold cereal you ate **All Bran**, **Fiber One**, **100% Bran**, or **All-Bran Bran Buds**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

This is a sample form. Do not use for scanning.

Over the past 12 months...

17d. How often was the cold cereal you ate **some other bran or fiber cereal** (such as Cheerios, Shredded Wheat, Raisin Bran, Bran Flakes, Grape-Nuts, Granola, Wheaties, or Healthy Choice)?

- Almost never or never
- About 1/4 of the time
- About 1/2 of the time
- About 3/4 of the time
- Almost always or always

17e. How often was the cold cereal you ate any **other type of cold cereal** (such as Corn Flakes, Rice Krispies, Frosted Flakes, Special K, Froot Loops, Cap'n Crunch, or others)?

- Almost never or never
- About 1/4 of the time
- About 1/2 of the time
- About 3/4 of the time
- Almost always or always

17f. Was **milk** added to your cold cereal?

- NO (GO TO QUESTION 18)
- YES

17g. What kind of **milk** was usually added?

- Whole milk
- 2% fat milk
- 1% fat milk
- Skim, nonfat, or 1/2% fat milk
- Soy milk
- Rice milk
- Other

17h. Each time **milk was added to your cold cereal**, how much was usually added?

- Less than 1/2 cup
- 1/2 to 1 cup
- More than 1 cup

18. How often did you eat **applesauce**?

- NEVER (GO TO QUESTION 19)
- 1-6 times per year
- 7-11 times per year
- 1 time per month
- 2-3 times per month
- 1 time per week
- 2 times per week
- 3-4 times per week
- 5-6 times per week
- 1 time per day
- 2 or more times per day

Question 19 appears in the next column

18a. Each time you ate **applesauce**, how much did you usually eat?

- Less than 1/2 cup
- 1/2 to 1 cup
- More than 1 cup

19. How often did you eat **apples**?

- NEVER (GO TO QUESTION 20)
- 1-6 times per year
- 7-11 times per year
- 1 time per month
- 2-3 times per month
- 1 time per week
- 2 times per week
- 3-4 times per week
- 5-6 times per week
- 1 time per day
- 2 or more times per day

19a. Each time you ate **apples**, how many did you usually eat?

- Less than 1 apple
- 1 apple
- More than 1 apple

20. How often did you eat **pears** (fresh, canned, or frozen)?

- NEVER (GO TO QUESTION 21)
- 1-6 times per year
- 7-11 times per year
- 1 time per month
- 2-3 times per month
- 1 time per week
- 2 times per week
- 3-4 times per week
- 5-6 times per week
- 1 time per day
- 2 or more times per day

20a. Each time you ate **pears**, how many did you usually eat?

- Less than 1 pear
- 1 pear
- More than 1 pear

21. How often did you eat **bananas**?

- NEVER (GO TO QUESTION 22)
- 1-6 times per year
- 7-11 times per year
- 1 time per month
- 2-3 times per month
- 1 time per week
- 2 times per week
- 3-4 times per week
- 5-6 times per week
- 1 time per day
- 2 or more times per day



Question 22 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

21a. Each time you ate **bananas**, how many did you usually eat?

- Less than 1 banana
- 1 banana
- More than 1 banana

22. How often did you eat **dried fruit** (such as prunes or raisins)? (*Please do not include dried apricots.*)

- NEVER (GO TO QUESTION 23)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

22a. Each time you ate **dried fruit**, how much did you usually eat?

- Less than 2 tablespoons
- 2 to 5 tablespoons
- More than 5 tablespoons

23. Over the past 12 months, did you eat **peaches, nectarines, or plums**?

- NO (GO TO QUESTION 24)
- YES

23a. How often did you eat **fresh peaches, nectarines, or plums WHEN IN SEASON?**

- NEVER
- 1–6 times per season
- 7–11 times per season
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

23b. How often did you eat **peaches, nectarines, or plums** (fresh, canned, or frozen) **DURING THE REST OF THE YEAR?**

- NEVER
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

23c. Each time you ate **peaches, nectarines, or plums**, how much did you usually eat?

- Less than 1 fruit or less than ½ cup
- 1 to 2 fruits or ½ to ¾ cup
- More than 2 fruits or more than ¾ cup

24. How often did you eat **grapes**?

- NEVER (GO TO QUESTION 25)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

24a. Each time you ate **grapes**, how much did you usually eat?

- Less than ½ cup or less than 10 grapes
- ½ to 1 cup or 10 to 30 grapes
- More than 1 cup or more than 30 grapes

25. Over the past 12 months, did you eat **cantaloupe**?

- NO (GO TO QUESTION 26)
- YES

25a. How often did you eat **fresh cantaloupe WHEN IN SEASON?**

- NEVER
- 1–6 times per season
- 7–11 times per season
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

25b. How often did you eat **cantaloupe** (fresh or frozen) **DURING THE REST OF THE YEAR?**

- NEVER
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

This is a sample form. Do not use for scanning.

Over the past 12 months...

25c. Each time you ate **cantaloupe**, how much did you usually eat?

- Less than ¼ melon or less than ½ cup
- ¼ melon or ½ to 1 cup
- More than ¼ melon or more than 1 cup

26. Over the past 12 months, did you eat **melon, other than cantaloupe** (such as watermelon or honeydew)?

NO (GO TO QUESTION 27)

YES

26a. How often did you eat **fresh melon, other than cantaloupe, WHEN IN SEASON?**

- NEVER
- 1–6 times per season
- 7–11 times per season
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

26b. How often did you eat **melon other than cantaloupe (fresh or frozen) DURING THE REST OF THE YEAR?**

- NEVER
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

26c. Each time you ate **melon other than cantaloupe**, how much did you usually eat?

- Less than ½ cup or 1 small wedge
- ½ to 2 cups or 1 medium wedge
- More than 2 cups or 1 large wedge



Question 27 appears in the next column

27. Over the past 12 months, did you eat **strawberries**?

NO (GO TO QUESTION 28)

YES

27a. How often did you eat **fresh strawberries WHEN IN SEASON?**

- NEVER
- 1–6 times per season
- 7–11 times per season
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

27b. How often did you eat **strawberries (fresh or frozen) DURING THE REST OF THE YEAR?**

- NEVER
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

27c. Each time you ate **strawberries**, how much did you usually eat?

- Less than ¼ cup or less than 3 berries
- ¼ to ¾ cup or 3 to 8 berries
- More than ¾ cup or more than 8 berries

28. Over the past 12 months, did you eat **oranges, tangerines, or clementines?**

NO (GO TO QUESTION 29)

YES

28a. How often did you eat **fresh oranges, tangerines, or clementines WHEN IN SEASON?**

- NEVER
- 1–6 times per season
- 7–11 times per season
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

Question 29 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

28b. How often did you eat **oranges, tangerines, or clementines** (fresh or canned) **DURING THE REST OF THE YEAR?**

- NEVER
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

28c. Each time you ate **oranges, tangerines, or clementines**, how many did you usually eat?

- Less than 1 fruit
 1 fruit
 More than 1 fruit

29. Over the past 12 months, did you eat **grapefruit?**

NO (GO TO QUESTION 30)

YES

29a. How often did you eat **fresh grapefruit WHEN IN SEASON?**

- NEVER
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per season | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per season | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

29b. How often did you eat **grapefruit** (fresh or canned) **DURING THE REST OF THE YEAR?**

- NEVER
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

Question 30 appears in the next column

29c. Each time you ate **grapefruit**, how much did you usually eat?

- Less than 1/2 grapefruit
 1/2 grapefruit
 More than 1/2 grapefruit

30. How often did you eat **pineapple?**

- NEVER (GO TO QUESTION 31)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

30a. Each time you ate **pineapple**, how much did you usually eat?

- Less than 1/4 cup or less than 1 medium slice
 1/4 to 3/4 cup or 1 medium slice
 More than 3/4 cup or more than 1 medium slice

31. How often did you eat **other kinds of fruit?**

- NEVER (GO TO QUESTION 32)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

31a. Each time you ate **other kinds of fruit**, how much did you usually eat?

- Less than 1/4 cup
 1/4 to 3/4 cup
 More than 3/4 cup

32. How often did you eat **COOKED greens** (such as spinach, turnip, collard, mustard, chard, or kale)?

- NEVER (GO TO QUESTION 33)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

Question 33 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

32a. Each time you ate **COOKED greens**, how much did you usually eat?

- Less than ½ cup
- ½ to 1 cup
- More than 1 cup

33. How often did you eat **RAW greens** (such as spinach, turnip, collard, mustard, chard, or kale)? *(We will ask about lettuce later.)*

- NEVER (GO TO QUESTION 34)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

33a. Each time you ate **RAW greens**, how much did you usually eat?

- Less than ½ cup
- ½ to 1 cup
- More than 1 cup

34. How often did you eat **coleslaw**?

- NEVER (GO TO QUESTION 35)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

34a. Each time you ate **coleslaw**, how much did you usually eat?

- Less than ¼ cup
- ¼ to ¾ cup
- More than ¾ cup

35. How often did you eat **sauerkraut or cabbage** (other than coleslaw)?

- NEVER (GO TO QUESTION 36)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

Question 36 appears in the next column

35a. Each time you ate **sauerkraut or cabbage**, how much did you usually eat?

- Less than ¼ cup
- ¼ to 1 cup
- More than 1 cup

36. How often did you eat **carrots** (fresh, canned, or frozen)?

- NEVER (GO TO QUESTION 37)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

36a. Each time you ate **carrots**, how much did you usually eat?

- Less than ¼ cup or less than 2 baby carrots
- ¼ to ½ cup or 2 to 5 baby carrots
- More than ½ cup or more than 5 baby carrots

37. How often did you eat **string beans or green beans** (fresh, canned, or frozen)?

- NEVER (GO TO QUESTION 38)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

37a. Each time you ate **string beans or green beans**, how much did you usually eat?

- Less than ½ cup
- ½ to 1 cup
- More than 1 cup

38. How often did you eat **peas** (fresh, canned, or frozen)?

- NEVER (GO TO QUESTION 39)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

Question 39 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

38a. Each time you ate **peas**, how much did you usually eat?

- Less than ¼ cup
- ¼ to ¾ cup
- More than ¾ cup

39. Over the past 12 months, did you eat **corn**?

NO (GO TO QUESTION 40)

YES

39a. How often did you eat **fresh corn WHEN IN SEASON**?

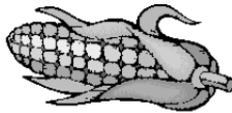
- NEVER
- 1–6 times per season
- 7–11 times per season
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

39b. How often did you eat **corn** (fresh, canned, or frozen) **DURING THE REST OF THE YEAR**?

- NEVER
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

39c. Each time you ate **corn**, how much did you usually eat?

- Less than 1 ear or less than ½ cup
- 1 ear or ½ to 1 cup
- More than 1 ear or more than 1 cup



Question 40 appears in the next column

40. How often did you eat **broccoli** (fresh or frozen)?

- NEVER (GO TO QUESTION 41)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

40a. Each time you ate **broccoli**, how much did you usually eat?

- Less than ¼ cup
- ¼ to 1 cup
- More than 1 cup

41. How often did you eat **cauliflower** or **Brussels sprouts** (fresh or frozen)?

- NEVER (GO TO QUESTION 42)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

41a. Each time you ate **cauliflower** or **Brussels sprouts**, how much did you usually eat?

- Less than ¼ cup
- ¼ to ½ cup
- More than ½ cup

42. How often did you eat **asparagus** (fresh or frozen)?

- NEVER (GO TO QUESTION 43)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

42a. Each time you ate **asparagus**, how much did you usually eat?

- Less than ⅓ cup or less than 4 spears
- ⅓ to ⅔ cup or 4 to 7 spears
- More than ⅔ cup or more than 7 spears

Question 43 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

43. How often did you eat **winter squash** (such as pumpkin, butternut, or acorn)?

- NEVER (GO TO QUESTION 44)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

43a. Each time you ate **winter squash**, how much did you usually eat?

- Less than ½ cup
 ½ to ¾ cup
 More than ¾ cup

44. How often did you eat **mixed vegetables**?

- NEVER (GO TO QUESTION 45)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

44a. Each time you ate **mixed vegetables**, how much did you usually eat?

- Less than ½ cup
 ½ to 1 cup
 More than 1 cup

45. How often did you eat **onions**?

- NEVER (GO TO QUESTION 46)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

45a. Each time you ate **onions**, how much did you usually eat?

- Less than 1 slice or less than 1 tablespoon
 1 slice or 1 to 4 tablespoons
 More than 1 slice or more than 4 tablespoons

Question 46 appears in the next column

46. Now think about all the **cooked vegetables** you ate in the past 12 months and how they were prepared. How often were your vegetables **COOKED WITH** some sort of fat, including oil spray? (Please do not include potatoes.)

- NEVER (GO TO QUESTION 47)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |



46a. Which fats were usually added to your vegetables **DURING COOKING**? (Please do not include potatoes. **Mark all that apply.**)

- | | |
|--|---|
| <input type="checkbox"/> Margarine (including low-fat) | <input type="checkbox"/> Corn oil |
| <input type="checkbox"/> Butter (including low-fat) | <input type="checkbox"/> Canola or rapeseed oil |
| <input type="checkbox"/> Lard, fatback, or bacon fat | <input type="checkbox"/> Oil spray, such as Pam or others |
| <input type="checkbox"/> Olive oil | <input type="checkbox"/> Other kinds of oils |
| | <input type="checkbox"/> None of the above |

47. Now, thinking again about all the **cooked vegetables** you ate in the past 12 months, how often was some sort of fat, sauce, or dressing added **AFTER COOKING OR AT THE TABLE**? (Please do not include potatoes.)

- NEVER (GO TO QUESTION 48)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 2 times per day |
| <input type="checkbox"/> 1-2 times per week | <input type="checkbox"/> 3 or more times per day |

Question 48 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

47a. Which fats, sauces, or dressings were usually added **AFTER COOKING OR AT THE TABLE**? (Please do not include potatoes. **Mark all that apply.**)

- | | |
|--|---|
| <input type="checkbox"/> Margarine (including low-fat) | <input type="checkbox"/> Salad dressing |
| <input type="checkbox"/> Butter (including low-fat) | <input type="checkbox"/> Cheese sauce |
| <input type="checkbox"/> Lard, fatback, or bacon fat | <input type="checkbox"/> White sauce |
| | <input type="checkbox"/> Other |

47b. If margarine, butter, lard, fatback, or bacon fat was added to your cooked vegetables **AFTER COOKING OR AT THE TABLE**, how much did you usually add?

- Did not usually add these
- Less than 1 teaspoon
- 1 to 3 teaspoons
- More than 3 teaspoons

47c. If salad dressing, cheese sauce, or white sauce was added to your cooked vegetables **AFTER COOKING OR AT THE TABLE**, how much did you usually add?

- Did not usually add these
- Less than 1 tablespoon
- 1 to 3 tablespoons
- More than 3 tablespoons

48. How often did you eat **sweet peppers** (green, red, or yellow)?

- NEVER (GO TO QUESTION 49)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

48a. Each time you ate **sweet peppers**, how much did you usually eat?

- Less than 1/4 pepper
- 1/4 to 1/2 pepper
- More than 1/2 pepper

Question 49 appears in the next column

49. Over the past 12 months, did you eat **fresh tomatoes** (including those in salads)?

- NO (GO TO QUESTION 50)
- YES

49a. How often did you eat **fresh tomatoes** (including those in salads) **WHEN IN SEASON**?

- NEVER
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per season | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per season | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

49b. How often did you eat **fresh tomatoes** (including those in salads) **DURING THE REST OF THE YEAR**?

- NEVER
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

49c. Each time you ate **fresh tomatoes**, how much did you usually eat?

- Less than 1/4 tomato
- 1/4 to 1/2 tomato
- More than 1/2 tomato

50. How often did you eat **lettuce salads** (with or without other vegetables)?

- NEVER (GO TO QUESTION 51)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

Question 51 appears on the next page

This is a sample form. Do not use for scanning.

Over the **past 12 months**...

50a. Each time you ate **lettuce salads**, how much did you usually eat?

- Less than ¼ cup
- ¼ to 1¼ cups
- More than 1¼ cups

50b. How often did the lettuce salads you ate include **dark green lettuce**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

51. How often did you eat **salad dressing** (including low-fat) **on salads**?

- NEVER (GO TO QUESTION 52)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

51a. Each time you ate **salad dressing on salads**, how much did you usually eat?

- Less than 2 tablespoons
- 2 to 4 tablespoons
- More than 4 tablespoons

52. How often did you eat **sweet potatoes** or **yams**?

- NEVER (GO TO QUESTION 53)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

52a. Each time you ate **sweet potatoes** or **yams**, how much did you usually eat?

- 1 small potato or less than ¼ cup
- 1 medium potato or ¼ to ¾ cup
- 1 large potato or more than ¾ cup

Question 53 appears in the next column

53. How often did you eat **French fries, home fries, hash browned potatoes, or tater tots**?

- NEVER (GO TO QUESTION 54)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

53a. Each time you ate **French fries, home fries, hash browned potatoes, or tater tots** how much did you usually eat?

- Less than 10 fries or less than ½ cup
- 10 to 25 fries or ½ to 1 cup
- More than 25 fries or more than 1 cup

54. How often did you eat **potato salad**?

- NEVER (GO TO QUESTION 55)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

54a. Each time you ate **potato salad**, how much did you usually eat?

- Less than ½ cup
- ½ to 1 cup
- More than 1 cup

55. How often did you eat **baked, boiled, or mashed potatoes**?

- NEVER (GO TO QUESTION 56)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

55a. Each time you ate **baked, boiled, or mashed potatoes**, how much did you usually eat?

- 1 small potato or less than ½ cup
- 1 medium potato or ½ to 1 cup
- 1 large potato or more than 1 cup

Question 56 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

55b. How often was **sour cream** (including low-fat) added to your potatoes, **EITHER IN COOKING OR AT THE TABLE?**

- Almost never or never (GO TO QUESTION 55d)
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

55c. Each time **sour cream** was added to your potatoes, how much was usually added?

- Less than 1 tablespoon
- 1 to 3 tablespoons
- More than 3 tablespoons

55d. How often was **margarine** (including low-fat) added to your potatoes, **EITHER IN COOKING OR AT THE TABLE?**

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

55e. How often was **butter** (including low-fat) added to your potatoes, **EITHER IN COOKING OR AT THE TABLE?**

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

55f. Each time **margarine** or **butter** was added to your potatoes, how much was usually added?

- Never added
- Less than 1 teaspoon
- 1 to 3 teaspoons
- More than 3 teaspoons

55g. How often was **cheese** or **cheese sauce** added to your potatoes, **EITHER IN COOKING OR AT THE TABLE?**

- Almost never or never (GO TO QUESTION 56)
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

55h. Each time **cheese** or **cheese sauce** was added to your potatoes, how much was usually added?

- Less than 1 tablespoon
- 1 to 3 tablespoons
- More than 3 tablespoons

56. How often did you eat **salsa**?

- NEVER (GO TO QUESTION 57)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

56a. Each time you ate **salsa**, how much did you usually eat?

- Less than 1 tablespoon
- 1 to 5 tablespoons
- More than 5 tablespoons

57. How often did you eat **catsup**?

- NEVER (GO TO QUESTION 58)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

57a. Each time you ate **catsup**, how much did you usually eat?

- Less than 1 teaspoon
- 1 to 6 teaspoons
- More than 6 teaspoons

58. How often did you eat **stuffing, dressing, or dumplings**?

- NEVER (GO TO QUESTION 59)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

58a. Each time you ate **stuffing, dressing, or dumplings**, how much did you usually eat?

- Less than ½ cup
- ½ to 1 cup
- More than 1 cup

Question 56 appears in the next column

Question 59 appears on the next page

This is a sample form. Do not use for scanning.

Over the **past 12 months...**

59. How often did you eat **chili**?

- NEVER (GO TO QUESTION 60)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

59a. Each time you ate **chili**, how much did you usually eat?

- Less than ½ cup
 ½ to 1¼ cups
 More than 1¼ cups

60. How often did you eat **Mexican foods** (such as tacos, tostados, burritos, tamales, fajitas, enchiladas, quesadillas, and chimichangas)?

- NEVER (GO TO QUESTION 61)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

60a. Each time you ate **Mexican foods**, how much did you usually eat?

- Less than 1 taco, burrito, etc.
 1 to 2 tacos, burritos, etc.
 More than 2 tacos, burritos, etc.

61. How often did you eat **cooked dried beans** (such as baked beans, pintos, kidney, blackeyed peas, lima, lentils, soybeans, or refried beans)? *(Please do not include bean soups or chili.)*

- NEVER (GO TO QUESTION 62)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

61a. Each time you ate **beans**, how much did you usually eat?

- Less than ½ cup
 ½ to 1 cup
 More than 1 cup

61b. How often were the beans you ate **refried beans, beans prepared with any type of fat, or with meat added**?

- Almost never or never
 About ¼ of the time
 About ½ of the time
 About ¾ of the time
 Almost always or always

62. How often did you eat **other kinds of vegetables**?

- NEVER (GO TO QUESTION 63)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

62a. Each time you ate **other kinds of vegetables**, how much did you usually eat?

- Less than ¼ cup
 ¼ to ½ cup
 More than ½ cup

63. How often did you eat **rice or other cooked grains** (such as bulgur, cracked wheat, or millet)?

- NEVER (GO TO QUESTION 64)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

63a. Each time you ate **rice or other cooked grains**, how much did you usually eat?

- Less than ½ cup
 ½ to 1½ cups
 More than 1½ cups

63b. How often was **butter, margarine, or oil** added to your rice or other cooked grains **IN COOKING OR AT THE TABLE**?

- Almost never or never
 About ¼ of the time
 About ½ of the time
 About ¾ of the time
 Almost always or always

Question 62 appears in the next column

Question 64 appears on the next page

This is a sample form. Do not use for scanning.

Over the **past 12 months...**

64. How often did you eat **pancakes, waffles, or French toast**?

- NEVER (GO TO QUESTION 65)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

64a. Each time you ate **pancakes, waffles, or French toast**, how much did you usually eat?

- Less than 1 medium piece
- 1 to 3 medium pieces
- More than 3 medium pieces

64b. How often was **margarine** (including low-fat) added to your pancakes, waffles, or French toast **AFTER COOKING OR AT THE TABLE**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

64c. How often was **butter** (including low-fat) added to your pancakes, waffles, or French toast **AFTER COOKING OR AT THE TABLE**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

64d. Each time **margarine** or **butter** was added to your pancakes, waffles, or French toast, how much was usually added?

- Never added
- Less than 1 teaspoon
- 1 to 3 teaspoons
- More than 3 teaspoons

64e. How often was **syrup** added to your pancakes, waffles, or French toast?

- Almost never or never (GO TO QUESTION 65)
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

Question 65 appears in the next column

64f. Each time **syrup** was added to your pancakes, waffles, or French toast, how much was usually added?

- Less than 1 tablespoon
- 1 to 4 tablespoons
- More than 4 tablespoons

65. How often did you eat **lasagna, stuffed shells, stuffed manicotti, ravioli, or tortellini**?
(Please do not include spaghetti or other pasta.)

- NEVER (GO TO QUESTION 66)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

65a. Each time you ate **lasagna, stuffed shells, stuffed manicotti, ravioli, or tortellini**, how much did you usually eat?

- Less than 1 cup
- 1 to 2 cups
- More than 2 cups

66. How often did you eat **macaroni and cheese**?

- NEVER (GO TO QUESTION 67)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

66a. Each time you ate **macaroni and cheese**, how much did you usually eat?

- Less than 1 cup
- 1 to 1½ cups
- More than 1½ cups

67. How often did you eat **pasta salad or macaroni salad**?

- NEVER (GO TO QUESTION 68)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

Question 68 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

67a. Each time you ate **pasta salad** or **macaroni salad**, how much did you usually eat?

- Less than ½ cup
- ½ to 1 cup
- More than 1 cup

68. Other than the pastas listed in Questions 65, 66, and 67, how often did you eat **pasta, spaghetti, or other noodles**?

NEVER (GO TO QUESTION 69)

- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

68a. Each time you ate **pasta, spaghetti, or other noodles**, how much did you usually eat?

- Less than 1 cup
- 1 to 3 cups
- More than 3 cups

68b. How often did you eat your pasta, spaghetti, or other noodles with **tomato sauce** or **spaghetti sauce made WITH meat**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

68c. How often did you eat your pasta, spaghetti, or other noodles with **tomato sauce** or **spaghetti sauce made WITHOUT meat**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

68d. How often did you eat your pasta, spaghetti, or other noodles with **margarine, butter, oil, or cream sauce**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

Question 69 appears in the next column

69. How often did you eat **bagels** or **English muffins**?

NEVER (GO TO INTRODUCTION TO QUESTION 70)

- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

69a. How often were the bagels or English muffins you ate **whole wheat**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

69b. Each time you ate **bagels** or **English muffins**, how many did you usually eat?

- Less than 1 bagel or English muffin
- 1 bagel or English muffin
- More than 1 bagel or English muffin

69c. How often was **margarine** (including low-fat) added to your bagels or English muffins?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

69d. How often was **butter** (including low-fat) added to your bagels or English muffins?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

69e. Each time **margarine** or **butter** was added to your bagels or English muffins, how much was usually added?

- Never added
- Less than 1 teaspoon
- 1 to 2 teaspoons
- More than 2 teaspoons

Introduction to Question 70 appears on the next page

This is a sample form. Do not use for scanning.

Over the **past 12 months...**

69f. How often was **cream cheese** (including low-fat) spread on your bagels or English muffins?

- Almost never or never (GO TO INTRODUCTION TO QUESTION 70)
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

69g. Each time **cream cheese** was added to your bagels or English muffins, how much was usually added?

- Less than 1 tablespoon
- 1 to 2 tablespoons
- More than 2 tablespoons

The next questions ask about your intake of breads other than bagels or English muffins. First, we will ask about bread you ate as part of sandwiches only. Then we will ask about all other bread you ate.

70. How often did you eat **breads or rolls AS PART OF SANDWICHES** (including burger and hot dog rolls)?

(Please do not include fast food sandwiches.)

- NEVER (GO TO QUESTION 71)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

70a. Each time you ate **breads or rolls AS PART OF SANDWICHES**, how many did you usually eat?

- 1 slice or ½ roll
- 2 slices or 1 roll
- More than 2 slices or more than 1 roll

70b. How often were the breads or rolls that you used for your sandwiches **white bread** (including burger and hot dog rolls)?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

70c. How often was **mayonnaise** or **mayonnaise-type dressing** (including low-fat) added to the breads or rolls used for your sandwiches?

- Almost never or never (GO TO QUESTION 70e)
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

70d. Each time **mayonnaise** or **mayonnaise-type dressing** was added to the breads or rolls used for your sandwiches, how much was usually added?

- Less than 1 teaspoon
- 1 to 3 teaspoons
- More than 3 teaspoons

70e. How often was **margarine** (including low-fat) added to the breads or rolls used for your sandwiches?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

70f. How often was **butter** (including low-fat) added to the breads or rolls used for your sandwiches?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

70g. Each time **margarine** or **butter** was added to the breads or rolls used for your sandwiches, how much was usually added?

- Never added
- Less than 1 teaspoon
- 1 to 2 teaspoons
- More than 2 teaspoons

71. How often did you eat **breads or dinner rolls, NOT AS PART OF SANDWICHES**?

- NEVER (GO TO QUESTION 72)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

Question 71 appears in the next column

Question 72 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

71a. Each time you ate **bread**s or **dinner rolls**, **NOT AS PART OF SANDWICHES**, how much did you usually eat?

- 1 slice or 1 dinner roll
- 2 slices or 2 dinner rolls
- More than 2 slices or 2 dinner rolls

71b. How often were the breads or rolls you ate **white bread**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

71c. How often was **margarine** (including low-fat) added to your breads or rolls?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

71d. How often was **butter** (including low-fat) added to your breads or rolls?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

71e. Each time **margarine** or **butter** was added to your breads or rolls, how much was usually added?

- Never added
- Less than 1 teaspoon
- 1 to 2 teaspoons
- More than 2 teaspoons

71f. How often was **cream cheese** (including low-fat) added to your breads or rolls?

- Almost never or never (GO TO QUESTION 72)
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

Question 72 appears in the next column

71g. Each time **cream cheese** was added to your breads or rolls, how much was usually added?

- Less than 1 tablespoon
- 1 to 2 tablespoons
- More than 2 tablespoons

72. How often did you eat **jam, jelly, or honey** on bagels, muffins, bread, rolls, or crackers?

- NEVER (GO TO QUESTION 73)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

72a. Each time you ate **jam, jelly, or honey**, how much did you usually eat?

- Less than 1 teaspoon
- 1 to 3 teaspoons
- More than 3 teaspoons

73. How often did you eat **peanut butter** or **other nut butter**?

- NEVER (GO TO QUESTION 74)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

73a. Each time you ate **peanut butter** or **other nut butter**, how much did you usually eat?

- Less than 1 tablespoon
- 1 to 2 tablespoons
- More than 2 tablespoons

74. How often did you eat **roast beef** or **steak IN SANDWICHES**?

- NEVER (GO TO QUESTION 75)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

Question 75 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

74a. Each time you ate **roast beef** or **steak IN SANDWICHES**, how much did you usually eat?

- Less than 1 slice or less than 2 ounces
- 1 to 2 slices or 2 to 4 ounces
- More than 2 slices or more than 4 ounces

75. How often did you eat **turkey** or **chicken COLD CUTS** (such as loaf, luncheon meat, turkey ham, turkey salami, or turkey pastrami)? *(We will ask about other turkey or chicken later.)*

- NEVER (GO TO QUESTION 76)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

75a. Each time you ate **turkey** or **chicken COLD CUTS**, how much did you usually eat?

- Less than 1 slice
- 1 to 3 slices
- More than 3 slices

76. How often did you eat **luncheon** or **deli-style ham**? *(We will ask about other ham later.)*

- NEVER (GO TO QUESTION 77)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

76a. Each time you ate **luncheon** or **deli-style ham**, how much did you usually eat?

- Less than 1 slice
- 1 to 3 slices
- More than 3 slices

76b. How often was the luncheon or deli-style ham you ate **light, low-fat, or fat-free**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

Question 77 appears in the next column

77. How often did you eat **other cold cuts** or **luncheon meats** (such as bologna, salami, corned beef, pastrami, or others, including low-fat)? *(Please do not include ham, turkey, or chicken cold cuts.)*

- NEVER (GO TO QUESTION 78)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

77a. Each time you ate **other cold cuts** or **luncheon meats**, how much did you usually eat?

- Less than 1 slice
- 1 to 3 slices
- More than 3 slices

77b. How often were the other cold cuts or luncheon meats you ate **light, low-fat, or fat-free**? *(Please do not include ham, turkey, or chicken cold cuts.)*

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

78. How often did you eat **canned tuna** (including in salads, sandwiches, or casseroles)?

- NEVER (GO TO QUESTION 79)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

78a. Each time you ate **canned tuna**, how much did you usually eat?

- Less than ¼ cup or less than 2 ounces
- ¼ to ½ cup or 2 to 3 ounces
- More than ½ cup or more than 3 ounces

78b. How often was the canned tuna you ate **water-packed**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

Question 79 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

78c. How often was the canned tuna you ate prepared with **mayonnaise** or **other dressing** (including low-fat)?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

79. How often did you eat **GROUND chicken** or **turkey**? (We will ask about other chicken and turkey later.)

- NEVER (GO TO QUESTION 80)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

79a. Each time you ate **GROUND chicken** or **turkey**, how much did you usually eat?

- Less than 2 ounces or less than ½ cup
- 2 to 4 ounces or ½ to 1 cup
- More than 4 ounces or more than 1 cup

80. How often did you eat **beef hamburgers** or **cheeseburgers** from a **FAST FOOD** or **OTHER RESTAURANT**?

- NEVER (GO TO QUESTION 81)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

80a. Each time you ate **beef hamburgers** or **cheeseburgers** from a **FAST FOOD** or **OTHER RESTAURANT**, what size did you usually eat?

- Small hamburger (such as a regular Burger King or McDonald's Hamburger)
- Medium (such as McDonald's or Burger King Double Burger or Cheeseburger)
- Large (such as Burger King Whopper or Double Whopper or a McDonald's Double Quarter Pounder)

Question 81 appears in the next column

80b. Each time you ate **beef hamburgers** or **cheeseburgers** from a **FAST FOOD** or **OTHER RESTAURANT**, how much did you usually eat?

- Less than 1 burger
- 1 burger
- More than 1 burger

80c. How often did you have **cheeseburgers** rather than **hamburgers**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

81. How often did you eat **beef hamburgers** or **cheeseburgers** that were **NOT FROM A FAST FOOD** or **OTHER RESTAURANT**?

- NEVER (GO TO QUESTION 82)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

81a. Each time you ate **beef hamburgers** or **cheeseburgers** that were **NOT FROM A FAST FOOD** or **OTHER RESTAURANT**, how much did you usually eat?

- Less than 1 patty or less than 2 ounces
- 1 patty or 2 to 4 ounces
- More than 1 patty or more than 4 ounces

81b. How often were these beef hamburgers or cheeseburgers made with **lean ground beef**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

82. How often did you eat **ground beef in mixtures** (such as meatballs, casseroles, chili, or meatloaf)?

- NEVER (GO TO QUESTION 83)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

Question 83 appears on the next page

This is a sample form. Do not use for scanning.

Over the **past 12 months...**

82a. Each time you ate **ground beef in mixtures**, how much did you usually eat?

- Less than 3 ounces or less than ½ cup
- 3 to 8 ounces or ½ to 1 cup
- More than 8 ounces or more than 1 cup

83. How often did you eat **hot dogs or frankfurters**? (Please do not include sausages or vegetarian hot dogs.)

- NEVER (GO TO QUESTION 84)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

83a. Each time you ate **hot dogs or frankfurters**, how many did you usually eat?

- Less than 1 hot dog
- 1 to 2 hot dogs
- More than 2 hot dogs

83b. How often were the hot dogs or frankfurters you ate **light or low-fat**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

84. How often did you eat **beef mixtures** (such as beef stew, beef pot pie, beef and noodles, or beef and vegetables)?

- NEVER (GO TO QUESTION 85)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

84a. Each time you ate **beef mixtures**, how much did you usually eat?

- Less than 1 cup
- 1 to 2 cups
- More than 2 cups

Question 85 appears in the next column

85. How often did you eat **roast beef or pot roast**? (Please do not include roast beef or pot roast in sandwiches.)

- NEVER (GO TO QUESTION 86)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

85a. Each time you ate **roast beef or pot roast**, how much did you usually eat?

- Less than 2 ounces
- 2 to 5 ounces
- More than 5 ounces

86. How often did you eat **steak** (beef)? (Please do not include steak in sandwiches)

- NEVER (GO TO QUESTION 87)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

86a. Each time you ate **steak** (beef), how much did you usually eat?

- Less than 3 ounces
- 3 to 7 ounces
- More than 7 ounces

86b. How often was the steak you ate **lean steak**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

87. How often did you eat **pork or beef spareribs**?

- NEVER (GO TO QUESTION 88)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

Question 88 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

87a. Each time you ate **pork** or **beef spareribs**, how much did you usually eat?

- Less than 4 ribs
- 4 to 12 ribs
- More than 12 ribs

88. How often did you eat **roast turkey, turkey cutlets, or turkey nuggets** (including in sandwiches)?

- NEVER (GO TO QUESTION 89)
- 1-6 times per year 2 times per week
- 7-11 times per year 3-4 times per week
- 1 time per month 5-6 times per week
- 2-3 times per month 1 time per day
- 1 time per week 2 or more times per day

88a. Each time you ate **roast turkey, turkey cutlets, or turkey nuggets**, how much did you usually eat? (Please note: 4 to 8 turkey nuggets = 3 ounces.)

- Less than 2 ounces
- 2 to 4 ounces
- More than 4 ounces

89. How often did you eat **chicken mixtures** (such as salads, sandwiches, casseroles, stews, or other mixtures)?

- NEVER (GO TO QUESTION 90)
- 1-6 times per year 2 times per week
- 7-11 times per year 3-4 times per week
- 1 time per month 5-6 times per week
- 2-3 times per month 1 time per day
- 1 time per week 2 or more times per day

89a. Each time you ate **chicken mixtures**, how much did you usually eat?

- Less than ½ cup
- ½ to 1½ cups
- More than 1½ cups

Question 90 appears in the next column

90. How often did you eat **baked, broiled, roasted, stewed, or fried chicken** (including nuggets)? (Please do not include chicken in mixtures.)

- NEVER (GO TO QUESTION 91)
- 1-6 times per year 2 times per week
- 7-11 times per year 3-4 times per week
- 1 time per month 5-6 times per week
- 2-3 times per month 1 time per day
- 1 time per week 2 or more times per day

90a. Each time you ate **baked, broiled, roasted, stewed, or fried chicken** (including nuggets), how much did you usually eat?

- Less than 2 drumsticks or wings, less than 1 breast or thigh, or less than 4 nuggets
- 2 drumsticks or wings, 1 breast or thigh, or 4 to 8 nuggets
- More than 2 drumsticks or wings, more than 1 breast or thigh, or more than 8 nuggets

90b. How often was the chicken you ate **fried chicken** (including deep fried) or **chicken nuggets**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

90c. How often was the chicken you ate **WHITE meat**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

90d. How often did you eat chicken **WITH skin**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

91. How often did you eat **baked ham** or **ham steak**?

- NEVER (GO TO QUESTION 92)
- 1-6 times per year 2 times per week
- 7-11 times per year 3-4 times per week
- 1 time per month 5-6 times per week
- 2-3 times per month 1 time per day
- 1 time per week 2 or more times per day

Question 92 appears on the next page

This is a sample form. Do not use for scanning.

Over the **past 12 months**...

- 91a. Each time you ate **baked ham** or **ham steak**, how much did you usually eat?
- Less than 1 ounce
 - 1 to 3 ounces
 - More than 3 ounces
92. How often did you eat **pork** (including chops, roasts, and in mixed dishes)? *(Please do not include ham, ham steak, or sausage.)*
- NEVER (GO TO QUESTION 93)
 - 1–6 times per year 2 times per week
 - 7–11 times per year 3–4 times per week
 - 1 time per month 5–6 times per week
 - 2–3 times per month 1 time per day
 - 1 time per week 2 or more times per day
- 92a. Each time you ate **pork**, how much did you usually eat?
- Less than 2 ounces or less than 1 chop
 - 2 to 5 ounces or 1 chop
 - More than 5 ounces or more than 1 chop
93. How often did you eat **gravy** on meat, chicken, potatoes, rice, etc.?
- NEVER (GO TO QUESTION 94)
 - 1–6 times per year 2 times per week
 - 7–11 times per year 3–4 times per week
 - 1 time per month 5–6 times per week
 - 2–3 times per month 1 time per day
 - 1 time per week 2 or more times per day
- 93a. Each time you ate **gravy** on meat, chicken, potatoes, rice, etc., how much did you usually eat?
- Less than ¼ cup
 - ¼ to ½ cup
 - More than ½ cup
94. How often did you eat **liver** (all kinds) or **liverwurst**?
- NEVER (GO TO QUESTION 95)
 - 1–6 times per year 2 times per week
 - 7–11 times per year 3–4 times per week
 - 1 time per month 5–6 times per week
 - 2–3 times per month 1 time per day
 - 1 time per week 2 or more times per day

Question 95 appears in the next column

- 94a. Each time you ate **liver** or **liverwurst**, how much did you usually eat?
- Less than 1 ounce
 - 1 to 4 ounces
 - More than 4 ounces
95. How often did you eat **bacon** (including low-fat)?
- NEVER (GO TO QUESTION 96)
 - 1–6 times per year 2 times per week
 - 7–11 times per year 3–4 times per week
 - 1 time per month 5–6 times per week
 - 2–3 times per month 1 time per day
 - 1 time per week 2 or more times per day
- 95a. Each time you ate **bacon**, how much did you usually eat?
- Fewer than 2 slices
 - 2 to 3 slices
 - More than 3 slices
- 95b. How often was the bacon you ate **light, low-fat, or lean**?
- Almost never or never
 - About ¼ of the time
 - About ½ of the time
 - About ¾ of the time
 - Almost always or always
96. How often did you eat **sausage** (including low-fat)?
- NEVER (GO TO QUESTION 97)
 - 1–6 times per year 2 times per week
 - 7–11 times per year 3–4 times per week
 - 1 time per month 5–6 times per week
 - 2–3 times per month 1 time per day
 - 1 time per week 2 or more times per day
- 96a. Each time you ate **sausage**, how much did you usually eat?
- Less than 1 patty or 2 links
 - 1 to 3 patties or 2 to 5 links
 - More than 3 patties or 5 links
- 96b. How often was the sausage you ate **light, low-fat, or lean**?
- Almost never or never
 - About ¼ of the time
 - About ½ of the time
 - About ¾ of the time
 - Almost always or always

Question 97 appears on the next page

This is a sample form. Do not use for scanning.

Over the **past 12 months**...

97. How often did you eat **fried shellfish** (such as crab, lobster, shrimp)?

- NEVER (GO TO QUESTION 98)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

97a. Each time you ate **fried shellfish**, how much did you usually eat?

- Less than 2 ounces
 2 to 4 ounces
 More than 4 ounces

98. How often did you eat **shellfish** (such as crab, lobster, shrimp) **that was NOT FRIED**?

- NEVER (GO TO QUESTION 99)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

98a. Each time you ate **shellfish that was NOT FRIED**, how much did you usually eat?

- Less than 1 ounce
 1 to 4 ounces
 More than 4 ounces

99. How often did you eat **salmon, fresh tuna or trout**?

- NEVER (GO TO QUESTION 100)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

99a. Each time you ate **salmon, fresh tuna or trout**, how much did you usually eat?

- Less than 2 ounces
 2 to 6 ounces
 More than 6 ounces

Question 100 appears in the next column

100. How often did you eat **fish sticks** or other **fried fish** (not including shellfish)?

- NEVER (GO TO QUESTION 101)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

100a. Each time you ate **fish sticks** or other **fried fish**, how much did you usually eat?

- Less than 2 ounces or less than 1 fillet
 2 to 7 ounces or 1 fillet
 More than 7 ounces or more than 1 fillet

101. How often did you eat **other fish that was NOT FRIED** (not including shellfish)?

- NEVER (GO TO INTRODUCTION TO QUESTION 102)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

101a. Each time you ate **other fish that was NOT FRIED**, how much did you usually eat?

- Less than 2 ounces or less than 1 fillet
 2 to 5 ounces or 1 fillet
 More than 5 ounces or more than 1 fillet

Now think about all the meat, poultry, and fish you ate in the past 12 months and how they were prepared.

102. How often was **oil, butter, margarine, or other fat** used to **FRY, SAUTE, BASTE, OR MARINATE** any meat, poultry, or fish you ate? (Please do not include deep frying.)

- NEVER (GO TO QUESTION 103)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

Question 103 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

102a. Which of the following **fats** were regularly used to prepare your meat, poultry, or fish? **(Mark all that apply.)**

- | | |
|--|--|
| <input type="checkbox"/> Margarine (including low-fat) | <input type="checkbox"/> Corn oil |
| <input type="checkbox"/> Butter (including low-fat) | <input type="checkbox"/> Canola or rapeseed oil |
| <input type="checkbox"/> Lard, fatback, or bacon fat | <input type="checkbox"/> Oil spray (such as Pam or others) |
| <input type="checkbox"/> Olive oil | <input type="checkbox"/> Other kinds of oils |
| | <input type="checkbox"/> None of the above |

103. How often did you eat **tofu, soy burgers, or soy meat-substitutes**?

- NEVER (GO TO QUESTION 104)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

103a. Each time you ate **tofu, soy burgers, or soy meat-substitutes**, how much did you usually eat?

- Less than ¼ cup or less than 2 ounces
 ¼ to ½ cup or 2 to 4 ounces
 More than ½ cup or more than 4 ounces

104. Over the past 12 months, did you eat **soups**?

- NO (GO TO QUESTION 105)
 YES

104a. How often did you eat **soup IN THE WINTER**?

- NEVER
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per winter | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per winter | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

104b. How often did you eat **soup DURING THE REST OF THE YEAR**?

- NEVER
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

Question 105 appears in the next column

104c. Each time you ate **soup**, how much did you usually eat?

- Less than 1 cup
 1 to 2 cups
 More than 2 cups

104d. How often were the soups you ate **bean soups**?

- Almost never or never
 About ¼ of the time
 About ½ of the time
 About ¾ of the time
 Almost always or always

104e. How often were the soups you ate **cream soups** (including chowders)?

- Almost never or never
 About ¼ of the time
 About ½ of the time
 About ¾ of the time
 Almost always or always

104f. How often were the soups you ate **tomato or vegetable soups**?

- Almost never or never
 About ¼ of the time
 About ½ of the time
 About ¾ of the time
 Almost always or always

104g. How often were the soups you ate **broth soups** (including chicken) **with or without noodles or rice**?

- Almost never or never
 About ¼ of the time
 About ½ of the time
 About ¾ of the time
 Almost always or always

105. How often did you eat **pizza**?

- NEVER (GO TO QUESTION 106)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

Question 106 appears on the next page

This is a sample form. Do not use for scanning.

Over the **past 12 months**...

105a. Each time you ate **pizza**, how much did you usually eat?

- Less than 1 slice or less than 1 mini pizza
- 1 to 3 slices or 1 mini pizza
- More than 3 slices or more than 1 mini pizza

105b. How often did you eat pizza with **pepperoni, sausage, or other meat**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

106. How often did you eat **crackers**?

NEVER (GO TO QUESTION 107)

- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

106a. Each time you ate **crackers**, how many did you usually eat?

- Fewer than 4 crackers
- 4 to 10 crackers
- More than 10 crackers

107. How often did you eat **corn bread or corn muffins**?

NEVER (GO TO QUESTION 108)

- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

107a. Each time you ate **corn bread or corn muffins**, how much did you usually eat?

- Less than 1 piece or muffin
- 1 to 2 pieces or muffins
- More than 2 pieces or muffins

108. How often did you eat **biscuits**?

NEVER (GO TO QUESTION 109)

- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

108a. Each time you ate **biscuits**, how many did you usually eat?

- Fewer than 1 biscuit
- 1 to 2 biscuits
- More than 2 biscuits

109. How often did you eat **potato chips** (including low-fat, fat-free, or low-salt)?

NEVER (GO TO QUESTION 110)

- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

109a. Each time you ate **potato chips**, how much did you usually eat?

- Fewer than 10 chips or less than 1 cup
- 10 to 25 chips or 1 to 2 cups
- More than 25 chips or more than 2 cups

109b. How often were the potato chips you ate **fat-free**? (*Please do not include reduced-fat chips.*)

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

110. How often did you eat **corn chips or tortilla chips** (including low-fat, fat-free, or low-salt)?

NEVER (GO TO QUESTION 111)

- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

Question 108 appears in the next column

Question 111 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

110a. Each time you ate **corn chips**, how much did you usually eat?

- Fewer than 10 chips or less than 1 cup
- 10 to 25 chips or 1 to 1½ cups
- More than 25 chips or more than 1½ cups

110b. How often were the corn chips or tortilla chips you ate **fat-free**? (Please do not include reduced-fat chips.)

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

111. How often did you eat **popcorn** (including low-fat)?

- NEVER (GO TO QUESTION 112)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

111a. Each time you ate **popcorn**, how much did you usually eat?

- Less than 2 cups, popped
- 2 to 5 cups, popped
- More than 5 cups, popped

112. How often did you eat **pretzels**?

- NEVER (GO TO QUESTION 113)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

112a. Each time you ate **pretzels**, how many did you usually eat?

- Fewer than 5 average twists
- 5 to 20 average twists
- More than 20 average twists

113. How often did you eat **peanuts, walnuts, seeds, or other nuts**?

- NEVER (GO TO QUESTION 114)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

113a. Each time you ate **peanuts, walnuts, seeds, or other nuts**, how much did you usually eat?

- Less than ¼ cup
- ¼ to ½ cup
- More than ½ cup

114. How often did you eat **energy, high-protein, or breakfast bars** (such as Power Bars, Balance, Clif, or others)?

- NEVER (GO TO QUESTION 115)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

114a. Each time you ate **energy, high-protein, or breakfast bars**, how much did you usually eat?

- Less than 1 bar
- 1 bar
- More than 1 bar

115. How often did you eat **yogurt** (NOT including frozen yogurt)?

- NEVER (GO TO QUESTION 116)
- 1–6 times per year
- 7–11 times per year
- 1 time per month
- 2–3 times per month
- 1 time per week
- 2 times per week
- 3–4 times per week
- 5–6 times per week
- 1 time per day
- 2 or more times per day

115a. Each time you ate **yogurt**, how much did you usually eat?

- Less than ½ cup or less than 1 container
- ½ to 1 cup or 1 container
- More than 1 cup or more than 1 container

Question 113 appears in the next column

Question 116 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

115b. How often was the **yogurt** you ate **low-fat** or **fat-free**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

116. How often did you eat **cottage cheese** (including low-fat)?

- NEVER (GO TO QUESTION 117)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

116a. Each time you ate **cottage cheese**, how much did you usually eat?

- Less than ¼ cup
- ¼ to 1 cup
- More than 1 cup

117. How often did you eat **cheese** (including low-fat, including on cheeseburgers or in sandwiches or subs)?

- NEVER (GO TO QUESTION 118)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

117a. Each time you ate **cheese**, how much did you usually eat?

- Less than ½ ounce or less than 1 slice
- ½ to 1½ ounces or 1 slice
- More than 1½ ounces or more than 1 slice

117b. How often was the cheese you ate **low-fat** or **fat-free**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

Question 118 appears in the next column

118. How often did you eat **frozen yogurt, sorbet, or ices** (including low-fat or fat-free)?

- NEVER (GO TO QUESTION 119)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

118a. Each time you ate **frozen yogurt, sorbet, or ices**, how much did you usually eat?

- Less than ½ cup or less than 1 scoop
- ½ to 1 cup or 1 to 2 scoops
- More than 1 cup or more than 2 scoops

119. How often did you eat **ice cream, ice cream bars, or sherbet** (including low-fat or fat-free)?

- NEVER (GO TO QUESTION 120)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

119a. Each time you ate **ice cream, ice cream bars, or sherbet**, how much did you usually eat?

- Less than ½ cup or less than 1 scoop
- ½ to 1½ cups or 1 to 2 scoops
- More than 1½ cups or more than 2 scoops

119b. How often was the ice cream you ate **light, low-fat, or fat-free ice cream or sherbet**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

120. How often did you eat **cake** (including low-fat or fat-free)?

- NEVER (GO TO QUESTION 121)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

Question 121 appears on the next page

This is a sample form. Do not use for scanning.

Over the **past 12 months...**

120a. Each time you ate **cake**, how much did you usually eat?

- Less than 1 medium piece
- 1 medium piece
- More than 1 medium piece

121. How often did you eat **cookies** or **brownies** (including low-fat or fat-free)?

- NEVER (GO TO QUESTION 122)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

121a. Each time you ate **cookies** or **brownies**, how much did you usually eat?

- Less than 2 cookies or 1 small brownie
- 2 to 4 cookies or 1 medium brownie
- More than 4 cookies or 1 large brownie

122. How often did you eat **doughnuts**, **sweet rolls**, **Danish**, or **pop-tarts**?

- NEVER (GO TO QUESTION 123)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

122a. Each time you ate **doughnuts**, **sweet rolls**, **Danish**, or **pop-tarts**, how much did you usually eat?

- Less than 1 piece
- 1 to 2 pieces
- More than 2 pieces

123. How often did you eat **sweet muffins** or **dessert breads** (including low-fat or fat-free)?

- NEVER (GO TO QUESTION 124)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

Question 124 appears in the next column

123a. Each time you ate **sweet muffins** or **dessert breads**, how much did you usually eat?

- Less than 1 medium piece
- 1 medium piece
- More than 1 medium piece

124. How often did you eat **fruit crisp**, **cobbler**, or **strudel**?

- NEVER (GO TO QUESTION 125)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

124a. Each time you ate **fruit crisp**, **cobbler**, or **strudel**, how much did you usually eat?

- Less than ½ cup
- ½ to 1 cup
- More than 1 cup

125. How often did you eat **pie**?

- NEVER (GO TO QUESTION 126)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

125a. Each time you ate **pie**, how much did you usually eat?

- Less than ¼ of a pie
- About ¼ of a pie
- More than ¼ of a pie

The next four questions ask about the kinds of pie you ate. Please read all four questions before answering.

125b. How often were the pies you ate **fruit pie** (such as apple, blueberry, others)?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

Question 126 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

125c. How often were the pies you ate **cream, pudding, custard, or meringue pie**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

125d. How often were the pies you ate **pumpkin or sweet potato pie**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

125e. How often were the pies you ate **pecan pie**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

126. How often did you eat **chocolate candy**?

- NEVER (GO TO QUESTION 127)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

126a. Each time you ate **chocolate candy**, how much did you usually eat?

- Less than 1 average bar or less than 1 ounce
- 1 average bar or 1 to 2 ounces
- More than 1 average bar or more than 2 ounces

127. How often did you eat **other candy**?

- NEVER (GO TO QUESTION 128)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

127a. Each time you ate **other candy**, how much did you usually eat?

- Fewer than 2 pieces
- 2 to 9 pieces
- More than 9 pieces

Question 128 appears in the next column

128. How often did you eat **eggs, egg whites, or egg substitutes** (NOT counting eggs in baked goods and desserts)? *(Please include eggs in salads, quiche, and soufflés.)*

- NEVER (GO TO QUESTION 129)
- 1–6 times per year 2 times per week
- 7–11 times per year 3–4 times per week
- 1 time per month 5–6 times per week
- 2–3 times per month 1 time per day
- 1 time per week 2 or more times per day

128a. Each time you ate **eggs**, how many did you usually eat?

- 1 egg
- 2 eggs
- 3 or more eggs

128b. How often were the eggs you ate **egg substitutes or egg whites only**?

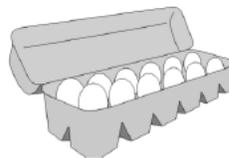
- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

128c. How often were the eggs you ate **regular whole eggs**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

128d. How often were the eggs you ate **cooked in oil, butter, or margarine**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always



Question 129 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

128e. How often were the eggs you ate part of **egg salad**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

129. How many cups of **coffee**, caffeinated or decaffeinated, did you drink (including coffee drinks such as Latte, Mocha, Frappuccino, etc.)?

- NONE (GO TO QUESTION 130)
- Less than 1 cup per month
- 1–3 cups per month
- 1 cup per week
- 2–4 cups per week
- 5–6 cups per week
- 1 cup per day
- 2–3 cups per day
- 4–5 cups per day
- 6 or more cups per day

129a. How often was the coffee you drank **decaffeinated**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

130. How many glasses, cans, or bottles of **COLD** or **ICED tea**, caffeinated or decaffeinated, did you drink?

- NONE (GO TO QUESTION 131)
- Less than 1 glass, can or bottle per month
- 1–3 glasses, cans or bottles per month
- 1 glass, can or bottle per week
- 2–4 glasses, cans or bottles per week
- 5–6 glasses, cans or bottles per week
- 1 glass, can or bottle per day
- 2–3 glasses, cans or bottles per day
- 4–5 glasses, cans or bottles per day
- 6 or more glasses, cans or bottles per day

130a. How often was the cold or iced tea you drank **decaffeinated** or **herbal**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

Question 131 appears in the next column

130b. How often was the cold or iced tea you drank **presweetened with either sugar or artificial sweeteners** (such as Splenda, Equal, Sweet'N Low or others)?

- Almost never or never (GO TO QUESTION 131)
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

130c. What kind of **sweetener** was added to your presweetened cold or iced tea most of the time?

- Sugar or honey
- Artificial sweeteners (such as Splenda, Equal, Sweet'N Low or others)

131. How many cups of **HOT tea**, caffeinated or decaffeinated, did you drink?

- NONE (GO TO QUESTION 132)
- Less than 1 cup per month
- 1–3 cups per month
- 1 cup per week
- 2–4 cups per week
- 5–6 cups per week
- 1 cup per day
- 2–3 cups per day
- 4–5 cups per day
- 6 or more cups per day

131a. How often was the hot tea you drank **decaffeinated** or **herbal**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

132. Over the past 12 months, did you add **sugar, honey or other sweeteners** to your tea or coffee (hot or iced)?

- NO (GO TO QUESTION 133)
- YES

132a. How often did you add **sugar** or **honey** to your coffee or tea (hot or iced)?

- Almost never or never (GO TO QUESTION 132c)
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

Question 132c appears on the next page
Question 133 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

132b. Each time **sugar** or **honey** was added to your coffee or tea, how much was usually added?

- Less than 1 teaspoon
- 1 to 3 teaspoons
- More than 3 teaspoons

132c. How often did you add **artificial sweetener** (such as Splenda, Equal, Sweet'N Low or others) to your coffee or tea?

- Almost never or never (GO TO QUESTION 133)
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

132d. What kind of **artificial sweetener** did you usually use?

- Equal or aspartame
- Sweet'N Low or saccharin
- Splenda or sucralose
- Herbal extracts or other kind

132e. Each time **artificial sweetener** was added to your coffee or tea, how much was usually added?

- Less than 1 packet or less than 1 teaspoon
- 1 packet or 1 teaspoon
- More than 1 packet or more than 1 teaspoon

133. Over the past 12 months, did you add **whiteners** (such as cream, milk, or non-dairy creamer) to your tea or coffee?

NO (GO TO QUESTION 134)

YES

133a. How often was **non-dairy creamer** added to your coffee or tea?

- Almost never or never (GO TO QUESTION 133d)
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

Question 133d appears in the next column

Question 134 appears on the next page

133b. Each time **non-dairy creamer** was added to your coffee or tea, how much was usually used?

- Less than 1 teaspoon
- 1 to 3 teaspoons
- More than 3 teaspoons

133c. What kind of **non-dairy creamer** did you usually use?

- Regular powdered
- Low-fat or fat-free powdered
- Regular liquid
- Low-fat or fat-free liquid

133d. How often was **cream** or **half and half** added to your coffee or tea?

- Almost never or never (GO TO QUESTION 133f)
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

133e. Each time **cream** or **half and half** was added to your coffee or tea, how much was usually added?

- Less than 1 tablespoon
- 1 to 2 tablespoons
- More than 2 tablespoons

133f. How often was **milk** added to your coffee or tea?

- Almost never or never (GO TO QUESTION 134)
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

133g. Each time **milk** was added to your coffee or tea, how much was usually added?

- Less than 1 tablespoon
- 1 to 3 tablespoons
- More than 3 tablespoons

133h. What kind of **milk** was usually added to your coffee or tea?

- Whole milk
- 2% milk
- 1% milk
- Skim, nonfat, or ½% milk
- Evaporated or condensed (canned) milk
- Soy milk
- Rice milk
- Other

Question 134 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

134. How often was **sugar** or **honey** added to foods you ate? (Please do not include sugar in coffee, tea, other beverages, or baked goods.)

- NEVER (GO TO INTRODUCTION TO QUESTION 135)
- | | |
|--|--|
| <input type="checkbox"/> 1-6 times per year | <input type="checkbox"/> 2 times per week |
| <input type="checkbox"/> 7-11 times per year | <input type="checkbox"/> 3-4 times per week |
| <input type="checkbox"/> 1 time per month | <input type="checkbox"/> 5-6 times per week |
| <input type="checkbox"/> 2-3 times per month | <input type="checkbox"/> 1 time per day |
| <input type="checkbox"/> 1 time per week | <input type="checkbox"/> 2 or more times per day |

134a. Each time **sugar** or **honey** was added to foods you ate, how much was usually added?

- Less than 1 teaspoon
 1 to 3 teaspoons
 More than 3 teaspoons

The following questions are about the kinds of margarine, mayonnaise, sour cream, cream cheese, and salad dressing that you ate. If possible, please check the labels of these foods to help you answer.

135. Over the past 12 months, did you eat **margarine**?

- NO (GO TO QUESTION 136)
 YES

135a. How often was the margarine you ate **light**, **low-fat**, or **fat-free** (stick or tub)?

- Almost never or never
 About ¼ of the time
 About ½ of the time
 About ¾ of the time
 Almost always or always

136. Over the past 12 months, did you eat **butter**?

- NO (GO TO QUESTION 137)
 YES

136a. How often was the butter you ate **light** or **low-fat**?

- Almost never or never
 About ¼ of the time
 About ½ of the time
 About ¾ of the time
 Almost always or always

Question 137 appears in the next column

137. Over the past 12 months, did you eat **mayonnaise** or **mayonnaise-type dressing**?

- NO (GO TO QUESTION 138)
 YES

137a. How often was the mayonnaise you ate **light**, **low-fat** or **fat-free**?

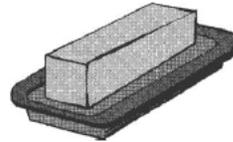
- Almost never or never
 About ¼ of the time
 About ½ of the time
 About ¾ of the time
 Almost always or always

138. Over the past 12 months, did you eat **sour cream**?

- NO (GO TO QUESTION 139)
 YES

138a. How often was the sour cream you ate **light**, **low-fat**, or **fat-free**?

- Almost never or never
 About ¼ of the time
 About ½ of the time
 About ¾ of the time
 Almost always or always



139. Over the past 12 months, did you eat **cream cheese**?

- NO (GO TO QUESTION 140)
 YES

139a. How often was the cream cheese you ate **light**, **low-fat**, or **fat-free**?

- Almost never or never
 About ¼ of the time
 About ½ of the time
 About ¾ of the time
 Almost always or always

Question 140 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

140. Over the past 12 months, did you eat **salad dressing**?

NO (GO TO INTRODUCTION TO QUESTION 141)

YES

140a. How often was the salad dressing you ate **light, low-fat or fat-free**?

- Almost never or never
- About ¼ of the time
- About ½ of the time
- About ¾ of the time
- Almost always or always

The following two questions ask you to summarize your usual intake of **vegetables and fruits**. Please do not include **salads, potatoes, or juices**.

141. Over the past 12 months, how many servings of **vegetables** (not including salad or potatoes) did you eat per week or per day?

- Less than 1 per week
- 1–2 per week
- 3–4 per week
- 5–6 per week
- 1 per day
- 2 per day
- 3 per day
- 4 per day
- 5 or more per day

142. Over the past 12 months, how many servings of **fruit** (not including juices) did you eat per week or per day?

- Less than 1 per week
- 1–2 per week
- 3–4 per week
- 5–6 per week
- 1 per day
- 2 per day
- 3 per day
- 4 per day
- 5 or more per day

143. Over the past month, which of the following foods did you eat **AT LEAST THREE TIMES**? (Mark all that apply.)

- Avocado, guacamole
- Cheesecake
- Chocolate, fudge, or butterscotch toppings or syrups
- Chow mein noodles
- Croissants
- Dried apricots
- Egg rolls
- Granola bars
- Hot peppers
- Jell-O, gelatin
- Mangoes
- Milkshakes or ice-cream sodas
- Olives
- Oysters
- Pickles or pickled vegetables or fruit
- Plantains
- Pork neck bones, hock, head, feet
- Pudding or custard
- Veal, venison, lamb
- Whipped cream, regular
- Whipped cream, substitute
- NONE

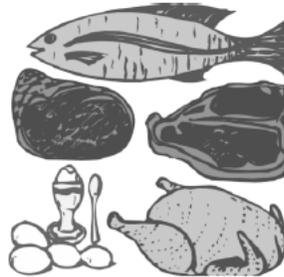
144. For **ALL** of the past 12 months, have you followed any type of **vegetarian diet**?

NO (GO TO INTRODUCTION TO QUESTION 145)

YES

144a. Which of the following foods did you **TOTALLY EXCLUDE** from your diet? (Mark all that apply.)

- Meat (beef, pork, lamb, etc.)
- Poultry (chicken, turkey, duck)
- Fish and seafood
- Eggs
- Dairy products (milk, cheese, etc.)



Introduction to Question 145 appears on the next page

This is a sample form. Do not use for scanning.

The next questions are about your use of vitamin pills or other supplements.

145. Over the past 12 months, did you take any **multivitamins**, such as One-a-Day-, Theragran-, Centrum-, or Prenatal-type multivitamins (as pills, liquids, or packets)?

- NO (GO TO INTRODUCTION TO QUESTION 147)
- YES

146. How often did you take **One-a-day-, Theragran-, Centrum- or Prenatal-type** multivitamins?

- Less than 1 day per month
- 1-3 days per month
- 1-3 days per week
- 4-6 days per week
- Every day

146a. Did your **multivitamin** usually contain **minerals** (such as iron, zinc, etc.)?

- NO
- YES
- Don't know

146b. For how many years have you taken **multivitamins**?

- Less than 1 year
- 1-4 years
- 5-9 years
- 10 or more years

146c. Over the past 12 months, did you take any **vitamins, minerals, or other herbal supplements** other than your multivitamin?

- NO

Thank you *very much* for completing this questionnaire! Because we want to be able to use all the information you have provided, we would greatly appreciate it if you would please take a moment to review each page making sure that you:

- Did not skip any pages and
- Crossed out the incorrect answer and circled the correct answer if you made any changes.

- YES (GO TO INTRODUCTION TO QUESTION 147)

Introduction to Question 147 appears in the next column

These last questions are about the vitamins, minerals, or herbal supplements you took that are **NOT** part of a One-a-day-, Theragran-, or Centrum-type of multivitamin.

Over the past 12 months...

147. How often did you take **Antacids** such as **Tums or Rolaids**?

- NEVER (GO TO QUESTION 148)
- Less than 1 day per month
- 1-3 days per month
- 1-3 days per week
- 4-6 days per week
- Every day

147a. When you took **Antacids** such as **Tums or Rolaids**, about how many tablets or lozenges did you take in one day?

- Less than 1
- 1
- 2
- 3
- 4 or more
- Don't know

147b. Was your antacid usually "extra strength"?

- NO
- YES
- Don't know

147c. For how many years have you taken **Antacids** such as **Tums or Rolaids**?

- Less than 1 year
- 1-4 years
- 5-9 years
- 10 or more years

148. How often did you take **Calcium** (with or without Vitamin D) (**NOT** as part of a multivitamin in Question 146 or antacid in Question 147)?

- NEVER (GO TO QUESTION 149)
- Less than 1 day per month
- 1-3 days per month
- 1-3 days per week
- 4-6 days per week
- Every day

Question 149 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

148a. When you took **Calcium**, about how much elemental calcium did you take in one day?
(If possible, please check the label for elemental calcium.)

- Less than 500 mg
- 500–599 mg
- 600–999 mg
- 1,000 mg or more
- Don't know

148b. Did your **Calcium** usually contain **Vitamin D**?

- NO
- YES
- Don't know

148c. Did your **Calcium** usually contain **Magnesium**?

- NO
- YES
- Don't know

148d. Did your **Calcium** usually contain **Zinc**?

- NO
- YES
- Don't know

148e. For how many years have you taken **Calcium**?

- Less than 1 year
- 1–4 years
- 5–9 years
- 10 or more years

149. How often did you take **Iron** (NOT as part of a multivitamin in Question 146)?

- NEVER (GO TO QUESTION 150)
- Less than 1 day per month
- 1–3 days per month
- 1–3 days per week
- 4–6 days per week
- Every day

149a. For how many years have you taken **Iron**?

- Less than 1 year
- 1–4 years
- 5–9 years
- 10 or more years

Question 150 appears in the next column

150. How often did you take **Vitamin C** (NOT as part of a multivitamin in Question 146)?

- NEVER (GO TO QUESTION 151)
- Less than 1 day per month
- 1–3 days per month
- 1–3 days per week
- 4–6 days per week
- Every day

150a. When you took **Vitamin C**, about how much did you take in one day?

- Less than 500 mg
- 500–999 mg
- 1,000–1,499 mg
- 1,500–1,999 mg
- 2,000 mg or more
- Don't know

150b. For how many years have you taken **Vitamin C**?

- Less than 1 year
- 1–4 years
- 5–9 years
- 10 or more years

151. How often did you take **Vitamin E** (NOT as part of a multivitamin in Question 146)?

- NEVER (GO TO INTRODUCTION TO QUESTION 152)
- Less than 1 day per month
- 1–3 days per month
- 1–3 days per week
- 4–6 days per week
- Every day

151a. When you took **Vitamin E**, about how much did you take in one day?

- Less than 400 IU
- 400–799 IU
- 800–999 IU
- 1,000 IU or more
- Don't know

151b. For how many years have you taken **Vitamin E**?

- Less than 1 year
- 1–4 years
- 5–9 years
- 10 or more years

Introduction to Question 152 appears on the next page

This is a sample form. Do not use for scanning.

Over the past 12 months...

The last two questions ask you about other supplements you took more than once per week.

152. Please mark any of the following **single supplements** you took more than once per week (NOT as part of a multivitamin in Question 147):

- | | |
|--|---|
| <input type="checkbox"/> B-6 | <input type="checkbox"/> Occu-vite/Eye health |
| <input type="checkbox"/> B-complex | <input type="checkbox"/> Potassium |
| <input type="checkbox"/> B-12 | <input type="checkbox"/> Selenium |
| <input type="checkbox"/> Beta-carotene | <input type="checkbox"/> Vitamin A |
| <input type="checkbox"/> Folic acid/folate | <input type="checkbox"/> Vitamin D |
| <input type="checkbox"/> Magnesium | <input type="checkbox"/> Zinc |

153. Please mark any of the following **herbal, botanical, or other supplements** you took more than once per week.

- | | |
|---|--|
| <input type="checkbox"/> Chondroitin | <input type="checkbox"/> Ginseng |
| <input type="checkbox"/> Coenzyme Q-10 | <input type="checkbox"/> Glucosamine/
chondroitin |
| <input type="checkbox"/> Echinacea | <input type="checkbox"/> Peppermint |
| <input type="checkbox"/> Energy supplements | <input type="checkbox"/> Probiotics |
| <input type="checkbox"/> Fish oil/omega 3's | <input type="checkbox"/> Saw palmetto |
| <input type="checkbox"/> Flaxseed/oil | <input type="checkbox"/> Soy supplement |
| <input type="checkbox"/> Garlic | <input type="checkbox"/> Sports supplements |
| <input type="checkbox"/> Ginger | <input type="checkbox"/> St. John's wort |
| <input type="checkbox"/> Ginkgo biloba | <input type="checkbox"/> Other |

Thank you *very much* for completing this questionnaire! Because we want to be able to use all the information you have provided, we would greatly appreciate it if you would please take a moment to review each page making sure that you:

- Did not skip any pages and
- Crossed out the incorrect answer and circled the correct answer if you made any changes.

26 Appendix O: Automated Self-Administered 24-hour Recall (ASA24)



Overview of the ASA24™ Respondent Web sites and Considerations Related to Data Security and Participant Confidentiality

Extensive evidence has demonstrated that 24-hour dietary recalls provide the highest quality, least biased dietary data. Traditional 24-hour recalls, however, are expensive and impractical for large-scale research because they rely on trained interviewers and multiple administrations to estimate usual intakes. As a result, researchers often make use of food frequency questionnaires, which are less expensive but contain substantial error.

To address this challenge, investigators at NCI created the Automated Self-administered 24-hour Recall (ASA24™) system, a freely-available, web-based tool that enables multiple automated self-administered 24-hour recalls. ASA24™ was developed under contract with Westat®, a social science research firm located in Rockville, MD, and builds on the Food Intake Recording Software System (FIRSt) developed by Dr. Tom Baranowski of the Baylor College of Medicine. An External Working Group provided advice about the needs and interests of potential users.

ASA24™ consists of a Respondent Web site used to collect recall data and a Researcher Web site used to manage study logistics and obtain data analyses. Two Respondent Web sites are currently available in English and Spanish: **ASA24™-2014** and **ASA24™-Kids-2014**. This document provides an overview of the methodology and main features of the ASA24™ Respondent sites, as well as information on security of the data collected and protections to the confidentiality of the participants of studies that make use of ASA24™. Images of the main Respondent site screens are also included.

ASA24™ Respondent Web site Methodology

Respondents are guided through the 24-hour recall interview using a modified version of the USDA's Automated Multiple-Pass Method (AMPM). The steps in the interview process include:

1. Meal-based Quick List
2. Meal Gap Review
3. Detail Pass
4. Forgotten Foods
5. Final Review
6. Last Chance
7. Usual Intake Question
8. Supplement Module (if selected by the researcher)

Meal-based Quick List

During the first pass of the interview, respondents are asked to provide a list of the foods and drinks consumed at each meal occasion for one of two possible 24-hour time periods, depending on the preference of the researcher: yesterday, from midnight to midnight; or, the past 24-hours based on the time of participant login. Respondents are able to browse food group categories to find their foods and drinks or search for a particular item. Foods and drinks

reported at each meal are recorded in the My Foods and Drinks panel within the instrument. This initial step is called the meal-based Quick List. In addition to selecting an eating occasion (e.g., breakfast, lunch, snack), respondents are also prompted to specify the time of the occasion before reporting the foods and drinks consumed. The researcher can opt to collect additional contextual information including where meals were eaten, television and computer use during meals, and whether the meal was eaten alone or with others.

Meal Gap Review

Once respondents finish creating their My Foods and Drinks list at the end of the Quick List step, they are asked if they consumed anything during any 3-hour gaps between eating occasions, and, for the midnight to midnight version, between midnight and the first eating occasion, and between the last eating occasion and midnight. A response of “Yes” to any gap will return the respondent to the Quick List to add the appropriate food(s) or drink(s).

Detail Pass

Respondents are asked for details about the foods and drinks they recorded during the Quick List, including form (e.g., raw), preparation methods (e.g., grilled or roasted), the amount eaten, and any additions (e.g., sugar, coffee cream, salad dressing). Researchers can also opt to ask the source (grocery store, farmer’s market, vending machine, etc.) of each food reported.

Forgotten Foods

Following the Detail Pass, a pop-up window appears with questions probing about the consumption of commonly forgotten foods and drinks (e.g., snack foods, fruits, vegetables, cheese, water, coffee, tea). Respondents must check either “Yes” or “No” for each food or drink probed. For any “Yes” response, the respondent will be returned to the Quick List to add the forgotten item(s).

Final Review

Respondents are prompted to review all of the foods and drinks reported for the intake day, and make edits and add meals, foods and drinks as necessary.

Last Chance

After the Final Review, a pop-up screen appears with an option to add food or drink items if respondents have still forgotten any. Again, respondents will be brought back to the Quick List to add more items; otherwise, they will move forward to the final question in the food and drink module.

Usual Intake Question

The final question asks: Was the amount of food that you ate yesterday more than usual, usual, or less than usual? This question probes whether this was a typical day’s intake.

Supplement Module (if selected by the researcher during study set-up)

Respondents are asked to provide information about the type and dose of supplements consumed by completing a Quick List, a Detail Pass, and a Final Review. Supplements include vitamins, minerals, and other supplements including prescription supplements. Respondents are able to browse supplement categories (e.g., Multi-Vitamin/Mineral, Calcium products, Herbal/Botanicals) or search for a particular supplement. The supplements included are based on those reported in the National Health and Nutrition Examination Survey.

ASA24™ Respondent Web Site Features

The ASA24™ Respondent Web site guides the participant through the completion of a 24-hour recall for the previous day, from midnight to midnight, using a dynamic user interface. The instrument:

- provides an animated guide and audio and visual cues to instruct participants and enhance use in low-literacy populations and with children (with options to turn off the guide and/or the audio);
- asks respondents to report eating occasion and time of consumption;
- includes optional modules to query where meals were eaten, whether meals were eaten alone or with others, and television and computer use during meals;
- flows as per modified USDA Automated Multiple-Pass Method (AMPM) 24-hour recall;
- allows respondents to report foods and drinks by browsing by category or searching from a list of food and drink terms derived from the National Health and Nutrition Examination Survey (NHANES);
- asks detailed questions about food preparation, portion size, and additions so that food codes from USDA's Food and Nutrient Database for Dietary Studies (FNDDS) can be assigned; it also provides an option to query respondents about food source;
- uses images to assist respondents in reporting portion size;
- allows the respondent to add or modify food and drink choices at multiple points during the interview;
- includes an optional module to query dietary supplement intake based on supplements reported in NHANES;
- is available in English and Spanish; and
- is compliant with Section 508 of the 1973 Rehabilitation Act.

The Respondent Web sites do not provide any direct feedback to respondents. Instead, researchers can obtain analysis files from the Researcher Web site and contact respondents with any findings they choose to share.

Data Security and Protections to Confidentiality of Participants using ASA24™

Researchers using ASA24™ do not provide the National Cancer Institute, Westat (the research firm that developed and maintains ASA24™), or the ASA24™ system with any identifying data for participants of their studies. Rather, researchers specify an identifier for each respondent and download system-generated usernames and encrypted passwords that they provide to respondents so that they may access the application.

ASA24™ also does not collect any identifying data directly from respondents. However, IP address information is accessed for the purpose of routing information between the server and the respondent's computer—often the IP address is that of the user's Internet Service Provider (ISP). IP addresses are not stored or tracked by ASA24™. However, logs of connections are kept in the hosting environment for audit trail purposes. This information is not mined in any way but would be available if there were a legal obligation to release it.

Response data are secured at the hosting site using industry standard security controls, including firewalls and encryption. All data entered into ASA24™ at the respondent's computer is encrypted by the internet browser (e.g., Internet Explorer, Firefox) before they are transmitted to our servers using Secure Socket Layer (SSL) Technology. SSL allows for the authentication of the sending and receiving computers.

Only a particular study's investigator(s) and the ASA24™ operations team can access response data. Access is gained through usernames and strong passwords.

ASA24 Respondent Web site Screen Shots

Figure 1: The participant can choose to complete ASA24 in either English or Spanish.

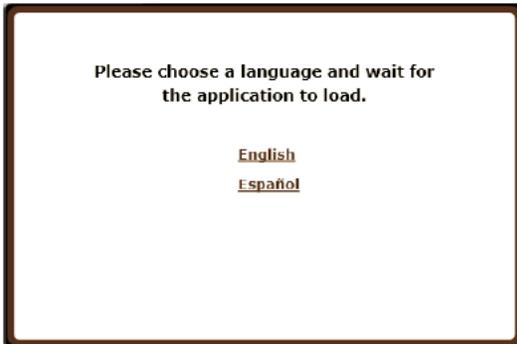


Figure 2: An introductory screen prompts the participant to report everything that she or he had to eat or drink yesterday.

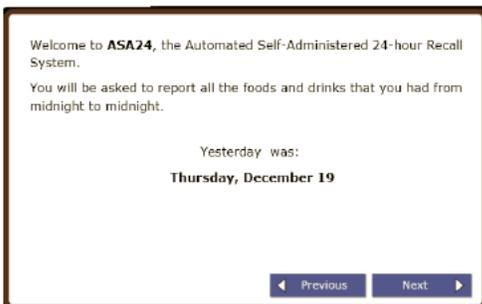


Figure 3: The main ASA24 screen is used to select foods and drinks to be added to My Foods and Drinks during the Quick Pass, and to add details and make changes. The animated guide provides an overview of the main ASA24 screen and gives instructions on how to report all foods, drinks, and supplements (if the optional Supplement Module is selected by the researcher) consumed either from midnight to midnight yesterday or for the past 24 hours, starting at the time of login (depending on the researcher preferences).



Figure 4: The meal details screen collects information on the eating occasion and time, and displays optional modules that can be selected by the researcher to query where meals were eaten, whether meals were eaten alone or with others, and television and computer use during meals. This is the first step in the meal-based Quick List.

Meal Details
Enter the details of the meal or snack you would like to report.

Meal or snack:

Time of meal or snack:
 AM PM

Location:

TV and computer use while eating and drinking:

Did you eat with anyone? Yes No Don't know

Figure 5: Participants complete the Quick List pass by browsing categories or searching for the foods and drinks they consumed. The food and drink terms are based on the National Health and Nutrition Examination Survey.

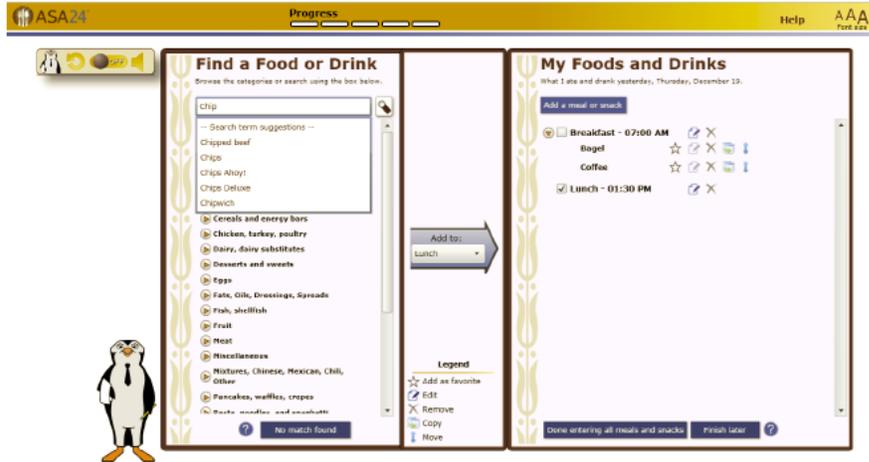


Figure 6: The foods and drinks that the participant reports during the Quick List are displayed in the My Foods and Drinks panel on the right of the main screen.

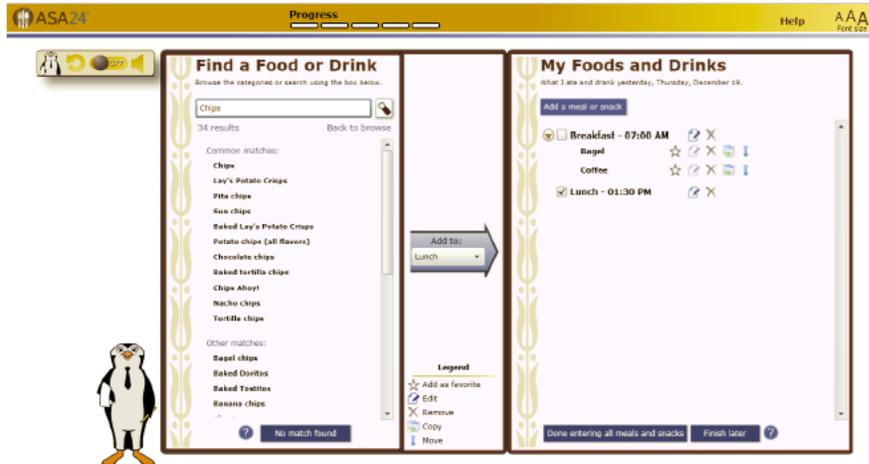


Figure 7: After the participant reports the foods and drinks consumed yesterday and selects Done entering all meals and snacks, the Meal Gap Review is displayed.



Figures 8a-c: The detail pass prompts the participant to report the details of each food and drink, including the specific type or how it was prepared, anything added to it, and the amount that was consumed.

Figure 8a.

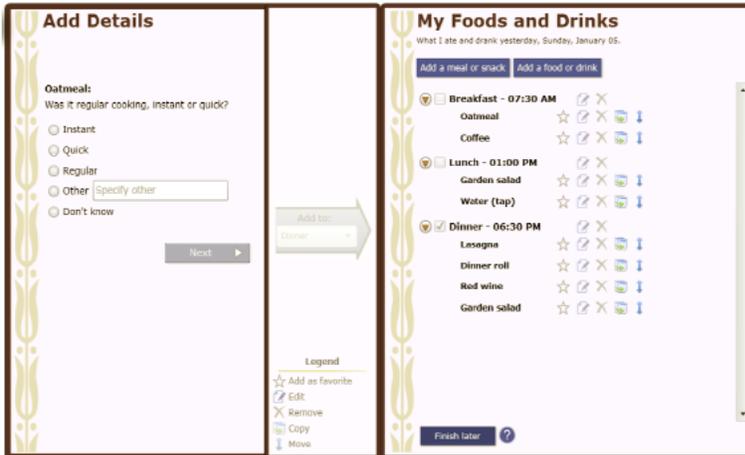


Figure 8b.

Oatmeal: How much did you actually eat?

Select the image that best represents the amount you ate at breakfast Sunday at 07:30 AM.

2 1/4 cups Less than 1/4 cup

2 cups 1/4 cup

1 3/4 cups 1/2 cup

1 1/2 cups 3/4 cup

1 1/4 cups 1 cup

Amount eaten:
3/4 cup

Previous Don't Know Next

Figure 8c.

Did you add anything to your Oatmeal that you haven't already reported?

Select all that apply.

Search or browse to find foods added to your Oatmeal at breakfast Sunday at 07:30 AM. Use the arrows to add or remove additions. If nothing was added or you have already reported the additions, select **Nothing Added** below.

Enter search term		
Butter	Almonds	
Cheese	Jordan almonds	
Cream, creamers	Macadamia nuts	
Egg	Mixed nuts	
Fruit	Mixed seeds	
Margarine, butter replacements	Pine Nuts	
Meal	Pistachio nuts	
Replacements, Protein	Pumpkin seeds	
Supplements	Sesame seeds	
Milk	Soy nuts	
Nuts, seeds	Squash seeds	
	Sugared almonds	
	Sunflower seeds	
	Walnuts	

Previous Don't Know Nothing Added Next

Figure 9: Once the Detail Pass is complete, the Final Review begins. The participant can make changes to the details for a given food or drink and add more foods and drinks if necessary.

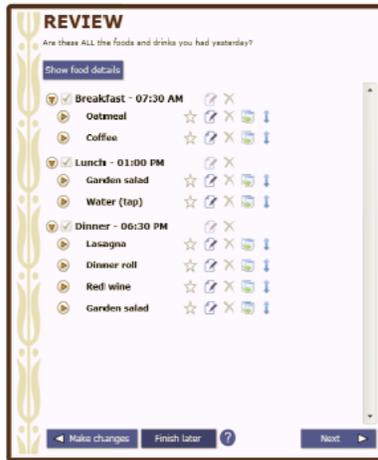


Figure 10: The forgotten foods pass queries the participant about frequently forgotten foods. Responding yes to one or more categories will result in a prompt to add the forgotten foods or drinks.

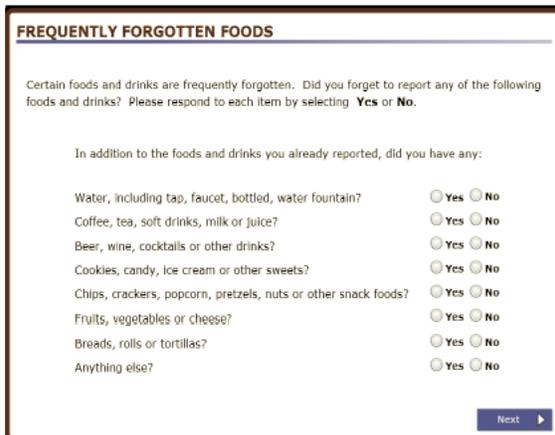


Figure 11: The final question in the food and drink module asks the participant whether the amount of foods and drinks consumed yesterday was usual.

AMOUNT EATEN YESTERDAY

The amount of food and drinks I had yesterday was:

Much more than usual
 Usual
 Much less than usual

Next >

Figure 12: If the Supplement Module is selected by the researcher during study set up, the participant will also be asked about the supplements, if any, that he or she took either from midnight to midnight yesterday or for the past 24 hours, starting at the time of login (depending on researcher preferences).

Find a Supplement

Browse the categories or search using the box below.

Enter search term

★ Favorites

- ▶ Antacids
- ▶ Calcium products
- ▶ Childrens
- ▶ Fiber Supplements
- ▶ Glucosamine products
- ▶ Herbal/Botanical Supplements
- ▶ Minerals
- ▶ Multi-Vitamin/Mineral
- ▶ Other Supplements
- ▶ Potassium Supplements
- ▶ Prenatal
- ▶ Vitamins

Add to:
Supplements

Legend

- ★ Add as favorite
- ✎ Edit
- ✕ Remove
- 📄 Copy
- 📁 Move

No match found

My Supplements

Supplements I took yesterday, Sunday, January 05.

✔ Supplements

Calcium 1200 mg (Unknown or Other Brand) ☆ ✎ ✕ 📄 📁

Done entering supplements Finish later ?

Figure 13: The Supplement Module collects details about each supplement reported.



Figure 14: Once the participant completes the food and drink module and the supplement module, if selected by the researcher during study set up, his or her responses are saved in the secure database and he or she can exit ASA24. Only the researcher(s) who are registered to that study and the ASA24 operations team can access the response data.



27 Appendix P: qADAM Questionnaire

Questions Used as Part of the qADAM Questionnaire

1. How would you rate your libido (sex drive)?
1(terrible) 2(poor) 3(average) 4(good) 5(excellent)
2. How would you rate your energy level?
1(terrible) 2(poor) 3(average) 4(good) 5(excellent)
3. How would you rate your strength/endurance?
1(terrible) 2(poor) 3(average) 4(good) 5(excellent)
4. How would you rate your enjoyment of life?
1(terrible) 2(poor) 3(average) 4(good) 5(excellent)
5. How would you rate your happiness level?
1(terrible) 2(poor) 3(average) 4(good) 5(excellent)
6. How strong are your erections?
(1= extremely weak 5= extremely strong)
1 2 3 4 5
7. How would you rate your work performance over the past 4 weeks?
1(terrible) 2(poor) 3(average) 4(good) 5(excellent)
8. How often do you fall asleep after dinner?
1(never) 2(1-2/week) 3(3-4/week) 4(5-6/week) 5(every night)
9. How would you rate your sports ability over the past 4 weeks?
1(terrible) 2(poor) 3(average) 4(good) 5(excellent)
10. How much height have you lost?
1(2" or more) 2(1.5-1.9") 3(1-1.4") 4(0.5-0.9") 5(none-0.4")

The quantitative ADAM questionnaire. *Int J Impot Res.* 2010 Jan; 22(1): 20–24.

[O Mohamed](#),¹ [R E Freundlich](#),¹ [H K Dakik](#),¹ [E D Grober](#),² [B Najari](#),³ [L I Lipshultz](#),¹ and [M Khera](#)^{1,*}

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PMCID: PMC2834355

29 Appendix R: Sun Exposure and Behaviour Inventory (SEBI v2)

Subject ID: _____

Survey Administration: 1st / 2nd

Date: _____

For **each question** listed, please check off the **ONE** answer that is the **BEST** response to the question.

A **sunburn** is defined as skin redness or pain which lasts at least one day after sun exposure.

1. Which of the following **BEST** describes your skin's reaction to **one hour of summer sun without sunscreen**?

- Always burns, never gets darker /tans (Very light skin, Caucasian)
- Always burns at first, but sometimes gets darker/tans with continued sun exposure (Light skin, Caucasian)
- Sometimes burns first, but always gets darker/tans with continued sun exposure (Medium skin, usually Caucasian)
- Rarely burns, gets darker/tans easily with sun exposure (Olive skin, may be of many race/ethnic backgrounds)
- Never burns, skin gets darker with sun exposure (Brown to dark-brown skin, may be of many race/ethnic backgrounds)
- Never burns, no darkening of skin color with sun exposure (Black skin, African ancestry)

2. How many times in your life have you had a **SUNBURN**?

- None
- 1-10
- 11-20
- More than 20

3. How many times in your life have you had a **SUNBURN that BLISTERED**?

- None
- 1-3
- 4-10
- More than 10

4. How many times in your life have you used a **tanning bed/booth/sunlamp**?

- None
- 1-10
- 11-50
- 51-100

- 101-500
- More than 500

5. Have you lived in an area with a **significantly sunnier climate** than Boston for six months or more?

- Yes
- No

IF yes, what city/state or country? _____ For how long?

- Less than 5 years
- 6-10 years
- 11-20 years
- More than 20 years

6. Please rate your **lifetime** sun exposure

	Very low	Low	Moderate	High	Very high
TOTAL sun exposure					
Exposure from OUTDOOR RECREATION					
Exposure from your JOB					

7. Which of the following **BEST** describes your **NATURAL** skin and hair color when you were a young adult (18-25)?

- Light skin, red or red-blond hair
- Light skin, blonde or light brown hair
- Light skin, brown or black hair
- Medium-tone skin, brown or black hair
- Brown skin, dark brown or black hair
- Black skin, dark brown or black hair

8. What is your eye color?

- Brown
- Blue, green, gray
- Hazel (brownish green)

Now, think about your current lifestyle to answer the remaining questions.

9. Think about what you do when you are outside during the summer on a warm sunny day.

	Never	Rarely	Sometimes	Often	Always
How often do you wear SUNSCREEN ?					

How often do you wear a SHIRT WITH SLEEVES that cover your shoulders?					
How often do you wear a HAT that shades your face, ears, and neck?					
How often do you stay in the SHADE or UNDER AN UMBRELLA?					
How often do you wear SUNGLASSES?					

10. What is the **Sun Protection Factor (SPF)** of the sunscreen that you use most often?

- Less than SPF 15
- SPF 15 or higher
- Don't know
- I don't use sunscreen

11. Does your sunscreen have both **UVA** and **UVB** protection?

- Yes
- No
- Don't know
- I don't use sunscreen

12. How often do you spend time in the sun or in a tanning bed/booth in order to get a tan or to feel good?

- Never
- Rarely
- Sometimes
- Often
- Always

13. Have you been tan in the last 12 months?

- Yes
- No

14. In the **SUMMER** (June, July, August), on average, how many hours per day are you **outside** between 10am and 4pm?

	Less than 1hour	1hour	2hours	3hours	4hours	5hours	6 hours
On WEEKDAYS (Monday-Friday)							
On WEEKENDS (Saturday and Sunday)							

15. In **NON-SUMMER** months (September to May), on average, how many hours per day are you **outside** between 10am and 4pm?

	Less than 1 hour	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
On WEEKDAYS (Monday-Friday)							
On WEEKENDS (Saturday and Sunday)							

30 Appendix S: Investigator Signature of Agreement

Investigator Signature of Agreement

The Eunice Kennedy Shriver National Institute of Child Health and Human Development
Reproductive Medicine Network

Title: Males, Antioxidants, and Infertility (MOXI) Trial

Version: 4.0

Principal Investigator:

I, *[Insert PI's name]*, the Principal Investigator for *[Insert Institute Name]*, hereby certify that I have read and agree to conduct this study in accordance with this protocol on behalf of all RMN Investigators and research staff from my site.

I will conduct the clinical study as described and will adhere to the *Code of Federal Regulations, Title 21 and Title 25, Part 46, Good Clinical Practices (GCP), International Conference on Harmonisation (ICH), and the Declaration of Helsinki. I have read and understood the contents of the Protocol.*

The signature of the investigator below indicates acceptance of the protocol and a complete understanding of the investigator commitments as outlined in Form FDA 1572, Statement of Investigator.

Principal Investigator's Signature

Date

Printed Name

Date

31 Appendix T: Data and Safety Monitoring Plan

DATA AND SAFETY MONITORING BOARD (DSMB) CHARTER

Males, Antioxidants, and Infertility (MOXI) Trial

1. Purpose and Responsibilities of the DSMB

The members of the Data and Safety Monitoring Board (DSMB) identified in this Charter for the MOXI study are responsible for safeguarding the interests of study participants, assessing the safety and efficacy of all study procedures, and shall monitor the overall conduct of the MOXI trial. This Committee will serve as an independent advisory group to the Director of NICHD, and is required to provide recommendations about starting, continuing, and stopping the MOXI trial.

This Committee is responsible for identifying mechanisms to complete various tasks that will impact the safety and efficacy of all study procedures, and overall conduct. The table below identifies the key areas where oversight is necessary and the ways in which the Committee for the MOXI trial will complete those tasks.

Basic Responsibility of DSMB	Method DSMB for MOXI will use to complete task
Familiarize themselves with the study protocol	<ul style="list-style-type: none">· Review study protocols and informed consent forms.
Monitor adverse events	<ul style="list-style-type: none">· Adverse Event: Review quarterly progress reports prepared by the DCC on behalf of RMN.· Serious Adverse Events: Review report submitted by the DCC on behalf of RMN within one week of the event if life threatening or fatal, or within two weeks otherwise. The DSMB will submit a report of their review to the NICHD Committee Coordinator within 7 business days if the SAE is life threatening or fatal, or within two weeks otherwise.
Monitor data quality	<ul style="list-style-type: none">· Conduct interim evaluations of the data.
Oversee participant recruitment and enrollment	<ul style="list-style-type: none">· Review interim progress reports prepared by the DCC on behalf of RMN.
Develop an understanding of the Study's risks and benefits	<ul style="list-style-type: none">· Review study protocols and related literatures.· Review interim reports of subject accrual and outcome measures provided by the DCC.· Assess the need to perform further in-depth evaluation of the benefits and risks of the study after reviewing each report.
Ensure the proper reporting occurs	<ul style="list-style-type: none">· Review and approve the meeting and reporting schedule listed in Section 5 of this DSMB charter.

2. Contacts

NICHD

Louis DePaolo, PhD, Program Officer
Charisee Lamar, PhD, MPH, RRT, Committee Coordinator
Esther Eisenberg, MD, MPH, Project Scientist

Data Coordination Center (DCC)

Heping Zhang, PhD, DCC Principal Investigator
Hao Huang, MD, DCC Data Manager

The Data Manager at the DCC will prepare and review the DSMB reports prior to submission to the DSMB, and will not be blind to treatment condition.

Lead Investigator

Anne Z. Steiner, MD, MPH

3. DSMB Members, Organizational Chart, & Communications

Members

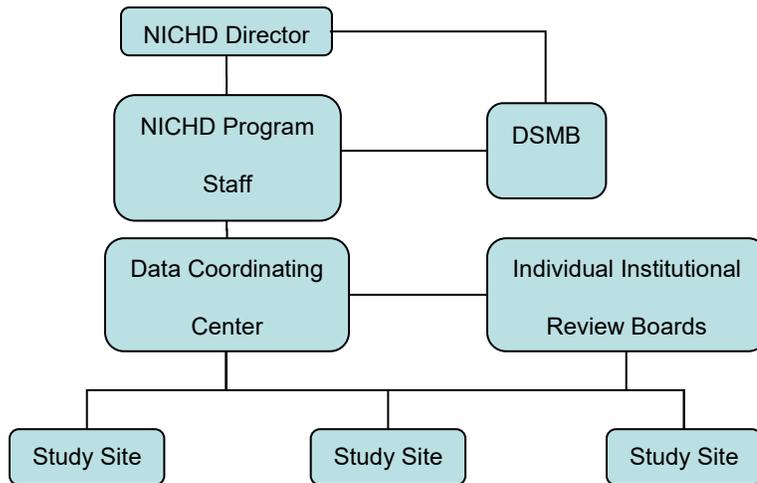
The DSMB for the MOXI trial is comprised of the members listed in the table below. In addition, their high level roles and responsibilities are identified in the table.

Name of Member	Role on DSMB	High Level Responsibilities
Frank Witter, MD	Chair of DSMB Voting member	<ul style="list-style-type: none">· Chair the DSMB discussion and prepare written recommendations to NICHD.· Ensure the safety of study subjects, the integrity of the research data.· Provide NICHD with advice on the ethical and safe progression of studies conducted in the RMN.· Advises on research design issues, data quality and analysis, and research participant protection for each prospective and on-going study.
Robert E. Brannigan, MD	Voting member	<ul style="list-style-type: none">· Ensure the safety of study subjects, the integrity of the research data.
Rev. Phillip Cato, PhD	Voting member	<ul style="list-style-type: none">· Provide NICHD with advice on the ethical and safe progression of studies conducted in the RMN.
PonJola Coney, MD	Voting member	<ul style="list-style-type: none">· Advises on research design issues, data quality and analysis, and research participant protection for each prospective and on-going study.
Lurdes Y.T. Inoue, PhD	Voting member	
Stacey A. Missmer, ScD	Voting member	

Only Voting members for this DSMB may attend closed sessions for this Committee. In addition, only Voting members will have access to unblinded data points for this Committee.

Organizational Chart

The following diagram illustrates the relationship between the DSMB and other entities in the MOXI study.



Communication

Communication for members of this DSMB will be primarily through the NICHD Program Office and, where applicable, the Data Coordination Center (DCC). Investigators from the MOXI study will not communicate directly with DSMB members about the study, except when making presentations or responding to questions at DSMB meetings or during scheduled conference calls.

4. Conflict of Interest and Compensation

It is extremely important that all members of the DSMB state any real or apparent conflicts of interests at the onset of the study. Members of the DSMB shall read the NICHD Clinical Research Guidance Document regarding Conflict of Interest and provide their signed summary of any COI for the study, at its onset, to the NICHD Committee Coordinator, Dr. Charisee Lamar. A table summarizing any COI within the DSMB is provided in the Appendix.

Prior to each meeting, all members of the RMN DSMB will have an opportunity to state whether they have developed any new conflicts of interest since the meeting. As a new COI is identified it must be documented in the table in the Appendix and a new signed summary of the COI should be provided to the NICHD Committee Coordinator. The Coordinator will forward the COI documentation to the DCC for record-keeping purposes.

If a new conflict is reported, the Coordinator and staff will determine if the conflict limits the ability of the DSMB member to participate in the discussion.

All DSMB members will be compensated for their role in supporting the committee. Compensation will include an honorarium for meeting attendance and any travel costs.

5. Meeting Schedule

DSMB meetings will be conducted quarterly. However, the DSMB may hold a meeting at any time in accordance with their mission. The NICHD Committee Coordinator will notify the DCC of any change in schedule.

6. Blinding

All summaries for DSMB reports will be presented in a blinded fashion, unless specified by the DSMB Chair.

7. Report Schedule and Content

The type of reports (full or brief) is indicated below, followed by a description of the contents of each type.

DSMB Report	Report Submission Date	Type of Report
1.	tbd	Brief
2.	tbd	Brief
3.	tbd	Brief
4.	tbd	Full
5.	tbd	Brief
6.	tbd	Full
7.	tbd	Brief
8.	tbd	Full
9.	tbd	Brief
10.	tbd	Full
11.	tbd	Brief

Brief DSMB reports will include the following summaries:

- overall actual versus projected enrollment accrual
- overall randomization update
- overall study drop-out rate
- serious adverse events
- primary outcome measures update

Full DSMB reports will include the following summaries:

- recruitment update (number screened) overall and by site

- enrollment update (enrolled defined as randomized to a treatment) overall and by site
- accrual status including actual enrollment compared to projections overall and by site
- randomization update (i.e., number assigned to each treatment arm)
- study drop-out rate for enrolled patients (number, reason, time point) overall and by site)
- pre-specified subset of baseline demographic data for enrolled patients
- safety data, adverse events, and serious adverse events
- number of case report forms expected
- number/percentage of expected case report forms received – overall and by site
- number of case report forms that are query clean
- primary outcome measures update

References

NIH Policy for Data and Safety Monitoring

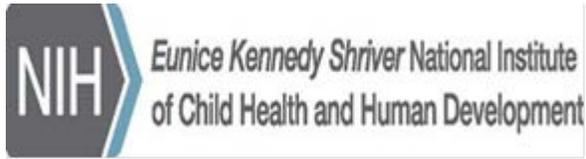
<http://grants.nih.gov/grants/guide/notice-files/NOT98-084.html>

Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-supported Multi-center Clinical Trials

<http://grants.nih.gov/grants/guide/notice-files/not99-107.html>.

Appendix: Summary of COI within the DSMB

DSMB Member Name	Date Submitted Signed COI	Was a COI Identified?	Will the Member Remain part of the Committee?
Robert E. Brannigan, MD			
Rev. Phillip Cato, PhD			
PonJola Coney, MD			
Lurdes Y.T. Inoue, PhD			
Stacey A. Missmer, ScD			
Frank Witter, MD			



Reproductive Medicine Network

Funded by *Eunice Kennedy Shriver* NICHD

Conflict of Interest Statement

Males, Antioxidants, and Infertility (MOXI) Trial

I, _____, assuming the role of _____
(insert role, for example: DSMB member)

for the _____
(insert project or study name)

agree to the following statements.

I agree to:

- protect the interests and safety of study participants;
- uphold the integrity of the research process including data collection and analysis to be as free from bias and preconception as I am able;
- adhere to the highest scientific and ethical standards, to comply with all relevant regulations and to eliminate or disclose, during my involvement with the proposed clinical research project, any real or apparent conflicts of interest.

In addition:

I declare that I, my spouse or dependent children, or organization with which I am connected, do/does not have any financial interest in the _____ study, where financial interested is defined by the DHHS, as anything of monetary value, including but not limited to, salary or other payments for services (for example, consulting fees or honoraria); equity interests (for example, stocks, stock options or other ownership interests); and intellectual property rights (for example, patents, copyrights and royalties from such rights).

The financial interest term does not include various items which can be found in The Federal regulation, PHS, DHHS Part 50--Policies of General Applicability; Subpart F- *Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding Is Sought*.

For Federal employees, financial interests that are allowable and require disclosure are:

Financial Interest Disclosure: Financial interest that require disclosure are stock holdings in pharmaceutical firms, medical device manufacturers, and biotechnology companies

Allowable Financial Interests: In a company that produces a product that is being evaluated by a study, participants may hold up to \$15,000 of stock; and up to an aggregate of \$25,000 of the stock of that company and its competitors who produce that (or a similar) product. As an alternative to individual stock holdings, participants may hold up to an aggregate of \$50,000 in sector mutual funds-including pharmaceutical/health care sectors.

For holdings in excess of these *de minimus* levels, a conflict of interest analysis needs to be conducted by NIH regarding the holding, the company producing the product being evaluated under the study, and its competitors, and, if a conflict exists, could lead to the need to withdraw from the study.

- I agree to not withhold any data related to the _____ study or to interfere with the analysis or publication of the study's results.
- I will not engage in activities that could be viewed as real or apparent COI, including but not limited to:
 - having a part-time, full-time, paid, or unpaid employee status of any organizations that are: (a) involved in the study under review; (b) whose products will be used or tested in the study under review, or whose products or services would be directly and predictably affected in a major way by the outcome of the study;
 - being an officer, member, owner, trustee, director, expert advisor, or consultant of such organizations;
 - being a current collaborator or associate of the principal investigator (applicable to potential members of data safety and monitoring boards);
 - having a scientific interest beyond that required for my role, where scientific interest is defined as having influence over the protocol, the study design, conducting the study analysis or any reporting related to the investigation (applicable to potential members of data safety and monitoring boards).

8.2 Data Collection and Management (including quality assurance/compliance measures)

8.2.1 Data Entry and Forms

Case Report Forms (CRFs) will be developed as the protocol is developed. They will also be implemented in a Web-based Oracle data management system. The Web data entry forms will be similar to the paper forms with the same questions. However, the Web forms usually have more flexibility than the paper forms, such as pull-down menus.

8.2.2 Features of Data Management System

Features of the data management system include study definition; different types of data entry (including double entries and complete audit trail); forms control; query capture, reporting, and resolution; dictionary coding of Adverse Events (AEs) and medical terms; and clinical data review Tools; and prepares data and CRF images to FDA e-Submission Standards. The end-user/reporting/ad hoc query front-end uses a standard Web browser, so that data entry and browsing can be done from any machine with Internet access, without purchase of special software. Login to this system will be through a secured Web server with the security under the protection of Yale Center for Clinical Investigations.

8.2.3 Data Security

A data server and Web server will be used. The data server will be managed by YNHH IT center and the website two servers will be separated and managed by Forte Research Systems. The web server will be accessible through a secured login, but the data server can only be accessed through the web server. For security purposes, no login to the data server will be permitted, and access to the back end is limited to authorized individuals. PHI, including patient names and addresses, will be locked and secured at the participating sites, and data will be linked through a unique identification number, which will be assigned after a patient is screened or enrolled. Access will be limited to authorized individuals (21 CFR 11.10(d)). Each user of the system will have an individual account. The user will log into the account at the beginning of a data entry session, input information (include changes) on the electronic record, and log out at the completion of the data entry session. The system will be designed to limit the number of log-in attempts and record unauthorized access log-in attempts. Individuals will work only under their own access key, and not share these with others. The system will not allow an individual to log onto the system to provide another person access to the system. Access key Users will be asked to change their passwords at established intervals commensurate with a documented risk assessment. This plan has been adapted from the guidelines for computerized systems used in clinical investigations established by the U.S. Department of Health and Human Services Food and Drug Administration.

8.2.4 Data Quality Control

Competency to perform procedure/tests in the protocol

The site PI will be responsible for ensuring that study related tests are performed by competent personnel. The criteria for determination of competency may vary between sites in the study.

biostatistics, epidemiology, infertility, gynecology, andrology and ethics. The NICHD Committee Coordinator is responsible for scheduling regular committee meetings, recording all meeting minutes and summarizing the committee recommendations for the Steering Committee and NICHD. Steering Committee members are prohibited from attending closed sessions of the DSMB. Open sessions may be attended by Steering Committee members or Chairperson when requested by NICHD and the DSMB.

The DSMB has quarterly teleconferences to review Network randomized trial protocols with respect to ethical and safety standards, monitors the safety of on-going clinical trials, monitors the integrity of the data with respect to original study design, and provides advice on study conduct. The DSMB periodically monitors data quality, including protocol adherence and adverse events. As outlined in the protocols, the DSMB will conduct interim evaluations of the data. It may recommend protocol modifications based on concern for subject welfare and scientific integrity.

8.5 Reporting

Administrative Reports will be prepared by the DCC - which include monthly and quarterly reports on accrual, data quality and study compliance - and presented to the Steering Committee and DSMB. Statistical reports include reports to the SC, DSMB and AB from the data analysis, and special reports for scientific manuscripts.

Statistical Reports will be generated in SAS. Reports are provided for DSMB reviews, and for final analysis of study results in preparation for scientific publications. The content of the interim reports will be very complete, and will serve as the template for the final report of each study, which in turn will form the basis of the publication of the results. Our proposed reports to the DSMB would include the following: a protocol description and history; accrual rates; site performance in terms of accrual; eligibility; protocol violations; data accuracy and minority representation; patient characteristics by treatment and site; and the rate of adverse experiences.

8.6 Obligation of the Investigator

8.6.1 IRB Review

The site PI is responsible for submitting the approved protocol and consent form to the IRB for review. The IRB must approve all aspects of the study as detailed in the protocol, including the patient informed consent form. It is anticipated that there will be minor site-specific changes in the consent form. The IRB must periodically review the status of the study at appropriate intervals not exceeding one year. The site PI will also be responsible for submitting revisions to the protocol to the IRB, as directed by the DCC, and promptly communicating serious adverse events that result during the study, to both the local IRB and the DCC. After the approval, the informed consent and IRB approval (or amendment) letters must be forwarded to the DCC.

8.6.2 Maintenance/Retention of site records

In order to comply with Good Clinical Practice (GCP) requirements, the investigators must maintain the master patient log that identifies all patients entered into the study for a period of

9 RMN Publications Policy

The publications policy proposes guidelines for publications that originate from our collaborative Reproductive Medicine Network. Decisions concerning publications shall be determined by consensus (majority vote) of the collaborating Principal Investigators (or designees) noted below as the "Network." This policy is designed to promote prompt, exact, quality publications and presentations of Network studies with appropriate academic recognition of those with significant contributions. Protocols are classified into three types: 'Main Study' (which may include major and minor publications), "Ancillary Study", and 'Pilot Study'. Additionally, there may be publications from concepts or ideas generated by the RMN ("Related Publications") or from other groups utilizing RMN data and/or specimens, known as "Outside Studies" (those utilizing data and/or specimens from the RMN studies). Abstract submissions to national meetings will also follow the publications policy below. The progress of publications (including presentations) will be a standing agenda note on all teleconferences and meetings. The Steering Committee will make the final decision regarding disputes with respect to analysis request approval, prioritization, presentation, authorship and/or manuscript submission.

9.1 Main Study

A Main Study is a Network study designed prospectively by an investigator independent of other studies. Generally, that investigator becomes Lead Investigator of the protocol and Chair of the Protocol Subcommittee. At the end of each Main Study, a primary analysis resulting in the primary manuscript and a number of secondary analyses is produced based on the research questions stated in the protocol. The Protocol Subcommittee Chair is the primary author of the primary analysis. A Main Study can generate major (related to the major hypotheses) and minor publications (relating to secondary hypotheses).

9.1.1 Major Publications

A major publication is defined as one reporting results of the major hypotheses tested. (For example: Does hMG/IVF increase cyclic fecundity in couples with unexplained or male factor infertility?)

a. Authorship

Publications will include the names of investigators from each RMU and the DCC rather than merely identify the "Reproductive Medicine Network". Each RMU and the DCC will have up to two authors per publication, ordinarily the PI and the Co-PI, but this may at times involve another investigator who has contributed to the study at his/her site, in lieu of the PI or Co-PI. The Principal Investigator at each RMU will be responsible for submitting the names of the two authors from that unit and designating them as either the primary and secondary authors of the unit. No more than 2 authors may represent a RMN site. An ancillary site (such as a SCCPIR) may only have 1 investigator. The Steering Committee Chair and NICHD Project Scientist will be authors. Occasionally, additional authors, both within and outside the RMN

It is anticipated that there will be up to 18-25 authors per major manuscript. The authorship order of the RMUs and outside sites will be based upon subject recruitment, data accuracy and promptness of data report according to the chart below:

Data accuracy will be ranked according to the rate of missing or false data entries/randomized subjects at each site. Inquiries that show data was accurately entered will not count against this rate of data inaccuracy. Each site's PI will be responsible for documenting the contributions to the study of that site's authors. In the event the journal editor requires fewer authors even after written documentation of the authors' contribution has been provided, the Steering Committee will vote on the authorship order which will include at a minimum the Lead Investigator and PI of the DCC (or his/her designee) in the positions listed above with the authorship order ending with the footnoted statement "for the Reproductive Medicine Network". The other authors will be referenced in the footnote and listed in the title page.

d. Acknowledgement Section

The acknowledgement section will include other investigators and study personnel who contributed substantially to the study by site, as well as members of the Advisory Board and the Data and Safety Monitoring Board. The designation will list the initials of the individuals followed by their highest degree (e.g. C. L. Gnatuk, J.A. Ober, R.N., etc.).

Significant contributions include but are not limited to protocol review, initiation and participation at each site, subject recruitment and enrollment, study conduct, data analysis, and preparation of the manuscript.

9.1.2 Minor Publications

Minor studies are defined as those in which the hypotheses would not be the main elements of Network studies, but in which the study data base would be utilized to test secondary hypotheses. (One example would be testing whether metformin use spares the dose of clomiphene resulting in lower dose needs.) Ideas for "minor studies" will, in general, be proposed by a single individual, who would direct all efforts leading to publication and representation. The results from minor studies would be handled similarly to those from major studies. The "Protocol" is defined as the Concept Protocol/study design of the hypothesis resulting in the publication.

Authorship will follow the Major Publications guidelines above with the exception that the individual leading the minor study would be the first author, followed by the ranked primary RMN investigators involved in developing the Concept Protocol. The Lead Investigator of the minor publication can propose additional investigators who contributed to the study, whose inclusion in the authorship will be voted on by the Steering Committee (majority vote of SC required for inclusion in authorship). Centers may wish to withdraw inclusion from authorship of publications

of minor studies in which only data are contributed, and this will be the decision of the individual site (RMU) PI.

9.2 Ancillary Study

An Ancillary Study is an observational study, conducted as a supplement to a Main Study. By definition, an Ancillary Study involves all or a subset of patients enrolled in a Main Study. An Ancillary Study does not involve any additional participants. To be defined as an Ancillary Study, there must be a need for collection of additional data not already collected in the Main Study. An Ancillary Study may also be designed by another Network investigator, who would serve as the lead investigator and primary author of the paper. Ancillary Studies may be a “single-center” or “multi-center”.

A “single-center” Ancillary Study is a study in which all data are collected, stored and analyzed at a single center. The center bears the additional cost of such a study. The study requires approval of the Main Study Protocol Subcommittee and the Steering Committee. The center conducting the study is responsible for the analysis and reporting of the results. Abstracts and manuscripts resulting from data from the single-center Ancillary Study are not subject to the RMN Publications Policies.

A “multi-center” Ancillary Study is defined as one for which data or material (such as specimens) are collected at more than one center, or additional funds for conduct of the study are provided by the NICHD RMN and the DCC provides data analysis. Multi-center Ancillary Studies require the approval of the Main Study Protocol Subcommittee and the Steering Committee.

Authorship will be as per Major Publications above with the exception that the individual leading the Ancillary Study and writing the paper would be the first author, followed by ranked RMN primary investigators, etc. A center not participating in the Ancillary Study would not receive authorship unless by majority vote of the Steering Committee.

9.2.1 *Publication Policy on Ancillary Papers*

Authorship

1. RMN will be included as the group author and the acknowledgement will define the entire RMN roster as provided by all PIs.
2. The SC Chair, the NICHD Project Scientist, and all PIs will be co-authors upfront. The order will be recommended by the lead author(s).
3. Based on the ICJME statement for authorship (http://www.icmje.org/ethical_1author.html), anyone who makes additional contributions that are documented and substantive will be co-authors. Correcting typos and making grammar suggestions may be below the threshold.
4. The responsibilities of the lead authors and the DCC: