Study Protocol

Version 2 (2017-9-5)

1. Name of the study:

The effect of zinc acetate lozenges on the rate of recovery from the common cold: a randomized trial (The HelZinki Study)

2. Researchers, collaborators, location, and time

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Co-investigators:

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Department of Public Health, University of Turku.

Tiina Pohjonen, MD, CEO,
Marianne Alho, MD, chief physician
Helsinki City Occupational Health office

Collaboration with:

The University Pharmacy (Yliopiston Apteekki), Helsinki
They will provide the zinc lozenges and placebo lozenges for the trial, and generate the randomization code

Place of the study:
Helsinki, Finland

Time of the trial:
Start of November 2017 to end of January 2018

Pre-registration of the trial:
ClinicalTrials.gov
https://clinicaltrials.gov

3. Introduction

Interest in zinc lozenges for the treatment of the common cold arose when the common cold symptoms of a 3-year-old girl with leukemia disappeared within a few hours after she had slowly dissolved a therapeutic zinc tablet in her mouth instead of immediately swallowing it as instructed [1]. The benefit seemed to be obtained from the slow dissolution of the tablet in her mouth, which implied that zinc has local effects in the pharyngeal region. This observation prompted the father of the child, George Eby, to conduct the first randomized double-blind placebo-controlled trial on zinc lozenges. Eby (1984) used zinc gluconate lozenges, providing 207 mg/day of elemental zinc, and they significantly shortened the duration of colds [1].

A series of zinc lozenge trials have been carried out since Eby's (1984) study but with varying results, which could be partly ascribed to the 7-fold variation in the daily dosage of elemental zinc in those trials [2]. The composition of the zinc lozenges between the trials also differed as some lozenges contained substances such as citrate, that tightly bind zinc ions, which prevented the release of free zinc. The variation in the levels of free zinc ions in the oro-pharyngeal region has been proposed as a factor that might explain the wide divergence between the results [3-10]. Eby hypothesised that zinc acetate might be a better constituent for lozenges than zinc gluconate, since acetate binds zinc ions less strongly [9,10]. Nevertheless, it is not clear whether the difference between zinc acetate and zinc gluconate has practical importance at the clinical level.

An early meta-analysis showed that 5 low-dose trials of zinc lozenges (<75 mg/day zinc) uniformly found no effect on the duration of colds [2]. Thus, most negative findings from zinc lozenge studies were simply explained by too low doses of elemental zinc. That meta-analysis [2] also calculated that three high-dose (>75 mg/day) zinc acetate trials [11-13] found on average a 42% reduction in the duration of colds, and 5 high-dose zinc gluconate trials found a 20% reduction in cold duration [1,14-17]. Thus, in that comparison Eby's proposal to favour zinc acetate seemed to get support.

However, one of the five above-cited high-dose zinc gluconate trials had lozenges that contained maltose and sorbitol as excipients [14], but these substances bind zinc, and thus the lack of benefit in that trial may be explained by those excipients [6,9,10,15]. Thus, there are factors that can confound the comparison of the efficacy of zinc acetate and zinc gluconate lozenges. A more recent meta-analysis concluded that there is no convincing evidence that lozenges composed of zinc acetate and zinc gluconate differ in their clinical effects in treating the common cold [18].

Two individual participant data (IPD) meta-analyses of the three high-dose zinc acetate lozenge trials [11-13] have been carried out. One of them calculated that zinc lozenges shortened the duration of cold by 3 days from the average of 7 days in the placebo groups [19]. Another IPD meta-analysis calculated that zinc lozenges increased the rate of recovery from the common cold 3-fold [20]. On the 5th day, 70% of the zinc patients of the three zinc acetate lozenge trials had recovered compared with 27% of the placebo patients [20]. These proportions are used as the basis for our sample size calculation (Item 7).

Although the zinc lozenges dissolved in the oro-pharyngeal region lead to the highest zinc levels in that region, a meta-analysis found no evidence that zinc acetate lozenges would have a greater effect on cold symptoms that originate in lower anatomical regions compared with those of the nasal region [21].

Further systematic reviews on zinc and the common cold have been published [22-24], but some of them have methodological problems [25-27], and the Cochrane review was recently withdrawn

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because of plagiarism [28].

After the Eby (1984) trial on zinc lozenges was published [1], Farr and Gwaltney (1987) speculated that the benefit reported by Eby might have been explained by the bad taste of the zinc lozenges [29]. However, the early findings of Eby (1984) are consistent with the findings in a number of later trials with numerous other research groups and bad taste does not seem a reasonable explanation for all the reported benefits. For example, none of the 3 high-dose zinc acetate lozenge trials reported bad taste to be a problem, there was no substantial difference between the zinc and placebo groups in the recorded adverse effects, and only a few drop-outs occurred [11-13]. In the most recent trial by Prasad (2008), a few participants identified the lozenges, but when the analysis was restricted to those who remained blinded at the end of the study, the efficacy of zinc lozenges was no less [13].

Zinc has been administered in the doses of 100-150 mg/day for various patient groups for months and 150 mg/day zinc is a standard treatment for Wilson's disease for the rest of the patient's life at the extreme. See Appendix 1 for references and details. Therefore the planned dose level of 78 mg/day for 5 days in the current protocol is not a concern for safety. In short term administration, zinc lozenges have caused adverse effects such as bad taste and taste disturbances, and stomach irritation. However, if a participant considers that the zinc lozenge of this trial tastes bad or irritates stomach, he or she can discontinue their usage.

The HelZinki trial is a pilot study to confirm that the specific lozenge is effective, and to test the feasibility of organizing a trial on zinc lozenges with the logistics that are being employed, so that symptom data are collected through internet, and sickness absence outcomes are collected through linkage to sickness absence records kept by the employer. If the result is positive, we plan to implement a larger trial on the following winter.

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4. Study participants

Participants are employees of the city of Helsinki, both men and women.

Inclusion criteria: ≥18 years, recollecting that they usually have had ≥1 colds per winter.

Exclusion criteria: pregnancy or lactation; chronic runny nose or chronic cough.

All employees in the chosen work-units of Helsinki City will be first contacted with an email advertisement in which the criteria for inclusion and exclusion will be described and employee's consistency with those criteria will be asked.

Included in the email will be an information sheet, which describes the background of the topic, rationale of the current study, and includes a brief description of the evidence of safety of zinc.

Included in the advertisement email will also be a link to a web-based informed consent form, which can be signed by the participants if they decide to participate in the trial. The web link leads to a program which records the signature of the informed consent through a bank or other high security personal identification method. The same web link will be used as the route for collecting data from the enrolled participants during the trial.
See Appendix 3 for the advertisement and information sheet. Only a Finnish version will be used since the study does not intend to capture non-Finnish speaking employees, a small minority group.
See Appendix 4 for the informed consent sheet. Only a Finnish version will be formulated.

Those who meet the inclusion and exclusion criteria, and are willing to participate and provide informed consent, will be enrolled until the minimum of 200 participants (100 + 100) is achieved.

There is no standard treatment for the common cold. Participation in the trial does not limit the possibility of the participants to use their usual health care services or OTC medicine usage during or after the 5 day intervention period.

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5. Methods

This is a randomized parallel-group two arm superiority trial with an allocation ratio 1:1, both participants and investigators blinded.

The randomization code will be generated at the University Pharmacy and the code will be maintained by them until the end of the trial period. The lozenge packages will be numbered with 3-digit codes that are used in the identification of the packages and linking the specific participant to the given package in the web-based data collection form. Zinc lozenge packages and placebo packages will be put to storage boxes so that a box contains an equal number of zinc and placebo packages in a haphazard order, and they will be distributed to participants in a haphazard order.

The zinc lozenge that will be used in the study is a commercial product available from the University Pharmacy, Helsinki, Finland:
https://www.yliopistonapteekki.fi/yritys/yritys (Company)

The product is labelled:
"YA sinkkiasetaatti 13 mg imeskelytabletti 60 kpl"
https://www.yliopistonapteekki.fi/ya-sinkkiasetaatti-13-mg-imeskelytabletti-60-kpl-65510.html

The product is classified as a "medical device" and it is not regulated according to the jurisdiction for medicines.

Each lozenge contains 13 mg elemental zinc as zinc acetate. The instruction in the commercial package for common cold patients is to dissolve slowly 6 lozenges per day in their mouth, which totals to 78 mg/day of elemental zinc, at most for 5 days. The same instruction will be used in this trial.

The University Pharmacy will prepare 100 placebo lozenge packages so that the placebo lozenges contain sucrose octaacetate, and they are similar with the zinc lozenges in visual appearance and in taste. 100 packages of zinc lozenges will be used as the active intervention. Each placebo and zinc package will be given a random 3-digit identification code, and the randomization key will be kept at the University Pharmacy until the study is concluded, or until there is a particular reason for opening the code for a singular participant. The packages will contain 30 lozenges (6/day×5 days).

After signing electronically the informed consent form, the enrolled participants will be sent one package of the lozenges, the kind of lozenge (placebo vs. zinc) being blinded for the researchers and the participant. The packages will be distributed directly to the participants since that allows a more rapid initiation of treatment compared with distributing the lozenges only after the participant actually contracts the common cold. On the other hand, this also means that many packages will not be used since all participants do not catch the cold during the winter. To decrease this problem, we will restrict to participants who usually have had ≥1 cold during previous Winters.

The package of lozenges will be distributed to the enrolled participants in November 2017. The participants will be instructed to keep the package readily available so that, when they catch the common cold, they will find the package and they can start to take the lozenges according to the instructions.

The participants will be instructed to start taking zinc lozenges as soon as they start to suffer from the first symptoms of the common cold, defined as their personal consideration that they have the

common cold. Thereby this definition for the "common cold" is most realistic for the general community. There is no rigorous biological definition of the common cold and the symptoms can be substantially variable. It is the person's subjective experience that makes him or her to, for example, meet a physician to ask for a sick leave for the common cold.

The participants will be instructed to take 6 lozenges daily over the time awake, evenly distributed, allowing the lozenge to dissolve in the mouth as slowly as possible. The duration of intervention is for the maximum of 5 days. If the symptoms disappear before 5 days, the participant may stop the usage of the lozenges.

There will be no limitations for other treatments that participants wish to use for treating their colds.

Participants will be requested to respond to a web-based symptom questionnaire daily from the first day of the treatment to the recovery from the common cold, or to a maximum of 2 weeks.

See Appendix 2 for the baseline (1st day) and follow-up symptom questionnaires.

After the study period, all participants who gave consent will be linked to employer's records of absences.

Given the delay in record updates in National registers, data linkage to
(1) hospitalisation records from the National Institute of Health and Welfare hospitalisation register,
(2) prescription records from Social Insurance Institute (KELA), and
(3) death records from Statistic Finland mortality register
will be requested in 2020. Participants who gave consent will be linked to these records using unique personal identification numbers assigned to all Finnish citizens.

Data from these registers will be collected for the time period from 1 month before the start of the intervention until 2 months after the start of the intervention. It is possible that some of the treatment effects are delayed and therefore data are collected for the period after the end of intervention. Data are also collected for 1 month before the common cold to allow a comparison of baseline balance of the groups and to allow considerations of potential health issues before the initiation of lozenge usage. Data of sick leaves in winter 2016-17 will also be collected to allow a comparison of the rate in the intervention period to a corresponding period in the preceding winter.

Primary outcome

The primary outcome is the duration of the common cold (time to recovery), which will be analyzed both as the rate of recovery on the basis of the time to recovery and as the duration as a continuous variable.

The *"beginning"* of the common cold is a personal judgement of the participant. There is no rigorous and universal definition of the common cold and the symptoms can be substantially variable. Viral respiratory infection can start with muscle ache and shivering without any nasal or throat symptoms, or cough. An algorithmic definition of the beginning of the common cold for the purpose of this kind of trial would be either complex or/and quite far from the set of symptoms considered as "the common cold" in the general community. In the general community, it is the

person's own judgement when he or she starts to take a pain killer or cough medicine etc. for the common cold, or considers that his or her condition is such as to tell to a friend that he or she has the common cold. Thereby this subjective definition for the "beginning" of the common cold is most relevant to the real life conditions for the basis to initiate common cold treatment.

On the 1st day of lozenge intervention, we will ask baseline data of the participants and 12 symptoms associated with the common cold, and for the occurrence of adverse effects, see Appendix 2.
On the following days until the day of recovery, or until 2 weeks after the initiation of lozenge intervention, we ask the participant to report on the symptoms and adverse effects, see Appendix 2.

In the quantification of symptom severity, we will use a scale from 0 to 3 with the following instructions:

0: Absent, 1: Mild, 2: Moderately severe, 3: Very severe. We will calculate a symptom score as a sum over all the symptoms which means that the maximum of the symptom score scale is 3×12 = 36 points.

For fever measured by a thermometer, we will use a dichotomized scale to classify that any measurement on a given day for ≥37.5°C indicates objective fever on that day, and no such recording indicates no measured fever. Measured fever is not included in the symptom score.

The definition for the "recovery" from the common cold is based on symptom reporting. The common cold is caused by diverse viruses which vary between Winters. The duration and the kind of symptoms differ between different viruses. Sometimes the common cold leads to long lasting cough or hoarseness and if the outcome is defined as full recovery (symptom score = 0), it is possible that a substantial proportion of participants do not recover within 2 weeks.
Therefore, before opening the randomization code, we will analyse the distribution of the symptom score and we will set the cut point for symptom score indicating recovery to such a level that <20% of participants have colds over 1 week. Although this decision influences the power of the study, the decision about cut point is made before opening the randomization code and thus the knowledge of the allocation to groups does not influence the decision.

Secondary outcomes

Secondary outcomes include:

- Objective fever
- Sickness absence
- Usage of antibiotics and/or asthma medication
- Complications such as sinusitis, bronchitis, otitis.

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6. Size of the trial and the time table

At least 200 participants will be enrolled to the trial, 100 to both trial arms.

The inclusion of participants will start in November 2017. The trial will be concluded at the end of January 2018.

7. Sample size

Based on an assumption that 60% of common cold patients in the zinc group and 30% in the placebo group recover by the 5th day, a sample size 23 + 23 common cold patients would be sufficient to reach an 80% power to find a difference between the trial groups with P(2-tailed) < 0.05.

The assumptions of rates of 60% and 30% are conservative compared with the findings in previous studies with zinc acetate lozenges, see Introduction (item 3; ref. [20]).

However, we enrol participants in their good health and not patients with the common cold. The number of participants enrolled does not directly translate to an equal number of common cold episodes occurring over the trial period in the study groups. Instead, many people will not catch a cold during the Winter. To decrease this problem we restrict to participants who usually have had ≥1 cold per Winter so that it is more likely that the included participants have a cold during the trial. For that reason, we also increase the sample size to 4-fold from the estimate calculated above, to at least 100+100 participants.

The increased sample size allows for the absence of common cold in many enrolled participants. In addition, it also allows for a proportion of participants to drop out and some other participants to have lost their lozenge package. Finally, the common cold is caused by a wide diversity of viruses, and it is possible that the effect of zinc varies for different viruses. This also justifies our conservative attitude to the use of the previous findings as the basis for our sample size calculation, and to increase the sample size to 4-fold compared with the calculation described in the first paragraph of this section.

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8. Analysis of data.

In our analysis, we will include only participants who caught the common cold during the trial period from November 2017 to January-February 2018. The zinc lozenge intervention is intended for treatment and participants who do not catch the common cold during the trial do not yield information about the treatment effects of zinc lozenges. Thus, they will be excluded from the analysis.

We will include participants in the analysis even if they discontinued taking lozenges or take less than instructed. In this respect, we will follow the intention to treat approach (ITT).
However, if a participant discontinues recording his or her symptoms (drop out), we cannot follow the ITT approach in the analysis of the subjective symptoms. However, we will use the ITT approach in collecting follow-up data from the registers.

Analysis of the primary outcome

The primary analysis of the primary outcome will be carried out by Cox's proportional hazards (PH) regression over 7 days from the initiation of the intervention. Although colds sometimes are longer than one week, if there is a substantial effect by zinc lozenges, we expect to see an effect within one week. In addition, the accuracy of participant's recording of daily followup data may decrease with time so that the recording is more accurate at the early days after the initiation of the intervention.

A second analysis of the primary outcome is by the t-test to compare the duration of the common cold as a continuous variable in the two trial arms.

Cox's PH regression will be preferred in our study since it is not influenced by drop-outs or by outliers (i.e., patients who happen to have colds that last exceptionally long, eg., long lasting cough or hoarseness). Outliers decrease the power of the t-test but they do not have a similar influence on Cox PH regression.

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Secondary analyses

Analysis of subgroups of the primary outcome, comparisons by:

- age,
- sex,
- baseline severity of this cold,
- type of work,
- delay between the start of the symptoms and the start of intervention,
- number of colds usually during the winter,
- usual length of colds,
- sick leave on the previous winter

If there are differences in the magnitude of effect between several subgroups, we will explore possible second or third level interactions between several subgroups and the treatment effect.

Analysis of secondary outcomes

Sickness absence: Absence from work due to sickness is indicated by recorded sickness absence. All participants will be linked to employer's registers of sickness absence and job contracts using unique identification numbers. Records of sickness absence starting during the common cold will be treated both as a dichotomous variable (sick leave or not) and as a continuous variable (the number of days absent). Consecutive and overlapping sickness absence spells will be merged. Participants with absence due to non-health related causes during the common cold will be excluded from the analysis. Sick leaves that start within 7 days after the initiation of treatment will be included in our analysis.

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9. Publication of the results

A manuscript of the study findings will be prepared after the study is concluded irrespective of whether the study finding is positive or negative, during Spring 2018. It will be submitted to a medical journal.

10. Insurance for possible adverse events

The intervention that is being examined is a commercial product being sold by University Pharmacy. University Pharmacy has insurance for its products. It covers also this kind of study.

11. Compensations for the participants

The participants will not be paid or given any compensation for their decision to participate in the study.
If the zinc lozenges appear to be effective, the participants who entered the placebo arm will be given two packages of the active lozenge after the trial is concluded as a compensation for their participation. This is in agreement with the item 34 of the Helsinki Declaration (2013).

12. Costs of the trial

The University Pharmacy will donate the zinc and the placebo lozenges. The University Pharmacy does not participate in the planning of the study, nor in the analysis of the results, nor is it involved in the publication of the results.

The work time allocated to the project by Harri Hemilä, Jari Haukka, Mika Kivimäki, and Jussi Vahtera will be covered by their salaries. The computers of the Helsinki City will be used for the collection of the data, and the computers of the Department of Public Health, Clinicum, Helsinki University will be used for the data analysis.

The work of Tiina Pohjonen and Marianne Alho from Helsinki City Occupational Health office will be covered by their salaries.

The time required by Jari Haukka to set up the web pages for filling and accepting the consent form, and entering the daily data over the 2-week period after the intervention will be covered by his salary.

Accordingly, this study can be conducted with minimal costs and there are no financial reasons why the study could not be carried out to the end as described in this study protocol.

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13. Instructions to the personnel of the trial

The packages of lozenges will be sent to the participants by Helsinki City internal mail or by regular mail by Harri Hemilä, Jari Haukka, and/or study manager (NN).

This trial does not involve active treatment of participants by a physician or nurse, or active measurements of the clinical variables of participants. The participants will report their common cold symptoms through the secure web connection. Therefore, no nurses or other technical personnel will be recruited for the trial.

14. Data base

Personal data of study participants are maintained and owned by University of Helsinki, Faculty of Medicine (Helsingin Yliopiston lääketieteellinen tiedekunta, Clinicum, Kansanterveystieteen laitos).

University of Helsinki is responsible for the storage and achieving of the data.

Description of research register is as a separate document.

Randomization is carried out by University Pharmacy, and code is kept safe by the same organization until the end of the trial period.

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15. Declarations of interests

None of the co-investigators has shares of companies that are involved in the production or selling of zinc lozenges. None of them has any other conflicts of interests related to this trial.

16. Appendices for the study protocol

The following appendices are included:

1. Evidence of safety of long term zinc administration.
2. The contents of the electronic data collection form; the first day and the following days.
3. The information sheet for patients ("Tiedote potentiaalisille koehenkilöille ja tutkittavan tiedote").
4. Informed consent form ("Suostumuslomake").

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17. References

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Appendix 1: Evidence of safety of long term high dose zinc administration.

The 78 mg/day dose of elemental zinc administered in this HelZinki study is substantially higher than the recommended daily intakes of 11 mg/day for men and 8 mg/day for women in the USA [1], and the recommended daily intakes of 9 mg/day for men and 7 mg/day for women in the Nordic countries [2]. However, zinc has been administered in doses of 100 to 150 mg/day to certain patient groups (not the common cold) for several months with few adverse effects [3-11].

Deficiency of copper has been reported as a consequence of long-term zinc supplementation [12,13], though a six-week experiment did not find any effect from 150 mg/day of zinc on plasma copper levels [14].

Because of the zinc and copper interaction, 150 mg/day of zinc is currently one of the standard treatments for Wilson's disease, which usually means taking such doses for the rest of the life of the patient [15-18]. In the treatment of Wilson's disease, zinc has had an excellent safety profile, though it has caused gastric irritation in 5-10% of the patients [16]. The usage of high dosage of zinc for long periods for the Wilson's disease patients indicates that zinc does not have serious adverse effects in the long term, except the deficiency of copper which is reversible.

Therefore, it seems highly unlikely that the dosage used in the current trial, 78 mg/day for 5 days might lead to long-term adverse effects. Furthermore, if a patient considers that the zinc lozenge of this trial tastes too bad or the lozenge seems to cause stomach irritation, he or she can discontinue the HelZinki trial.

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Appendix 2: The contents of the electronic data collection forms.

Finnish version on pages 4-6.
Suomenkielinen versio sivuilla 4-6.

[Data collection forms; these will be filled electronically through internet/intranet
Some explanations are written in brackets, they will not be written in the final data collection form]

Collection of baseline information and data of symptoms of participants on Day 1 of zinc lozenge treatment.
[The following baseline data will be collected on the first day the participant started to take lozenges. If a participant does not catch a cold during the trial period, then no baseline or followup data will be collected for him or her, and such a participant is not included in our analysis]

- ID:
- Email:
- Tel:
- Code number on the package:

Baseline data collected on Day 1

- Age (yr)
- Sex (M / F)
- Type of work (office / school /day care)
- Daily contact with young children in own family or in the job (Yes / No)
- Usual number of colds during the recent Winters (1 / ≥2)
- Did you have sick leave because of the common cold in the last winter (Y /N)
- Do you consider that usually your colds are short or long (short / long)
- Do you have regular asthma medication? (Y / N)
- Has a physician ever prescribed to you inhalatory asthma medication for the common cold? (Y / N)
- Have you had sinusitis within 5 years? (Y / N)
- Have you had bronchitis within 5 years? (Y / N)

- After having used the lozenge today, do you have an opinion whether your lozenge may be zinc or placebo (no opinion / zinc / placebo)

Symptoms associated with the common cold on Day 1

Please, give a score to the following respiratory symptoms:

[Scales 0 to 2 (or 3) will be used with instructions:]
0: absent, 1: mild (lievä oire), 2: moderately severe (varsin voimakas oire), 3: very severe (hyvin voimakas oire)

- nasal drainage (nuha) (0-3)
- nasal congestion (nenän tukkoisuus), (0-3)
- sneezing (aivastelu), (0-3)
- scratchy throat (kurkun karheus), (0-3)
- sore throat (kurkkukipu), (0-3)
- cough (yskä), (0-3)
- headache (päänsärky), (0-3)
- hoarseness (äänen käheys), (0-3)
- muscle ache (lihaskipu), (0-3)
- shivering or feverish (vilutusta tai kuumeen tunnetta) (0-3)
- tiredness (väsymystä) (0-3)
- difficulty in concentration (vaikeutta keskittyä) (0-3)

  [The above 12 symptoms will be summed to a "symptom severity score" which is used to define the end of the common cold. In addition, in secondary analysis they can be analyzed as we wish, eg, as separate symptoms and as the symptom severity score.
  Objective fever is not included in the symptom score.]

- measured fever (kuume mitattuna) (≥37.5°C any time during the day) (Y / N)

How many hours was the delay between the start of the symptoms and the start of taking lozenges (# hours)

How many lozenges did you take today (#)

For treating the common cold, did you use today:
cough medicines? (Y / N)
nasal decongestants? (Y / N)
pain killers? (Y / N)

Did you take sick leave today because of the common cold.

Did you observe any possible adverse effects of the treatment.

- taste problems, which kind: (open window for free text)
- stomach problems, which kind: (open window for free text)
- other problems, which kind: (open window for free text)

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Collection of data on symptoms daily until symptoms disappear or for the maximum of 2 weeks

Cold symptoms on Day X

- nasal drainage (nuha) (0-3)
- nasal congestion (nenän tukkoisuus), (0-3)
- sneezing (aivastelu), (0-3)
- scratchy throat (kurkun karheus), (0-3)
- sore throat (kurkkukipu), (0-3)
- cough (yskä), (0-3)
- headache (päänsärky), (0-3)
- hoarseness (äänen käheys), (0-3)
- muscle ache (lihaskipu), (0-3)
- shivering or feverish (vilutusta tai kuumeen tunnetta) (0-3)
- tiredness (väsymystä) (0-3)
- difficulty in concentration (vaikeutta keskittyä) (0-3)

- objective fever (kuume mitattuna) (≥37.5°C any time during the day) (Y / N)

How many lozenges did you take today (#)

For treating the common cold, did you use today:
cough medicines? (Y / N)
nasal decongestants? (Y / N)
pain killers? (Y / N)

Did you take sick leave today because of the common cold.

Did you observe any possible adverse effects of the treatment.

- taste problems, which kind: (open window for free text)
- stomach problems, which kind: (open window for free text)
- other problems, which kind: (open window for free text)

[If the "symptom severity score" is 0 or 1 indicating strict recovery from the common cold, the web-based form will inform the patient about the recovery from the common cold according to the trial definitions, the participant will be informed that his or her treatment is ended and the patient will be asked:]

Your symptoms have disappeared to the extent that in this study you are considered to have recovered, and you do not need to take lozenges any more, and more data will not be collected from you.

Did you consider that the lozenges you used were beneficial (Yes/No)

Liite 2: Suomenkielinen kyselylomake

[Hakasuluissa selityksiä]

[Alkutietojen ja oiretietojen keräys ensimmäisenä päivänä eli sinkki-imeskelytablettien käytön aloituspäivänä]

- Sosiaaliturvatunnus:
- Sähköpostiosoite:
- Puhelinnumero
- Pakkauksen koodinumero:

[Alkutietojen keräys 1. päivänä]

- Ikä (vuosia)
- Sukupuoli (Mies / Nainen)
- Työn luonne (toimisto / koulu / päivähoito)
- Onko päivittäin kontakteja nuoriin lapsiin perheessä tai työssä (Kyllä / Ei)
- Kuinka monta flunssaa talvessa Sinulla on ollut yleensä (1 / ≥2)
- Oliko sinulla sairaslomaa viime talvena flunssan johdosta (K /E)
- Koetko, että flunssasi ovat yleensä lyhyitä tai pitkiä (lyhyitä / pitkiä)
- Onko sinulla säännöllinen astmalääkitys? (K /E)
- Onko lääkäri koskaan kirjoittanut sinulle reseptin hengitettävälle astmalääkkeelle flunssan yhteydessä? (K /E)
- Onko sinulla ollut poskiontelotulehdus 5 vuoden sisällä? (K /E)
- Onko sinulla ollut keuhkoputkentulehdus 5 vuoden sisällä? (K /E)
-

- Kun olet tänään imeskellyt tutkimuksen imeskelytablettia, onko sinulla mielipidettä sen suhteen, onko kyseessä sinkki-imeskelytabletti vai lume(plasebo)-imeskelytabletti (ei mielipidettä / sinkki / lume)

[Ensimmäisen päivän oiretietojen keräyslomake]

Asteikolla 0 - 3, arvioi seuraavien flunssaoireiden voimakkuus:

0: ei oiretta
1: lievä oire
2: varsin voimakas oire
3: hyvin voimakas oire

- nuha (0-3)
- nenän tukkoisuus (0-3)
- aivastelu (0-3)
- kurkun karheus (0-3)
- kurkkukipu (0-3)
- yskä (0-3)
- päänsärky (0-3)
- äänen käheys (0-3)
- lihaskipu (0-3)
- vilutusta tai kuumeen tunnetta (0-3)
- väsymystä (0-3)
- vaikeutta keskittyä (0-3)

- Mittasitko tänään kuumetta ≥ 37,5°C missään vaiheessa päivää (K / E)

Kuinka monta tuntia oli aikaa oireiden alkamisen ja imeskelytablettien käytön aloituksen välillä (# tuntia)

Kuinka monta imeskelytablettia otit tänään (#)

Käytitkö tänään flunssan hoitoon:
Yskänlääkettä? (K / E)
Lääkettä nenän tukkoisuuteen? (K / E)
Kipulääkettä? (K / E)

Olitko tänään pois työstä flunssan johdosta? (K / E)

Huomasitko imeskelytableteista haittavaikutuksia:

- makuhaittaa, millaista: (avoin ikkuna vapaalle tekstille)
- vatsan ärsytystä, millaista: (avoin ikkuna vapaalle tekstille)
- muita ongelmia, millaista: (avoin ikkuna vapaalle tekstille)

[Oiretietolomake päiville 2-14, lopetus aiemmin, jos oireet poistuvat]

Asteikolla 0 - 3, arvioi seuraavien flunssaoireiden voimakkuus:

0: ei oiretta
1: lievä oire
2: varsin voimakas oire
3: hyvin voimakas oire

- nuha (0-3)
- nenän tukkoisuus (0-3)
- aivastelu (0-3)
- kurkun karheus (0-3)
- kurkkukipu (0-3)
- yskä (0-3)
- päänsärky (0-3)
- äänen käheys (0-3)
- lihaskipu (0-3)
- vilutusta tai kuumeen tunnetta (0-3)
- väsymystä (0-3)
- vaikeutta keskittyä (0-3)

- Mittasitko tänään kuumetta $\geq 37{,}5°C$ missään vaiheessa päivää (K / E)

Kuinka monta imeskelytablettia otit tänään (#)

Käytitkö tänään flunssan hoitoon:
Yskänlääkettä? (K / E)
Lääkettä nenän tukkoisuuteen? (K / E)
Kipulääkettä? (K / E)

Olitko tänään pois työstä flunssan johdosta? (K / E)

Huomasitko imeskelytableteista haittavaikutuksia:

- makuhaittaa, millaista: (avoin ikkuna vapaalle tekstille)
- vatsan ärsytystä, millaista: (avoin ikkuna vapaalle tekstille)
- muita ongelmia, millaista: (avoin ikkuna vapaalle tekstille)

[Jos oireindeksi ("symptom severity score") on 0 tai 1, koehenkilö luokitellaan toipuneeksi ja ilmoitetaan että tutkimus loppuu ja kysytään, kokiko hän imeskelytabletista apua]

Flunssaoireesi ovat kadonneet siinä määrin, että tutkimuksessa luokittelemme sinut toipuneeksi. Sinun ei enää tarvitse käyttää imeskelytabletteja. Emme enää kerää oiretietoja sinulta.

Koitko, että imeskelytableteista oli sinulle hyötyä? (K /E)

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Appendix 3. The recruitment and information sheet intended for participants.

Tämä tiedote postitetaan sähköpostitse rajatulle henkilöryhmälle Helsingin kaupungin työntekijöitä.

SÄHKÖPOSTIN OTSIKKO:

Haluatko osallistua tutkimukseen, jossa selvitetään sinkki-imeskelytablettien vaikutusta flunssan kestoon.

SÄHKÖPOSTIN TEKSTI:

Helsingin yliopiston ja Helsingin kaupungin työterveyshuollon yhteistyönä tehdään ensi talvikautena tutkimus, jossa selvitetään sinkki-imeskelytablettien tehoa flunssan hoidossa. Alempana on tutkimuksen kuvaus.

Sinkki-imeskelytabletit ovat turvallisia itsehoitovalmisteita, jotka eivät edellytä reseptiä. Keskeinen kysymys on se, onko niillä tehoa flunssaa vastaan.

Tutkimukseen etsitään täysi-ikäisiä koehenkilöitä, joilla on **talvisin tavallisesti vähintään yksi flunssa.**

Tutkimukseen **ei oteta** henkilöitä, jotka ovat raskaana tai imettävät, tai joilla on krooninen nuha tai yskä.

Jos nämä vaatimukset toteutuvat, ja jos sinua kiinnostaa tutkimukseen osallistuminen, lue alla oleva tutkimuksen kuvaus.

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TUTKIMUKSEN KUVAUS

Flunssa on yksi keskeisimpiä lyhyiden sairaslomien syitä. Sille ei ole vakiintunutta hoitoa, joka lyhentäisi taudin kestoa. Jos flunssalle löytyy tehokas hoito, on sillä paljon kansanterveydellistä ja kansantaloudellista merkitystä.

Eräissä aiemmissa tutkimuksissa sinkki-imeskelytabletit ovat lyhentäneet koehenkilöiden flunssan kestoa, mutta joissakin tutkimuksissa imeskelytableteista ei ole ollut hyötyä.
Erot voivat selittyä käytetyillä tableteilla, niin että tehottomissa tableteissa sinkki on ollut sellaisessa kemiallisessa muodossa, josta se ei ole päässyt vapautumaan nieluun. Esimerkiksi sitruunahappo sitoo sinkki-ionin niin tiukasti, ettei sinkki vapaudu imeskelyn yhteydessä nieluun. Eräissä tutkimuksissa sinkki-imeskelytableteissa on ollut sitruunahappoa, mikä selittää sen, ettei tableteista ollut hyötyä.

Talven 2017-2018 tutkimuksen tarkoituksena on selvittää yli 200 koehenkilön tutkimuksessa, onko sinkki-imeskelytabletti tehokas flunssaa vastaan ja tarkoitus on myös varmistaa, että oiretietojen keräys saadaan toteutettua sähköisesti.
Tähän tutkimukseen osallistuminen on vapaaehtoista. Voitte kieltäytyä osallistumasta tutkimukseen, keskeyttää osallistumisenne tai peruuttaa suostumuksenne syytä ilmoittamatta milloin tahansa tutkimuksen aikana.
Jos tablettien imeskelyn lopettaa, toivomme silti oirekirjanpidon jatkamista.
Halutessaan senkin saa luonnollisesti lopettaa.

Tutkimuksen koehenkilöt valitaan Helsingin kaupungin työntekijöiden joukosta.

Koehenkilöt jaetaan satunnaisesti kahteen ryhmään. Toisen ryhmän jäsenille annetaan yllä kuvattu purkki sinkki-imeskelytabletteja ja toisen ryhmän jäsenille annetaan purkki saman näköisiä ja saman makuisia tehottomia lume (plasebo)-imeskelytabletteja, joissa ei ole sinkkiä.
Sinkkitableteissa on 13 milligrammaa (mg) sinkkiä.

Purkit jaetaan marraskuun 2017 alussa ja tarkoitus on säilyttää purkkia talven aikana esillä niin, että ensimmäisen flunssan alkaessa koehenkilö aloittaa mahdollisimman pian imeskelytablettien käytön 6 tablettia päivässä mahdollisimman hitaasti imeskellen enintään 5 päivän ajan. 6 tabletissa on yhteensä 78 mg sinkkiä. Jos flunssa menee ohi, voi tablettien käytön lopettaa ennen 5-päivän takarajaa.

Ravitsemussuositusten ohjeistama sinkkimäärä on 7-9 mg päivässä, johon verrattuna 78 mg päivässä on suuri annos. Monissa tutkimuksissa, joissa on tutkittu muita sairauksia kuin flunssa, potilaille on annettu 150 mg sinkkiä päivässä jopa kuukausien ajan. Sama annos 150 mg/pv on Wilsonin taudin (eräs perinnöllinen sairaus) yksi vakiintunut hoito. Sen johdosta ei ole aiheellista epäillä että 5 päivän kestoinen 78 mg päivässä annos sinkkiä voisi aiheuttaa merkittäviä haittoja. Jotkut flunssapotilaat ovat kokeneet, että sinkkitabletit maistuvat pahalta ja joillekin on tullut mahan ärsytystä. Jos sellaiset ongelmat ovat hankalia, koehenkilö voi keskeyttää hoidon.

Tutkimuksessa ei rajoiteta muiden flunssalääkkeiden, esim. kipulääkkeiden, nuhalääkkeiden ja yskänlääkkeiden käyttöä.

Tutkimukseen osallistumisesta ei makseta korvausta. Jos sinkki-imeskelytabletit osoittautuvat tehokkaaksi, plasebo-ryhmän koehenkilöille jaetaan tutkimuksen jälkeen kaksi purkkia niitä

korvauksena tutkimukseen osallistumisesta.

Tutkimuksen valmistumisen jälkeen tuloksista informoidaan koehenkilöitä sähköpostitse.

Tutkijoilla ei ole sidonnaisuuksia lääketeollisuuteen tai muita sidonnaisuuksia, jotka liittyvät tähän tutkimukseen. Yliopiston apteekki rahoittaa käytettävät sinkki-tabletit, mutta ei osallistu tutkimuksen suunnitteluun eikä tulosten tulkintaan.

Sinkki-imeskelytabletit ovat turvallisia käsikauppalääkkeitä. Mikäli tutkimuksen yhteydessä kuitenkin ilmaantuu odottamattomia haittavaikutuksia, kattaa Yliopiston apteekin vakuutus sellaiset tapahtumat.

Tutkimuksen rekisterinpitäjä on Helsingin yliopisto, joka vastaa tutkimuksen yhteydessä tapahtuvan henkilötietojen käsittelyn lainmukaisuudesta. Jari Haukka ja Harri Hemilä vastaavat rekisteristä. Tutkimuksessa henkilöllisyytenne on ainoastaan Helsingin yliopiston tutkijoiden tiedossa ja he ovat salassapitovelvollisia. Tutkimusrekisteristä on laadittu henkilötietolain mukainen rekisteriseloste ja tämän linkin kautta pääsee katsomaan rekisteriselostetta:
(tähän laitetaan linkki rekisteriselosteeseen).

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Mika Kivimäki, professori, Helsingin yliopisto
Jussi Vahtera, professori, Turun yliopisto

Tutkimuksen organisointiin osallistuvat
Helsingin kaupungin työterveyden toimitusjohtaja Tiina Pohjonen
sekä
työterveyshuollon ylilääkäri Marianne Alho
marianne.alho@hel.fi
Heille ei anneta tietoa siitä kuka tutkimukseen osallistuu.

Jos SINÄ haluat osallistua tutkimukseen, avaa seuraava web sivu ja täytä suostumuslomake.

Toimitamme sinkkitabletti-purkin tutkimukseen osallistujille marraskuun alussa.

(tähän laitetaan linkki suostumuslomakkeeseen)

Appendix 4. Informed consent form.

[Suostumuslomake joka toteutetaan web-muodossa, niin että koehenkilölle annetaan linkki, jonka kautta hän pääsee sivulle, jossa nämä asiat kuvataan ja kysytään]

Suostumuslomake

Tutkimuksen nimi:
Sinkki-imeskelytablettien vaikutus flunssasta toipumisen nopeuteen
(The effect of zinc acetate lozenges on the rate of recovery from the common cold: a randomized trial: The HelZinki Study)

Tutkittavan nimi:

Henkilötunnus:

Helsingin kaupungin sisäposti-osoite:

Kotiosoite:

Puhelinnumero:

Tutkimuksessa selvitetään, voiko sinkki-imeskelytableteilla lyhentää flunssan kestoa.

Tutkittavan tiedote on lähetetty sinulle sähköpostitse, mutta se on lisäksi nähtävissä tällä sivulla: (tutkittavan tiedote kopio linkki).

Olen perehtynyt "tutkittavan tiedote" selvitykseen ja saanut riittävästi tietoa tutkimuksesta ja sen yhteydessä suoritettavasta tietojen keräämisestä, käsittelystä ja luovuttamisesta. Minulla on ollut riittävästi aikaa harkita tutkimukseen osallistumista.

Ymmärrän, että tähän tutkimukseen osallistuminen on vapaaehtoista.
Minulla on oikeus milloin tahansa tutkimuksen aikana ja syytä ilmoittamatta keskeyttää tutkimukseen osallistuminen tai peruuttaa suostumukseni tutkimukseen. Tutkimuksen keskeyttämisestä tai suostumuksen peruuttamisesta ei aiheudu minulle kielteisiä seuraamuksia, eikä se vaikuta asemaani terveydenhuollon asiakkaana.
Minulla on oikeus milloin tahansa ennen tutkimuksen päättymistä peruuttaa suostumus, ja voin päättää että minusta siihen mennessä kerättyjä tietoja ei tuolloin käytetä enää osana tutkimusta.

Annan luvan siihen, että tutkimuksessa käsitellään henkilötietojani.
Annan luvan siihen, että tutkimuksessa kerätään tietoja työterveyshuollon rekisteristä ja KELAsta reseptilääkkeiden käytöstä alkaen 1 kuukausi ennen sinkki-imeskelytablettien käyttöä ja 2 kuukauden ajan imeskelytablettien käytön alkamisen jälkeen, sekä sairaspoissaolotietoja talvelta 2016-2017.
Jotkin hoidon vaikutukset voivat tapahtua viiveellä ja sen vuoksi tietoja kerätään 2 kuukautta

hoitovaiheen jälkeen. Tietojen kerääminen flunssaa edeltävältä jaksolta mahdollistaa edeltävän terveystilan arvioinnin.

Tietojen keräämisen yhteydessä tutkimuksessa käytetään henkilötietoja, mutta tulosten analysoinnin yhteydessä henkilötiedot korvataan koodilla. Tiedosto, jossa on henkilötiedot, tuhotaan 2 vuoden päästä tutkimuksen lopettamisen jälkeen.

Tutkimusrekisteristä on laadittu henkilötietolain mukainen rekisteriseloste ja alla olevan linkin kautta pääsee katsomaan rekisteriselostetta.
(tähän linkki)

Hyväksyn yllä kuvatun tietojen keräämisen, ja kerättyjen tietojeni säilyttämisen ja analysoinnin tutkimuksessa.

Tämän lomakkeen allekirjoituksella vahvistan, että osallistun tässä asiakirjassa kuvattuun tutkimukseen ja suostun vapaaehtoisesti tutkittavaksi.
Annan luvan minua koskevien yllä kuvattujen tietojen hankkimiseen.
(Automaattinen päiväys ohjelmasta)

Täytän tämän lomakkeen suojatun web-yhteyden kautta ja
tällä klikkauksella hyväksyn lomakkeen kokonaisuutena, allekirjoittamista vastaavasti
(klikkauskohta)

Tämän lomakkeen hyväksymisesi jälkeen lähetämme Sinulle vahvistuksen, että olemme vastaanottaneet suostumuksesi osallistua tutkimukseen.