

**Effect of a Cold Water Immersion (CWI) on Pain in People with Gouty Arthritis: A
Community Based Randomized Controlled Trial**

Unique Protocol ID: N201912052

April 26, 2020

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1. Introduction

Gouty arthritis is a type of autoinflammatory arthritis (Rock et al., 2014) that generates higher pain (Carroll et al., 2018). Although the hospitalization rate in people with rheumatoid arthritis has declined, gout is growing (Fields, 2019). Gouty arthritis causes inflammation pain with only minimum movement in the joint. The inflammatory process causes central sensitization that can lead to chronic-long-term pain (Harth & Nielson, 2019). The pain among people with gouty arthritis is shown to negatively correlate with the physical function that encompasses reduced peak ankle joint angular mobility velocity, foot-specific disabilities, and impairment. It will probably represent the weakness of gait and experience disability (Carroll et al., 2018). People with gouty arthritis were found to have 1.18-times more likely to have a poor physical function (Burke et al., 2015). As such, we can conclude that gout arthritis diseases will lead to inferior extremity impairment, foot-specific disabilities, raises intolerance foot pain, physical inactivity, and joint mobility reduction.

Currently, intermittent drugs use for pain relief is suggested to contribute to the renal impairment side effect. Consequently, the renal impairment is attributed to the under-excretion of uric acid, kidney stones, and progress with many comorbidities (Fields, 2019; Padang, Muiriden, Schumacher, Darmawan, & Nasution, 2006). Furthermore, terminal renal insufficiency has also long been implicated as a common cause of death in gout (Padang et al., 2006). However, we found that there is a limited study that investigated non-pharmacological intervention among people with gouty arthritis (Abhishek & Doherty, 2018).

The pain among people with gouty arthritis has also been shown to increase the degree of depression and psychological distress (Harth & Nielson, 2019). The prior studies conveyed the more pain will produce a huger degree of anxiety and depression (Fu et al., 2017; Hilderink, Burger, Deeg, Beekman, & Oude Voshaar, 2012; Lin, Zhang, & Ma, 2018). A significant relationship was also found between stress and the incidence of gouty arthritis in Southeast Celebes, Indonesia, in 2017 (Jaliana, Suhadi, La Ode, & Sety, 2018). Also, the high levels of pain, psychological distress, anxiety, and depression among people with gouty arthritis were found as the risk factor of poor Quality of Life (QOL) (Chandratre et al., 2018; Fu et al., 2017; Singh et al., 2017). Multiple studies reflect the impact of gout on life quality and its association with higher mortality (Chandratre, Mallen, Roddy, & Liddle, 2016; DiBonaventura, Andrews, Yadao, & Kahler, 2012; Fields, 2019). However, non-pharmacological therapy remains has been seldom studied among people with gouty arthritis on QOL, stress, anxiety, and depression. Therefore, non-pharmacologic treatment is vital in supporting people with gouty arthritis who are increased pain, reduced Quality of life, stress, anxiety, and depression.

A significant decrease of TNF- α level and considerable improvement of clinical severity of pain, duration of morning stiffness, and the degree of self-reported fatigue among people with Rheumatoid Arthritis (RA) were also founded in cryotherapy twice a day for ten days at -160⁰C on the knee joint and 4 hours later on the joint of both hands (Jastrzābek, Straburzyńska-Lupa, Rutkowski, & Romanowski, 2013). Cold therapy (cryotherapy) application has been proven as useful adjuvant therapy on alleviating pain among people with gouty arthritis. A previous studies that applied the topical ice therapy on patients people with gouty arthritis who had experienced previous gouty flare attacks, showed a symptomatic improvement after 1 week of treatment (19 minutes on each treatment) compared to before topical ice therapy and control group (Schlesinger,

2006; Schlesinger et al., 2002). This cooling therapy reduces hyperemia and has also been presented to decrease experimental crystal-induced inflammation (Schlesinger, 2006). Since the application of cooling therapy is limited in short duration, Schlesinger (2006) suggested that the reaction of inflammatory arthritis among people with gouty arthritis should be assessed frequently in the future study. Moreover, the effects of topical ice therapy and cryotherapy have not been conducted in the community setting, an innovative and relevant cooling therapy with a multi-center-community setting to estimate its effect on people with gouty arthritis is strongly recommended.

Cold Water Immersion (CWI) is categorized as one of the Cryotherapies (Bleakley et al., 2012). CWI therapy has a twofold reduction of inflammation. Firstly, it attenuates metabolic processes in stressed tissues and slowing cytokine and myokine up-regulation that mediate inflammation. Second, CWI induces microvasculature vasoconstriction by perfusing stressed tissue; consequently, it reduces the circulatory exposure of tissue access to inflammatory cells (White & Caterini, 2017). CWI was defined as water immersion to a temperature of up to 15°C (Bleakley et al., 2012). A prior study has been proven that a short term effect of CWI therapy significantly reduced the level of pressure pain among 12 males (Klich, Krymski, Michalik, & Kawczyński, 2018). On the other hand, low temperature could induce gout crystal formation (Albar, 2007). As there was a controversial result of low temperature on joint crystal inflammation (Albar, 2007; Schlesinger, 2006), it was suggested to modify the CWI therapy on 20-30°C. Moreover, the CWI (20-30°C) therapy has not been done among people with gouty arthritis worldwide.

Meanwhile, the high prevalence of gouty arthritis has been presented in North Celebes, Indonesia (Health Research and Development Agency, 2013). Moreover, patients frequently

presented too late for effective therapy; consequently, the chronic topical gout has contributed to the permanent deformities and impairments. When disability develops, and patients become dependent on their families. Data showed that more than 50% of patients had observed tophi for 7 to 9 years before presenting for treatment. It was due to the lack of information among people with gouty arthritis and primary healthcare professionals, and the lack of availability of urate-lowering drugs in community health centers (CHC) in Indonesia (Padang et al., 2006). These empirical issues indicate that the marked clinical and economic impact of gouty arthritis and the requirements of further research on successful gout management. Due to the previous studies limitation on cooling therapy, we aim to fill the gaps to investigate a unique analysis of the CWI (20-30°C) therapy effect on pain, joint mobility, stress, anxiety, depression, QOL (encompasses PCS and MCS), physical activity (MET-h/week) in the multicenter-community setting with randomized controlled trial study design.

2. Methods

2.1. Design

The randomized control trial study with two parallel-intervention-groups was employed to examine the effect of CWI (20-30°C) therapy. All participants were randomly assigned to either CWI (20-30°C) therapy intervention group or the control group. Block random sampling was then employed to generate the intervention and control group sequence. All participants were assessed on their pain as the primary outcome, joint mobility, stress, anxiety, depression, QOL including overall quality of life, physical component summary (PCS), and mental component summary (MCS), physical activity (metabolic equivalent of task-hour/week; MET-h/week) at three time points: before the intervention, 2nd and 4th-week of the intervention. Due to the nature of the intervention, it is only possible to blind the evaluator of the study. The CONSORT diagram of this

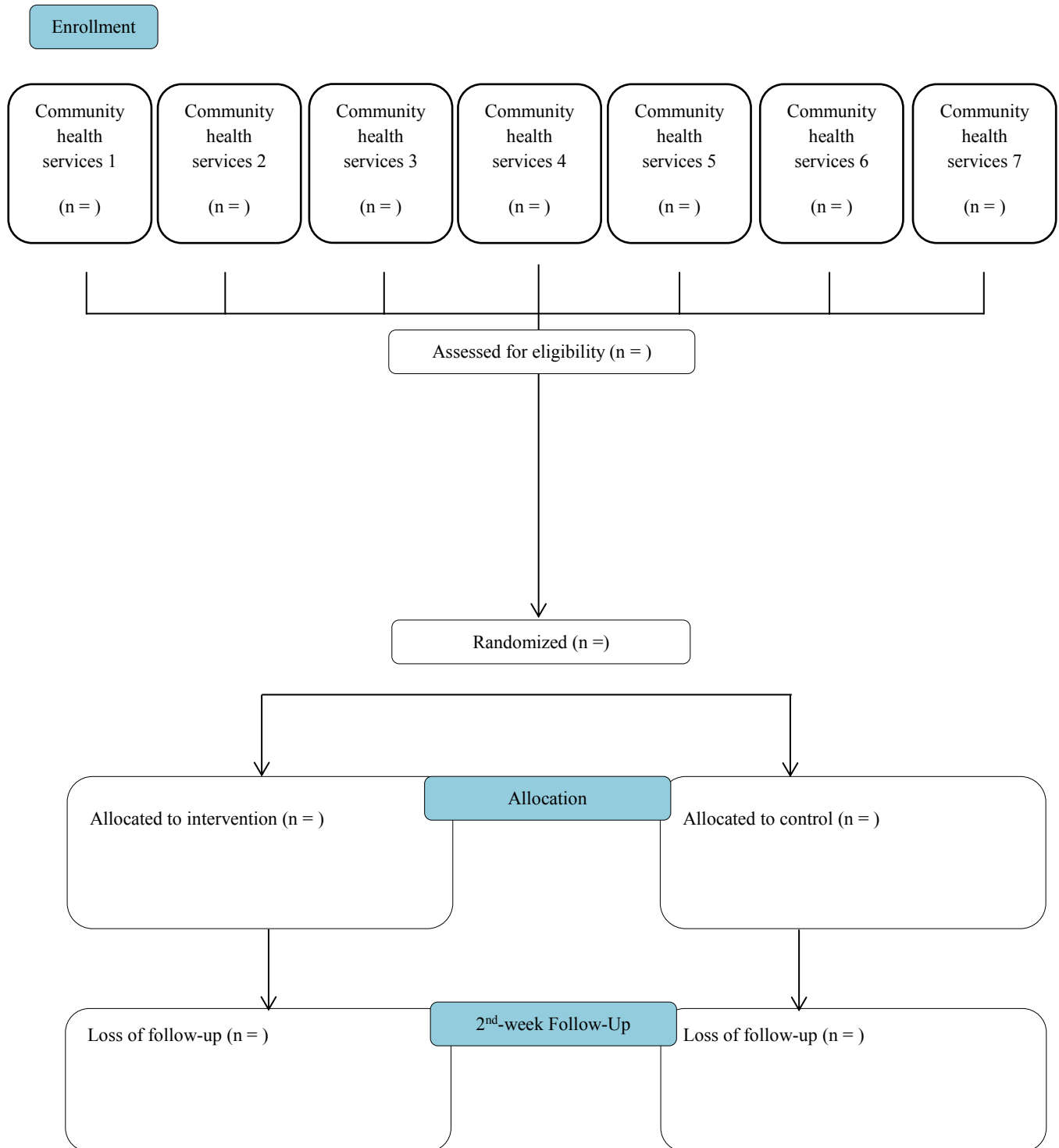
study is exhibited in Figure 1. The study protocol was reviewed and approved by the Institutional Review Board Ethics Committee of Taipei Medical University (N201912052), Taipei, Taiwan, and Universitas Kristen Satya Wacana, Salatiga, Indonesia (187/PE/KEPK.UKSW/2019), and conformed to the provisions of the *Declaration of Helsinki*. Written informed consent was obtained from each participant after they had received both verbal and written information about the research.

2.2. Setting and Participant

The sample calculation utilized G-Power 3.1 software with the alpha level (α) of 0.01, power ($1-\beta$) of 0.80 (Cohen, 1998), and the effect size is 0.9 (Klich et al., 2018), the total estimated sample size required 31 in each group. An estimated 20% dropout rate increases; the sample size is 36 for each group.

This research was conducted at North Celebes, Indonesia. Participants were recruited using the multi-stage sampling method. North Celebes Province was conveniently selected in the first stage sampling, which had the highest prevalence of gouty arthritis. North Celebes province was stratified it into 15 regions. In the second stage, two regions of fifteen regions were randomly selected, including urban and rural areas. Tomohon City is the one urban area that has been able to engage in this partnership. Seven Community Health Service (CHS) centers in Tomohon City have been randomly chosen in the final level. The inclusion criteria included (1) people with gouty arthritis in the knee or ankle or metatarsophalangeal or metacarpophalangeal or olecranon bursa or wrist, (2) participants were Indonesian nationals and aged ≥ 18 years, (3) they had visited a clinic of the Public CHS of Tomohon City, and (4) they had agreed to participate in the study. Participants, who self-reported the presence of other types of inflammatory arthritis, including RA

or spondyloarthritis, were excluded from the study. The data source of diagnoses was their medical records in the Public CHS of Tomohon City.



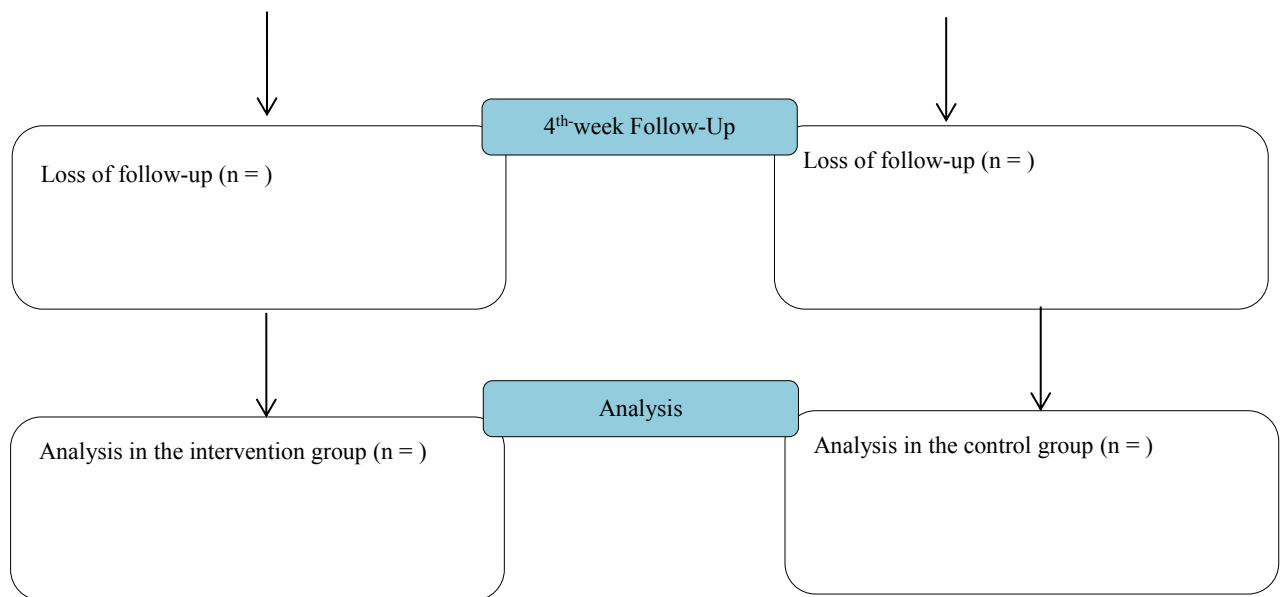


Figure 1. Flow of participants

2.3. Cold Water Immersion Intervention and Procedures

The participants maintained their daily activities during the intervention. When daily activity ended, the intervention was begun. CWI therapy immersed the whole part of the inflamed target joints in the water at 20-30°C for 20 minutes/day. The intervention was continued for four weeks. The researchers work together with the nurses of Community Health Services (CHS) to give the intervention. The nurses provide data that contains people who are diagnosed with gouty arthritis. Thereby, started with the participants' recruitment, intervention, and evaluation, the researchers collaborated with the CHS nurses to approach participants.

2.4. Measurements

2.4.1. Participants characteristic

Four qualified professional nurses collected all the data. Blood pressure and BMI were examined in a standardized medical examination. Demographic data were collected by using a self-designed questionnaire. The questionnaire included the demographic characteristics of the participant, including age, gender, marital status, educational level, income, occupation, family gout history, gouty arthritis drug consumption, alcohol consumption, and smoking status (Tsai et al., 2007). The translated food frequency questionnaire was employed with Cronbach's alpha as 0.95 (Nilawati, Nugraheni, & Frieda, 2005).

2.4.2. Pain

The Visual Analog Scale (VAS) instrument has 10 centimeters length. The standard scale anchored by "no pain" marked as a score of 0 and the "worst imaginable pain" marked as a score of 10 cm (Huskisson et al., 1974; Scott & Huskisson, 1976). The higher score identifies greater pain intensity. The reliability test showed that VAS was good ($r = 0.94$, $p = 0.001$) (Ferraz et al., 1990). The reliability test of the VAS instrument has been done in Indonesia with the Cronbach's alpha as 0.89 (Suwendar et al., 2017).

2.4.3. Joint mobility

The range of knee joint motion was calculated using an International Standard Orthopedic Measurement (ISOM) goniometric. Its method using the Sagittal Frontal Transverse Rotation (SFTR) system to an accuracy of 1° (Dorwart, Hansell, & Schumacher, 1974). Goniometry provides an objective assessment tool to measure the range of motion (Rose & Norton, 1987). The validity and reliability of Goniometry are 0.98 and 0.97, respectively (Rose & Norton, 1987). The validity score of the Indonesian

version is 0.97, and the Cronbach alpha as 0.51 (Hafiyah, 2013).

2.4.4. Stress, anxiety, depression

The Depression Anxiety Stress Scale (DASS-21) questionnaire is used to measure the negative states of three mental health conditions: depression, anxiety, and stress using a self-report 4-point Likert scale. Data was collected by reflecting thoughts, feelings, and behavior (Oei, Sawang, Goh, & Mukhtar, 2013). The result will be defined by the total scores of responses from the 7-item subscale of this questionnaire. The Cronbach's alphas of Indonesian translated is 0.72 to 0.87 (Susilowati, Isahak, & Harncharoen, 2016).

2.4.5. Quality of Life (QOL)

The 36 Health Survey (SF-36) questionnaire was employed to estimate QOL. It included Physical Component Summary (PCS), Mental Component Summary (MCS). Total QOL range from 0 to 100 (Rias et al., 2020). The Indonesia version of the SF-36 questionnaire has tested the reliability with the Cronbach's alphas 0.7 (Salim, Yamin, Alwi, & Setiati, 2015)

2.4.6. Physical activity (MET-h/week)

The physical activity level was investigated as metabolic equivalent of task (MET)-hr/week by calculating the arbitrary units of summing the products of the separate components using the formula: (MET)-hr/week score =(MET level x hours x times/week) (Rias et al., 2020) We then estimated physical activity levels based on the exercise type (that is divided into the following categories: mild (e.g., yoga, bowling, or floor-sweeping), moderate (e.g., gym, baseball, or badminton), and strenuous exercise (e.g., hiking, soccer, or running)), duration in hours and exercise frequency

they presented during a typical week. We multiplied the amount of mild, moderate, and strenuous exercise hours and duration by 3, 5, and 9. By summing the exercise pattern of the separate things, we measured total weekly physical activity in arbitrary units (Rias et al., 2020).

2.5. Statistical Analysis Plan

The Chi-square and t-test were employed to analyze the homogeneity of subject characteristics between the experimental and control group. The Generalized Estimating Equation (GEE) model was applied to compare the differences pain, joint mobility, stress, anxiety, depression, QOL (included PCS and MCS), physical activity quantity (MET-h/week) within four weeks intervention between the intervention and control group. The interaction between group and time was also further analyzed to determine if the mean differences in their pain, joint mobility, stress, anxiety, and depression, QOL, and physical activity between groups differed significantly over time. $P < 0.05$ was applied as statistically significant. The per-protocol method was employed to deal with the missing data. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) vers. 25.0 (Chicago, IL, USA). Besides, Structural Equation Modeling (SEM) was also employed to analyze the mediating effect between variables through the Analysis of Moment Structures (AMOS) vers. 24. Then we evaluate the measurement and structural models by utilizing the goodness fit index (Hair et al., 2014).

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Name of the Trial :

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Implementation Institution:

Taipei Medical University, Department of Nursing College

Contact person: Maria Dyah Kurniasari/ +62 82 226 886 16 9

Tel : +62 82 226 886 16 9

Principal investigator: Professor Hsiu Ting Tsai

Co-investigator: Maria Dyah Kurniasari

Contact person in case of emergency: Maria Dyah Kurniasari/ +62 82 226 886 16 9

Name of participant :

Gender :

Age :

Chart Number :

Mail Address :

Phone Number :

Name of contact person in case of emergency/relationship to the participant :

Maria Dyah Kurniasari

Mail Address : Kartini Street, No 11A, Salatiga City, Central Java, Indonesia

Phone Number : +62 82 226 886 16 9

1. Background for the trial/research and drug/medical device/product status

Gouty arthritis is a type of autoinflammatory arthritis (Rock et al., 2014) that generates higher pain (Carroll et al., 2018). Gouty arthritis causes inflammation pain with only minimum movement in the joint. The inflammatory process causes central sensitization that can lead to chronic-long-term pain (Harth & Nielson, 2019). The pain among people with gouty arthritis is shown to negatively correlate with the physical function that such as reduced peak ankle joint mobility, foot-specific disabilities, and impairment. It will probably

represent experience disability (Carroll et al., 2018). People with gouty arthritis were found to have 1.18-times more likely to have a poor physical function (Burke et al., 2015). As such, we can conclude that gout arthritis diseases will lead to foot-specific disabilities, raises intolerance foot pain, physical inactivity, and joint mobility reduction.

Currently, intermittent drugs use for pain relief is suggested to contribute to the kidney impairment side effect. Consequently, the renal impairment is attributed to the under-excretion of uric acid, kidney stones, and progress with many comorbidities (Fields, 2019; Padang, Muirden, Schumacher, Darmawan, & Nasution, 2006). Furthermore, terminal kidney impairment has also long been implicated as a common cause of death in gout (Padang et al., 2006). However, we found that there is a limited study that investigated non-pharmacological intervention among people with gouty arthritis (Abhishek & Doherty, 2018).

The pain among people with gouty arthritis has also been shown to increase the degree of depression and psychological distress (Harth & Nielson, 2019). The prior studies conveyed the more pain will produce a huger degree of anxiety and depression (Fu et al., 2017; Hilderink, Burger, Deeg, Beekman, & Oude Voshaar, 2012; Lin, Zhang, & Ma, 2018). A significant relationship was also found between stress and the incidence of gouty arthritis in Southeast Celebes, Indonesia, in 2017 (Jaliana, Suhadi, La Ode, & Sety, 2018). Also, the high levels of pain, psychological distress, anxiety, and depression among people with gouty arthritis were found as the risk factor of poor Quality of Life (QOL) (Chandratre et al., 2018; Fu et al., 2017; Singh et al., 2017). Multiple studies reflect the impact of gout on life quality and its association with higher mortality (Chandratre, Mallen, Roddy, & Liddle, 2016; DiBonaventura, Andrews, Yadao, & Kahler, 2012; Fields, 2019). However, non-pharmacological therapy remains has been seldom studied among people with gouty arthritis on QOL, stress, anxiety, and depression. Therefore, non-pharmacologic treatment is vital in supporting people with gouty arthritis who are increased pain, reduced Quality of life, stress, anxiety, and depression.

A considerable improvement of clinical severity of pain, duration of morning stiffness, and the degree of self-reported fatigue among people with Rheumatoid Arthritis (RA) were also founded in cryotherapy twice a day for ten days at -160⁰C on the knee joint and 4 hours later on the joint of both hands (Jastrzabek, Straburzyńska-Lupa, Rutkowski, & Romanowski, 2013). Cold therapy (cryotherapy) application has been proven as useful a complementary therapy on reduce pain among people with gouty arthritis. A previous studies that applied the

topical ice therapy on patients people with gouty arthritis who had experienced previous gouty pain, showed an improvement after 1 week of treatment (19 minutes on each treatment) compared to before topical ice therapy and participants who did not received the topical ice therapy as the control group (Schlesinger, 2006; Schlesinger et al., 2002). This cooling therapy reduces inflammation (Schlesinger, 2006). Since the application of cooling therapy is limited in short duration, Schlesinger (2006) suggested that the reaction of inflammatory arthritis among people with gouty arthritis should be assessed frequently in the future study. Moreover, the effects of topical ice therapy and cryotherapy have not been conducted in the community setting, an innovative and relevant cooling therapy with a multi-center-community setting to estimate its effect on people with gouty arthritis is strongly recommended.

Cold Water Immersion (CWI) is categorized as one of the Cryotherapies (Bleakley et al., 2012). CWI therapy has a twofold reduction of inflammation (White & Caterini, 2017). CWI was defined as water immersion to a temperature of up to 15°C (Bleakley et al., 2012). A prior study has been proven that a short term effect of CWI therapy significantly reduced the level of pressure pain among 12 males (Klich, Krymski, Michalik, & Kawczyński, 2018). On the other hand, low temperature could induce gout progression (Albar, 2007). As there was a controversial result of low temperature on joint crystal inflammation (Albar, 2007; Schlesinger, 2006), it was suggested to modify the CWI therapy on 20-30°C. Moreover, the CWI (20-30°C) therapy has not been done among people with gouty arthritis worldwide.

Meanwhile, the high prevalence of gouty arthritis has been presented in North Celebes, Indonesia (Health Research and Development Agency, 2013). Moreover, patients frequently presented too late for effective therapy; consequently, the chronic topical gout has contributed to the permanent deformities and impairments. When disability develops, and patients become dependent on their families. Data showed that more than 50% of patients had observed tophi for 7 to 9 years before presenting for treatment. It was due to the lack of information among people with gouty arthritis and primary healthcare professionals, and the lack of availability of urate-lowering drugs in community health centers (CHC) in Indonesia (Padang et al., 2006). These empirical issues indicate that the marked clinical and economic impact of gouty arthritis and the requirements of further research on successful gout management. Due to the previous studies limitation on cooling therapy, we aim to fill the gaps to investigate a unique analysis of the CWI (20-30°C) therapy effect on pain, joint mobility, stress, anxiety, depression, QOL (encompasses PCS and MCS), physical activity

(MET-h/week) in the multicenter-community setting with randomized controlled trial study design.

2. Purpose for the trial/research

To investigate a unique analysis of the CWI (20-30°C) therapy effect on pain, joint mobility, stress, anxiety, depression, QOL (encompasses PCS and MCS), physical activity (MET-h/week) in the multicenter-community setting with randomized controlled trial study design.

3. Inclusion and exclusion criteria

The inclusion criteria included (1) people with gouty arthritis in the knee or ankle or metatarsophalangeal or metacarpophalangeal or olecranon bursa or wrist, (2) participants were Indonesian nationals and aged ≥ 18 years, (3) they had visited a clinic of the Public CHS of Tomohon City, and (4) they had agreed to participate in the study. Participants, who self-reported the presence of other types of inflammatory arthritis, including RA or spondyloarthritis, were excluded from the study. The data source of diagnoses was their medical records in the Public CHS of Tomohon City.

4. Procedures and relevant tests for the trial/research

- The participants maintained their daily activities during the intervention. When daily activity ended, the intervention was begun. CWI therapy immersed the whole part of the inflamed target joints in the water at 20-30°C for 20 minutes/day. The intervention was continued for four weeks.
- In addition, the participants will fill the questionnaire (Pain level; Quality of life; Depression, anxiety, stress; Joint mobility; Physical activity) for three times point pre trial, middle and post trial. Filling questionnaire take around 15 minutes.

I agree to be checked the medical record when necessary.

Signature: _____ Date: _____ (year/ month/ day)

5. Possible adverse effects and damage, and standard procedures for handling

A mild risk maybe happen during the participant filled out these questionnaires such as discomfort, fatigue, and headache. Hence, there is no significant risk in this research. If there is

an adverse effect or damage the participant should be sent to the nearest hospital as soon as possible by the researcher.

1. Expected effects/results from the trial/research and possible/potential business benefits

The participant will get some benefit such as reduce pain level, depression, anxiety, stress, increased the quality of life, joint mobility and physical activity.

7. Alternative treatment options

The participant remains receive the regular treatments

8. Things should be avoided or restricted during participating in the trial/research

Since, there is no significant harmful effect in this study, there is no things should be avoided or restricted during participating in the trial/research.

9. Confidentiality and the process about handling trial/research materials/specimens collected after the trial/research

Taipei Medical University will classify your data as secrets based on legal regulations. You understand that sponsor of this project; Ministry of Health and TMU-JIRB have the right to review your data under ethical requirement for confidentiality.

All test results and diagnoses made in this trial/research will be labeled with a project serial number and your name will be taken off from all labels. We will keep your privacy, while the above-mentioned institutes have the right to review your data according to legal regulations. Your identification will be confidential in all publications associated with this trial/research.

After the end of the trial/research, your information/data will be stored (including names of country, city, institute, department, lab and person in charge, all applicable to international institutes), and Hsiu Ting Tsai/Taipei Medical University will keep the information/data for 5 years (no more than 20 years). We will process the information/data according to your choice.

Do you agree to provide your information/data for use in other medical trial/research?

☐ Yes

☐ I will provide my information/data to Hsiu Ting Tsai/Taipei Medical University or authorize Maria Dyah Kurniasari/Taipei Medical University for further research including those do not meet the definition of biomedical research by human biological database regulatory rules. (Another informed consent form that is reviewed and approved by TMU-JIRB will be signed for this purpose).

☐ No

☐ Information/data will be destroyed by Hsiu Ting Tsai/Taipei Medical University or authorize Maria Dyah Kurniasari/Taipei Medical University.

If there is remainder of your specimen after the end of the trial/research, it will be stored (including names of country, city, institute, department, lab and person in charge, all applicable to international institutes), and Hsiu Ting Tsai/Taipei Medical University or authorize Maria Dyah Kurniasari/Taipei Medical University will keep the specimens for 5 years(no more than 20 years). We will process the remainder of specimens according to your choice.

Do you agree to provide your specimens for use in other medical trial/research?

☐ Yes

☐ I will provide my specimens to Hsiu Ting Tsai/Taipei Medical University or authorize Maria Dyah Kurniasari/Taipei Medical University for further research including those do not meet the definition of biomedical research by human biological database regulatory rules. (Another informed consent form that is reviewed and approved by TMU-JIRB will be signed for this purpose).

☐ No

☐ Specimens will be destroyed by Hsiu Ting Tsai/Taipei Medical University or authorize Maria Dyah Kurniasari/Taipei Medical University.

10. Withdrawal/termination of the trial/research, and disposal of specimens and related information in such conditions.

The decision of participation in the current trial/research is yours, and you may withdraw your permission at any time during the trial/research without any reason. There will be no negative impacts on your continual health care by the current physician and hospital. In addition, by signing this consent form you also understand the possibility that principal

investigator or the sponsor may halt the trial when necessary. This is not going to post any negative impacts on your continual care by the current physician and hospital either.

If the tests of your specimens and filled physical questionnaires as well as scales are completed at the time of your withdrawal from this trial/research, the information will be kept and analyzed as described in this informed consent. Hsiu Ting Tsai and Maria Dyah Kurniasari will have all rights on the use and copyright of these results. Your specimens will be destroyed upon your withdrawal.

11. Damage compensation and insurance

- (1) Hsiu Ting Tsai and Maria Dyah Kurniasari are liable to compensation for damage directly related to the use of agent in this trial/research as described in the previous sections. Damage includes all adverse events, side effects or injury. Please inform principal investigator if any adverse event, side effect or injury that is directly related to the current trial/research happens. Kandao Public Hospital will provide medical care. You are exempt from medical care expenses for adverse event, side effect or injury that is directly related to the current trial/research.
- (2) You will not lose any legal rights by signing this informed consent form.
- (3) This project is not covered by insurance. If you do not want to expose to the risk, you may deny the enrollment or withdraw your agreement anytime during the trial period. For such decisions we will not ask for a reason and your rights will not be affected.

12. Rights and obligations of the participant.

- (1) All cost related to the trial/research is covered by the current trial/research.
- (2) The trial/research didn't Provide any grants or gifts.
- (3) During the trial/research, we will timely provide all significant findings that are related to your personal well-being and that may change your willingness to stay in the trial/research.
- (4) During the trial/research period, you will be referred to Professor Hsiu Ting Tsai (Professor and director of Post-Baccalaureate Program in Nursing/Taipei Medical University) and Maria Dyah Kurniasari/International student of Ph.D program for research-related medical care. Please feel free to contact Professor Hsiu Ting Tsai (Professor and director of Post-Baccalaureate Program in Nursing/Taipei Medical University) and Maria Dyah Kurniasari/International student of Ph.D program at +62 82 226 886 16 9 if there is any question during the research period.

- (5) If you have any question on the nature of this research, on participants' rights, or on the possible damage directly related to participation in the trial/research, please contact TMU-JIRB at any time at 02-66382736 ext 1728 or email: tmujirb@gmail.com.
- (6) Besides the above situation, any individual who is unaffiliated with the research study such as current, prospective, or past research participants or their designated representatives, permits to discuss problems and concerns; obtain information from TMU-JIRB, we can also offer input with an informed individual who is unaffiliated with the specific research protocol or plan. If necessary, please contact TMU-JIRB at 02-66382736 ext. 1728 or email: tmujirb@gmail.com.

13. Signature

Disclaimer from participant

I have been explained about the above information, and have been provided opportunities to clarify all questions related to the trial/research. I understand and agree to participate in the trial/research, and a copy of the informed consent has been provided to me. I will contact Maria Dyah Kurniasari/International student of Ph.D program, Taipei Medical University at +62 82 226 886 16 9 if there is any question in the future.

Name of participant (print) _____

Date of birth _____

Signature _____

Date _____

Name of the proxy when applicable (print) _____ (If applicable)

Signature _____

Relationship to participant _____

Date _____

For any person who is asked to sign this informed consent because participant himself/herself or his/her legal proxy cannot sign this informed consent at this time, please print your name and specify your relationship to the participant.

Name (Print) _____

Relationship to the participant _____

National ID Number _____

Contact number _____

Mail Address _____

Signature _____

Date _____

Disclaimer from the Principal investigator

I guarantee that either I or an authorized member in my trial/research team has explained about the purpose, procedure, possible risks and benefits to the person listed above. All questions have been properly answered.

Name of the PI / co-investigator: Hsiu Ting Tsai

Signature_____

Date_____

Name of the researcher that explains about the research: Maria Dyah Kurniasari

Signature_____

Date_____

Witness for orally informed consent

(If the participant cannot read the above documents, and the full document is explained by a researcher orally, a witness is required for the process.)

I hereby certify the principal investigator (or a researcher in the trial/research) has thoroughly explained about the trial/research to the participant.

Name of the witness (Print): Maria Dyah Kurniasari

National ID number: 3308085503910001

Contact number: +62 82 226 886 16 9

Mail address: Kartini Street, No 11A, Salatiga City, Central Java, Indonesia

Signature_____

Date_____

©If subjects, legal representatives, auxiliary personnel or anyone who has the right to agree all have difficulty to read, the discussion related to the agreement of the subject should be fully participated in by a witness. After confirming the agreement of subjects, legal representatives, auxiliary personnel or anyone who has the right to agree are all out of their free will, a signature should be put on the agreement as well as remark the date. Testing/ research relevant personnel must not be the witness.