Cost-effectiveness and implementation process of a running-related injury prevention program (RunIn3): Protocol of a randomized controlled trial

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Background: Running is one of the most popular and accessible physical activities in the world. However, running-related injuries are unfortunately very common. Scientific evidence is limited and scarce regarding cost-effectiveness and implementation process of interventions for running-related injuries prevention. Thus, the objective of this study will be to investigate the effectiveness, cost-effectiveness and implementation process of a running-related injury prevention program (RunIn3).

Methods: This is the protocol of a pragmatic hybrid type 1 randomized controlled trial. There will be 530 runners over 18 years old, without running-related injuries in the last 3 months from São Paulo, Brazil. This program will be delivered online with two broad actions: (1) to provide feedback on individual training characteristics and running-related injury risk; and (2) providing/enhancing knowledge, skills and self-efficacy on running-related injury preventive behaviors. The primary outcome will be the proportion of runners reporting running-related injuries. The secondary outcomes will be preventive behaviors, direct and indirect costs, and implementation outcomes. The main effectiveness analysis on the primary outcome will be performed using linear probability mixed models in order to allow outcome changes over time and to yield the absolute risk reduction between-groups.

Discussion: The main hypothesis of this study is that the RunIn3 program will be effective in reducing the running-related injury risk and in promoting preventive behavior, either by increasing the frequency of healthy behaviors or by reducing the frequency of risk behaviors. Moreover, if the RunIn3 program is effective in reducing the running-related injuries risk, we believe that this effect would go alongside with a reduction of societal costs.

Trial registration: Clinicaltrials.gov (NCT03892239) Registered 5 February 2019 - Prospectively registered, https://clinicaltrials.gov/ct2/show/NCT03892239.

1. Introduction

Running is one of the most popular types of physical activity worldwide [1-3]. Studies suggest that running promotes improvements in health indicators [1], morbidity [4], mortality [3,5-7] and it is cost-effective for the prevention of cardiovascular diseases [8]. Unfortunately, running-related injuries (RRI) are very common [9-12]. RRI incidents are associated with pain; absence from training; increased use of medical resources; productivity loss; and costs [9-12].

The incidence of RRI in novice and recreational runners are estimate in 17.8 injuries per 1000 h of running and 7.7 injuries per 1000 h of running, respectively [13]. Therefore, runners could benefit from RRI prevention programs [11,13,14]. There are several RRI prevention programs [15-21]. However, a Cochrane review [22] has shown that the evidence from the existing prevention programs is limited and scarce.

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2. Methods

2.1. Trial design and setting

This is the protocol of a pragmatic hybrid type 1 randomized controlled trial. The study will be conducted in the state of Sao Paulo, Brazil. A flowchart presenting a process overview of the study design can be found in Fig. 1.

2.2. Ethics and dissemination

This study was approved by the Research Ethics Committee of the Universidade Cidade de Sao Paulo in October 2018 (#79841318.3.0000.0064). The trial protocol was prospectively registered on ClinicalTrials.gov (NCT03892239).

2.3. Target study population

We will include: (A) runners aged 18 years or older; (B) with a running experience of at least three months; (C) residents of the state of Sao Paulo; (D) no RRI at baseline; and (D) no history of RRI in the past three months (Fig. 1). Advertisements of the trial will be displayed in different types of social media by the authors’ personal accounts, running groups, running influencers and other stakeholders. We will also promote the study in public parks and running events in Sao Paulo.

2.4. Interventions

2.4.1. Intervention group

Participants assigned to the intervention group will receive the full RunIn3 program, which is structured as a two-part intervention. Part 1 consists of advice on a ‘safe’ (i.e., lower RRI risk) range of biweekly running exposure progression. The advice will be delivered every two weeks and in relative measures, meaning that the crude running exposure advised may differ between the biweekly periods. Part 2 consists of providing information and knowledge on RRI prevention. Only the intervention group will receive the intervention part 2. The delivery of part 2 will be done using conventional texts (including scientific references supporting the information provided), infographics and/or videos. The content of each information package is evidence-based and was determined during the development of the RunIn3 program using a participatory approach (i.e., including the target population in the process). The detailed part 2 interventions and mode of delivery are available in Table 1.

2.4.2. Comparison group

Participants assigned to the comparison group will receive the follow-up questionnaires as the same manner as the intervention group. After filling out the running exposure and the RRI questionnaires, the comparison group will receive advice on a ‘safe’ (i.e., lower RRI risk) range of biweekly running exposure progression. The advice will be delivered every two weeks in relative measures, meaning that the crude running exposure advised may differ between the biweekly periods. This advice will be equal to the part 1 of the RunIn3 program delivered to the intervention group. However, no further information and/or intervention will be provided to the comparison group. We believe that providing feedback on running exposure progression could mimic the information that runners could find themselves in the Internet, establishing then a sort of ‘usual or standard information’ as a comparison group in this primary prevention study.

2.5. Randomisation and blinding

Runners will be invited to access the website of the project to gather further information about the study (http://runin3.com.br), including the eligibility criteria. After enrolment, participants will have access to a self-report screening questionnaire to confirm eligibility. Eligible runners will be directed to an online consent form for final inclusion. In case the participants do not match the eligibility criteria or do not consent, they will be directed to an acknowledgment webpage explaining why they could not participate. Included participants will receive a username and password in order to register in the RunIn3 website and at this moment the participant will be randomized. Simple randomization will be performed automatically with a programmed and automated online system embedded in the website ensuring the concealed allocation. The outcome assessment, the delivery of intervention and the data analysis of this study will be blinded, since the outcome assessment and the delivery of the intervention will be performed by an a priori programmed and automated online system with no human influence in these processes during the study, and the data analysis will be performed by a person who will possess only the dataset blinded to the groups identification.
2.6. Measurement/outcomes

2.6.1. Baseline questionnaire

After registration, the participants will receive an e-mail containing a link for the baseline questionnaire. This questionnaire is aimed at collecting personal data (age, sex, weight, height, occupation and level of education), running experience and history of RRI over the last 12 months (i.e., previous RRI). The questionnaire is available in Appendix A.

2.6.2. Follow-up questionnaires

The participants will receive an e-mail containing a link for the questionnaires embedded in the RunIn3 website when they become available. For each biweekly questionnaire, if no response is received within approximately 10 days, a reminder will be sent encouraging the participant to retroactive respond to the unanswered questionnaire. The outcome measures of follow-up questionnaires are detailed in Table 2.

2.6.3. Primary outcome

The primary outcome of this trial will be the proportion of runners reporting RRI. RRI’s will be assessed through the four key questions of the Brazilian version of the Oslo Sports Trauma Research Center Questionnaire on Health Problems (OSTRC-BR): (1) difficulty/discomfort in running during training and/or running events due to RRI; (2) reduced...
The participants can login in the RunIn3 website to access the contents. The economic evaluation questionnaire will be applied every six weeks from the 8th to the 50th week. The preventive behavior and implementation questionnaire will be applied at 5th, 15th, 27th, and 51st weeks from baseline. The economic evaluation questionnaire will be applied every six weeks from the 8th to the 50th week.

2.6.4. Secondary outcomes

The secondary outcomes will be preventive behavior (understanding the runner’s beliefs about RRI prevention and detecting changes in running behavior), implementation (adherence, appropriateness, penetration, adoption and fidelity), and health economics (implementation costs, healthcare utilization costs, patient/family costs, and lost productivity cost). The preventive behavior and implementation questionnaire will be applied at 5th, 15th, 27th, and 51st weeks from baseline. The economic evaluation questionnaire will be applied every six weeks from the 8th to the 50th week.

2.7. Study schedule/participant timeline

The contents will be available during the scheduled week of delivery. The participants can login in the RunIn3 website to access the contents. Nevertheless, an e-mail will be sent to the participants of the intervention group notifying that a new content was published in the website and providing the link to access the new content. After published in the website, the content will be available until the end of the study, meaning that the participants of the intervention group will have access to any published content at any time. The schedule for each content delivery and the application of the data collection questionnaires is presented in Table 3.

Firstly, the participants will receive the intervention every two weeks. As described earlier, the economic evaluation questionnaire will be applied every six weeks. During the 2-week period when the economic evaluation questionnaire is applied, the follow-up questionnaire will also be applied. Therefore, during the 2-week period when the participant receives the economic evaluation questionnaire, there will be no intervention content/material provided in order to minimize the possible burden of too many tasks to comply within the 2-week period. All contents will be delivered during the first six months of the program implementation. After this period, each content will be reinforced for the next six months, completing one year of program implementation. There is evidence suggesting that reinforcement may enhance the effectiveness of interventions [35,36].

| Table 1 | Detailed part 2 interventions. |
|---|---|
| Intervention | Mode of delivery |
| (1) Biweekly progression of running exposure: importance, translation of scientific evidence into practice and how to implement | text and infographic |
| (2) Importance of warm-up and stretching exercises and translation of scientific evidence into practice | text |
| (3) How to perform warming-up exercises | text and video |
| (4) Differentiation of symptoms: inflammation | text |
| (5) Differentiation of symptoms: delayed onset muscle soreness | text |
| (6) Foot strike patterns: rearfoot, midfoot and forefoot | text |
| (7) Running shoes: pronation, neutral, supination, maximalist, minimalist and conventional shoes | text |
| (8) Conditioning exercises: importance and translation of scientific evidence into practice | text |
| (9) How to perform conditioning exercises | text and video |

| Table 2 | Outcome measures. |
|---|---|
| Running-related injury (RRI) – Primary outcome |
| Running exposure | (1) Running frequency (total running sessions during the 2-week period) |
| | (2) Running distance (total kilometers run during the 2-week period) |
| | (3) Running duration (total minutes run during the 2-week period) |
| | (4) Running intensity (average perceived effort of running during the 2-week period) |
| | (5) Participation in running events (i.e., races) |
| | (6) Number of running events |
| | (7) Total time spent on running events during the 2-week period (minutes) |
| | (8) Total distance on running events during the 2-week period (kilometers) |
| | (7) Running intensity during running events (average perceived effort of running during running events in the 2-week period) |
| | The full questionnaire is available in Appendix B. |

Preventive behavior and implementation

The preventive behavior questions are based on the Integrated Behavior Model which is composed of five determinants: intention to perform the behavior; knowledge and skills to perform behavior; attitude; subjective norm; and perceived behavioral control. Intention reflects the motivational factors influencing the behavior [49-51], and it will be assessed by question 4. Knowledge and skills reflect the knowledge and skills necessary to perform the behavior. Even if there is a positive intention to behave for a specific behavior, it is still possible for an individual to lack the knowledge and skills necessary to perform that behavior. For example, a runner may have developed an intention to perform conditioning exercises but may not know exactly how to do this. Even if she does identify a mechanism or action to improve muscle conditioning, using elastic bands for example, she may not know how to do the exercise, especially which movements will be best for runners. This lack of knowledge and skills can prevent her from performing the behavior.

Knowledge and skills will be assessed by question 6 [44]. Attitude reflects the beliefs about the consequences of the behavior [49-51], and it will be assessed by questions 2 and 7. Subjective norm reflects the beliefs on what others think about the person’s behavior [49-51], and it will be assessed by question 10. Perceived behavioral control reflects the perceived ease or difficulty in performing the behavior [49-51], and it will be assessed by questions 5 and 6.

The implementation outcomes considered in the preventive behavior and implementation questionnaire are ‘adherence’ and ‘appropriateness’. Adherence is the extent to which a person ‘uptake’ the intervention considering a dynamic process influenced by the context [52], and it will be assessed by question 3. Appropriateness reflects the perceived fit, relevance or compatibility regarding the intervention [53], and it will be assessed by questions 8, 9 and 11. The content below and the full questionnaire is available in Appendix D.

Preventive behavior and implementation questionnaire

(1) What do you believe it can prevent RRI? [open question with no limits of characters]  
(2) 7-point Likert agreement scale from –3 (completely disagree) to +3 (completely agree) regarding the following statement: ‘Since I am participating in this study, I pay more attention/I am more aware of RRI prevention’  
(3) ‘What components of the program did you implement in the last weeks?’*  
(4) ‘What components of the program do you plan to implement in the next weeks’*  
(5) Likert scale from –3 (very difficult) to +3 (very easy) regarding the following question: ‘Do you believe it is easy or difficult to prevent RRI?’  
(6) Likert scale from –3 (very difficult) to +3 (very easy) regarding the following question: ‘How difficult is it to use the RRI prevention program?’  
(7) Likert scale from –3 (no, I don’t) to +3 (yes, I do) regarding the following question: ‘Do you believe the RRI prevention program is helping you to prevent RRI?’  
(8) ‘Which program components do you believe are helping you the most in preventing RRI?’*  
(9) ‘Which program components do you believe are helping you the least in preventing RRI?’*  
(10) Likert scale from –3 (not supportive at all) to +3 (very supportive) regarding the following question: ‘Do your family, friends, trainer/coach or running colleagues support you in using the RRI prevention program?’  
(11) ‘Which of the strategies to disseminate program information did you like/prefer the most?’ (multiple choice question with the following answer options: texts, infographics, videos, none, I did not receive any information material)”
clinically relevant [38]. Therefore, we hypothesized an average effect as a result of a prevention program is considered to be realistic and time used in the...have reported RRI proportions of about 30% [9,11]. There...prospective cohort studies with biweekly repeated measurements...controlled trials with a repeated measurement longitudinal design [37,38].

### 2.8. Sample size

The sample size was estimated based on calculations for randomized controlled trials with a repeated measurement longitudinal design [37,38]. Previous prospective cohort studies with biweekly repeated measurements have reported RRI proportions of about 30% [9,11]. Therefore, the reference value for the mean proportion of RRI measured over time used in the a priori sample size calculation was 30%. A preventative effect representing an overall sports injuries risk reduction of about 25% as a result of a prevention program is considered to be realistic and clinically relevant [39]. Therefore, we hypothesized an average effect size of about 25% risk reduction; that is, the hypothesized mean proportion of RRI in the intervention group would be 22.5%. Considering an \( \alpha = 0.05, \beta = 0.20, 26 \) repeated measurements (every two weeks over one year), a within-person correlation coefficient of 0.3 [9,10] and a lost to follow up of 50% (according to our experience, a 1-year follow-up in primary prevention trials may result in a significant decline in the response rate), a sample size of 265 participants was suggested for each group, resulting in a total of at least 530 individuals to be included in the study.

### 2.9. Statistical analysis

Descriptive analyses will be performed for baseline data. Distributions will be evaluated by histogram inspection. Follow-up data will be summarized using mixed models in order to account for repeated measurements. Linear mixed models will be performed for continuous variables. Linear probability mixed models will be used for dichotomous or categorical data using dummy variables. In the descriptive analysis, the RRI rate will be estimated by taking the number of new RRI reported during the 1-year follow-up divided by the total person-time running exposure measured in hours, and it will be reported as RRI per 1000 h of running exposure [40]. The uncertainty around all estimates will be expressed as 95% confidence intervals, unless otherwise specified. All analysis will be performed in R [41] and will follow the intention-to-treat principles.

The analysis of the primary outcome will be performed by linear probability mixed models. The preventive behavior will be analyzed by a qualitative method for opened question and linear mixed models for change behavior outcomes. The implementation outcomes will be analyzed partly by linear probability mixed models and partly by a descriptive analysis, depending on when repeated measurements were...
applied. Finally, the main outcome of the economic evaluation analysis will be measured by the incremental cost-effectiveness ratio (ICER). The full statistical analysis plan can be found in Table 4.

### 3. Discussion

Through the advancement of technology, online strategies have been widely explored in healthcare [42, 43]. Online strategies may also assist in the implementation of sports injury prevention programs [29]. For example, the TrailS6 online RRI prevention program was effective in preventing RRI, reducing about 13% of RRI risk in six months [29]. However, the TrailS6 RRI prevention program was investigated only in trail runners, which make it difficult to generalize for runners in general [29]. Moreover, the INSPIRE trial has shown that an online intervention delivered at baseline had no preventive effect on RRI in recreational runners (risk difference of 0.8; 95% CI -3.1 to 4.6) [34]. This scenario raised the following question: 'are online educational/advice programs aimed at preventing RRI really effective in general?'. We believe that answering this research question would be of great value for public health, for the sports injury prevention community and for the runners themselves. Therefore, we have developed and proposed the RunIn3 trial in order to add scientific evidence to this topic and to help answering the abovementioned research question.

The RunIn3 RRI prevention program was developed following the Intervention Mapping (IM) framework [27]. The program is based on behavioral and social science theories aimed at changing health behavior. The theory used in this study was the Integrated Behavior Model [44]. Therefore, we believe that the RunIn3 program may be effective in reducing the risk of RRI and in promoting preventive behavior, either by increasing the frequency of healthy behaviors or by reducing the frequency of risk behaviors. The hypothesis regarding the RunIn3 effectiveness on reducing the RRI risk is supported by the TrailS6 study, that has shown a mean preventive effect of 13.1% in trail runners [29]. We believe that increase in RRI prevention knowledge may reduce the expenses related to healthcare utilization resources to acquire RRI preventive information as foot strike pattern or running shoes. Finally, if the RunIn3 program is effective in reducing the risk of RRI, we believe that this effect would go alongside with a reduction in the expenses regarding the utilization of healthcare resources and even work absenteeism, leading to reductions in societal costs.

The design of this study precludes the blinding of participants due to the nature of the interventions, which can be considered a limitation of this study since it can increase the risk of performance bias [45]. The RunIn3 RRI prevention program will have no therapist to deliver the intervention. Since the delivery of the intervention will be blinded, one could consider that therapists would also be blinded. However, we suggest that the ‘blind therapist’ characteristic assessed by some risk of bias tools should not be applicable to this study. Another limitation regarding the online characteristic of the design of this study is that it will only be possible to recruit runners who have access to the Internet. Although a relevant limitation, we believe that most runners who live in the state of Sao Paulo, Brazil, have access to the Internet.

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### Contributors

LH was involved in the conceptualization of the study. PMB, CSV, GMO, GCM and LH were involved in designing and conducting the study. PMB, CSV, GMO, GCM and LH were involved in the drafting and revision of the manuscript for intellectual content and all approved the final version of the article.

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**Table 4**: Statistical analysis plan.

| Primary outcome | Secondary outcomes |
|-----------------|-------------------|
| Preventive behavior | **Preventive behavior** |
| For question 1 answers of the preventive behavior questionnaire, the data processing will be performed in two steps: (1) two researchers will independently categorize the terms written by the participants into codes; and (2) two researchers will have a discussion to categorize the codes. In case of disagreements, a third researcher will adjudicate and suggest a consensus. The R Qualitative Data Analysis (RQDA) package will be used to assist in the transcriptions, coding and categorization performed in the qualitative analysis [37]. Afterward, a descriptive quantitative analysis will be performed in order to summarize the codes and categories. To understand which behavioral change strategies the participants will adopt, we developed questions based on the Integrated Behavior Model [44]. The Integrated Behavior Model has a proximal component: intention to perform the preventive behavior that will be analyzed using linear probability mixed models with dummy variables created for each category of the RunIn3 that the runners intend to perform in the next two weeks (question 4 of the preventive behavior and implementation questionnaire); and distal components: knowledge and skills (question 6), attitude (questions 2 and 7), subjective norm (question 10) and perceived behavioral control (questions 5 and 6) that will be analyzed using linear mixed models. Time and the interaction term composed of group and time will be included as independent variables in the fixed effects part of the model. The results of the linear probability mixed models will be presented as absolute probability difference (APD) between groups and the 95% CI. The results of the linear mixed models will be presented as mean difference between groups and the 95% CI. |
| Implementation outcomes | Besides appropriateness and adherence assessed by the 'preventive behavior and implementation' questionnaire, penetration, adoption, fidelity and implementation costs will also be analyzed [31]. Appropriateness and adherence to each RunIn3 component will be analyzed using linear probability mixed models using dummy variables yielded from answers to questions 3 (adherence), 8, 9 and 11 (appropriateness). Time and the interaction term composed of group and time will be included as independent variables in the fixed effects part of the model in order to adjust the estimates for the baseline measurements. A study ‘id’ variable composed of a unique value identifying each participant will be included in the random effects part of the model. The results will be presented as APD between groups and the 95% CI. |

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Penetration will be estimated taking the number of total users who accessed the RunIn3 website by the number of users who accessed the registration webpage (i.e., those who were interested in participating in the study). The number of users will be estimated by the number of different Client-ID addresses that accessed the RunIn3 website given by Google Analytics. Adoption will be estimated taking the number of runners from the intervention group presenting an adherence rate ≥ the average adherence rate divided by the number of runners in the intervention group. Fidelity will be analyzed taking the number of components that were implemented as intended by the number of total RunIn3 components. The results will be presented as relative frequencies reported as percentages and the 95% CI.

Implementation costs will be analyzed taking all costs related to the implementation of the RunIn3 RRI prevention program. Since costs are considered right skewed data, we will analyze the implementation costs by bootstrapping the data with 10, 000 replications as recommended for economic evaluations [38]. The results will be presented as the mean of the observed data and the bias-corrected and accelerated 95% CI obtained by the bootstrap samples. Moreover, we will also analyze the implementation costs using a Bayesian approach with noninformative priors, because we believe that a Bayesian sampling distribution using Markov chain Monte Carlo sampling might perform better than bootstrapping [59]. The results will be summarized based on sampling from the posterior distributions using five chains with 20,000 interactions after disregarding the initial 5,000 interactions of each chain. The results will be presented as mean, median, and the 95% CrI.

Cost-effectiveness analysis

The cost-effectiveness analysis will be performed from a societal perspective. Therefore, the total societal cost (i.e. healthcare utilization, patient/family care, lost productivity and implementation costs) will be considered. The main outcome of the economic evaluation analysis will be the incremental cost-effectiveness ratio (ICER), taking the between-group difference in total societal cost divided by the between-group difference in RRI proportion (ARR). Missing data in costs will be handled by generating 10 datasets with imputed data using the Multiple Imputation by Chained Equations (MICE) procedure. The imputation model will include age, sex, body mass index, level of education, running experience, previous RRI, running exposure data, the available costs data and all available effect measure values. The results of the 10 imputed datasets will be pooled following the Rubin’s rule [60, 61]. The uncertainty around the between-group difference in costs and the ICER will be estimated by bias-corrected and accelerated bootstrapping with 10,000 replications and will be presented as the proportion of the replicated ICERs in each cost-effectiveness plane quadrant. A cost-effectiveness acceptability curve will be performed in order to provide information on the probability of the RunIn3 prevention program in being cost-effective compared to the comparison group for different willingness-to-pay threshold values [62]. Sensitivity analyses will be performed to investigate the robustness of the cost-effectiveness analysis. Firstly, the analyses will be performed considering only the maintenance costs (i.e., domain and server annual costs) of the implementation structure, excluding costs related to the creation of the RunIn3 website. The costs related to the creation of the website will be excluded in this sensitivity analysis because this is a 1-time payment of a high monetary value that has an enormous impact in a 1-year time horizon, but in, let’s say, five years it would be substantially mitigated or even negligible. Secondly, the analyses will be performed considering only those runners who present an adherence rate ≥ the average adherence rate within the RunIn3 prevention program. Thirdly, complete-case analyses will be performed excluding participants with missing data for costs and effects in order to investigate the influence of missing data and/or the imputations in the analyses. Finally, the cost-effectiveness analyses will be performed considering a Bayesian approach with noninformative priors. There is evidence suggesting that a Bayesian sampling distribution using Markov chain Monte Carlo sampling might perform better than bootstrapping [59]. The results will be summarized based on sampling from the posterior distributions using five chains with 20,000 interactions after disregarding the initial 5,000 interactions of each chain. The 100,000 interactions (i.e., 20,000x5) will be used to estimate the ICER posterior distribution, which will be summarized based on sampling from the posterior distributions using five chains with 20,000 interactions after disregarding the initial 5,000 interactions of each chain. The results will be presented as mean, median, and the 95% CrI.

Ethical approval

This study was approved by the Research Ethics Committee of the Universidade Cidade de São Paulo (UNICID), CAAE: 97841318.3.0000.0064.

Transparency

The authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted. Any discrepancies from the study as planned have been explained.

Declaration of competing interest

The authors declare that they have no competing interest of any nature.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2021.100726.

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