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Review

OARSI Clinical Trials Recommendations: Design and conduct of clinical trials for primary prevention of osteoarthritis by joint injury prevention in sport and recreation

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SUMMARY

The risk of post-traumatic osteoarthritis (PTOA) substantially increases following joint injury. Research efforts should focus on investigating the efficacy of preventative strategies in high quality randomized controlled trials (RCT). The objective of these OARSI RCT recommendations is to inform the design, conduct and analytical approaches to RCTs evaluating the preventative effect of joint injury prevention strategies.

Recommendations regarding the design, conduct, and reporting of RCTs evaluating injury prevention interventions were established based on the consensus of nine researchers internationally with expertise in epidemiology, injury prevention and/or osteoarthritis (OA). Input and resultant consensus was established through teleconference, face to face and email correspondence over a 1 year period.

Recommendations for injury prevention RCTs include context specific considerations regarding the research question, research design, study participants, randomization, baseline characteristics, intervention, outcome measurement, analysis, implementation, cost evaluation, reporting and future considerations including the impact on development of PTOA.

Methodological recommendations for injury prevention RCTs are critical to informing evidence-based practice and policy decisions in health care, public health and the community. Recommendations regarding the interpretation and conduct of injury prevention RCTs will inform the highest level of evidence in the field. These recommendations will facilitate between study comparisons to inform best practice in injury prevention that will have the greatest public health impact.

Introduction

Osteoarthritis (OA) is a leading cause of severe chronic pain and disability worldwide resulting in a significant public health impact, the knee joint contributing to over 80% of this burden[1–5]. The burden of OA is well established and expected to grow, with projections estimating that OA currently affecting one in eight will affect one in four individuals in Canada for example, by 2040[5]. By

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2040, the associated economic burden is projected to rise 6-fold from close to $200 billion in 2015[5]. Current pharmacological, non-pharmacological and surgical management of OA alleviates symptoms but does not prevent disease progression. Although the cause of OA is complex, it is thought to result from the interaction between multiple risk factors, including joint injury and obesity[6–9]. In order to reduce the economic and personal burden of OA, it is essential that research efforts focus on understanding these modifiable risk factors and on investigating the efficacy of preventative strategies in high quality randomized controlled trials (RCT).

Among youth, participation in sport is the leading cause of injury requiring medical attention[10,11]. Knee and ankle injuries account for 35–40% of all injuries sustained through participation in youth sport and recreation and consistent findings are found in adults[10,11]. These injuries are associated with an increased risk of PTOA[12,13]. A meta-analysis examining the risk of knee OA following knee injury provides evidence of a 4-fold increased risk of developing PTOA 12–20 years after a knee injury, compared to the uninjured population[12]. In addition, a meta-analysis examining the risk of hip OA following hip injury, suggests a 5-fold increased risk of developing PTOA compared to the uninjured population in a similar time frame[12]. It is estimated that more than 50% of individuals with an anterior cruciate ligament (ACL) tear or meniscus injury may go on to develop knee OA after 10–15 years[6,13]. Further, joint injury has been shown to have physical, emotional, and economic impacts on individuals[14].

The innumerable benefits of physical activity, including participation in sport and recreational activities, to overall physical and mental health have been abundantly researched and documented[15]. Physical activity is essential for normal muscle and joint health, and may be protective against obesity and OA[16]. In North America, rates of adolescent inactivity and obesity are on the rise and there is evidence that after sustaining an injury, young athletes stop participating in sport[17,18]. Systematic review evidence confirms that there is a significant increased risk of OA in overweight and obese individuals[12]. The significant consequences of injury in the contribution to PTOA inform the need for rigorous evaluation of primary injury prevention strategies to reduce the risk of injury, subsequent overweight/obesity and PTOA.

These OARSI RCT recommendations aim to inform the design, conduct and analytical approaches to RCTs evaluating the preventative effect of joint injury primary prevention. Specific attention is directed to the unique consideration in RCTs evaluating injury prevention strategies that are designed to reduce the risk of joint injury in sport and recreation where the burden of joint injury is significant. Changes in clinical and preventive practice need to be governed by evidence. Evidence from RCTs is considered to be strong, but meta-analyses combining data from multiple RCTs to optimally demonstrate size of the effect are vital as this is considered the highest level of evidence. Consistent methodology across RCTs is needed to make meta-analyses feasible. Sport and recreational injury prevention is an area where there has only been a relatively recent history of RCTs. As such, there are few meta-analyses of measures to prevent joint injury. An international focus on RCTs and subsequent meta-analyses in sport-related joint injury prevention, given the strong link to PTOA, are essential. This improved evidence-base could assist to inform health care practitioners, sport and health administrators, legislators, athletes, coaches, parents, and the public to make evidence-informed decisions regarding the prevention of joint injury in the broad communities in which we promote physical activity through sport and recreation.

In order to recommend optimal design, conduct and analyses related to joint injury prevention RCTs, this paper adopts a structured approach with sub-sections that each address the following elements: research question, research design, participant recruitment, randomization, baseline characteristics, intervention, outcome measurement, consideration for analysis, implementation, economic evaluation, RCT reporting, and future directions. These guidelines are not intended to replace RCT reporting guidelines, such as the CONSORT statement. Rather, they provide additional guidance specifically for RCTs related to joint injury prevention to supplement the broader principles identified through the CONSORT statement.

The injury prevention RCT working group identified to contribute to these recommendations with the support of an OARSI steering committee establishing “Recommendations for the Conduct of Randomized Clinical Trials in Osteoarthritis”. International experts in the field were asked to contribute in the development of these injury prevention RCT recommendations based on a breadth of interdisciplinary research and clinical expertise with representation internationally. The working group members contributed to the literature reviewed, consensus discussion regarding section content and final approval of the manuscript.

Specifying the research question

Clear and concise identification of the problem to be addressed and specification of the related research question are important. The initial purpose statement may be broad. In the context of injury prevention to prevent PTOA, the purpose statement will identify the number of joint injuries to be avoided in a particular population and over a specific timeframe. In developing any research question, identifying the Population, Intervention, Comparison, Outcomes of interest and Time or duration of study (PICOT) as defined by Guyatt *et al.* (2008) is important[19]. For example, the public health burden of anterior cruciate ligament knee injuries in female youth athletes is significant and higher than in other subgroups[20]. In identifying a gap in knowledge in the literature, a primary research question and associated approach to the optimal RCT design can be determined. Examples of primary research questions including the PICOT elements may include: “What is the efficacy of a team-based neuromuscular training program in reducing lower extremity injury rates in female youth soccer players compared to a standard of practice warm-up over one season of play?” and “What is the effectiveness of an individually targeted neuromuscular training program in high risk youth sport participants with a history of previous knee injury compared to a standard return-to-play program across two seasons of play?” Verhagen *et al.*[21] and Emery *et al.*[22] provide examples of similar research questions which allow for economic evaluation alongside the evaluation of an injury prevention program in volleyball and youth basketball players, respectively. Emery *et al.*[23,24] also provide examples of questions relating to the examination of the dose response effect of a balance training program in improving dynamic balance ability in high school physical education and soccer participants.

Secondary research questions can also be posed to align with the primary question such as “What is the cost-effectiveness of a team based neuromuscular training program in female youth soccer players?” and “Is there a dose–response effect based on reported adherence to a team based neuromuscular training program in female youth soccer players?” Measuring and evaluating the effect of adherence in RCTs evaluating the preventative effect of interventions in primary and secondary injury prevention in sport is critical to informing the implementation context of such interventions[25–27].

The public health impact of the intervention being evaluated should be considered when determining the appropriate research question in primary injury prevention. An RCT in primary joint

injury prevention should significantly demonstrate: 1) reduction of sport injury frequency and rates; and 2) the potential to inform policy and/or practice in the public health context. For a research question to be answered in a primary prevention RCT, the intervention and control groups, the intended intervention and primary and secondary outcome(s) (dependent variables) must be operationally defined and precisely measurable.

In RCTs for sport injury prevention, the outcome "sport injury" requires a clear definition concisely operationalized. The use of sport-specific injury definitions based on available consensus agreements may facilitate comparisons between studies. Examples of consensus statements for sports injury definitions have been developed for a number of sports such as rugby, soccer and athletics[28–30]. For example, soccer specific recommendations are made regarding how the incidence of match and training injuries should be reported, including a checklist of issues and information that should be included in published reports of soccer studies of football[29]. The ability to identify the impact of reduced injury rates on the development of post-traumatic osteoarthritis (PTOA) will be more challenging and will require an additional longitudinal design approach for longer term outcomes.

The intervention group and the comparison/control group also require clear operationalization. Description of different trial groups needs to include details related to both the intervention and control components and delivery mechanisms. In the case of an exercise intervention, details should also include the specific aims of the program, duration of program, length of session, intensity, progression levels and number of repetitions of each component[21–24,31]. In addition to a primary outcome such as the preventative effect in reducing the risk of injury, an exercise training program could also have secondary outcomes. For example, secondary outcomes may aim to improve sport performance in an athletic population (e.g., win/loss/tie record, balance, agility, alignment, aerobic capacity and/or muscle strength).

The feasibility of addressing a research question using an RCT design may relate to participant recruitment, community engagement (coaches, administrators, parents, players), expertise of individuals delivering the intervention, timelines, available funds, previous evidence, and ethical considerations. The relevance of distinguishing between an efficacy and effectiveness trial is essential when defining the research question. Efficacy refers to the benefit of an intervention under controlled and ideally randomized conditions whereas effectiveness refers to the benefit of an intervention under "real world" conditions and considers the implementation context[25,32]. One must always of course consider the feasibility of delivery of clinical or community interventions beyond the context of the conditions and personnel available for a highly controlled RCT. Research questions informing the implementation context are critical identifying barriers and facilitators of uptake, adherence and maintenance[33]. There are several examples of mixed methods approaches which include a qualitative component to inform such barriers and facilitators[31,34–36]. For example, alongside an RCT, Finch *et al.*[31] provide valuable feedback from players about the content and focus of exercise-training programs in youth Australian Rules Football that will directly inform the delivery of similar, or more successful, programs in the future.

Research design

For primary or secondary injury prevention, as in other fields, the purpose of randomization in an RCT is to produce comparable groups with respect to known and unknown risk factors[37]. In a two-armed RCT, participants are typically randomly assigned to an intervention (treatment) or comparison (control) groups. Well-conducted RCTs, with true randomization, allocation concealment, and blinding when possible, will have the greatest influence on both practice and policy in health care[37]. Examples of this in primary sport injury prevention include the establishment of best practice neuromuscular training interventions recommended in youth sport such as soccer and European team handball[24,26,44,45]. Other RCT designs used in primary prevention can include three-armed trials (i.e., typically one control group and two different intervention groups). Examples of this may include RCTs evaluating different intervention delivery mechanisms, with a focus on implementation context[24,33,39].

Another possible trial design for primary joint injury prevention is a factorial design where one or more additional independent variables are considered and participants are randomly assigned to different combinations and/or levels of the interventions. An example of this was a cluster-RCT examining the effectiveness of mouth guard use in Australian Football where, in addition to a "usual practice" control arm, the mouth guard type was considered (e.g., custom vs standard)[40]. A cluster RCT will be the ideal design if an intervention is delivered at a group (cluster) level such as a team. This design, however, can be associated with statistical inefficiencies that will be discussed in the considerations for analysis section.

A crossover design in which participants first receive one intervention and then crossover to the other intervention after a washout period may also be considered in a primary joint injury prevention RCT. A crossover design can control for potential influences of individual differences on inherent injury risk, however, there may also be several disadvantages. These include the potential for carry over effects from the first intervention to the second and temporal effects (e.g., learning and physiological responses to exercise) that could influence the outcome over time[41]. Unlike conventional RCTs, for example those aimed at the treatment of OA symptoms, the primary outcome of interest in an injury prevention trial is a traumatic and irreversible event (e.g., knee injury). As such, crossover designs may be difficult and may not adequately evaluate the effectiveness of an intervention based on the inherent methodological limitations. The irreversibility of control group injuries may also present an ethical dilemma for those who believe that those injuries could have been prevented by the intervention being studied.

The perceived benefit of injury prevention programs may be an impediment to the recruitment of RCT participants, due to reluctance on the part of sport participants, parents, and/or coaches to be included in a control group which does not participate in the injury prevention program. This concern can be addressed in comparing an injury prevention intervention to the usual standard of practice[22,26,40–43]. If the results of such an RCT inform the preventative effect of an intervention, this intervention can then be subsequently offered to the control group.

Study participants

Assessment of the generalizability of the results of injury prevention RCTs to a broader target population relies on appropriate reporting of inclusion and exclusion criteria for the sampling frame, the availability of potential study participants that meet those criteria, and the sampling methodology. Probability sampling ensures a process of random selection of study participants. Simple random sampling methods may be used in which every individual has an equal probability of selection[37]. Computer generated randomization is often used to generate a random list of individual participants based on unique study identification numbers. Stratified random sampling can also be employed in order to recruit a sample that reflects a similar distribution of study participants on

factors that may be differentially distributed in the population (e.g., sex, level of play)[22,24]. The number of strata should be small and there will likely be heterogeneity on other covariables within each strata (e.g., functional movement patterns, previous injury history). Cluster sampling will often require consideration in primary prevention RCTs if individuals are sampled because of their membership in specific groups (i.e., teams, families, schools)[37]. The number of clusters is ideally large and homogeneity within clusters requires assessment. There are significant methodological implications of clustering to consider in the study design and analysis including the need for an increased sample size to ensure similar power to a study randomizing individuals[46]. Clustering may also reduce the power to examine specific injury outcomes (e.g., ACL, ankle, severe injury) which will be less frequent than overall injury outcomes, especially if the study duration is short (e.g., over one season of play).

A random sample is highly desirable and the first preference. There are several examples of injury prevention RCTs where a random selection of individuals or teams is reported across sports such as youth basketball, soccer and school sport[22–24,26]. It is not always possible, however, to obtain a random sample and, as such, non-probability sampling is often used. An example of non-probability sampling in injury prevention would be convenience sampling (e.g., recruitment through posters, social media, and websites). Notably, volunteers may significantly differ on the outcome of interest from individuals not choosing to volunteer and thus may not be representative of the target population[37]. Other potential recruitment methodologies include consecutive sampling (e.g., recruiting consecutive patients attending a clinic) and snowball sampling (e.g., sampling through identification of additional participants through participants already recruited). In the case of non-probability sampling, one cannot assume that the sample will be representative of the target population and thus the study results cannot be generalized. The possibility of non-participation in sport injury prevention RCTs is evident in some sport populations and the reason for non-participation should be considered in evaluating the representativeness of the sample[47]. Notwithstanding the sampling approach, characteristics of RCT participants and non-participants should be described and compared, to highlight where there may be any systematic biases.

The a-priori sample size estimate informing participant recruitment for any injury prevention RCT should have adequate power to detect a desired and clinically relevant effect size. The sample size is typically based on desired effect sizes for the primary, and sometimes secondary, research questions and outcomes of interest as well as prior knowledge of the study population. The sample size estimation should consider *P*-value corrections (e.g., Bonferroni's) if the RCT is confirmatory and interim analyses are planned. There are multiple resources available to inform appropriate sample size estimation[37,46,48–50]. Sample size considerations must include outcome variable type (e.g., multiple injuries, proportion, time to injury), clinically relevant effect size, level of error (Type I and II) tolerable, as well as other methodological details (e.g., paired data, cluster, repeated measures, multiple comparisons, non-adherence, expected drop-outs and consideration of multiple co-variables in analysis).

Randomization

Random allocation of study participants is aimed at producing study groups that are comparable with respect to known and unknown risk factors. However, validating such assumptions for statistical analyses is critical[37]. There is the possibility of bias if the randomization procedure does not produce balance on baseline risk factor profiles across trial groups. Restricting the sample on a potentially relevant confounding variable (e.g., sex, age) will ensure that there is no imbalance on this variable, but will also minimize the generalizability of study results beyond the homogeneous group being studied. For example, studies examining the protective effect of an ACL prevention strategy often restrict recruitment to female athletes given the significantly greater risk of ACL injury in females[51]. Stratified random sampling can also be used to increase the probability of study group equivalency on the variables upon which the sampling is stratified (e.g., sex, level of play), however limiting the ability to analyze that co-variable as an independent risk factor[22,26]. Block randomization or matching can be considered to ensure equal study group size and enhance the possibility of equivalency between study groups on known confounders[37]. An important limitation of matching is that it removes the possibility of examining differential effects based on the matching variable. Cluster randomization can be considered if individuals enter a study in the context of a group (e.g., team, clinic, family, school, or classroom). In this case, the entire group is the unit of randomization and the study intervention is allocated by that group (e.g., team).

In justifying a cluster-RCT, the lack of statistical efficiency relative to an individual design including the same number of participants must be considered[46]. A cluster design may be considered to reduce the risk of contamination between study groups. For example, contamination could arise if individual-level randomization is used when individuals belong to the one group but are then randomized to different conditions. When this occurs, there is potential for their behaviors to be influenced by those allocated to other conditions and not just to the specific condition they were allocated to. If the rate of contamination is expected to be large (e.g., in the context of a team training program), then individual randomization may not be efficient. In other cases, the rate of contamination could be considerably smaller (e.g., in a trial of ankle brace prescription) and individual randomization might be considered feasible. Efficiency of implementation at a group-level (e.g., when a training program is to be delivered by coaches to all members of a team) and enhancement of adherence to an intervention through team participation should be considered in considering a cluster-RCT design. The loss of efficiency in a cluster RCT arises because the variability in outcomes in individuals within a cluster is much smaller than those across different clusters (e.g., members of a given team are more likely to be similar to each other than they would be to members from a completely different team)[46]. Moreover, the actions and responses in relation to the required condition of individuals within a cluster are usually related because of group influences that lead to decreased statistical power. Greater similarities within a cluster can also arise if participants select the cluster to which they belong (e.g., selection of sport team may be related to socio-economic status or socio-cultural context). This can introduce additional bias, especially if such selection occurs after groups have been randomized to RCT conditions. In addition, other important covariates and effect modifiers are likely to be similar within a cluster (e.g., sport facility, coaching) and ongoing interaction between participants within a cluster may lead to similarities in outcomes.

Cluster randomization is favored when cluster sizes are small and contamination is expected to be large[46]. When clusters are large ($n > 100$), individual randomization is more efficient unless contamination between study group programs is expected to be so severe that it is not a practical alternative[46]. Outcomes among participants from smaller clusters (e.g., teams) also tend to be more similar than outcomes among participants from larger clusters (e.g., schools) leading to greater efficiency in randomizing by smaller rather than larger clusters. Multiple levels of clustering may also have to be considered (e.g., classrooms and schools). In determining

the unit of randomization, one must consider statistical power, the need for independence in outcomes between different units of randomization, the need to avoid contamination, administrative and financial feasibility, the method of delivery of the intervention, and the anticipated effect of the intervention.

Randomization sequence generation should be completed by an individual, often a biostatistician, external to the study team to ensure removal of investigator bias and to ensure blinding of treatment allocation. Allocation concealment (i.e., method used to implement random allocation in which the sequence is concealed at recruitment and until the intervention is assigned) is also important to minimize potential recruitment bias[52]. Selection bias associated with participant drop-out, particularly if the reasons for drop-out are related to the study outcome and/or drop-out rates are differential between study groups, requires consideration. As such, reasons for drop-out should be recorded for interpretation.

Baseline characteristics

Baseline characteristics of participants require measurement to both allow for evaluation of baseline comparability of study groups before the commencement of the intervention, and to assess any changes from baseline. In sport injury prevention RCTs, these may include potential risk factors or prognostic factors (e.g., age, sex, physiological maturity, previous injury history, level of play, physiological measures, socioeconomic status). Comparisons at baseline should be based on consideration of the prognostic strength of the variables measured and the size of any chance imbalances that have occurred[52]. Baseline imbalances may be avoided by stratification at the time of randomization or controlled for in the analysis[37,52].

Meeuwisse *et al.*[53] developed a model for research in injury prevention in sport which highlights the recursive and dynamic nature of risk and etiology of injury (Fig. 1).

This model highlights that risk factors for injury can change over time through repeated exposure to sport, whether such exposure produces adaptation, mal-adaptation, injury or complete/incomplete recovery from injury. As such, a linear approach to the analysis of risk factors may not be appropriate, particularly if risk factors are not stable over time. In an adolescent population, it may be that a change in a baseline co-variable over the study period may be the risk factor of interest (e.g., skeletal maturity, menses). Given the restriction of injury prevention RCTs conducted over one season of play only, to date there are no examples considering change in baseline covariables, with the exception of injury occurrence during a season[24,26]. The RCT design should ideally include intermittent longitudinal measurements if baseline covariates are expected to change over time (e.g., every 6 months). In addition, analysis strategies must be selected that will allow for the inclusion of time-dependent covariates (e.g., generalized estimating equations or generalized linear mixed models).

Intervention

Many of the interventions evaluated in sport-related joint injury prevention RCTs are exercise interventions. In contrast, rule, equipment and policy change interventions are often evaluated using alternative observational or quasi-experimental designs that are subject to selection bias, although there are some exceptions[40,42,43]. The intervention of interest requires clear delineation of the details related to the intervention (e.g., components of an exercise intervention) including motivational components (e.g., educational sessions, campaigns, performance enhancement, verbal feedback), mechanism of delivery, length and timeframe of a program (e.g., frequency, intensity and duration of components), and definition of adherence (also referred to in the literature as compliance). Clear delineation of details of the intervention is a pre-requisite for future informative meta-analyses. The comparison group may be a true control if this is deemed ethical in the context of current standard of practice, or may be an alternate intervention based on the current standard of practice[40]. In the case of a true control group, interpretation of study results can be limited as differences found between groups may not be attributed to the components of the intervention alone, but can be attributed to time and/or interaction with study team in the intervention group (e.g., Hawthorne effect)[37]. Contamination will be introduced if participants are aware of the intervention details of the other study group and blinding participants to these details may be warranted[20,54]. An alternative is to ensure the control intervention mimics the study intervention with respect to delivery, length and timeframe, and differs only on specific components under study[22,24,26]. In multiple component intervention RCTs (e.g., orthotics plus exercise, balance training plus other agility training), interpretation of the results

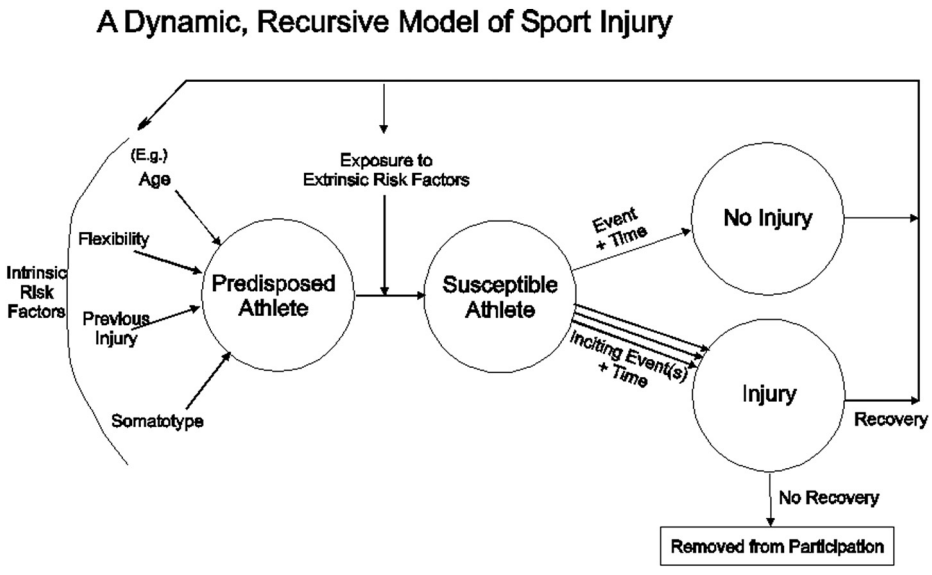

Fig. 1. A dynamic model of etiology in sport injury (reproduced with permission)[53].

must consider the interaction of the multiple components. This design allows for determining individual and joint effects, for example if an educational part added to the exercise intervention, is more effective than exercise alone.

Evaluation of adherence to a study intervention is important when considering dose–response based on quantity of intervention performed or adhered to. Adherence is commonly self-reported by study participants or coaches, however, evaluation by study personnel through intermittent observation or through measurement of a secondary variable is ideal (e.g., measurement of balance ability in a balance training injury prevention strategy; random observations of player behaviors)[22–24,44]. Attendance at a certain number of sessions is not necessarily the best measure of adherence since the effort made during the sessions may vary widely between individuals. Additional confirmatory detail of intervention adherence can be captured with an observational component evaluating individual participation performance (quantity and quality) and/or an objective evaluation of improvement from the intervention (e.g., improvement in time to complete an agility task, improvement in correct number of landings after a jump).

Outcome measurement

RCT outcome definitions require clarity and detail to facilitate interpretation of study results and comparisons with other studies. Potential sources of measurement bias should be considered in the measurement planning stages of any RCT in injury prevention. Blinding evaluators to study group allocation is ideal to minimize bias associated with measurement of outcomes, but this may not always be possible (e.g., use of a brace). The reliability and validity of all outcome measures requires consideration. If a measurement is unreliable, then study groups may be more similar on the outcome measure of interest and treatment effect may be biased towards the mean[26]. To minimize measurement bias, it is important to calibrate all study instruments as well as establish intra-rater and inter-rater reliability in the case of multiple raters which is often the case in a large community RCT study. In sport injury prevention RCTs, the outcome is typically number of injuries or injury rate (e.g., number of injuries/1000 exposure hours). Consensus statements on definition of injury developed in this field facilitate the comparisons between studies[28,29]. In sport injury prevention research, valid injury surveillance methodology has been established in numerous sport settings and should be inclusive of baseline data on individual baseline characteristics (e.g., medical history, performance measurements), injury outcomes, and exposure data (e.g., training and competition participation hours)[55]. These injury data collection methods require adaptation for use and validation in specific populations and contexts (i.e., youth, school, sport-specific) where the feasibility and validity may differ from the population in which the injury surveillance methodology was originally developed and validated[56]. Lack of completeness in collection of all data points is a common limitation in community–based RCTs (elite and recreational sport populations). Minimizing missing data is reliant on the surveillance support available and may include self-report (e.g., via email, web-based entry, SMS), trained personnel or volunteers, and/or medically trained personnel (e.g., physiotherapist or physician). If there is missing data, appropriate methods of imputation are possible[57]. In examining joint injury outcomes relevant to PTOA (e.g., meniscus, ACL injury), injury assessment by a trained medical professional is ideal, if feasible. Consideration of the relevant injury definitions (e.g., acute injury, chronic injury, specific diagnosis, subsequent injury) will inform the injury surveillance methodology used. Novel data collection methodologies could include online or SMS technologies to facilitate the collection of some injury data (e.g., pain) that may not be ideally captured through standard reporting methods[58].

In injury prevention RCTs, a defined injury measurement is typically the a-priori primary outcome of interest upon which an RCT is powered. The study injury definitions should include reporting definition (e.g., inclusive of all injury data captured) and analysis definitions (e.g., sub-categories which may be more specific to primary or secondary research questions such as lower extremity injury, time loss injury or injury requiring medical attention). Injury outcome definitions may also consider multiple independent injury outcomes, time to injury, specific diagnoses, severity of injury (e.g., time loss), re-injury, and/or subsequent injury[59,60]. In particular, specific injury definitions, including subsequent injury, will have an effect on the study results and interpretation[61]. Secondary outcomes of interest may also be considered (e.g., performance, adherence). An example of an RCT evaluating the 11+ (soccer-specific neuromuscular training program) in youth soccer demonstrated greater improvement in functional performance and reduced injury risk in players who demonstrated greater adherence to the program[24]. If a secondary outcome of interest is measured at baseline and follow-up, the change in this variable (i.e., visual analogue scale pain score, quality of life measure, performance measures, adherence) may be considered as a secondary outcome of interest and the RCT should be powered to measure this as well as the primary outcome. Change in an outcome between baseline and follow-up is often associated with less variability than the actual measurement and also considers differences between participants at baseline[26].

While high quality RCTs are targeted at the prevention of health problems, adverse effects of interventions cannot be excluded. It is therefore essential to collect and report such effects. Verhagen *et al.*[21] reported an increase in the number of reported knee problems in an RCT evaluating an ankle sprain prevention exercise intervention. Just as side effects of clinical treatments, which may have rare adverse events that must be disclosed, injury prevention trials should completely and transparently report adverse effects of interventions. These may include pain, muscle soreness, other joint injury, and non-musculoskeletal medical outcomes.

In the collection of follow-up measurements, the study design should include mechanisms to minimize the possibility of missing data and/or invalid data and appropriate approaches to handling such missing data[57]. Strategies to ensure this include validation and pre-testing of all study forms, adequate training and standardization of data collection and data entry procedures, monitoring of data quality and data entry, and random data audits by an external data monitoring committee[37].

Considerations for analysis

Appropriate selection of statistical analysis techniques in any sport injury prevention RCT is critical to inform appropriate interpretation of results. Analysis may be either intent-to-treat alone or intent-to-treat complemented by a per-protocol analysis, depending on the research question. An intent-to-treat analysis compares study groups based on their study group allocation and is recommended to avoid selection bias. Per-protocol analysis compares participants completing the intervention and those not completing. This approach introduces selection bias but may provide some insights into dose response considerations. Statistical considerations and techniques in the analysis of data from RCTs with a diversity of outcome measure types considered in primary prevention RCTs (i.e., proportions, continuous, repeated measures, clustering, time to event, count) have been reported previously[26,37,46,48–50,62]. An effect measure usually provides additional information beyond

whether or not a significant difference between study groups was reported. Effect measures of interest in prevention RCTs should consider exposure to risk (e.g., hours of participation) and be expressed as an injury rate ratio (IRR) when comparing injury rate in the intervention group and the control groups. Statistical techniques to consider multiple independent outcomes (e.g., Poisson regression or negative binomial regression) are frequently considered in injury prevention RCTs[22–26,56]. Alternative effect estimates include Hazard Ratios (e.g., considering time to injury), Risk Ratios (e.g., considering incidence proportions) or Odds Ratios (e.g., comparing odds of injury). Multivariate analyses should be considered to adjust for any covariate imbalance at baseline (e.g., previous injury, sex, age) and to examine effect modification (i.e., varying level of effect based on the level of another covariate)[37]. Sub-group analyses to examine the effect modification of covariates such as age, sex, and previous injury should be considered in the planning stages of the RCT as there are considerable sample size implications. *Post-hoc* analyses should be avoided due to the significant statistical implications of multiple comparisons[37]. Identification of common outcomes is critical to inform future meta-analyses. Analyses (including multiple outcomes and interim analyses) should be planned a priori in order to minimize bias and comply with the standard of practice for registering of RCTs in clinical trials registries and publication of protocol papers. Registering a trial (prior to inclusion of the first participant) is often a pre-requisite for publication.

Analytical considerations related to participant drop-out or withdrawal from an RCT require consideration. This includes reporting of participants recruited who are subsequently determined as ineligible, non-adherence to intervention contamination, poor quality or missing data and occurrence of competing events (e.g., mortality, injuries that do not meet the injury definition). An intention to treat analysis is critical to informing effectiveness of an intervention as it considers an analysis in which participants are included in the study group in which they are assigned[26,37]. If contamination or non-adherence is predicted, then the sample size estimation should consider the probability of each because either can be associated with loss of statistical power[37]. Withdrawal related to participants subsequently being determined as ineligible (e.g., other medical concern) or drop-outs should be minimized in the study design by making every effort to establish eligibility prior to randomization and to minimize loss to follow-up. If data are missing, the reason for this should be investigated, as any technique to impute missing data is based on the assumption that the reason for the missing data is not related to the outcome. Missing data may be imputed using various techniques such as EM algorithm, bootstrapping and multiple imputation[37,57,63]. Outliers should always be examined for plausibility (e.g., physiological, psychological, biomechanical) as well as for potential errors in recording or data entry before data is discarded. Decisions regarding outliers can be made based on a sensitivity analysis comparing results with and without inclusion of the outlier. If the results vary considerably based on inclusion of outliers, then results should be interpreted with caution. All major competing events (i.e., mortality, non-sport related injury) require reporting in order to explain withdrawal from the study.

Despite the evidence addressing appropriate design and analysis of cluster RCTs[64], only some sport injury prevention intervention trials have addressed clustering appropriately in the design and analysis[21–24,26,34,40,44,45]. In youth soccer, for example, cluster RCTs have considered clustering in the sample size estimation and recruitment methodology and have controlled for clustering by team in the analyses[24,26]. The "CONSORT Statement cautions: Extension to cluster randomization trials"[65] in the reporting of such study results is often ignored. Inappropriate individual-level analysis and poor reporting of cluster RCTs may lead to erroneous results, misleading conclusions, and often overstated practice and policy recommendations[55].

As there is a need to interpret results in injury prevention RCTs at the level of individual participants, there are numerous approaches to cluster adjusted analyses that could be considered. For example, when comparing incidence proportions in two groups, a standard chi-square test can be adjusted for the clustering of responses within a cluster[46]. In order to account for the imbalance on baseline covariates, however, provided the number of clusters is sufficiently large, multiple regression methods may be used to increase the precision with which the intervention effect is estimated[46]. A Generalized Estimating Equation (GEE) extension of logistic regression or appropriate adjustment for the effects of clustering in a Poisson regression or survival analysis may be considered[37,66].

Other considerations

Implementation

The implementation of injury prevention research into practice has garnered attention in recent years[27,67,68] However, wide-scale implementation of cost-effective intervention measures and treatment protocols under real life conditions proves to be an ongoing challenge and cannot be addressed solely in the context of an RCT[69]. Various implementation research frameworks for sports injury prevention have been postulated, of which the Translating Research into the Injury Prevention Practice (TRIPP) Framework is arguably the most widely adopted and should be considered[27]. The TRIPP framework is in essence an addendum to the original 'Sequence of Prevention' which included; 1. establishing the extent of the problem (surveillance), 2. establishing etiology (risk factors) and mechanisms of injury, 3. developing preventive measures, and 4. evaluating preventive measure[70].

The TRIPP framework describes two additional steps that are required to translate evidence of effectiveness to practice[27]. The additional steps include a description of the intervention context to inform implementation strategies and evaluation of the effectiveness of preventive measures in the implementation context[27]. Implementation starts with the description of the context for which the original intervention was developed in order to inform implementation strategies. This description is necessary to understand how the outcomes of RCT studies can be rephrased into actions that can be successfully transferred to a real-world context of on-field sports. In order to inform implementation strategies, effectiveness reports should at least describe the type of sport or activity, age groups, level of play, and organizational structure in which the original intervention was evaluated. It is also highly recommended to perform a process evaluation alongside a controlled effectiveness trial. Although multiple approaches to do so exist, we recommend the RE-AIM framework (Reach Efficacy Adoption Implementation Maintenance Framework) for this purpose[71,72]. The RE-AIM framework designed by Glasgow *et al.*[72] is originally developed to evaluate the public health impact of health promotion interventions. This framework describes five interacting dimensions that identify the translatability and feasibility of a program[71]. There has only been limited attention to these in published sports injury prevention trials to date, so this will be an area requiring further development in the future[71,74].

Cost-evaluation

The value of economic evaluation of injury prevention research has been acknowledged, adding a relevant layer of information to

preventive outcomes by including insights into the financial input and outcomes of preventive approaches. This information aids policy makers in their decision to advocate a specific intervention, but also helps health professionals and patients to make decisions in clinical practice. A more efficient use of limited financial resources results in optimal care for more individuals. As yet, only a handful of full economic evaluations in the field of sport medicine have been published[75–78]. Cost effectiveness evaluations can be carried out alongside an RCT and sample sizes should consider both the clinical evaluation as well as the economic analysis. However, issues surrounding the nature of cost data hamper power calculations with the combined incremental cost-effectiveness ratio (ICER) as the outcome measure[79–81]. Cost data are skewed (i.e., no or low costs for most study participants) and consequently display a greater variance than clinical effects. This is a challenge as 'regular' sample size calculations are often based upon parametric assumptions including normal distribution of expected difference between groups. As a result, sampling in cost effectiveness studies is typically based upon clinical outcomes alone and additional study participants are not required to evaluate costs in an RCT[82]. Efficiency should be considered in order to address a cost-effectiveness research question. An ideal research question values the incremental costs and effects of an intervention against a "control condition". To draw meaningful clinical inferences from the results, one should consider standard of care practice as the control condition for the comparison[83].

RCT reporting

The revised CONSORT statement in 2010, including a 25-item CONSORT checklist, was intended to provide guidance in the reporting of RCTs to facilitate the interpretation of the design and conduct of published RCTs in order to assess the validity of results[52]. In addition, CONSORT extensions (non-pharmacologic treatment and cluster randomized trials) further inform the reporting of relevant RCTs in injury prevention[84,85]. Subsequently the SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) guidelines, a guideline for minimum content of an RCT protocol, were published[86]. The 33-item SPIRIT checklist focuses on content and recommends a full description for planning an RCT, not how to design or conduct an RCT. The SPIRIT recommendations aim to facilitate planning of high-quality protocols to enhance the transparency and completeness of protocols for the benefit of investigators, trial participants, patients, sponsors, funders, research ethics committees or institutional review boards, peer reviewers, journals, trial registries, policymakers, regulators, and other key stakeholders[86]. The CONSORT, CONSORT extensions or SPIRIT checklist[52,84–86] are highly recommended also to ensure the publication of the highest quality RCTs in primary injury prevention in addition to other trial types (e.g., non-pharmacological and pharmacological RCTs in OA). Submitting these checklists is a requirement for publication in many journals.

Future directions

The implications of the research question, design, methods, and analysis in injury prevention RCTs are critical to informing the interpretation and development of injury prevention trials that will ultimately inform evidence-based practice and policy decisions in health care, public health and the community. Recommendations regarding the interpretation and conduct of injury prevention RCTs including the design, methods and analyses will inform the highest level of evidence in the field. In addition, these recommendations will facilitate between study comparisons to inform best practice in injury prevention that will have the greatest public health impact.

The aim of these OARSI recommendations is to inform the conduct of RCTs in injury prevention. Once injury has occurred, however, it is imperative that those individuals who are at high risk to develop OA are identified. There is some research suggesting that signs of early PTOA can be identified at 3–10 years post intra-articular injury[9,87]. PTOA prevention strategies require development and evaluation to inform the prevention of onset and progression of OA. This was beyond the scope of these recommendations, however further research is needed in the field to inform the future development of such guidelines.

Summary recommendations for the design and conduct of injury prevention RCTs:

1 Conduct of primary and secondary prevention RCTs incorporating a mixed methods approach with a focus on the implementation context to inform practice and policy
2 Increased focus on secondary negative and beneficiary outcomes including performance, other health outcomes, economic consequences, intervention adherence and intervention maintenance
3 Ongoing validation of injury surveillance methodologies in multiple settings, including novel methodologies
4 Prevention RCTs should include standardized injury definitions where available, rigorous analytic plans, program adherence, important confounders, secondary outcomes and cluster adjustment where appropriate

Author contributions

CAE was responsible for the conception and design of the development of these guidelines, including writing the first draft of the manuscript. EMR, EV, CFF, KB, BS, KS, JK, and LSL contributed to the development of these guidelines. All authors had full access to the manuscript at all stages of development and contributed to the critical revision of the manuscript and approved the final manuscript.

Competing interests statement

CAE, EMR, EV, CFF, KB, BS, KS, JK, and LSL have no competing interests to disclose.

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