PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Criteria for Return to Sport after Anterior Cruciate Ligament reconstruction with lower reinjury risk (CR'STAL study): protocol for a prospective observational study in France
AUTHORS	Rambaud, Alexandre; SEMAY, Bertrand; Samozino, Pierre; Morin, Jean-Benoît; Testa, Rodolphe; Philippot, Rémi; Rossi, Jérémy; Edouard, Pascal

VERSION 1 - REVIEW

REVIEWER	David Logerstedt, Assistant Professor of Physical Therapy University of the Sciences Samson College of Health Sciences Philadelphia, PA USA
REVIEW RETURNED	01-Dec-2016

GENERAL COMMENTS	Thank you for the opportunity to review this interesting research protocol. Safe return to sports and high level activities is important to many individuals and it is our duty to try to ensure that athletes are adequately rehabilitated prior to release to sports. I have some major concerns that should be addressed. Recently, Kyritsis (BJSM, 2016) and Grindem (BJSM 2016) reported on reinjury rates and likelihood ratios of reinjury after ACL reconstruction using specific clinical criteria (similar to the clinical criteria suggested here). Kyritsis et al reported that those with lower hamstrings to quad ratio and those who did not pass all discharge criteria had a greater risk of ACL graft rupture. Grindem et al reported that athletes who failed the RTS criteria were more likely to sustain a reinjury than those that passed all criteria. Secondly, in addition, to the clinical and self-report criteria, the investigators are proposing measuring postural and running mechanics using COP and GRF. As these measures are likely much more sensitivity to small differences, they will likely be able to discriminate smaller differences between those that reinjure compared to those that don't. Therefore, these measures may contribute more to the prediction model. However, what are the clinical utility of these measures? Most clinicians don't have access or know how to interpret these measures in the clinic. Additionally, how would clinicians use this information to make treatment decisions to address these impairments? In regards to the running and sprinting measures, while asymmetries were found during a case report, I am unclear how measuring a sagittal plane activities like forward running, might be a surrogate for determining reinjury risk in athletes that participate and usually are injured in pivoting and cutting. Paterno et al (AJSM 2010, 2014) has

	demonstrated reinjury risk and contributing factors using the drop jump maneuver. Lastly, the investigators are proposing testing at 6, 9, and 12 months post reconstruction. Why not test athletes when they are cleared to return to sports versus specific time points? Such as, what if you test an athlete at 6 months who has not returned to sports but then is cleared to return at 7 months. How do account for changes that occur from month 7 to month 9, when he is tested next? Additionally, how are athletes cleared to return to sport? You cannot use your testing criteria to clear athletes to return to sport as this would in essence result in selection bias. Athletes would have to return using other criteria, not the ones being assessed. Below are specific comments to the manuscript: P7, L27: Self-report questionnaires are not subjective. They are validated, objective data of an individual's self-report of perceived function. Please change accordingly. P8, L53: As "48" starts a sentence, it should be in word format. P9,L30-31: Anderson et al does not make any specific recommendations for a cutoff score for the IKDC. Logerstedt et al (JOSPT, 2014) used the 15th percentile of sex- and age-matched normal population values for cutoffs for the IKDC. P9, L32: I might suggest adding the ACL-RSI as it addresses more movement-related fear compared to the TSK-11 which addresses more pain-related fear. P9, L56: change "gender" to "sex" P14, L23: Why did you not include the 6-meter timed hop? The 6-meter timed hop has been shown to have predictive value for both non-operative and post-operative function after ACL injury. P17, L20: How many patients are you proposing? It seems a little unrealistic to suggest only a 10% dropout rate over a 3 year period. P17, L23: Remove the "0" before "20%". P19, Table 3: "Tork" should be spelled "Torque". P19, Table 3: Lynch et al did not propose a cutoff for hamstrings/quadriceps ratio in this article. Please check your references.

REVIEWER	Clare Ardern Linköping University, Sweden
REVIEW RETURNED	13-Dec-2016

GENERAL COMMENTS	Thank you for asking me to read and comment on this manuscript. I note it has been through one round of revisions – thanks for your work revising the paper. It's great to see a study tackling a key issue/question in ACL injury management. This is an important study as many people propose return to sport criteria, yet there are few high quality prospective studies to guide practitioners in their decision making regarding return to sport discharge criteria. With this in mind, I was surprised that you didn't refer to Krytsis et al. (http://bjsm.bmj.com/content/50/15/946) and Grindem et al. (http://bjsm.bmj.com/content/50/13/804) when building the rationale for your study. I think these are key papers and have important implications for your study. I also think they can help you build a really strong argument for your study.

	There were also some grammatical and language expression issues that affected the flow or understanding of the text (e.g. “all variables which will be validated criteria to return to sport or biomechanical significant to avoid wacky variables”). I think the manuscript would benefit from careful editing to improve readability. INTRODUCTION/RATIONALE There’s a few statements in the introduction that I’m not sure are totally accurate: For many athletes, returning to the pre-injury sport is an important measure of their satisfaction with the outcome of ACL reconstruction. However, not for all athletes (https://www.ncbi.nlm.nih.gov/pubmed/27020461) - consider moderating this in your introduction. “Fewer than 1 in 6 return to competitive sport” – evidence from systematic reviews suggests 1 in 2 return to competitive sport (https://www.ncbi.nlm.nih.gov/pubmed/25157180). “The longer the patient waits to return to competition, the more his socio-professional and familial environment will diminish his motivation to return” – it is hypothesised that work and family commitments might influence the decision to return or not return to sport, but I don’t think we have hard evidence for this yet. “Returning to sport too late seems to decrease the chances of returning to the pre-injury level of performance” – is there a reference to support this statement? You comment that it is necessary to define the optimal timeline for return to sport, but I’m not sure that your study allows this. Is it even possible to determine a ‘one-size-fits-all’ timeline? I respectfully suggest that the return to sport timeline needs to be individualised for each athlete, taking into consideration the individual’s goals, experiences, ‘risk factors’ and concerns. I’m not sure that you need to get into this argument to build your rationale. Similarly, the comment that “it is surprising that the more objective tests are the least used while the least objective tests are the most used” needs elaboration if you’re making this a key point in your rationale (although, again, I’m not sure you need to go here). In general, the introduction is very long, and I’m not sure that it needs to be. With all the detail I found the rationale for your study got a bit lost – perhaps consider streamlining this section to build a strong, succinct rationale. METHOD Why do you propose to evaluate static knee laxity? It’s pretty well established that this measure has no relationship to patients’ self-reported outcome or to function. I’m not convinced that it will give you much useful information. Similarly, I’m interested to know why you have chosen to include the Tampa Scale for Kinesiophobia. Recently, the ACL-Return to Sport after Injury scale (ACL-RSI) has emerged as the best psychological predictor of returning to the pre-injury sport after ACL reconstruction (TSK scores were not related to returning to sport in a multivariable model) (https://www.ncbi.nlm.nih.gov/pubmed/23733635). I wonder if a condition-specific and sport-relevant measure of psychological readiness to return to sport might be more appropriate for your population than the TSK, which was developed for people with chronic pain. I’m also intrigued by the assessment of running and sprinting on the

	treadmill. Cutting and pivoting movements are far more challenging movements (and replicate a common ACL injury scenario) for patients, so I wonder whether only assessing straight-line running will give enough information. I understand there are always limitations to lab-based research, but it seems you might be missing an important part of the return to sport picture by not examining a more challenging movement that more closely mimics the common non-contact ACL injury scenario. The recent consensus statement on return to sport recommends return to sport criteria include tasks that replicate the specific demands of the sport. Given that a key inclusion criterion for your study is participation in pivoting and/or contact sport, it seems that you might be missing some critical elements for return to sport. Along the same lines, is the static balance test challenging enough? I'm concerned you might have problems with ceiling effects. Please consider basing your rehabilitation program on the recently published guidelines (http://bjsm.bmj.com/content/50/24/1506) – these are an update to the approaches you cite, and are based on the best current evidence. I also wonder if it might be important to include an earlier follow-up. The first follow-up you propose is at 6-months post-operative, but by this time, many patients have either finished rehabilitation or have very limited contact with their physiotherapist/rehabilitation practitioner. Is there scope within your study to do this? The protocol reads like you plan to conduct the tests in the same order for each participant and each measurement occasion. Why not randomise the order? Please clarify the power and sample size calculations on page 18 – how many participants are needed for the study? How many explanatory variables do you plan to include in your multivariable model? I found Table 3 confusing. In the "criterion to return to sport" column, this is what you would deem is a "pass" on the test? The reference is for the test itself or the criterion to return to sport? What is the point of the "Variables" column? The Marx and Tegner scale scores are typically analysed as continuous variables, not discrete as you have written. Please clarify this information. Regarding the statistical analysis, it seems that you are planning to look at change over time? Why do you propose to use repeated measures ANOVA for this and not a more robust Generalised Estimating Equations or Linear Mixed Models approach? Similarly, GEE would work well instead of the simple logistic regression for the assessment of predictive factors. One advantage of GEE is that it allows the inclusion of a random intercept coefficient. The sentence "all variables which will be validated criteria to return to sport or biomechanical significant to avoid wacky variables" doesn't make sense to me – could you please clarify what you mean? Do you plan to check for multicollinearity? How do you plan to assess model fit? Do you plan to register the study? DISCUSSION You are using a multivariable not multivariate approach – please

	amend this at the bottom of page 22. The final 2 sentences of the discussion might need to be moderated. It makes the assumption that your return to sport criteria will improve recovery, facilitate safe return to play, prevent short- and long-term consequences of re-injury, and reduce health care costs, but I don't know that you are assessing all of these aspects in your study. Perhaps more appropriate to write that we could hypothesise that superior return to sport criteria might help achieve all of these things?

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1 COMMENTS:

Ms. Ref. No.: bmjopen-2016-015087
Title: "CR'STAL study: Criteria for Return to Sport after ACL reconstruction with lower re-injury risk. A prospective observational study protocol"
BMJ Open

Reviewer Name: David Logerstedt, Assistant Professor of Physical Therapy
Institution and Country: University of the Sciences, Samson College of Health Sciences, Philadelphia, PA USA
Please state any competing interests: None declared

Thank you for the opportunity to review this interesting research protocol. Safe return to sports and high level activities is important to many individuals and it is our duty to try to ensure that athletes are adequately rehabilitated prior to release to sports. I have some major concerns that should be addressed.
R: Thank you for these supportive comments, and your suggestions for improving the present manuscript. We hope that we have now addressed your concerns and are very pleased that you can see some clinical implications for the care of ACL reconstruction patients.

Recently, Kyritsis (BJSM, 2016) and Grindem (BJSM 2016) reported on reinjury rates and likelihood ratios of reinjury after ACL reconstruction using specific clinical criteria (similar to the clinical criteria suggested here). Kyritsis et al. reported that those with lower hamstrings to quad ratio and those who did not pass all discharge criteria had a greater risk of ACL graft rupture. Grindem et al. reported that athletes who failed the RTS criteria were more likely to sustain a reinjury than those that passed all criteria.
R: Thank you for this very important comment. Indeed, these two articles are very important and represent a relevant basis for our study problematic and aims. We unfortunately overlooked these articles in the previous version, since the manuscript was written before their publication. However, following your comment and given their relevance, they have been added to this revised version. Moreover, an update review of the topic has been made, in order to avoid the risk of missing other relevant articles.

Secondly, in addition, to the clinical and self-report criteria, the investigators are proposing measuring postural and running mechanics using COP and GRF. As these measures are likely much more sensitivity to small differences, they will likely be able to discriminate smaller differences between

those that reinjure compared to those that don't. Therefore, these measures may contribute more to the prediction model. However, what are the clinical utility of these measures? Most clinicians don't have access or know how to interpret these measures in the clinic. Additionally, how would clinicians use this information to make treatment decisions to address these impairments?
R: We acknowledge the current partial accessibility to these measures in the clinic today, and we thank you for offering us the opportunity to expose our point of view regarding this.
The practice of medicine, especially sports medicine, is moving to a more objective measures based practice. More and more, decisions are now taken after a global assessment of the patient's condition using many different parameters (such as biology, biomechanics, psychology, or environmental factors). Consequently, we can observe a growing interest for biomechanical assessment in sport medicine (such as isokinetics, gait analysis, running treadmill…). This is associated with the ready availability of these tools, at affordable prices, able to provide this information (COP, running biomechanics, muscle power production during tasks...). Some of them are even available for smartphones, tablets and game consoles (MyJump2, MySprint, Runmatic, Wii Balance Board, Microsoft Kinect…). Indeed, the Nintendo Wii Balance Board, used by Hatton et al (2016) and Clark et al (2014), allows good testing of postural outcomes with good test-retest reliability and validity (Clark 2010). New mobile apps, like Mysprint or Runmatic have recently been validated (Romero-Franco 2016, Balsalobre-Fernandez 2016) as a method of measuring specific biomechanic parameters (without GRF measures) using only a smartphone or tablet.
Therefore, one of our goals here is to identify which of these numerous parameters is/are the most useful to assist the practitioner in making the decision regarding a return to sport, and then to present it/them to the medical community and to those with a stake in the return to sport decision in a way that will be useful for clinical practice and not only in the laboratory.

In regards to the running and sprinting measures, while asymmetries were found during a case report, I am unclear how measuring a sagittal plane activities like forward running, might be a surrogate for determining reinjury risk in athletes that participate and usually are injured in pivoting and cutting. Paterno et al. (AJSM 2010, 2014) has demonstrated reinjury risk and contributing factors using the drop jump maneuver.
R: Indeed, the analysis described by Paterno et al. (AJSM 2010, 2014) is closer to that of sports activity, and sagittal plane activities are not representative of cutting and pivoting activities.
Our approach is quite different here. Our analysis focuses on the power production and pattern during a running and sprinting task. These tasks represent an important step before return to pivoting and cutting activities. We therefore chose to analyze these aspects.
Moreover, the use of a running treadmill is very safe for these patients, and is often used early in the rehabilitation program. Considering the concern of applicability in daily practice, we have already mentioned mobile apps such as MySprint and Runmatic, which have recently been validated (Romero-Franco 2016, Balsalobre-Fernandez 2016) and are able to provide these analyses in field conditions. Moreover, control of sagittal plane activities, like straight-line runs and sprints, is indeed a major step in the recovery process and need to be considered before a return to sport can be envisaged. We therefore chose to analyze these aspects using the cross over test.

Lastly, the investigators are proposing testing at 6, 9, and 12 months post reconstruction. Why not test athletes when they are cleared to return to sports versus specific time points? Such as, what if you test an athlete at 6 months who has not returned to sports but then is cleared to return at 7 months. How do account for changes that occur from month 7 to month 9, when he is tested next?
R: Thank you very much for this relevant comment. The period before a return to sport varies greatly with the sport, patients, and pathologies. For pivot shift sports, some patients will return to sport at 6 months after surgery and others at 12 months. Therefore, we wanted to analyze all the parameters during this 6-month period, to have an evaluation of the subjective and objective parameters, as close

as possible to the date of return to sport. In addition, the change in these parameters also seems interesting.
As our aim is to determine the criteria or association of criteria which can help the decision to RTS with the lowest risk of reinjury, we will first perform a descriptive analysis to explore the changes in these parameters from 6 to 12 months post-surgery, and secondly an exploratory data analysis will be made using the data from the evaluation at 6 months and the last evaluation before the return to sport.
Exploratory data analysis (data mining), will allow us to determine models and patterns from the available data. It includes descriptive data mining algorithms for finding interesting patterns in the data, like associations, clusters and subgroups, but also predictive data mining algorithms, which result in models that can be used for prediction and classification. This procedure will give us the opportunity to specify which is the most accurate time point to assess the patient for RTS.
Furthermore, for many years, the 'expected' RTS has been 6 months after surgery. However, considering the already-mentioned paper from Grindem et al. (2016), it currently seems to be safer to wait until the 9th month after ACLR. This trend comforts us in our choice not to perform our test assessments only at 6 months post-op, but also to include other testing times. Moreover, it highlights the need of an individualized timeline after ACLR.
Lastly, patients usually have an appointment with their surgeon and/or their sports physician at these different time points. So, these evaluations, fitting this timeline, could be widely and easily applicable in the clinic.

Additionally, how are athletes cleared to return to sport? You cannot use your testing criteria to clear athletes to return to sport as this would in essence result in selection bias. Athletes would have to return using other criteria, not the ones being assessed.
R: Thank you for highlighting this lack of information in our manuscript. This key point has now been added to the manuscript. The decision to return to sport is taken by an independent sport physician, blinded from the results of all the tests except the isokinetic assessment as this has been used in daily practice for many years. This bias has been acknowledged in the discussion and will be considered when interpreting our results.

Below are specific comments to the manuscript:

P7, L27: Self-report questionnaires are not subjective. They are validated, objective data of an individual's self-report of perceived function. Please change accordingly.
R: Thank you for your relevant comment. Indeed, Patient Reported Outcomes Measures (PROMs, as IKDC subjective form) are objective measures of subjective parameters. This has been corrected accordingly in the manuscript.

P8, L53: As "48" starts a sentence, it should be in word format.
R: This has been corrected.

P9,L30-31: Anderson et al. does not make any specific recommendations for a cutoff score for the IKDC. Logerstedt et al. (JOSPT, 2014) used the 15th percentile of sex- and age-matched normal population values for cutoffs for the IKDC.
R: Thank you for highlighting this inaccuracy. This has been corrected.

P9, L32: I might suggest adding the ACL-RSI as it addresses more movement-related fear compared

to the TSK-11 which addresses more pain-related fear.
R: Thank you for your very relevant comment. Indeed, we acknowledge recent literature appears to favor ACL-RSI for evaluating psychological readiness to return to sport in ACL. That is why we have added ACL-RSI to our protocol as you suggested. However, as the factors assessed are different, the TSK-11 will still be used in this protocol as we believe that movement-related fear can influence RTS and the risk of re-injury. Indeed these two scores seem to be complementary as reported by Ardern et al. (2014): ACL-RSI is used to evaluate psychological readiness to RTS while TSK-11 is used to evaluate fear of injury.

P9, L56: change “gender” to “sex”
R: This has been corrected.

P14, L23: Why did you not include the 6-meter timed hop? The 6-meter timed hop has been shown to have predictive value for both non-operative and post-operative function after ACL injury.
R: We have chosen to use only distance-based tests, as did other authors like Kyritsis et al. (2016). We think that the use of a chronometer may induce a higher measurement bias than a simple distance measurement. Moreover, multiplication of the tests will induce a higher fatigue effect, which we wanted to avoid.

P17, L20: How many patients are you proposing? It seems a little unrealistic to suggest only a 10% dropout rate over a 3 year period.
R: Ten cases (i.e. reinjury) are needed to support one explanatory variable. Given the reinjury rate (about 20%) and the risk of dropout (10%), we calculated that 50 patients should be included to test one explanatory variable. Among all the explanatory variables presented in Table 3, if we choose to test 5 variables at most, we need to include 250 patients. These variables will be chosen from the exploratory data analysis. Given the very specific population and the optimized follow up, we hope that we will have a low percentage of dropouts.

P17, L23: Remove the “0” before “20%”.
R: This has been corrected.

P19, Table 3: “Tork” should be spelled “Torque”.
R: This has been corrected.

P19, Table 3: Lynch et al. did not propose a cutoff for hamstrings/quadriceps ratio in this article. Please check your references.
R: Table 3 has been modified. The columns indicating the criteria and their references have been deleted in order to indicate only the variables studied and their characteristics, simplifying the understanding of the table.
We have also checked the references of the article and have made the necessary changes in the manuscript.

REVIEWER 2 COMMENTS:

Ms. Ref. No.: bmjopen-2016-015087
Title: “CR’STAL study: Criteria for Return to Sport after ACL reconstruction with lower re-injury risk. A prospective observational study protocol”
BMJ Open

Reviewer Name: Clare Ardern
Institution and Country: Linköping University, Sweden
Please state any competing interests: None declared

Dear Authors,
Thank you for asking me to read and comment on this manuscript. I note it has been through one round of revisions – thanks for your work revising the paper. It’s great to see a study tackling a key issue/question in ACL injury management. This is an important study as many people propose return to sport criteria, yet there are few high quality prospective studies to guide practitioners in their decision making regarding return to sport discharge criteria.
R: Thank you for your supportive comments. We are very pleased that you have seen our protocol as a high quality prospective study. We have again revised our manuscript, and we hope that this version will satisfy your expectations.

With this in mind, I was surprised that you didn’t refer to Krytsis et al. (http://bjsm.bmj.com/content/50/15/946) and Grindem et al. (http://bjsm.bmj.com/content/50/13/804) when building the rationale for your study. I think these are key papers and have important implications for your study. I also think they can help you build a really strong argument for your study.
R: Thank you for your relevant suggestion. Indeed, these two papers have comforted us in our approach as they represent the basis for our aims and methods. We unfortunately did not reference them in our initial manuscript as the last version was written before their online publication. However, following your suggestion, we have included these two key papers in our references, and an update review has been performed to avoid this risk.

There were also some grammatical and language expression issues that affected the flow or understanding of the text (e.g. “all variables which will be validated criteria to return to sport or biomechanical significant to avoid wacky variables”). I think the manuscript would benefit from careful editing to improve readability.
R: It has been checked and corrected by colleagues and by a native English-speaking professional. We hope this revised version will satisfy the level of English language expected.

INTRODUCTION/RATIONALE
There’s a few statements in the introduction that I’m not sure are totally accurate: For many athletes, returning to the pre-injury sport is an important measure of their satisfaction with the outcome of ACL reconstruction. However, not for all athletes (https://www.ncbi.nlm.nih.gov/pubmed/27020461) - consider moderating this in your introduction.
R: Thank you for your suggestion. This has been moderated and included in our introduction.

“Fewer than 1 in 6 return to competitive sport” – evidence from systematic reviews suggests 1 in 2 return to competitive sport (https://www.ncbi.nlm.nih.gov/pubmed/25157180).
R: Thank you for your clarification. This has been modified and referenced accordingly in our

manuscript.

“The longer the patient waits to return to competition, the more his socio-professional and familial environment will diminish his motivation to return” – it is hypothesised that work and family commitments might influence the decision to return or not return to sport, but I don’t think we have hard evidence for this yet. “Returning to sport too late seems to decrease the chances of returning to the pre-injury level of performance” – is there a reference to support this statement?
R: Thank you for giving us the opportunity to improve our manuscript.
We have altered the affirmation: “The longer the patient waits to return to competition, the more his socio-professional and familial environment will diminish his motivation to return”.....
For “Returning to sport too late seems to decrease the chances of returning to the pre-injury level of performance”: it is a personal point of view. When we say "return to sport too late" we mean return to sport at competition level, and when it exceeding 1 year postoperative. It is an observation from our daily practice which is not supported by scientific literature.
We have clarified and modified these statements in the manuscript.

You comment that it is necessary to define the optimal timeline for return to sport, but I’m not sure that your study allows this. Is it even possible to determine a ‘one-size-fits-all’ timeline? I respectfully suggest that the return to sport timeline needs to be individualised for each athlete, taking into consideration the individual’s goals, experiences, ‘risk factors’ and concerns. I’m not sure that you need to get into this argument to build your rationale.
R: Indeed, we acknowledge that there is no optimal ‘one-size-fits-all’ timeline about RTS after ACLR. Actually, our approach is closer to a ‘patient's tailored’ decision. Consequently, this has been modified in the manuscript. To do this, we will use Data Mining. Such statistical approach allows the determination of models and patterns from the available data. It includes descriptive data mining algorithms for finding interesting patterns in the data, like associations, clusters and subgroups, but also predictive data mining algorithms, which result in models that can be used for prediction and classification. This way of proceeding will give us the opportunity to specify which is the most accurate time point to assess the patient for RTS. So, we hope to progressively move towards a more individualized decision.

Similarly, the comment that “it is surprising that the more objective tests are the least used while the least objective tests are the most used” needs elaboration if you’re making this a key point in your rationale (although, again, I’m not sure you need to go here). In general, the introduction is very long, and I’m not sure that it needs to be. With all the detail I found the rationale for your study got a bit lost – perhaps consider streamlining this section to build a strong, succinct rationale.
R: Thank you for all your relevant comments about our introduction. Following your comment, we have simplified and shorten the introduction. We hope that this has improved it.

METHOD
Why do you propose to evaluate static knee laxity? It’s pretty well established that this measure has no relationship to patients’ self-reported outcome or to function. I’m not convinced that it will give you much useful information.
R: Thank you to giving us the opportunity to clarify this. While we acknowledge that static laximetry has no relationship to patients’ self-reported outcome or function, we also believe that laxity plays a role in instability and thus to injury risk.
Moreover, we are using an innovative laximeter that provides dynamic curves for ligament resistance during the application of progressive anterior tibial force.

We also aim to analyze the status of the static stabilizers.

Similarly, I'm interested to know why you have chosen to include the Tampa Scale for Kinesiophobia. Recently, the ACL-Return to Sport after Injury scale (ACL-RSI) has emerged as the best psychological predictor of returning to the pre-injury sport after ACL reconstruction (TSK scores were not related to returning to sport in a multivariable model) (https://www.ncbi.nlm.nih.gov/pubmed/23733635). I wonder if a condition-specific and sport-relevant measure of psychological readiness to return to sport might be more appropriate for your population than the TSK, which was developed for people with chronic pain.
R: Thank you for your very relevant comment. Indeed, we acknowledge recent literature appears to favor ACL-RSI for evaluating psychological readiness to return to sport in ACLR. That is why we have added ACL-RSI to our protocol as you suggested. However, as the factors assessed are different, the TSK-11 will still be used in this protocol as we believe that movement-related fear can influence RTS and the risk of re-injury. Indeed these two scores seem to be complementary as reported by Ardern et al. (2014): ACL-RSI is used to evaluate psychological readiness to RTS while TSK-11 is used to evaluate fear of injury.

I'm also intrigued by the assessment of running and sprinting on the treadmill. Cutting and pivoting movements are far more challenging movements (and replicate a common ACL injury scenario) for patients, so I wonder whether only assessing straight line running will give enough information. I understand there are always limitations to lab-based research, but it seems you might be missing an important part of the return to sport picture by not examining a more challenging movement that more closely mimics the common non-contact ACL injury scenario. The recent consensus statement on return to sport recommends return to sport criteria include tasks that replicate the specific demands of the sport. Given that a key inclusion criterion for your study is participation in pivoting and/or contact sport, it seems that you might be missing some critical elements for return to sport. Along the same lines, is the static balance test challenging enough? I'm concerned you might have problems with ceiling effects.
R: We agree that cutting and pivoting movements are far more challenging and are closer to those of the sport activity, while sagittal plane activities are not representative of cutting and pivoting activities. We have therefore included the Cross-Over Hop Test (COHT) to assess the cutting movement capabilities of the patient. (Noyes 1991) The COHT imposes both predominant sagittal plane forces and rotation forces on the frontal plane of the knee. In addition, it is a test that highlights not only the instability of the knee, but also muscle extensibility, muscle strength and power, proprioception, neuromuscular control, dynamic balance, and agility (Clark 2001).
Concerning straight line running, our approach here is quite different. Our analysis focuses on power output and mechanical pattern during a running and sprinting task. The use of a running treadmill is very safe for these patients, even early on in their recovery. This choice is also explained by the need of applicability in daily practice: there exist some very affordable mobile apps MySprint and Runmatic, which have recently been validated (Romero-Franco 2016, Balsalobre-Fernandez 2016) and are able to provide similar analyses.
Moreover, control of sagittal plane activities as required for straight-line runs and sprints, is a major step in the recovery process necessary for a return to sport and we feel that they need to be taken into consideration.
Lastly, we acknowledge that the single-leg static balance test is not very challenging. We have consequently modified our protocol, referring to work by Culvenor 2016, and now assess balance during a single-leg squat. Moreover, the stabilometry assessment is easy to carry out in clinical practice and gives relevant information about postural control. Thank you for your pertinent comments, which have helped us to improve our protocol.

Please consider basing your rehabilitation program on the recently published guidelines (http://bjsm.bmj.com/content/50/24/1506) – these are an update to the approaches you cite, and are based on the best current evidence.
R: Thank you for your suggestion. Part of the protocol has been modified in the manuscript, following your recommendation.

I also wonder if it might be important to include an earlier follow-up. The first follow-up you propose is at 6-months post-operative, but by this time, many patients have either finished rehabilitation or have very limited contact with their physiotherapist/rehabilitation practitioner. Is there scope within your study to do this?
R: Indeed, you are right, some patients have completed their rehabilitation at the 6th month after surgery. However, none of them could not be cleared to return to pivoting sports before the 6-month mark. As our study focuses on return to sport, and not on assessing the results of rehabilitation, we have not planned to add an earlier follow-up at this stage, but this could be an interesting part of another study. Lastly, as we use the Cross-Over Hop Test to assess cutting capabilities, it is not possible to perform a complete assessment before 6 months after surgery.

The protocol reads like you plan to conduct the tests in the same order for each participant and each measurement occasion. Why not randomise the order?
R: Thank you for this interesting suggestion. This choice of ours was deliberate. Indeed, the running, sprinting and isokinetic assessments are very tiring for the patients. If we randomize the order, then a patient may start the assessment with the isokinetic test, and subsequent tests could then be influenced by a huge effect of tiredness.

Please clarify the power and sample size calculations on page 18 – how many participants are needed for the study? How many explanatory variables do you plan to include in your multivariable model?
R: Ten cases (i.e. reinjury) are needed to explain one explanatory variable. Given the reinjury rate (about 20%) and the risk of dropout (10%), we calculated that 50 patients should be included to test one explanatory variable. Given the very specific population and the optimized follow-up, we are hoping that we will have a low percentage of dropouts.
Among all the explanatory variables presented in Table 3, if we choose to test 5 variables maximum, we need to include 250 patients. These variables will be chosen by the exploratory data analysis.
Moreover, data mining will be used to build a predictive model if possible. Data mining will allow us to find models and patterns from the available data. It includes descriptive data mining algorithms for finding interesting patterns in the data, like associations, clusters and subgroups.
The aim of our model, if possible, is Predictive modeling to build a predictive model for a target variable, based on explanatory variables. But data Mining also includes Attribute selection and most machine learning algorithms allow us to learn which are the most appropriate attributes (predictor variables) to use for making decisions. Most methods for Attribute selection involve the space of attributes for the subset which is most likely to predict the best class.
The use of this exploratory data analysis will be inspired by some of the work done by Combes & Azema. (10.1016/j.dss.2012.10.016) and Esfandiari et al. 2014 (10.1016/j.eswa.2014.01.011). On the other hand, this method does not exclude the classical statistical analyses for the creation of a model. Lasting, depending on our variables, we will use the appropriate statistical tests.

I found Table 3 confusing. In the “criterion to return to sport” column, this is what you would deem is a

"pass" on the test? The reference is for the test itself or the criterion to return to sport? What is the point of the "Variables" column? The Marx and Tegner scale scores are typically analysed as continuous variables, not discrete as you have written. Please clarify this information.
R: Table 3 has been modified. We have deleted the column "variables", "criterion to return to sport" and "reference". The aim of the last column was to justify the use of these variables but was obviously unclear and confusing. The Marx and Tegner scale measurements are ordinal but, as you have rightly reminded us, these variables are treated as continuous. Thank you for this clarification.

Regarding the statistical analysis, it seems that you are planning to look at change over time? Why do you propose to use repeated measures ANOVA for this and not a more robust Generalised Estimating Equations or Linear Mixed Models approach? Similarly, GEE would work well instead of the simple logistic regression for the assessment of predictive factors. One advantage of GEE is that it allows the inclusion of a random intercept coefficient. The sentence "all variables which will be validated criteria to return to sport or biomechanical significant to avoid wacky variables" doesn't make sense to me – could you please clarify what you mean? Do you plan to check for multicollinearity? How do you plan to assess model fit?
R: Thank you for your excellent advice. After consulting with statisticians, the development of our model will use exploratory data mining. We will therefore perform a data analysis using the classification method to define the variables of our model explaining our outcome (injury or not). After performing a correlation matrix and calculating colinearity using linear regression, we will calculate several Generalized Linear Models if possible: Linear Regression, Generalized Estimating Equations, Generalized Linear Mixed Model, according to the characteristics of our variables

Do you plan to register the study?
R: Yes, this study will be registered on ClinicalTrials.gov. This registration is currently in progress.

DISCUSSION
You are using a multivariable not multivariate approach – please amend this at the bottom of page 22.
R: Thank you for your comment. This has been corrected.

The final 2 sentences of the discussion might need to be moderated. It makes the assumption that your return to sport criteria will improve recovery, facilitate safe return to play, prevent short- and long-term consequences of re-injury, and reduce health care costs, but I don't know that you are assessing all of these aspects in your study. Perhaps more appropriate to write that we could hypothesise that superior return to sport criteria might help achieve all of these things?
R: Thank you for your suggestion. This has been modified in the manuscript.

VERSION 2 – REVIEW

REVIEWER	David Logerstedt, Assistant Professor of Physical Therapy University of the Sciences, USA
REVIEW RETURNED	15-Feb-2017

GENERAL COMMENTS	Again thank you for the opportunity to review this research protocol. In regards to the primary outcomes, it is still unclear to me which is the primary outcome: Determining factors to predict return to sport or determining factors that predict reinjury. These are two very different questions and may require different methodologies to determine.

	This leads me to my second point. I want to follow up on the running measures. It may be appropriate for determining return to activity, as power is typically related to performance measures but still is unclear to me how this data may be relevant to reinjury risk in cutting and pivoting athletes. Additionally, you mentioned the validated mobile apps as potential for clinical use. Why not use one of these vs a lab-based, less-clinically relevant method? In regards to measurement time periods, I still think that you may miss valuable changes that may occur between 6-9 months and 9-12 months as compared to when athletes actually return to sport. Furthermore, this is only going to answer if results at 6, 9, or 12 months can predict return to sports or reinjury, but it does not answer your hypothesis of the optimal time frame. As a follow-up to the decision making of return to sport by an independent sports physician, how can you reassure that the physician is not using the criteria from Grindem or Kyritsis to determine return to sport? Can this result in an unforeseen bias?

REVIEWER	Clare Ardern Linköping University, Sweden
REVIEW RETURNED	01-Mar-2017

GENERAL COMMENTS	Thank you for your hard extensive work revising the manuscript – I believe it is improving with each round. But I still have some problems with the manuscript. I've outlined the key issues that I think you need to consider, plus given a few (more minor) comments on specific parts of the text. 1. I still find it difficult to see a clear rationale. All the pieces are there, and each point you make is fine, but I still don't see it pulled together in a clear way. What is really meant by optimal individualised timeline. The impression I have is that essentially you are taking some existing clinical criteria, and some novel measurements (that maybe focus more on sport-specific elements and less on impairments) and trying to validate them as predictors of safe return to play. And in particular, you are focusing on young, pivoting sport athletes, who we might say are an 'at risk' group of patients. It's really important to be clear about the population you are targeting (and why), and why the measures you have chosen might be important. Again, I think you have most of this information, but it is a bit buried, and difficult for the reader to follow a clear line of reasoning. 2. I'm a little unclear about your primary outcome: in the abstract you state that it is any reinjury (graft rupture, contralateral ACL rupture or any other time loss injury), but in the method, it you focus on ACL re-injury. Please clarify this. 3. I'm not sure the approach for sample size calculation is the best, and suggest you look at Bahr & Holm Br J Sports Med 2003;37(5):384-92 for some guidance. The ACL re-injury rate that you have used in the power analysis seems fairly high. Why did you choose this Swedish study and not use meta-analysis data? My other concern is about how realistic it is that you will have 50 ACL re-injuries in the study period. How many potentially eligible participants are there?

	4. Why is it not possible to outline which statistical modeling method you will use now? You know the characteristics of the variables that you will include in the model. Also, is data mining a robust approach when you only plan to include 250 patients? Is there a risk that your analysis could be nothing more than a fishing expedition? SPECIFIC COMMENTS I think you should qualify that "when can I get back to my sport" is one of the most frequent questions, not the only question. Please refer to participants and patients, rather than subjects. "Subject" has a negative connotation that people have been 'subjected' to something unpleasant. The inclusion criteria mention a pre-injury Tegner level of 4, and in brackets you say that this is competition training > 3 times per week. Please check this, because my understanding was that Tegner 4 was recreational sport only. Please be clearer about why you exclude patients older than 35 years. Please clarify whether the single leg squat tests of postural control will be done with eyes open or closed. In the description of the hop tests (page 17), it is unclear whether participants have the chance to do the hop test again should they fail any of the attempts. Please clarify this. It would be helpful to be clearer about which muscle groups you are testing with isokinetic dynamometry (ideally on page 18 or 19 when you first mention the tests. You state that the study will be registered on ClinicalTrials.gov, but you have already started. Is it possible to register when the study has already commenced? Your comment in the discussion about the biomechanical analysis detecting ANY asymmetry is a pretty big call. Maybe delete the word "any"?

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: David Logerstedt, Assistant Professor of Physical Therapy
Institution and Country: University of the Sciences, USA
Please state any competing interests: None declared

Again thank you for the opportunity to review this research protocol.

In regards to the primary outcomes, it is still unclear to me which is the primary outcome: Determining factors to predict return to sport or determining factors that predict reinjury. These are two very different questions and may require different methodologies to determine.
Indeed, these are two different questions. We have built our methodology to answer the following

question: What is the criterion or association of criteria to determine the time to allow the decision to return to sport with the lowest possible risk of reinjury ? Considering your relevant comment, the aim of the study has been clarified in the manuscript (Page 10): “The aim of the present study is therefore to determine which criteria or combination of criteria could allow the decision to return to sport with the lowest possible risk of reinjury.” Our aim is not focused on the prediction but on the decision.

This leads me to my second point. I want to follow up on the running measures. It may be appropriate for determining return to activity, as power is typically related to performance measures but still is unclear to me how this data may be relevant to reinjury risk in cutting and pivoting athletes.
We agree that cutting and pivoting movements are far more challenging and are closer to the sport activity, while the sagittal plane activities are not representative of the cutting and pivoting activities. Our approach is quite different here from the prediction of ACL reinjury only. We aim to determine which criteria or combination of criteria could allow the decision to return to sport with the lowest possible risk of reinjury. Our primary outcome is “any reinjury during the follow up period, defined as a graft rupture, a contralateral ACL rupture, or any injury necessitating an interruption of training and requiring a medical consultation”, this includes other lower limb injuries such as muscular injuries. Indeed, a history of an ACLR is a risk factor for developing a repeat hamstring strain (Koulouris AmJSM 2007, de Visser BJSM 2012), hindering return to sport and the future practice of sport. Considering that, we hypothesize here that the running and sprinting analysis could provide valuable information.
In addition, running is the first step through the return to sport. And the use of a running treadmill is very safe for these patients early during the recovery. As we start the assessments from 6 months after surgery, the need of a discriminating test between patients with deficits and patient without deficit while they are running in a straight line seems important to us, especially to assess their capacity to return to performance. Regarding only hop-tests at 6 months after surgery, the majority of patients require additional rehabilitation (Gokeler et al., KSSTA 2017), so using only hop-tests isokinetics analysis, could not be sufficient to discriminate patients that have a higher deficit at 6 months than the majority.
Lastly, as there is a gap in the literature about recovery of a normal running and sprinting pattern after ACLR during RTS, this analysis could show some interesting results.
In conclusion, we will use the running and sprint running analyses as a first early discriminant test to authorize return to sport.

Additionally, you mentioned the validated mobile apps as potential for clinical use. Why not use one of these vs a lab-based, less-clinically relevant method?
Thank you for this very relevant suggestion. The treadmill gives us the opportunity of a more complete analysis of the running and sprinting biomechanisms, with variables that are not measured by the mobile apps. Although this analysis will not be applicable directly in a clinical use, this study can help to determine parameters which can then be evaluated by simple field devices.

In regards to measurement time periods, I still think that you may miss valuable changes that may occur between 6-9 months and 9-12 months as compared to when athletes actually return to sport. Furthermore, this is only going to answer if results at 6, 9, or 12 months can predict return to sports or reinjury, but it does not answer your hypothesis of the optimal time frame.
We acknowledge that the best way to really individualize the time-line for a return to sport should be to assess patients every two-weeks or at least every month. Unfortunately, given the number of evaluations and the duration of each session that does not seem feasible, as we try to plan a reasonable protocol for scientists, clinicians and, of course, patients. Indeed, we will miss some information between each time point, however we could, in a further study, increased analyses’

frequency in some period regarding our results. This way to proceed seems more realistic in our clinical practice than a repeated long assessment every two-weeks during 6 months.

As a follow-up to the decision making of return to sport by an independent sports physician, how can you reassure that the physician is not using the criteria from Grindem or Kyritsis to determine return to sport? Can this result in an unforeseen bias?
The current trend on this topic and growing scientific knowledge could influence the decision of the return to sport by the physician. However, the physician will base his decision only on his own clinical examination and the results of the isokinetic tests as described in the protocol, and as his own habits. As this physician is the same for all the patients, it will be the same decision-making scheme for all of them.
In addition, the physician and the patient are blinded from the results of the many other parameters (such as questionnaires, instrumented laximetry, balance tests, hop-tests, running and sprinting biomechanics), the risk of an unforeseen bias is very low.
While we will interpret our results, we will take into account the role of theses parameters in the decision to return to sport or not.

REVIEWER 2 COMMENTS:

Ms. Ref. No.: bmjopen-2016-015087
Title: “CR’STAL study: Criteria for Return to Sport after ACL reconstruction with lower reinjury risk. A prospective observational study protocol”
BMJ Open

Reviewer: 2
Reviewer Name: Clare Ardern
Institution and Country: Linköping University, Sweden
Please state any competing interests: I have no competing interests

Thank you for your hard extensive work revising the manuscript – I believe it is improving with each round. But I still have some problems with the manuscript. I’ve outlined the key issues that I think you need to consider, plus given a few (more minor) comments on specific parts of the text.
Thank you for your supportive comment. We are very pleased to read that you have seen an improvement in our manuscript after your initial comments. We have considered your new comments, so that the key issues you outlined could be addressed.

1. I still find it difficult to see a clear rationale. All the pieces are there, and each point you make is fine, but I still don’t see it pulled together in a clear way. What is really meant by optimal individualised timeline. The impression I have is that essentially you are taking some existing clinical criteria, and some novel measurements (that maybe focus more on sport-specific elements and less on impairments) and trying to validate them as predictors of safe return to play. And in particular, you are focusing on young, pivoting sport athletes, who we might say are an ‘at risk’ group of patients. It’s really important to be clear about the population you are targeting (and why), and why the measures you have chosen might be important. Again, I think you have most of this information, but it is a bit buried, and difficult for the reader to follow a clear line of reasoning.

Thank you for your relevant suggestions. We have modified part of introduction to clarify it regarding your comments.
Concerning the measurements we use, we observed during RTS after ACLR muscle injuries in our clinical practice and this observation is reinforced by the literature. Indeed, a history of an ACLR is a

risk factor for developing a repeat hamstring strain(Koulouris 2007) hindering RTS and the future practice of sport. This muscle group plays an important role in the protection of knee joint but also in sprint performance and cutting drills. As hamstrings, as other muscular groups, are essential to running and sprinting biomechanics (Morin et al. 2015 Frontiers in Physiology https://doi.org/10.3389/fphys.2015.00404), our approach could help more clearly define the criteria necessary to assess a safe return to sport. We trust theses innovative criteria could be helpful in the decision for patients who want return to sport.
Concerning the population we target, we are focusing on patients who have a high risk of reinjury and have a high demand to return to sport. Wiggins et al. (Wiggins 2016), in a systematic review and meta-analysis, had found 15% of second ACL reinjury rate, with 7% for the ipsilateral ACL and 8% for the contralateral reinjury rate. However, if patients were younger and wanted to return to sport, the secondary ACL injury was 23%. That why we focus our patient group as young athletes, practicing sport/pivot/cutting sport in competition. Furthermore, these patients are very motivated to participate in our assessment-set and follow up. The introduction has been improved in consequence.

2. I'm a little unclear about your primary outcome: in the abstract you state that it is any reinjury (graft rupture, contralateral ACL rupture or any other time loss injury), but in the method, it you focus on ACL reinjury. Please clarify this.
Indeed, in the abstract, we have defined the primary outcome as "any reinjury during the follow up period, defined as a graft rupture, a contralateral ACL rupture, or any injury necessitating an interruption of training and requiring a medical consultation". Even so, in the methods (Page 22), the primary outcome is similarly defined as "the occurrence of reinjury during the 3-year follow-up. A reinjury is defined as a rupture of the transplant or the contralateral ACL, or any injury requiring the sporting activity to cease and necessitating a consultation and/or medical care."
We have, however, clarified this point in our "Power and sample considerations" (line 41) where this could be unclear, and define clearly reinjury also in the "Follow-up after ACL surgical reconstruction" part, to avoid any misunderstanding.

3. I'm not sure the approach for sample size calculation is the best, and suggest you look at Bahr & Holm Br J Sports Med 2003;37(5):384-92 for some guidance. The ACL reinjury rate that you have used in the power analysis seems fairly high. Why did you choose this Swedish study and not use meta-analysis data? My other concern is about how realistic it is that you will have 50 ACL reinjuries in the study period. How many potentially eligible participants are there?
Thanks for your relevant suggestion. As we have previously clarified, our primary outcome is not only the ACL injuries but any injury that requires the sporting activity to cease and a consultation and/or medical care. This explains why we choose a fairly high rate of injuries. In addition, our population is different from the general population as the participants are playing pivot and/or contact sport at a regional or national level, which expose to a higher risk of reinjury (Wiggins et al. 2016). The authors report a reinjury rate up to 23% in young population that RTS while they focus only on ACL injury (graft rupture or contralateral ALC injury).
In our study the reinjury is not limited to ACL injury, so a rate of 20% reinjury using the definition we use and our specific population doesn't seem to be over-evaluated.
Thank you for your very interesting suggestion the sample size calculation. Unfortunately, the methods described by Bahr & Holm are not applicable in our protocol as they described a sample size calculation when using a univariate Cox regression, which is quite different from our statistical methods. As we use multiple tests, at different time point, we cannot apply a Cox Regression to our results. Indeed, the univariate Cox regression, doesn't offer the possibility to adjust to different risk factors. Bahr & Holm state themselves that: "It is possible to perform power calculations taking additional risk factors into account, but these more complicated models are beyond the scope of this review". However, authors highlight the need of a large population to perform this analysis, which is what we aim with 275 patients. Moreover, more than 500 ACLR are to be performed each year in our region, so we could be able to reach this objective in 3 years.

4. Why is it not possible to outline which statistical modeling method you will use now? You know the characteristics of the variables that you will include in the model. Also, is data mining a robust approach when you only plan to include 250 patients? Is there a risk that your analysis could be nothing more than a fishing expedition?
The exploratory data analysis using Data Mining techniques is more and more used in medical research (Esfandiari et al., Witten et al., Combes et al.). Based on these previous works, a Principal Components Analysis will be performed for each population (injured and uninjured) in order to observe which parameters most characterize these two populations. Then a Hierarchical clustering of the previous variables found will help to understand the most important criteria differentiating these two populations.
As our principal outcome is the occurrence of any injuries that hinder the optimal RTS (graft rupture, contralateral ACL rupture, or any other injury necessitating an interruption of training and requiring a medical consultation), we could observe some variability of asymmetry, that leads to these different injuries. That is why this innovative statistical analysis seems very relevant.
According to the statisticians of our team, data mining is feasible on our sample and recommended with our approach (Boyer et al. DOI:10.1371/journal.pone.0167352, Clermont et al. : DOI :10.1123/jab.2016-0218). Furthermore, with 275 patients with 3 evaluations for each, we can expect to have 825 evaluations.
Perhaps this new approach will only give a trend, but it could give us other criteria in line with our definition of reinjury.
We understand that the use of data mining methods looks like "a fishing expedition", which is why we will also do a classic analysis of our data. We will pay close attention to the clinical significance of the variables that will be proposed.
There are many studies on criteria for RTS and we believe that a new statistical approach as well as new criteria (biomechanical) could help answer this question that many clinicians are still asking.

SPECIFIC COMMENTS
I think you should qualify that “when can I get back to my sport” is one of the most frequent questions, not the only question.
Thank you for your suggestion. Indeed, this question is one of the most frequent but not the only one. This has been modified in the manuscript.

Please refer to participants and patients, rather than subjects. “Subject” has a negative connotation that people have been ‘subjected’ to something unpleasant.
This comment offers us the opportunity to present our protocol with a better connotation to the people involved in our research project. The manuscript has been modified. The term “subjects” have been retained when referring to the general population, are they are nor patients, and neither of the participants.

The inclusion criteria mention a pre-injury Tegner level of 4, and in brackets you say that this is competition training > 3 times per week. Please check this, because my understanding was that Tegner 4 was recreational sport only.
Thank you for your relevant comment. This contradiction has been corrected. Indeed, the lower score possible with competition participation is 7.

Please be clearer about why you exclude patients older than 35 years.
Thank you to give us the opportunity to explain our chose. Patients over 35 years are more likely to present early signs of arthritis that could induce a confusion bias in our findings.
In addition, in a qualitative investigation of the decision to return to sport after ACLR, Tjond et al.

(AJSM, 2014) have stated the important role of lifestyle change in the decision not to return to play after surgery. The authors stated that the younger patients are more likely to “place a high priority on sport”, with “fewer conflicting commitments”. Similarly, this chose avoid confusion bias on our results. Lastly, the results of the meta-analysis of Wiggins et al. show that the more concerned population at risk of reinjury is the youngest population.

Please clarify whether the single leg squat tests of postural control will be done with eyes open or closed.
As described in the cited reference, the single-leg squat will be done with eyes open. This has been added in the manuscript.

In the description of the hop tests (page 17), it is unclear whether participants have the chance to do the hop test again should they fail any of the attempts. Please clarify this.
The patient has to do 3 valid hop for each attempt. That means that in case of a failure, the patient has to one more chance to do the hop-test again. This has been clarified in the manuscript.

It would be helpful to be clearer about which muscle groups you are testing with isokinetic dynamometry (ideally on page 18 or 19 when you first mention the tests.
Thanks again to give us the opportunity to improve our manuscript. This information is given in the manuscript page 20 line 5: “isokinetic quadriceps and hamstring muscle strength assessment will be performed last”. To clarify, this has been added page 20, line 23: “The range of knee motion will be set from 80° for a safe, comfortable, comparative assessment of quadriceps (extensor) and hamstrings (flexors) muscles”.

You state that the study will be registered on ClinicalTrials.gov, but you have already started. Is it possible to register when the study has already commenced?
After verification in the Frequently Asked Questions page of ClinicalTrials.gov (https://clinicaltrials.gov/ct2/manage-recs/faq#after), yes, it is possible to register a study at any time. Moreover, the registration is currently under process.

Your comment in the discussion about the biomechanical analysis detecting ANY asymmetry is a pretty big call. Maybe delete the word “any”?.
Thank you for your relevant suggestion. This has been modified in the manuscript.