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PHASE IV STUDY EVALUATING THE SAFETY AND CLINICAL EFFICACY OF ELDERBERRY EXTRACT IN PATIENTS WITH INFLUENZA: A RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL

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INVESTIGATOR'S SIGNATURE PAGE

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The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Investigator: Michael Macknin, M.D.

Signed: _____ **Date:** _____

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ABBREVIATIONS

[Abbreviations or acronyms frequently used in the protocol]

Example Abbreviations	
FDA	Food and Drug Administration
CRF	Case Report Form
IRB	Institutional Review Board
AE	Adverse Event
SAE	Serious Adverse Event
DAIDS	Division of AIDS Adverse Event Grading Table
PHI	Protected Health Information

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RESEARCH SCHEMA

PHASE IV CLINICAL ACTIVITY/SAFETY

1. **Patients will be screened, and influenza polymerase chain reaction positive patients ages 5 and above in the first 48 hours of symptoms will be enrolled at the time of presentation to Emergency Rooms at Main Campus, Fairview and Hillcrest Hospitals of Cleveland Clinic Health Care System.**
2. **Patients will be randomized in a double-blind placebo-controlled trial to treatment with Elderberry Extract (Sambucol^{R}) or Placebo 15 ml. 4 times a day for 5 days ages 13 and above, and 15 ml 2 times a day for 5 days for ages 5-12. All patients will also be offered a prescription for standard of care oseltamivir or baloxavir marboxil (Xofluza) treatment.**
3. **Daily telephone questionnaires documenting compliance, symptoms, and side effects will be obtained until patients are completely recovered from influenza for 24 hours or reach 21 days from date of enrollment. All daily information will be recorded on a case report form, and then entered into REDCap Cloud.**

1 INTRODUCTION

1.1 Background

We propose to conduct a randomized, double-blind, placebo-controlled trial of elderberry extract in a group of 65-100 patients with documented influenza who have been prescribed or offered a prescription for oseltamivir or baloxavir marboxil (Xofluza) .

A recent evidence-based systematic review by the Natural Standard Research Collaboration concluded that there is good scientific evidence that elderberry extract supplementation provides effective relief for the symptoms of influenza.[1-4]) The fact all previously published elderberry extract supplementation studies have been small, did not have intent-to-treat analysis, and were not published in high impact journals probably helps explain why their findings have not been generally recognized by the medical community and lay-public.

The "CDC estimates that influenza in the United States has resulted in between 9.2 million and 60.8 million illnesses, between 140,000 and 710,000 hospitalizations and between 12,000 and 56,000 deaths annually since 2010. [5] If elderberry extract supplementation is shown to be associated with improvement of symptoms of influenza there could be a beneficial impact on health in the United States and the world.

1.2 Investigational Agent [if applicable] Information provided by manufacturer describing investigational drug.

See attachments below:

Part 1.pdf Part 2.pdf Part 3.pdf Part 4.pdf

1.3 Preclinical data

A recent review of elderberry describes its potential mechanisms of action. Elderberry has been reported "to modulate the inflammatory cytokines IL-1 and TNF-alpha in vitro, increase human basophil secretion of IL-4, IL-13, and histamine, inhibit macrophage release of proinflammatory cytokines, and contain flavonoids reported to possess antioxidant activity.[1]" Sambucol® inhibits influenza A and B, HIV, and herpes simplex in vitro and in a randomized, placebo-controlled trial was associated with increased hemagglutination inhibition titers to influenza B infections in vivo.[1,2,6]

A small study showed chimpanzees supplemented with prophylactic Sambucol® 10 ml once daily for approximately six months had less than 1/3 the days of flu-like symptoms compared with a placebo supplemented group. [7] When symptoms occurred the dosage was increased to 15 ml twice daily, and the duration of illnesses were twice as long in the placebo group compared to the Sambucol® supplemented group.[7]

Another review of the antiviral properties of black elder products states, Sambucus nigra (black elder) flowers have been approved by Commission E of the German Federal Institute for Drugs and Medical Devices for the treatment of viral infections, but other parts of the plant have not. While the fruit is not on the FDA GRAS (generally recognized as safe, as the flowers are) list or approved by the German Commission E, analysis of flowers and cooked fruit have consistently indicated safety; other parts of the plant are less suitable for use."[6] Sambucol® uses only cooked fruit from the black elderberry plant.

1.4 Clinical Data to Date

There are four published peer-reviewed randomized double-blind placebo-controlled clinical trials with relevance to the protocol under development. Two, in 27 and 60 patients, demonstrated shortening of the duration of proven influenza by approximately 4 days with elderberry extract supplementation versus placebo ($p<0.001$ in both studies)[2,3]

Another trial evaluated 64 patients with three or more of the following "flu-like symptoms": fever, headache, muscle aches, coughing, nasal mucus discharge, and nasal congestion. [4] By 48 hours of supplementation, "9 patients (28%) in the elderberry extract supplemented group were void of all symptoms, 19 patients (60%) showed complete relief from some symptoms, and had only one or two mild symptoms" (1/10 on a visual analogue scale). No patient in the placebo group achieved complete recovery, and only 5 patients (16%) showed improvement in one or two symptoms ($p<0.001$ for all symptoms). Most patients in the placebo group remained the same or worsened over the 48-hour monitoring period.

The fourth study of elderberry extract evaluated supplementation before, during and after air-travel in 312 passengers.(8) More cold episodes occurred in the placebo group (17 vs. 12) but that did not reach statistical significance ($p=0.4$). "Placebo group participants had a significantly longer duration of cold episode days 117 vs.57, $p=0.02$) and the average symptom score over these days was also significantly higher (583 vs. 247, $p=0.05$)."

A fifth study, by A. Rao and L. Vitetta, entitled "A prospective, double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of a complementary medicine formulation, to help reduce duration and severity of cold and flu symptoms in otherwise healthy adults", with a goal of enrolling 120 cold and 80 flu episodes, completed enrollment in Australia on 5/22/2017. Preliminary results shared by Qayyum Adil, Ph.D. of PharmaCare® in Australia were, "Cold and Influenza relief: cold and influenza duration reduced by 30% (3 day equiv). Symptom severity 35% reduction (participants felt better, faster) using 15mL 4x daily."

1.5 Dose Rationale and Risk/Benefits

The route of administration, dosage, dosage regimen, and dosage period rationale is based upon two previous studies using Sambucol® supplementation for influenza. [2, 3]. Sambucol® supplementation decreased duration of symptoms by approximately 4 days. The only side effect reported in these studies was bad taste in one patient. The only reported side effects in the 312 air travelers study were 3 placebo patients each with one symptom, either itchy throat, fatigue, or kidney pain, and 2 elderberry patients, one with fatigue and one with cold symptoms. Also, there have been twenty-six years of clinical experience with Sambucol® as an over-the-counter supplement now available on six continents, with 21 years availability in the United States. There are no reported serious adverse effects, and dosage recommendations outside the United States are available for ages 2 and above (http://www.cpginteractive.com/sam/faqs.html) and for ages 5 and above in the United States. Subjects' risks under this protocol are minimal, and the potential benefits to the subjects and society are great.

2 STUDY OBJECTIVES

Determine if elderberry extract supplementation shortens the duration and decreases the severity of influenza symptoms in patients who have been prescribed or offered a prescription of oseltamivir or baloxavir marboxil (Xofluza) for documented influenza infection.

3 STUDY DESIGN

3.1 General Design

This is a Phase IV randomized, double-blind, placebo-controlled trial of elderberry extract supplementation versus placebo. Sixty-five to one hundred patients with Roche^{R} cobas^{R} Liat^{R} polymerase chain reaction documented influenza, with at least 2 moderate influenza symptoms as defined below, and who have been prescribed or offered a prescription for oseltamivir or baloxavir marboxil will be randomized to also receive elderberry extract supplementation or placebo.

3.2 Study Endpoints

Baseline data will be obtained at time of presentation including eligibility criteria, medical history, and current influenza symptoms.

Symptoms will be recorded using the scoring system described in a meta-analysis of "all published and unpublished Roche-sponsored randomized placebo-controlled, double-blind trials of oseltamivir treatment in adult influenza" ([9]). "The primary outcome will be time to alleviation of all symptoms. Seven influenza symptoms (nasal congestion, sore throat, cough, aches and pains, fatigue, headaches, and chills or sweats)" will be graded by severity as "absent" (0), "mild" (1), "moderate" (2), or "severe" (3). Alleviation will be defined to arise when all symptoms scored as absent or mild, and remain so for at least 21.5 hours." The secondary endpoints will be the time to alleviation and to complete resolution of individual and all symptoms. Patients will be followed daily until all symptoms have completely resolved and fever has remained less than 100° F for 24 hours, or for a maximum of 21 days if symptoms have not yet completely resolved for 24 hours.

3.3 Primary Safety Endpoints

The conditions or symptoms that will be recorded from day of presentation until influenza symptoms are resolved include; dry mouth, bad taste, nausea, vomiting diarrhea, constipation, abdominal pain,, rash, difficulty breathing, decreased drinking, dizziness and any other symptoms not previously recorded under study endpoints as outlined above. Patient symptoms and severity of illness will be monitored daily using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE GRADING TABLE). See appendix one for all case report forms. Study patients will be asked to call for any worsening influenza symptoms or new conditions or symptoms reaching Grade 3 or 4. See also section 8 safety and adverse events.

4 SUBJECT SELECTION AND WITHDRAWAL

4.1 Inclusion Criteria

Patients are eligible to be included in the study if they meet **all** of the following criteria:

[1] Males or females ≥ 5 years of age

[2] With 48 hours or less of an influenza illness documented by polymerase chain reaction

[3] Have AT LEAST 2 of the following 7 influenza symptoms (nasal congestion, sore throat, cough, aches and pains, fatigue, headaches, and chills or sweats) graded as either moderate or severe

[4] Have been prescribed or offered a prescription of oseltamivir or baloxavir marboxil (Xofluza)

[5] Have access to a phone

[6] Subjects are capable of giving informed consent or have an acceptable legally authorized representative capable of giving consent on the subject's behalf with informed assent given by subject.

4.2 Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria:

[1] Known allergy to elderberry extract, oseltamivir, or baloxavir marboxil (Xofluza)

[2] Use of antibiotic or antiviral medication on presentation to the study

[3] Women who are pregnant, breastfeeding women, or do not agree to appropriate contraception (abstinence, hormonal, intrauterine device, and barrier) to prevent pregnancy during the study.

[4] Patients with HIV

[5] Patients with cystic fibrosis

[6] Patients currently taking Elderberry Extract or Sambucol

4.3 Subject Recruitment and Screening

Study personnel in the Main Campus, Hillcrest and Fairview emergency rooms will be notified of all positive influenza polymerase chain reaction testing obtained in the emergency rooms. Study personnel will then screen these patients' charts for eligibility. Those patients interested in enrolling and willing to provide written informed consent will be enrolled in the study.

At Main Campus, Hillcrest and Fairview Emergency Rooms handouts explaining the study and home management of influenza will be placed where the polymerase chain reaction testing is performed. Potentially eligible patients testing positive for influenza will be given a copy of the handout by study staff or staff ordering or performing test.

The only laboratory testing required to meet inclusion criteria will be positive influenza rapid test polymerase chain reaction, and in women of childbearing potential a negative urine pregnancy test.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Patients may withdraw from the trial at any time and for any reason. Some possible reasons for early withdrawal include the following:

- Development of a medical condition or need for concomitant treatment that precludes further participation in the trial
- Unacceptable toxicity or any adverse event that precludes further participation in the trial
- The investigator removes the patient from the trial in the best interests of the patient
- Study completion or discontinuation
- Patient withdraws consent to continued participation in the trial

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

We will continue to collect data on subjects until they are well or for 21 days if they are not entirely well only if they agree to accept our follow-up phone calls. We will call and leave messages three times before concluding a subject is truly lost to follow-up.

5 STUDY SUPPLEMENT

5.1 Description

Thick reddish-brown liquid and each 15 ml of the oral liquid contains Sambucus Nigra (Black Elderberry) fruit juice equivalent to 5.7 grams.

5.2 Supplement Regimen

Patients will be given their randomly assigned study supplement and instructed to take 15 ml orally of medication, in measuring dispenser provided, four times a day for 5 days for ages 13 and above and 15 ml two times a day for ages 5-12 for 5 days.

5.3 Method for Assigning Subjects to Supplement Groups

Treatment assignment will be made by computer generated randomization with stratification based on age 5-12 or 13 and above.

5.4 Preparation and Administration of Study Medication

Study active and placebo medications will be prepared by PharmaCare® in Australia and mailed in 120 ml bottles with 2-3 bottles per patient of either Elderberry Extract or Placebo contained in boxes identifying the bottles in that box as either active or placebo medication.

Medications will be stored in locked areas at room temperature in a storage area in the study emergency room area with temperature monitors and daily temperature logs. Medications will be distributed by study personnel under the supervision of the Cleveland Clinic Investigational Pharmacy. The first dose of study medication will be administered by study personnel before the patients leave their presenting hospital. Subsequent doses will be administered at home by patients and their families in study provided medicine dispensers used to measure proper dosage.

5.5 Subject Compliance Monitoring

Daily phone calls will monitor the patients' symptoms, new medications or treatments, and compliance with the study medication regimen until reported complete resolution of patients' symptoms for 24 hours, or after 21 days of the study, whichever occurs first. Patients requiring follow-up pregnancy tests will have the testing performed at the Cleveland Clinic laboratory of their choice. Any patient who fails to comply with monitoring will be called three times in an effort to help with compliance with the study protocol. Patients' study medications and empty bottles remaining will be returned by stamped, addressed envelopes provided at the time of enrollment to the Main Campus based study coordinator. At that time remaining medicine will be measured prior to disposal by the investigational pharmacy.

5.6 Prior and Concomitant Therapy

All medications taken at study enrollment will be recorded on the case report forms and then into REDCap Cloud, and any changes in medications will be recorded daily throughout the study. All patients

will be discouraged from taking any cold or flu preparations except for acetaminophen and ibuprofen as needed for pain and/or fever until they have completed the study and are completely well.

5.7 Packaging

Every study patient will be given two (for patients ages 5-12 years old) or three (for patients ages 13 and above) 120 ml bottles of their study medication labeled as below:

Subject Name: _____
Subject Study Number: _____
Contents: 120 ml of Elderberry Extract or Placebo
Directions for use: Ages 5-12: Take 15 ml by mouth two times daily for five days
Ages 13 and above: Take 15 ml by mouth four times daily for five days
Protocol Title: Elderberry Extract or Placebo for Influenza
Sponsor, Investigator name: Cleveland Clinic Foundation, Michael Macknin, MD
Contact phone number, and address: 216-445-4876, 9500 Euclid Ave. Cleveland, Ohio 44195
Manufacturer: PharmaCare Laboratories Pty Ltd
Batch #: TPA xxxxxxx/TPP xxxxxxx
Expiration Date: mm/yyyy
Storage Conditions: Store below 77ºF
Caution: New Drug Limited by United States Law to Investigational Use

5.8 Blinding of Study Medication

A randomization scheme will be developed via computer algorithm with stratification by age (5 to 12 years old and ≥13 years old). Investigational pharmacy personnel not involved in patient contact or data collection directly observed and supervised by the statistician will write the numbers on the appropriate bottles of medications.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Study Medication

PharmaCare ®will ship the product to the Cleveland Clinic investigational pharmacy.

Upon receipt of the study medication, an inventory will be performed and a medication receipt log filled out and signed by the investigational pharmacy personnel accepting the shipment. The investigational pharmacist will count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study supplement product in a given shipment will be documented in the study files. The investigator will notify study sponsor of any damaged or unusable study medication that were supplied to the investigator's site.

5.9.2 Storage

There are no special storage or handling requirements. All supplies will be stored at room temperature between 55-77° F locked in a designated storage area for each study site emergency room with temperature monitors and logs.

5.9.3 Dispensing, Return, and Destruction of Study Medications

Medications will be assigned and dispensed to each subject consecutively at the study site of enrollment.

At the completion of the study, participants are instructed to return by mail any used or unused study medication and Oseltamivir or baloxavir marboxil (Xofluza) to the CCF Main Campus. The study coordinator will perform a final reconciliation of medication dispensed, medication consumed, and medication remaining. This reconciliation will be logged in REDCap Cloud. Any discrepancies noted will be investigated, resolved, and documented prior to the destruction of any medication. All returned medications will be disposed of on site in accordance with Cleveland Clinic Pharmacy Disposition or Disposal of Investigational Drugs Policy and will be documented in the study files.

6 STUDY PROCEDURES

6.1 Pre-registration and Screening

If patients are eligible and interested in participating we will review the informed consent with them, and their families if necessary, and obtain written informed consent or assent, depending upon patients' ages.

6.2 Visit 1

Visit 1 will be completed at the same visit for registration and screening. A nasopharyngeal swab will be obtained for Roche^{R} cobas^{R} Liat^{R} PCR assays for influenza A&B prior to enrollment in study to confirm all study patients have documented influenza.

Informed consent, and assent when indicated, will be obtained prior to completing any study related assessments. Eligibility for the study will be confirmed and baseline data will be obtained.

All women of childbearing potential will have a urine pregnancy test before starting and upon completion of the study. Pregnancy tests will be done following standard Cleveland Clinic operating procedures and documented in the electronic medical record, the case report forms and REDCap Cloud. The result of the pregnancy test(s) will be disclosed to the minor subject and their parent(s)/legal guardian.

Patients will be instructed on how to return unused study medication in the provided stamped envelope addressed to the study coordinator, and for women of childbearing potential how to obtain an end of study pregnancy test at the most convenient Cleveland Clinic laboratory.

Patients will be given their randomly assigned study medication and instructed to give 15 ml of medication, in a measuring cup provided, 4 times a day for 5 days for ages 13 and above and 15 ml 2 times a day for ages 5-12 for 5 days. They will be given their first dose of study medication prior to leaving the emergency room.

Patients will be asked to please avoid taking any additional cold or influenza medications if possible. They will be told they may take ibuprofen or acetaminophen for pain or fever. They will be asked to report daily all medications taken not reported on their day 1 visit. Taking additional medications will not disqualify patients from the study other than taking prescription antibiotics or antivirals prior to the start of the study.

Patients will receive daily phone calls to remind them to take each dose of their study medication and to answer their daily surveys (see Appendix 1). All patients who do not answer their daily surveys on the first call, will receive two additional phone call attempts to have the survey answered.

6.3 Visit 2, etc.

After the initial in-person study visit at the time of enrollment, all subsequent visits will be by telephone. As previously outlined, women of childbearing potential will have an end of study urine pregnancy test to be arranged at a nearby Cleveland Clinic Laboratory.

Study Assessments

Procedure	Screening/Baseline Visit One	Daily Phone Call Until Well	Final Study Visit
Confirm Inclusion/Exclusion Criteria	X		
Obtain Informed Consent	X		
Nasopharyngeal swab for PCR test for influenza A&B, RSV	X		
Urine Pregnancy Test for Women of Childbearing Potential	X		X
Screening/Enrollment Questionnaire	X		
Dispense Study Medication	X		
Daily (Symptom) Questionnaire	X	X	X
Record Side Effects/AE/SAE		X	
Study Drug Return			X

Laboratory Procedures

Roche^{R} cobas^{R} Liat^{R} PCR assays for influenza A&B and RSV on day of entry into study. This is CLIA waived testing.

Urine pregnancy testing initially will be done using a point of care pregnancy test per standard Cleveland Clinic procedures. The end of study pregnancy testing will be done per usual protocol at Cleveland Clinic outpatient laboratories.

7 STATISTICAL PLAN

7.1 Sample Size Determination

Duration of influenza was chosen as our primary outcome because previous studies described beneficial effects of elderberry extract on this outcome (1-4) and published data is available on the elderberry extract manufactured by the company supplying elderberry extract for our study to use to calculate our sample size.(3) Forty-six total influenza positive patients randomized at a 1:1 ratio with 23 active and 23 placebo patients are needed for a power of 90% to detect a mean difference in duration of illness of at least two days with a Type I error rate of 0.05, assuming standard deviations of 1.3 and 2.5 days in the supplement and placebo groups respectively.(3) Sixty-five to one hundred patients will be enrolled in our study. We are assuming a cautious estimate of nearly a 30% dropout rate.

7.2 Statistical Methods

Study groups will be compared on duration of illness using a two-sample unequal variance t-test; the data will be transformed (such as by log-transformation) to meet distributional assumptions, and the mean

difference between groups with 95% confidence interval will be reported. Secondary analyses will assess the time to resolution of individual symptoms, and compare study groups on adherence to protocol and side effects using two-sample t-tests and Chi-square tests as appropriate. These analyses will be performed on an intent-to-treat basis. All tests will be two-tailed and performed at a significance level of 0.05. SAS 9.4 software will be used for all analyses.

7.3 Subject Population(s) for Analysis

All-randomized population: Any subject randomized into the study, regardless of whether they received study drug

8 SAFETY AND ADVERSE EVENTS

8.1 Definitions As Defined by Cleveland Clinic IRB-60 Adverse Event Reporting

The Institutional Review Board requires Investigators to monitor and report Adverse Events. The Institutional Review Board is responsible to assess changes in risk to ensure safety protections of human subjects.

An **Unanticipated Problem Involving Risks to Participants or Others** is any event that (1) is unforeseen, (2) caused harm or placed a person at increased risk of harm, and (3) is related to the research procedures.

An **Adverse Event (AE)** is any untoward or unfavorable medical occurrence, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptoms, or disease. Adverse events can encompass both physical and psychological harms.

An **Internal Adverse Event** (AE) is an untoward medical occurrence, which occurs to participants in research conducted by Cleveland Clinic and/or Cleveland Clinic is the IRB of record.

A **Serious Adverse Event (SAE)** is any adverse experience that results in any of the following outcomes:

- death
- a life-threatening experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

An **Unexpected Adverse Event** means any AE not previously known or included in the current Investigator's Brochure, consent form or other risk information.

Related/Possibly Related means there must be reasonable evidence to suggest the event was caused by the drug, device or investigational intervention.

8.2 Recording of Adverse Events

At each daily contact, using questionnaires in Appendix 1,the investigator will seek information on adverse events detailing any Grade 1 through 4 DAIDS side effects as defined in Section 14.1, pages 24-25. Patients will be instructed to contact the study personnel at 216-445-4876 for all suspected Grade 3 or 4 side effects (First calling 911 for Grade 4 side effects and contacting study personnel once able) Patients will then be triaged as appropriate to their primary medical provider or urgent or emergency care facilities. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will also be recorded in the source document.

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events

A serious adverse event will be reported to the study investigator/sponsor by telephone within 24 hours of the event. A Serious Adverse Event (SAE) form must be completed by the investigator and faxed to the study sponsor, Dr. Michael Macknin within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and facsimile to: Michael Macknin 216-445-4876, 216-445-3523 respectively.

At the time of the initial report, the following information will be provided:

- Study Identifier
- Study Center
- Subject Number
- A description of the event
- Date of onset
- Current Status
- Whether study supplement was discontinued
- Reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Significant new information on ongoing serious adverse events will be provided promptly to the study sponsor.

8.3.1 IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) will be submitted to the CCF IRB per the guidelines located in the CCF IRB Standard Operating Procedures under IRB-60 in manual. Copies of each report and documentation of IRB notification and response will be filed in the regulatory binder.

The following four types of events will be reported to the Cleveland Clinic IRB:

1. Adverse events which are serious, unexpected, and related or possibly related to participation in the research.
2. Serious adverse events that are expected in some subjects, but are determined to be occurring at a significantly higher frequency or severity than expected.
3. Other unexpected adverse events, regardless of severity, that may alter IRB analysis of the risk versus potential benefit of the research and, as a result, warrant consideration of substantive changes in the research protocol or informed consent process/document.
4. Unanticipated Problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB."

8.3.2 FDA Notification by Sponsor (if applicable)

The study investigator/sponsor shall notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the supplement as soon as possible but no later than 7 calendar days from the sponsor's original receipt of the information.

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the adverse event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

8.4 Unblinding Procedures

The safety of the subject always comes first, we will seriously consider if unblinding the study therapy is necessary to ensure a subject's safety. If unblinding study supplement on a subject is deemed necessary, the study biostatistician will unblind the subject and documentation of this in the subject's source document will be completed. In most cases, the unblinding will be part of managing an SAE, and will be reported with the SAE, however, in cases where unblinding was not associated with an SAE, such actions should be reported in a timely manner. We will use the same timeline requirements for investigator reporting of SAEs, (notification of sponsor within 24 hours by phone or fax, followed by a written narrative of the event within 48 hours.)

8.5 Stopping Rules

Stopping rules will not be used in this study.

8.6 Medical Monitoring

The Principal Investigator and Monitor will oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.7 Criteria for Withdrawal of Patient from Study.

Patients may choose to withdraw from the study at any time.

Patients with DAIDS Grade 4 symptoms, felt to be due to a study medication side effect by their physician of record, will be withdrawn from the study with ongoing follow-up of symptoms until the patient's acute symptoms resolve.

If patients become too ill to tolerate oral study medication they will be withdrawn from the study with ongoing follow-up of symptoms until the patient's acute symptoms resolve.

If patients develop an allergy to study medication or become pregnant during the study they will be withdrawn from the study with ongoing follow-up until their acute symptoms resolve.

9 DATA HANDLING AND RECORD KEEPING

9.1 Confidentiality and Privacy

Information about study subjects will be kept confidential and managed according to the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke authorization for use of PHI.

The required HIPAA language for subject authorization (included as part of the informed consent form) as found in the CCF IRB consent form template.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documentation. Examples include but are not limited to: original documents, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, copies or transcriptions of electronic records certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy and laboratories, etc.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study (in hard copy or electronic format). All data requested on the CRF must be recorded in EPIC as the source document.

9.4 Records Retention

The investigator will retain study essential documents for 6 years with the source documents in EPIC being retained indefinitely.

10 STUDY MONITORING, AUDITING AND INSPECTING

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities deemed necessary. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all study-related documents and study related facilities (for example, pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit."

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and Institutional compliance and quality assurance groups of all study related documents (for example, source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (for example, pharmacy, diagnostic laboratory, etc.). Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable Institutional compliance and quality assurance offices.

11 ETHICAL CONSIDERATIONS

This study will be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor [if applicable] before commencement of this study. The investigator should provide a list of IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision

12 PUBLICATION PLAN

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study. Note: Sponsor is Investigator

13 REFERENCES

1. Ulbricht C, Basch E, Cheung L, et al. An evidence-based systematic review of elderberry and elderflower (Sambucus nigra) by the Natural Standard Research Collaboration. Journal of Dietary Supplements 2014;11(1):80-120
2. Zakay-Rones Z, Varsano N, Zlotnik M, et al. Inhibition of several strains of influenza virus in vitro and reduction of symptoms by an elderberry extract (Sambucus nigra L.) during and outbreak of influenza B Panama. The Journal of Alternative and Complementary Medicine 1995;1(4):361-36
3. Zakay-Rones Z, Thom E, Wollan T, Wadstein J. Randomized study of the efficacy and safety of oral elderberry extract in the treatment of influenza A and B virus infections. The Journal of International Medical Research 2004;32:132-140

4. Kong F. Pilot study on a proprietary elderberry extract: efficacy in addressing influenza symptoms. Online Journal of Pharmacology and PharmacoKinetics 2009;5:32-43
5. Disease Burden of Influenza|Seasonal Influenza (Flu)|CDC www.cdc.gov/flu/about/diseaseburden.htm updated 5/16/17
6. Porter RS, Bode RF. A Review of the Antiviral Properties of Black Elder (*Sambucus nigra* L.) Products. Phytotherapy Research 2017;31:533-554
7. Burge B, Mumcuoglu M, Simmons T. The effect of Sambucol on flu-like symptoms in chimpanzees: prophylactic and symptom-dependent treatment. International Zoo News 1999;46: 16-19
8. Tiralongo E, Wee SS, Lea RA. Elderberry supplementation reduces cold duration and symptoms in air-travelers: a randomized double-blind placebo controlled-clinical trial. Nutrients 2016;8, 182; doi:10.3390/nu8040182
9. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomized controlled trials. Lancet 2015;385:1729-1737
10. People at High Risk of Developing Flu-Related Complications www.cdc.gov/flu/about/disease/high_risk.htm updated 8/25/16

14 ATTACHMENTS

14.1 Screening/Enrollment Questionnaire

SCREENING/ENROLLMENT QUESTIONNAIRE

Inclusion Criteria
Mark if Yes

1) ____Patients ages 5 and above
2) ____With 48 hours or less of an influenza illness documented by polymerase chain reaction
3) ____ Have AT LEAST 2 of the following 7 influenza symptoms (nasal congestion, sore throat, cough, aches and pains, fatigue, headaches, and chills or sweats) graded as either moderate or severe
4) ____Who have been prescribed or offered a prescription for oseltamivir or baloxavir marboxil
5) ____Who have access to a phone
6) _____Subjects are capable of giving informed consent or have an acceptable legally authorized representative capable of giving consent on the subject's behalf with informed assent given by subject.

Exclusion Criteria (mark if NO)

1. ____ Known allergy to elderberry extract, oseltamivir or baloxavir marboxil
2. ____ Use of antibiotic or antiviral medication on presentation to the study
3. ____ Pregnant women
4. ____ Breastfeeding women

5. ____ Women who do not agree to appropriate contraception (abstinence, hormonal, intrauterine device, and barrier) to prevent pregnancy during the study.
6. ____ Patients with HIV
7. ____ Patients with cystic fibrosis

____ CHECK HERE TO CONFIRM ALL ABOVE ARE NEGATIVE
____ CHECK HERE TO CONFIRM URINE PREGNANCY TEST NEGATIVE IF APPLICABLE

Additional Information Recorded on All Patients at the Time of Enrollment

Study number _____
Birth Date _____
Sex _____
Race _____
Tobacco use _____
Allergies _____

High Risk Criteria
Patients considered at high risk from influenza (10)
Mark if Yes, Leave Blank if No, then Circle or Write-in specific illness***IF More than one possible Answer**

1. ____ Adult 65 years of age and older
2. ____ Resident of nursing homes and other long-term care facilities
3. ____ American Indian or Alaskan Native*****

People who have medical conditions including:

4. ____ Asthma
5. ____ Neurological and neurodevelopmental conditions [including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy (seizure disorders), stroke, muscular dystrophy, or spinal cord injury].*****
6. ____ Chronic lung disease (such as chronic obstructive pulmonary disease [COPD])*****
7. ____ Heart disease*****
8. ____ Blood disorders (such as sickle cell disease) *****
9. ____ Endocrine disorders (such as diabetes or thyroid) *****
10. ____ Kidney disorders*****
11. ____ Liver disorders*****
12. ____ Metabolic disorders (such as inherited metabolic disorders and mitochondrial disorders)*****
13. ____ Weakened immune system due to disease or medication (such as people with cancer, or those on 20 mg/day of prednisone or more for more than 14 days)*****
14. ____ People younger than 19 years of age who are receiving long-term aspirin therapy
15. ____ People with extreme obesity (body mass index [BMI] of 40 or more)

PLEASE LIST ALL MEDICATIONS AND DOSAGES AND HOW OFTER YOU TAKE THE MEDICINE. PLEASE INCLUDE PRESCRIPTION AND OVER-THE-COUNTER MEDICATIONS INCLUDING IBUPROFEN (MOTRIN, ADVIL), ACETAMINOPHEN (TYLENOL), COLD AND FLU PREPARATIONS, AND HERBAL AND OTHER COMPLEMENTARY MEDICATIONS, VITAMINS, MINERALS AND SUPPLEMENTS

_____
_____

_____
_____

All other medical illnesses not previous recorded

_____

_____

Influenza vaccine status up to date YES_____NO_____
If NO and <9 y.o. was one vaccine given this year YES____NO____
Weight at day of presentation_____
Highest measured temperature during day of presentation_____

Symptom Score (9):
0=NONE or Baseline 1=MILD 2=MODERATE 3=SEVERE

Nasal congestion _____
Sore throat _____
Cough _____
Aches and pains _____
Fatigue _____
Headaches _____
Chills and sweats _____

Symptoms are graded by severity as "absent" (0), "mild" (1), "moderate" (2), "severe" (3)
Presence or absence of possible **other conditions or symptoms at baseline** AND their severity:

SYMPTOM
SEVERITY OF SYMPTOM
NONE=0 MILD=1 MODERATE=2 SEVERE=3
BAD TASTE ____
DRY MOUTH ____
ABDOMINAL PAIN ____
NAUSEA ____
VOMITING ____
DIARRHEA ____
CONSTIPATION ____
DIZZINESS ____
HEADACHE ____
RASH ____
DIFFICULTY BREATHING ____
DECREASED DRINKING ____
LIST ANY OTHERS WITH SEVERITY OF ANY SYMPTOM
_____
_____

VITAL SIGNS IN EMERGENCY ROOM, N/A IF ALL NOT AVAILABLE

_____ TEMPERATURE ^{0}F
_____WEIGHT

_____ PULSE
_____ RESPIRATORY RATE
_____ BLOOD PRESSURE
_____ PULSE OXIMETRY
ABNORMAL PHYSICAL EXAMINATION FINDINGS, N/A IF ALL NOT AVAILABLE
GENERAL APPEARANCE_____
SKIN_____
LYMPH_____
HEENT_____
CHEST_____
COR_____
ABD_____
GENIT_____
NEUROMUSC_____

In addition, every day patients are in the study starting from the first contact to the first day they are back to their baseline symptom level they will be asked to use the Division of AIDS (DAIDS) scale for grading the severity of adult and pediatric adverse events version 1.0, December 2004: clarification August 2009. Unlike the Symptom Score above, there are specific definitions of Grades 1-4 as outlined below.

Grade 1 Mild is defined as "Symptoms causing no or minimal interference with usual social & functional activities".

Grade 2 Moderate is defined as "Symptoms causing greater than minimal interference with usual social and functional activity".

Grade 3 Severe is defined as "Symptoms causing inability to perform usual social and functional activity".

Grade 4 Potentially Life-Threatening is defined as "Symptoms causing inability to perform basic self-care functions OR medical of operative intervention indicated to prevent permanent impairment, persistent disability or death".

The patients will be asked to call immediately the study personnel mobile phone at 216-445-4876 for any suspected side effects at Grades 3. These patients will be referred by the principal investigator to their primary care physician, or urgent or emergency care facilities as appropriate with follow-up of their acute symptoms by the principal investigator or study coordinators until these symptoms resolve.

ATTENTION

PATIENTS WILL BE TOLD TO CALL 911 FOR ALL GRADE 4 SYMPTOMS. After their health care needs are met for Grade 4 symptoms we will ask that they please call study line for follow-up and study personnel will also keep in touch with them daily until they are well.

WRITE TIME_____AM or PM AND DATE ____ OF FIRST HAVING 2 MODERATE SYMPTOMS OF INFLUENZA

TIME_____AM or PM AND DATE_____ FIRST DOSE OF STUDY MEDICATION GIVEN AT ENROLLMENT

Guess after first dose of medication if receiving: Elderberry __OR Placebo_____

_____ **CHECK TO CONFIRM** PATIENTS TOLD TO KEEP ALL EMPTY AND/OR PARTIALLY FILLED STUDY MEDICATION, OSELTAMIVIR (TAMIFLU[R]), OR BALOXAVIR MARBOXIL (XOFLUZA) BOTTLES FOR THE FINAL STUDY VISIT AND RETURN OF UNUSED MEDICINE IN POSTAGE PAID ENVELOPES PROVIDED AT ENROLLMENT. RECORD GUESS IF GIVEN ACTIVE OR PLACEBO MEDICATION

14.2 Daily (Symptom) Questionnaire

DAILY (SYMPTOM) QUESTIONNAIRE

SYMPTOMS QUESTIONNAIRE (PLEASE NOTE IF SYMPTOM USUALLY PRESENT, SUCH AS A RUNNY NOSE WITH NASAL ALLERGIES, CONSIDER THAT BASELINE LEVEL OF SYMPTOM AS SYMPTOM BEING NONE, AND EACH SUBSEQUENT LEVEL A PROGRESSIVELY HIGHER LEVEL)

SYMPTOM SCORE SYMPTOMS WRITE NUMBER
SYMPTOM SEVERITY
NONE=0 MILD=1 MODERATE=2 SEVERE=3

NASAL CONGESTION	____
SORE THROAT	____
COUGH	____
ACHES AND PAINS	____
FATIGUE	____
HEADACHES	____
CHILLS OR SWEATS	____

HIGHEST MEASURED TEMPERATURE IN PAST 24 HOURS _____

IF TODAY IS THE FIRST DAY OF ILLNESS THAT ALL SYMPTOMS ABOVE ARE NONE OR MILD AND THEY HAVE BEEN ALLEVIATED FOR 21.5 HOURS, PLEASE RECORD THE BEST GUESS OF THE TIME THIS ALLEVIATION OF ALL SYMPTOMS OCCURRED

BEST GUESS OF TIME ALL SYMPTOMS HAD BEEN NONE OR MILD FOR 21.5 HOURS

TIME _____AM or PM DATE _____

POSSIBLE NEW CONDITIONS OR SYMPTOMS QUESTIONNAIRE

SYMPTOM	**SEVERITY OF SYMPTOM** **NONE=0 MILD=1 MODERATE=2 SEVERE=3**
BAD TASTE	____
DRY MOUTH	____
ABDOMINAL PAIN	____
NAUSEA	____
VOMITING	____
DIARRHEA	____
CONSTIPATION	____

DIZZINESS ____
HEADACHE ____
RASH ____
DIFFICULTY BREATHING ____
DECREASED DRINKING ____
LIST ANY OTHERS WITH SEVERITY OF ANY SYMPTOM
_____
_____

TOTAL NUMBER OF DOSES OF STUDY MEDICATION TAKEN TODAY _____

TOTAL NUMBER OF DOSES OF OSELTAMIVIR (TAMIFLU^{R}) OR BALOXAVIR MARBOXIL (XOFLUZA) TAKEN TODAY_____

PATIENTS TOLD TO KEEP STUDY MEDICATION AND OSELTAMIVIR OR BALOXAVIR MARBOXIL EMPTY, PARTIALLY FILLED, OR FULL BOTTLES FOR MAILING IN STAMPED ADDRESSED ENVELOPE PROVIDED _____

REVIEWED PROPER DISPOSAL OF STUDY MEDICATION BY MAILING BACK IN STAMPED ADDRESSED ENVELOPE PROVIDED AT TIME OF ENROLLMENT_____

PLEASE LIST ALL MEDICATIONS AND NUMBER OF DOSAGES AND DOSE TAKEN TODAY EXCEPT FOR USUAL DAILY MEDICATIONS REPORTED AT START OF STUDY. PLEASE INCLUDE OVER-THE-COUNTER MEDICATIONS SUCH AS IBUPROFEN (MOTRIN, ADVIL), ACETOMINOPHEN (TYLENOL), COLD AND FLU PREPARATIONS, AND HERBAL AND OTHER COMPLEMENTARY MEDICATIONS, VITAMINS, MINERALS, DIETARY SUPPLEMENTS AND NEW PRESCRIPTION MEDICATIONS.

PLEASE NOTE REASON(S) THESE NEW MEDICATIONS WERE STARTED

In addition, every day patients are in the study starting from the first contact to the first day they are back to their baseline symptom level they will be asked to use the Division of AIDS (DAIDS) scale for grading the severity of adult and pediatric adverse events version 1.0, December 2004: clarification August 2009. Unlike the Jackson Score above, there are specific definitions of Grades 1-4 as outlined below.

Grade 1 Mild is defined as "Symptoms causing no or minimal interference with usual social & functional activities".

Grade 2 Moderate is defined as "Symptoms causing greater than minimal interference with usual social and functional activity".

Grade 3 Severe is defined as "Symptoms causing inability to perform usual social and functional activity".

Grade 4 Potentially Life-Threatening is defined as "Symptoms causing inability to perform basic self-care functions OR medical of operative intervention indicated to prevent permanent impairment, persistent disability or death".

The patients will be asked to call immediately to call the study personnel mobile phone at 216-445-4876 for any suspected side effects at Grades 3. These patients will be referred by the principal investigator to their primary care physician, or urgent or emergency care facilities as appropriate

with follow-up of their acute symptoms by the principal investigator or study coordinators until these symptoms resolve.

PATIENTS WILL BE TOLD TO CALL 911 FOR ALL GRADE 4 SYMPTOMS. After their health care needs are met for Grade 4 symptoms we will ask that they please call study line for follow-up and study personnel will also keep in touch with them daily until they are well.

ON LAST DAY OF STUDY CONFIRM ALL SYMPTOMS RESOLVED AND TEMPERATURE (<100^{0}F) FOR 24 HOURS AND ALSO RECORD:

BEST GUESS OF EXACTLY WHEN ALL SYMPTOMS AND FEVER HAD BEEN RESOLVED FOR 24 HOURS TIME_____AM/PM DATE_____
GUESS WHETHER STUDY MEDICATION WAS ELDERBERRY_____ OR PLACEBO_____
WAS YOUR GUESS BASED *MOSTLY* BECAUSE OF:
YOUR RESPONSE TO TREATMENT____
TASTE OF MEDICATION____
OR SPECIFY SOMETHING ELSE_____

NUMBER OF BOTTLES OF STUDY MEDICATION REMAINING TO NEAREST ¼ _____
NUMBER OF BOTTLES TO NEAREST ¼ OR TABLETS OF OSELTAMIVIR (TAMIFLU^R) OR BALOXAVIR MARBOXIL (XOFLUZA) REMAINING_____
CONFIRM STUDY MEDICATIONS REMAINING WILL BE MAILED IN STAMPED ENVELOPE PROVIDED AT ENROLLMENT _____

RESULTS OF PREGNANCY TESTING IN women of childbearing potential:
POSITIVE_____NEGATIVE_____

ONCE MEDICATION RETURNED RECORD:
ELDERBERRY EXTRACT OR PLACEBO REMAINING IN ML_____
OSELTAMIVIR OR BALOXAVIR MARBOXIL PILLS _____ OR ML_____ REMAINING

14.3 Poster/Handout

PLEASE NOTE: APPENDIX 2 BELOW TO BE KEPT AT EMERGENCY ROOM INFLUENZA TESTING MACHINES TO BE DISTRIBUTED TO ALL PATIENTS WHO TEST POSITIVE FOR INFLUENZA. SIDE ONE WILL INCLUDE STUDY INFORMATION WITH INFLUENZA INFORMATION ON FLIP SIDE

VOLUNTEERS NEEDED
FOR ELDERBERRY EXTRACT FOR INFLUENZA STUDY

Please help us understand if a liquid from cooked elderberries will help decrease the duration and severity of your flu symptoms

Previous studies have shown Elderberry extract to reduce duration of influenza by 3-4 days (versus 1 day with standard therapy)

Volunteers will receive either Elderberry extract or a placebo medication

Daily phone calls will be made to monitor symptoms and medication adherence

Financial compensation will also be provided

Cleveland Clinic

This study was approved by the Institutional Review Board at the Cleveland Clinic

Version 2/14/2018

YOU MAY QUALIFY! IF YOU ARE:

- At least 5 years old
- Confirmed to have influenza within 48hrs of first symptoms
- Prescribed or offered a prescription for Oseltamivir (Tamiflu)
- Have access to a phone

YOU WILL NOT QUALIFY! IF YOU ARE:

- Allergic to elderberry or Oseltamivir (Tamiflu)
- Currently using an antibiotic or antiviral medication
- Currently taking Elderberry Extract or Sambucol
- Pregnant
- Breastfeeding
- Women of childbearing potential who do not agree to contraception during the study
- HIV
- Cystic Fibrosis

Qualified? Interested?

Want to hear more?

Let your ER representative know or call the Elderberry Study Team at

216-445-4876

INFLUENZA (FLU) AND YOU FROM THE CENTERS FOR DISEASE CONTROL

What is the flu?

The flu is an illness caused by flu viruses. The flu may make people cough and have a sore throat and fever. They may also have a runny or stuffy nose, feel tired, have body aches, chills, headaches or show other signs they are not well. Two less common symptoms, especially in adults, are vomiting and diarrhea. The flu happens every year and is more common in the fall and winter in the U.S. People of all ages can get the flu, from babies and young adults, to the elderly.

How does the flu spread?

People who have the flu can spread the virus by coughing or sneezing. Droplets released when a sick person coughs, sneezes, or talks can land in the mouths or noses of people who are nearby. The droplets can also be inhaled into the lungs. People may also catch the flu by touching their mouth or nose after touching something with the virus on it, such as doorknobs, tables, or an infected person's dirty hand. *Frequent hand washing and covering the mouth and nose with tissues during coughs and sneezes are the best ways to prevent the spread of flu.*

What should I do if I get sick?

If you become ill with influenza symptoms you should stay home and avoid contact with other people except to seek medical care. Most people are able to recover at home from flu without additional medical care. It is important to drink enough fluids to avoid becoming dehydrated. Acetaminophen (Tylenol®), Ibuprofen (Advil®, Motrin®) may help with pain and fever. *Do not give Aspirin to people under age 20 with flu because of the risk of serious liver injury.*

How sick do people get with the flu?

Some people get very sick and others do not. Most people who get sick get better without seeing a doctor or taking medicine. However, some people can get very sick from the flu and can die. Many of the people who get very sick are older than 65 years or have a medical condition such as: diabetes, heart disease, asthma, or kidney disease, or are pregnant. Children younger than 5 years of age are also at greater risk.

EMERGENCY WARNING SIGNS - SEEK MEDICAL CARE IMMEDIATELY

Children	Adults
• Fast breathing or trouble breathing • Bluish skin color • Not drinking enough fluids • Not waking up or not interacting • Being so irritable that the child does not want to be held • Flu-like symptoms improve but then return with fever and worse cough • Fever with a rash	• Flu-like symptoms improve but then return with fever and worse cough • Difficulty breathing or shortness of breath • Pain or pressure in the chest or abdomen • Sudden dizziness • Confusion • Severe or persistent vomiting

Are there medicines to treat infection with flu?

Yes. Antiviral drugs are prescription medicines (pills, liquid or an inhaled powder) that fight against the flu in your body. While a flu vaccine is the first and most important step in preventing flu, antiviral drugs are a second line of defense to treat the flu if you get sick. Antiviral drugs are not sold over-the-counter; you must have a prescription to get them. Antiviral drugs are not a substitute for vaccination.

How long should I stay home if I'm sick?

CDC recommends that you stay home for at least 24 hours after your fever is gone except to get medical care or for other necessities. (Your fever should be gone without the use of a fever-reducing medicine.) Stay away from others as much as possible to keep from making others sick. *Continue to cover coughs and sneezes and wash hands even after you return to work.* It is important to know even if you don't have a fever, you may have flu and be contagious.

Version 1/9/2018

14.4 Patient Take Home Checklist

Cleveland Clinic

PARTICIPANT TAKE HOME INSTRUCTIONS & JOURNAL

Study Title: The Effect of Elderberry Extract on Symptoms of Patients with Influenza: A Randomized, Double-Blind, Placebo-Controlled Trial

Contact:

Michael Macknin, MD Office phone #(216) 444-5512 After Hours phone #(216) 445-4876	Stephanie Stoianoff, Study Coordinator Office phone #(216) 444-0231

DAILY STUDY LOG

	Temperature/Time	Medication Time 1	*Medication Time 2	*Medication Time 3	Medication Time 4
Day 1	/				
Day 2	/				
Day 3	/				
Day 4	/				
Day 5	/				
*Day 6	/				
*Day 7	/				
*Day 8	/				
*Day 9	/				
*Day 10	/				
*Day 11	/				
*Day 12	/				
*Day 13	/				
*Day 14	/				
*Day 15	/				
*Day 16	/				
*Day 17	/				
*Day 18	/				
*Day 19	/				
*Day 20	/				
*Day 21	/				

*if necessary

If a checkmark appears in the box below, you are required to have a urine pregnancy test after you are well in order to complete your participation. See the back of this page for instructions.

☐

Please list any current medications_____

_____

_____

_____

_____

_____

Please list any symptoms experienced_____

_____

_____

_____

_____

_____

_____

_____

Medication Schedule for Patients Enrolled in the Study

	Morning 9:00am	Mid-Day 1:00pm	Afternoon 5:00pm	Night 9:00pm
Patient age 5-12 years old	X			X
Patient age 13 years and older	X	X	X	X

*We request that you take ONLY acetaminophen (Tylenol) and ibuprofen (Motrin or Advil) for pain and fever as needed. Please do NOT take any over-the-counter cold or influenza medications. You will be asked to report any medications that you took during the study.

SEEK MEDICAL CARE FOR THESE EMERGENCY WARNING SIGNS – CALL 911 IF SIGNS SEEM LIFE THREATENING OR SEVERE

Children

- Fast breathing or trouble breathing
- Bluish skin color or fever with a rash
- Not drinking enough fluids
- Not waking up or not interacting
- Being so irritable that the child does not want to be held
- Flu-like symptoms improve but then return with fever and worse cough

Adults

- Flu-like symptoms improve but then return with fever and worse cough
- Difficulty breathing or shortness of breath
- Pain or pressure in the chest or abdomen
- Sudden dizziness
- Confusion
- Severe or persistent vomiting

Cleveland Clinic

Important Pregnancy Testing Information for Patients Enrolling in the Study

Before we can enroll you as a participant, all women of childbearing potential will be asked to take a urine pregnancy test at the Emergency Department as a positive result will disqualify you from participation. A second pregnancy test will be required at the conclusion of your participation in the study.

All women of child bearing potential enrolled in the study are asked to go within 48 hours of the end of the study to the most convenient Cleveland Clinic outpatient laboratory for a Food and Drug Administration mandated urine pregnancy test. During the final study phone call, all women of child bearing potential will be reminded to walk-in to any Cleveland Clinic Outpatient Laboratory for pregnancy testing. They will be helped, if needed, to locate the most convenient laboratory site. When you arrive at the laboratory, to minimize any waiting time, let the front desk personnel know you are there for a urine test that has already been ordered. If the urine testing is not performed within 48 hours from the end of the study, a reminder phone call from study personnel will be made.

*****The results from the pregnancy test(s) will be disclosed to the child AND to their parent(s)/legal guardian.**