Research Protocol: Clinical Trial

Project title:

`` *Muscle injury RTP design in football; effects of backward design vs forward design . A randomized controlled trial.´´*

Version NO 1, date 25/05/2025

Project promoter: Oscar Vicente Rodríguez

Main researcher: Oscar Vicente Rodríguez

Collaborating researchers: José María Villalón Alonso, Olga Velasco Roldán, Carles Pedret Carballido

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6-Ethical and legal aspects

6.1-Compliance with the following standards is required: Good Clinical Practice, the Declaration of Helsinki, the Oviedo Convention, and Law 3/2018 of December 5, 2018, on the protection of personal data and the guarantee of digital rights. Regulations on the management of medical records must also be followed.

6.2-Informed Consent Form (Annex 1 and 2)

6.3-Confidentiality of the information collected in the context of the study.

6.4-Handling of biological samples in accordance with Law 14/2007 and Royal Decree 1716/2011

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1-Project Background and Justification

*"Return-to-play" (*RTP) is an English term that corresponds to "return to competition" (1). It is important to understand that this return is a constant, dynamic, and personalized decision-making process (2). The main objective of RTP is not to predict the exact moment of an athlete's return; rather, it is to prevent new injuries. For this, adequate decision-making is necessary (3). There are several important steps in the process, including correct diagnosis, strict control of workloads, and intelligent management of modifiers intrinsic to the sport that can lead to anxiety and stress (4).

Muscle tissue is tremendously dynamic and vulnerable to injury, especially in sports (5), where it accounts for 31% of all injuries and 30% of re-injuries (6). Due to the wide range of muscle groups and the numerous factors that influence injury, recovery time for these injuries varies greatly, even for injuries that occur in the same muscle or muscle group (7).

Muscle injuries are inherently associated with sports exposure (8), representing a very high percentage (6). According to the latest scientific publications, little progress has been made in the study of RTP, and it may have even gone in the wrong direction (9-11). Currently, only a few studies (12, 13) adequately address RTP and focus on monitoring the process. Due to the lack of consensus on RTP design, several questions arise.

How are the pieces of the RTP puzzle organized and managed?(1)

How are RTP processes evaluated today?

How should RTP be understood? Should it be understood statically, as a checklist, or as a constant decision-making process involving the player?(3)

As previously mentioned, the RTP process should not become a guessing game because it could cause anxiety (4) and stress for the player and their environment. The design and structure of the RTP process could significantly impact the success or failure of an athlete's recovery decision-making process.

2-Study hypothesis

H_0=The regression design (14, 15) of the RTP is the most appropriate since it positively influences the variables.

H_A=The regressive RTP design is not the most appropriate, as it significantly influences the variables in a detrimental way. The progressive RTP design (16,17) is more appropriate because it significantly influences the variables in a beneficial way.

3-Objectives

Main objective: To evaluate the design of the RTP process for muscle injuries in sport.

Specific objectives:

-Compare two RTP designs and evaluate how their design influences the player's anxiety (4).

-Identify variables that may be altered, sleep quality and cortisol level (18), when choosing a regressive or progressive RTP design.

-Establish direction in the design of the RTP process.

-Complete clinical guidelines (5) on muscle injuries in sports with a focus on return-to-play (RTP) design.

4-Type of study

This is a randomized, double-blind, single-center controlled clinical trial. There will be two groups: a control group and an intervention group.

5-Material and methods

5.1-Scope of study

The study will be carried out in the work environment of the principal investigator and doctoral student at the University of the Balearic Islands (UIB) and Club Atlético de Madrid. The study will focus on the first and B teams, which are both based at the Ciudad Deportiva del Cerro del Espino in Majadahonda, Madrid. The study will be included in the principal investigator's doctoral thesis.

5.2-Definition of Study Subjects

The study subjects will be all players from the first team or team B who suffer a muscle injury diagnosed by MRI. At the time of injury, they will be randomly assigned to either the control group (following a regressive RTP design) or the intervention group (following a progressive RTP design). Masking will be double-blind.

5.3-Selection and removal of subject

Male soccer players diagnosed with a muscle injury via magnetic resonance imaging (MRI) during the three-year study period will be included in the trial. They will all belong to the same club and be between 18 and 40 years old.

The study will exclude muscle injuries that do not cause players to miss training or competitions. Also excluded are cases in which patients voluntarily decide not to participate in the study or abandon the return-to-play (RTP) process due to transfers or other exceptional causes.

5.4-Recruitment of participants

Since they are all players from the same club and suffer muscle injuries, they will be included in the control and intervention groups throughout the three-year trial period. The following section will explain that the sampling technique is consecutive and that subjects can participate in the study several times as long as they have a muscle injury diagnosed by resonance. Relapses of the same injury or injuries in the same or different muscle groups will also be included in the sample. Dr.

José María Villalón Alonso, the head of the club's medical service and collaborating researcher, will be in charge of recruiting the participants. After the diagnostic test (MRI) is performed and the diagnosis and prognosis are established, the participants will be handed over to the recovery specialists, who will design the RTP. The specialists and the participants (players) will be blinded in the same way.

5.5-Allocation/randomization procedure

Assignment to the control and intervention groups will be done in a simple, randomized manner. Subjects with muscle injuries have the same 50% probability of being assigned to the control group or the intervention group, regardless of previous assignments.

5.6-Justification of sample size

We will carry out a type of consecutive sampling based on the average probability that a soccer player will suffer a muscular injury. This means that each player will suffer an average of 0.6 muscular injuries per season (7). In a team of 25 players, this averages to 15 muscular injuries per season. By contrasting this data with the club's database, we can verify the accuracy of this estimate. According to this statistical data, the population from which we will extract the sample will be the total number of muscle injuries suffered by the two teams of Club Atlético Madrid over three years, that is.

0.6 (injuries) x 50 (players) x 3 years = 90 muscle injuries. Using the Grammo sample calculator with a relative error of 5% and a 95% confidence interval, we will calculate the necessary sample size for the sample to be representative, which will be N = 74.

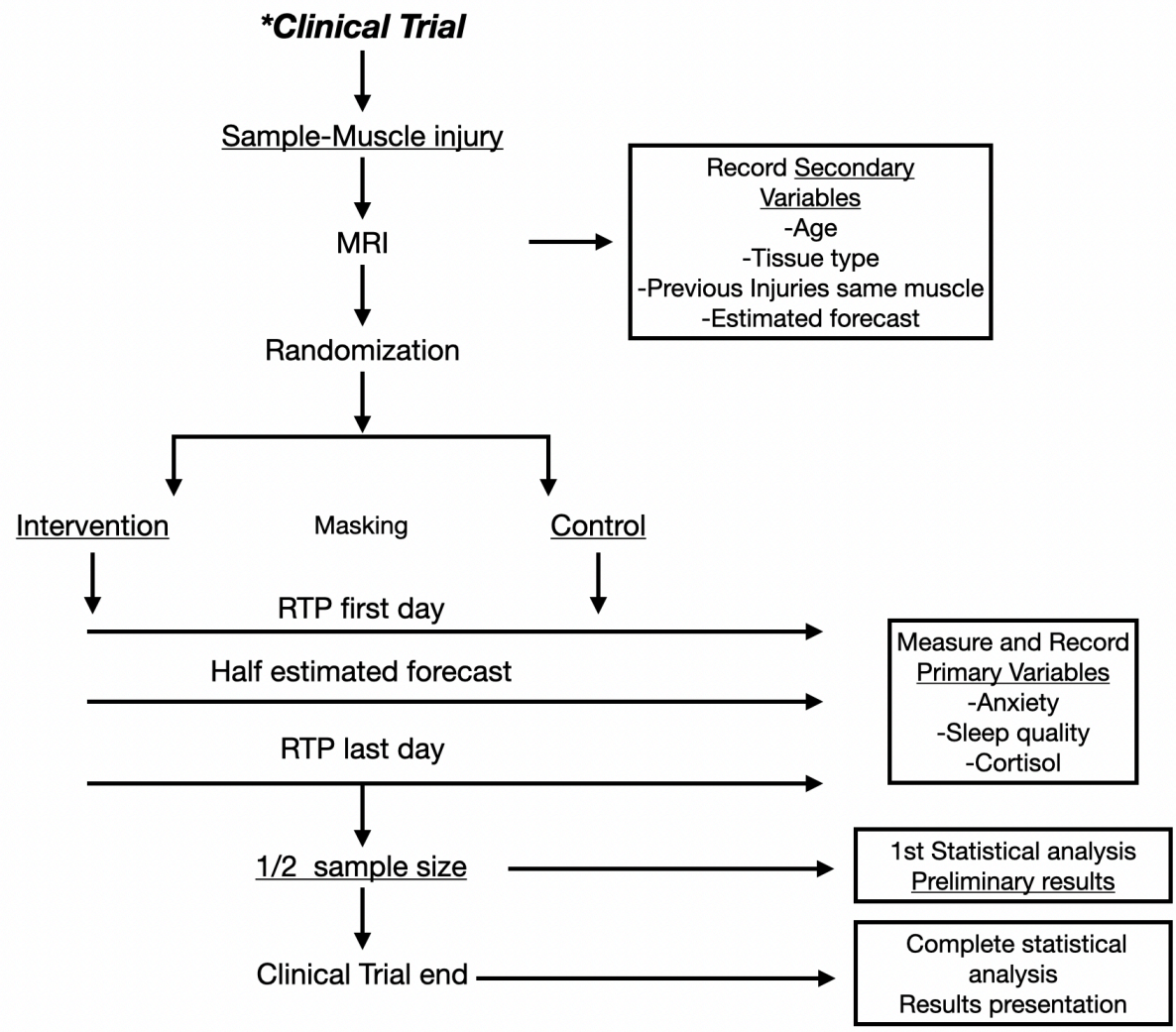
5.7-Primary and secondary variables

Primary Variables	*TYPE*	*MEASUREMENT TOOL*
Player **anxiety** (4)	(Qualitative ordinal) 4 categories Mn/Mi/Mo/S, codificada en 1/2/3/4	**GAD-7** Scale (19) *Protocol*
Sleep quality (20)	(Qualitative ordinal) 4 categories P/A/B/O, codify in 1/2/3/4	**Oura Ring**, (21) *Protocol*
Stress/Cortisol (18)	(Quantitative continue) in ng/mL	**Kit Cortisol Elisa** (22) *Protocol*

Secondary Variables	*TYPE*	*TYPE*
Age	(Quantitative discrete)	**Date of birth**
Tissue involved(5)	(Qualitative nominal) 3 categories MFJ/MTJ/T, codify 1/2/3	**MRI**
Previous injuries to the same muscle. (23)	(Qualitative nominal) dichotomous: Yes/Not, codify 0/1	**Clinical History**
Estimated Sports Absence **Forecast** (24)	(Quantitative discrete) in weeks	**MRI Inform(24)**

5.8-Description of the intervention

Subjects with muscle injuries assigned to the control group will follow a regressive return-to-play (RTP) design, while those assigned to the intervention group will follow a progressive RTP program. The independent (secondary) variables will be recorded in the database after diagnosis with an MRI. Subsequently, the dependent (main) variables will be measured and recorded at the beginning, middle, and end of the RTP period. The following scheme illustrates the dynamics of the clinical trial.



5.9-Timeline and expected completion date. Distribution of tasks among the members of the research team.

-05/2025 to 08/2025 Task 1 Literature review, design (sample size calculation, protocols, intervention/control group and randomization) following CONSORT statement (25), approval by the Ethics Committee and registration of the clinical trial.

-08/2025 to 09/2025 Task 2 Collection and preparation of the material; questionnaires, cortisol salivary kit, Oura Ring, creation of the database by categorizing and coding the variables for optimal operation and registration.

-09/2025 Task 3 Start the trial, recruitment with consecutive sampling (muscle injury episode), MRI, randomization, registration and measurement of variables.

-03/2027 Task 4 It is estimated that half of the necessary sample size has been reached: approximately 37 subjects with muscle injury. The first statistical analysis will be carried out to observe preliminary results.

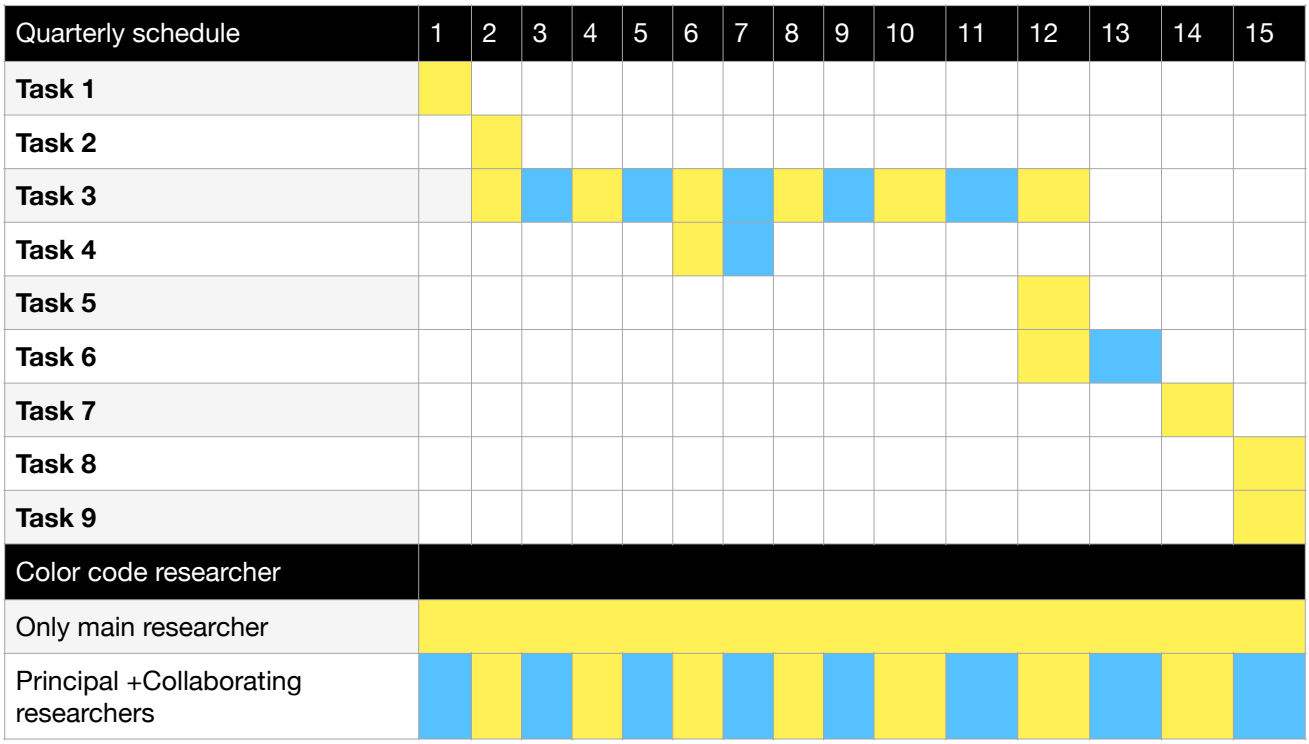
-09/2028 Task 5 After three years it is expected to have reached the N=74 size necessary for the sample to be representative.

-09/2028-12/2028 Task 6 Complete statistical analysis.

-12/2028-02/2029 Task 7 Writing the manuscript with the results obtained.

-02/2029-05/2029 Task 8 Submission to journal, corrections by reviewers and publication.

-05/2029-06/2029 Task 9 Presentation of results at an international congress.



5.10- Statistical analysis plan

-Phase 1: Levene's test to test the equality of variances between control and intervention groups.

-Phase 2: Student's t-test to determine whether there is a significant difference between the means of the control and intervention groups and to establish the H_0 or H_A as true.

-Phase 3: Perform a bivariate study between the dependent variable anxiety and the independent variable estimated prognosis, through Pearson's correlation coefficient.

-Phase 4: Conduct a multivariate study through multiple regression between the dependent variable sleep quality and the independent variables age, type of affected tissue and the variable cortisol level.

-Phase 5: To perform a multivariate study through a simple linear regression between the dependent variable anxiety and the independent variable previous injuries in the same musculature.

6-Ethical and legal aspects

6.1-The investigator must comply with the Good Clinical Practice Standards, the Declaration of Helsinki, the Oviedo Convention, and the December 5, 2018, Law 3/2018 on the protection of personal data and the guarantee of digital rights, as well as the regulations for managing clinical histories.

The investigator undertakes to comply with the aforementioned rules throughout the development of the research protocol, as well as in the presentation to this ethics committee, for which the investigator has obtained a Good Clinical Practice (GCP) certificate. The collaborating investigators also have this GCP certificate.

6.2-Informed Consent Form (Annex 1 and 2)

Both the patient information sheet and the informed consent form are attached in Annexes 1 and 2.

6.3-Confidentiality of the information collected in the context of the study.

Data Controller: Óscar Vicente Rodríguez

TLF: 699 874 059

Email: oscarvicente90@gmail.com

Purpose of data collection: Clinical and epidemiological research.

Maximum period of data retention: The data will be kept for four years (three years for the duration of the study and one extra year for future research).

Processing, communicating, and transferring the personal data of all participating subjects will comply with the provisions of Organic Law 3/2018 of December 5 on the protection of personal data and the guarantee of digital rights.

In accordance with the aforementioned legislation, you may exercise your rights of access, rectification, deletion, opposition, and limitation of data processing. You may also transfer your data to an authorized third party (data portability). For more information, please contact the principal investigator responsible for processing at oscarvicente90@gmail.com or at C/Moreno Torroba 10, 1o B, CP. 28220 Majadahonda, Madrid.

Your data will be computerized and incorporated into an automated personal data system that complies with all security measures for restricted access, as described in this document.

To guarantee the confidentiality of the obtained information:

Your data and the sample will be identified by a code, and only the study physician and their collaborators will be able to relate this data to you and your medical history. Therefore, your identity will not be disclosed to anyone except in case of medical emergency or legal or administrative requirement.

Only the essential data necessary for the study will be transmitted to third parties and other countries. In no case will the data contain information that can directly identify you, such as your name, initials, address, or social security number. If this transfer occurs, it will be for the aforementioned study purposes and will guarantee confidentiality with at least the level of protection guaranteed by the legislation in force in our country.

Access to your personal information will be restricted to the study physiotherapist, collaborators, health authorities, the Balearic Islands Research Ethics Committee, and authorized personnel when required to verify the study's data and procedures, always maintaining confidentiality in accordance with current legislation.

You may contact the Spanish Data Protection Agency with any claims related to the processing of your personal data.

6.4-Handling of biological samples in accordance with Law 14/2007 and Royal Decree 1716/2011

Saliva samples to determine cortisol levels will be collected at the Ciudad Deportiva Atlético de Madrid clinic on three occasions: at the beginning of the RTP, after the magnetic resonance diagnosis, in the middle of the established prognosis, and the day before the end of the RTP. The analysis will be performed at the same clinic, where, at the end of the cortisol measurement, the saliva will be discarded and only the recorded cortisol value will be kept.

Any risks associated with the procedure used to collect these samples are covered by the study insurance.

The samples will be coded and treated confidentially throughout this study. A code will be used to link the samples to you, and only the investigator and his staff will be able to decipher it to preserve your anonymity.

If additional data or samples are needed, your physiotherapist will contact you again to request your cooperation.

You will be informed of the reasons, and your consent will be requested again if necessary.

You will not receive any financial benefits from donating samples or transferring data, nor will you be entitled to commercial benefits from discoveries resulting from the research.

The samples will be analyzed at the Ciudad Deportiva Atlético de Madrid laboratory and stored for four years in case additional analyses related to the study's objectives are necessary. The person responsible for the samples will be the study promoter during this process.

At the end of the investigation, your sample may be destroyed.

-Destroyed

-Anonymized (i.e., the link between the sample and you will be completely destroyed so that neither the researcher nor any other team member will be able to identify who the sample belongs to again).

-Incorporated into a collection managed by researcher Óscar Vicente Rodríguez at Ciudad Deportiva Atlético de Madrid for continued use in the "Stress and Muscle Injury" study. - Stored in the biobank.

It may be stored in the Ciudad Deportiva Atlético de Madrid biobank for use in other research, possibly unrelated to the initial study for which consent was given. The biobank may transfer samples for authorized projects, possibly abroad, with prior favorable opinions from the scientific and biobank ethics committees. You may contact the biobank to obtain information on the projects in which your samples have been used.

6.5-Insurance policy or justification of absence for experimental studies

Mr. Óscar Vicente Rodríguez is the principal investigator with D.N.I. No. 35572548N, and member no. 1224, is registered in the Collective Policy of Professional Civil Responsibility, to which the Official College of Physiotherapists of the Balearic Islands adheres, with policy number 531000009 from A.M.A. (Agrupación Mutual Aseguradora — La Mutua de los Profesionales Sanitarios). Annex 3.

6.6-Commitment to publish results

The principal investigator is committed to publishing the results, regardless of their nature, since there is no conflict of interest. The present trial will be part of the principal investigator's (doctoral student) thesis. Therefore, this fact guarantees the publication of the results, which will improve the design of the RTP process.

7-Financial Report and Sources of Financing

Resources	**€/ at 3 years**
Staff	
Statistical analysis team University of the Balearic Islands	0 €
Radiologist MRI report (Free to club)	0 €
Specific resources	
Kit Elisa Cortisol Saliva (96 tests) 3 x 345.15€	1035.45€
MRI radiological tests (Free for club)	0 €
Ethics Committee of the CEIm, University of the Balearic Islands fee exempt	0 €
Devices	
Oura Ring (Quality of sleep) 2 x 400€.	800 €
The cost of the data logging tablet and GAD-7 is 2 x 700€.	1400 €
TOTAL TO BE COVERED BY THE MAIN RESEARCHER	**3235.45€**

The project has no private funding other than that provided by the main researcher, Oscar Vicente Rodríguez, as explained in the table above. The MRI and radiological report expenses are free for the club due to the nature of the entity itself, without any conflict of interest. The same happens with the team of statisticians that can be used for the analysis of results, which are part of the UIB, and collaborate with doctoral theses, and therefore works that are included in them as will be this essay. In relation to the CEIm of the Balearic Islands, this trial will be exempt from fees, (presented in the documentation) as it is part of studies of the Doctoral School of the UIB.

8-Data Collection Notebook (Annex 3)

The type of variables, their coding and measurement tools are explained in the tables in section 5.7-Main and secondary variables. The data collection notebook is attached as Annex 3. The GAD-7 anxiety measurement scale (19) is attached as Annex 4, the Cortisol measurement protocol with the Elisa test (22) Annex 5, the sleep quality measurement scale (21) Annex 6, and as for the estimated prognosis (radiological report) the classification of muscular lesions (24) is attached as Annex 7.

Annex 1

PATIENT INFORMATION SHEET FOR THE CONDUCT OF CLINICAL TRIALS

(Version No. 1, May 25, 2025)

Study title:```Muscle injury RTP design in football; effects of backward design vs forward design . A randomized controlled trial.''

Protocol code:

Sponsor: Óscar Vicente Rodríguez

Principal Investigator: Óscar Vicente Rodríguez

Position, unit, center: Physiotherapist Club Atlético de Madrid

Telephone: 699 874 059
E-mail: oscarvicente90@gmail.com

Introduction

We are writing to inform you about a study in which you are invited to participate. The study has been approved by the Balearic Islands Drug Research Ethics Committee in accordance with current legislation and will be conducted according to the principles outlined in the Helsinki Declaration and the standards of good clinical practice.

Our only intention is for you to receive sufficient and accurate information so that you can decide whether or not to participate in this study. Please read this information sheet carefully, and we will clarify any doubts you may have after the explanation. You may also consult the people you deem appropriate. If you have any questions, please contact Óscar Vicente Rodríguez.

General description

This clinical trial aims to evaluate the design of the return-to-play (RTP) process for muscle injuries. We will also attempt to establish causal relationships between variables.

To this end, a review of the literature was conducted and two models were identified. The most widely used model in sports, which aims to predict RTP time in a regressive manner by establishing clear, specific objectives based on the hypothetical discharge date (hereafter referred to as the control group).

The other working model, which is less popular, is one in which the objectives are set according to evolution, progressively and without being so inflexible. This model will be called the intervention group.

Once patients are diagnosed with a muscle injury via magnetic resonance imaging, they will be randomly assigned to the control or intervention group. Masking will be double-blind, meaning neither the patient nor the principal investigator will know which RTP design has been implemented.

During the RTP process, the following independent variables will be recorded at the beginning: age, type of tissue involved, previous injuries to the same muscle group, and estimated prognosis in weeks. Then, the dependent variables—cortisol, sleep quality, and anxiety—will be measured at three points in the RTP process: the beginning, middle, and end. These measurements will then be recorded in the database.

The required sample size is N = 74.

Alternative treatments

Both regressive and progressive RTP designs are generally used within an athlete's recovery.

The principal investigator of the study, Physiotherapist Oscar Vicente Rodriguez will give you more information if you wish.

Other relevant information

If any new information concerning the study's designs that could affect your willingness to participate is discovered during your participation, your physician will communicate it to you as soon as possible.

If you withdraw your consent to participate in the study, no new data will be added to the database, and you may request that all identifiable samples previously retained be destroyed to prevent further analysis.

Study managers may continue to use the information collected about you up to that point, unless you object.

You should also be aware that you may be withdrawn from the study if the study leaders deem it appropriate for safety reasons or due to an adverse event, or if they determine that you are not complying with established procedures. In either case, you will receive an adequate explanation for your withdrawal.

If you are withdrawn from the study for any of these reasons, your physician will prescribe treatment for your condition.

Al firmar la hoja de consentimiento adjunta, se compromete a cumplir con los procedimientos del estudio que se le han expuesto.

Benefits and risks of participating in the study

The benefits obtained from their participation in the study include improved RTP designs that are better adjusted to specific muscle injuries and beneficial interactions with dependent variables such as cortisol, sleep quality, and anxiety.

The risks associated with participation are minimal and do not increase with respect to the general RTP process design.

Saliva samples will be stored during the analysis process and then destroyed; the results will be kept for three years.

Insurance

The study's promoter, member number 1224, has a Collective Professional Liability insurance policy with the Official College of Physiotherapists of the Balearic Islands. The policy number is 531000009 with the company Agrupación Mutual Aseguradora — La Mutua de los Profesionales Sanitarios. It complies with current legislation and covers all damages that may occur in relation to participation in the study.

Confidentiality

Responsible for treatment: Óscar Vicente Rodríguez

TLF: 699 874 059

Email: oscarvicente90@gmail.com

Purpose of data collection: Clinical and epidemiological research.

Maximum period of data retention: The data will be kept for four years (three years for the duration of the study and one extra year for future research).

Processing, communicating, and transferring the personal data of all participating subjects will comply with the provisions of Organic Law 3/2018 of December 5 on the protection of personal data and the guarantee of digital rights.

In accordance with this legislation, you may exercise your rights of access, rectification, deletion, opposition, and limitation of data processing. You may also transfer your data to an authorized third party (data portability). For more information, please contact the principal investigator responsible for processing at oscarvicente90@gmail.com or at C/ Moreno Torroba 10, 1º B, CP. 28220 Majadahonda, Madrid.

Your data will be processed electronically and incorporated into an automated personal data system that complies with all security measures for restricted access, for the purpose described in this document.

To guarantee the confidentiality of the obtained information:

Your data and the sample will be identified by a code, and only the study physician and collaborators will be able to relate such data to you and your clinical history.

Therefore, your identity will not be disclosed to anyone except in the event of a medical emergency or if required by health administration or legal authorities.

Only the data necessary to conduct the study will be shared with third parties and other countries. In no case will the data contain information that can directly identify you, such as your name, initials, address, or social security number. If this transfer occurs, it will be for the aforementioned study purposes and to ensure confidentiality with at least the level of protection guaranteed by the legislation in force in our country.

Access to your personal information will be restricted to the study physiotherapist, collaborators, health authorities, the Balearic Islands Research Ethics Committee, and authorized personnel when required to verify the study's data and procedures, always maintaining confidentiality in accordance with current legislation.

You may contact the Spanish Data Protection Agency with any claims related to the processing of your personal data.

Financial compensation

Participation in the study is free of charge, and you will be reimbursed for any additional expenses, such as meals and travel.

Your physiotherapist will not receive any financial compensation for your participation in the study, and he or she has declared no conflict of interest.

Voluntary participation

You should know that your participation in this study is voluntary. You may choose not to participate, or you may change your mind and withdraw your consent at any time without providing an explanation. You may also request the destruction of the sample without affecting your relationship with your doctor or your treatment.

If you revoke your consent, no new data will be collected or new analyses performed on the sample. However, this revocation will not affect the research carried out up to this point.

Collection of biological samples

Saliva samples to determine cortisol levels will be collected at the Ciudad Deportiva Atlético de Madrid clinic on three occasions: at the beginning of the RTP, after the magnetic resonance diagnosis, halfway through the established prognosis, and the day before the RTP ends. The analysis will be performed at the same clinic, where, at the end of the cortisol measurement, the saliva will be discarded and only the recorded cortisol value will be kept.

Any risks associated with the procedure used to collect these samples are covered by the study insurance.

The samples will be coded and treated confidentially throughout this study. Only the investigator and his staff will be able to link the code to your identity.

If additional data or samples are needed, your physical therapist will contact you to request your cooperation. You will be informed of the reasons and asked for your consent again, if necessary.No percibirá ningún beneficio económico por la donación de las

muestras y la cesión de los datos aportados, ni tendrá derecho sobre posibles beneficios Commercial discoveries may result from the research.

The samples will be analyzed in the Ciudad Deportiva Atlético de Madrid laboratory and stored for four years in case additional analyses related to the study's objectives are necessary. The person responsible for the samples will be the study promoter during this process.

At the end of the research period, your sample may be:

- Destroyed

- Anonymized (i.e., the link between the sample and you will be completely destroyed so that neither the researcher nor any other team member will be able to identify to whom your sample belongs again).

-Incorporated into a collection managed by researcher Óscar Vicente Rodríguez at the Ciudad Deportiva Atlético de Madrid so that it can continue to be used in the "Stress and Muscle Injury" study and line of research.´

The samples are stored in the Ciudad Deportiva Atlético de Madrid biobank for use in other research projects, which may be unrelated to the initial study for which consent was given. The biobank may provide the samples to authorized projects, possibly abroad, with prior approval from the scientific and ethics committees. You may contact the biobank to obtain information on projects in which your samples were used.

Acknowledgment

No matter what you decide, the sponsor and research team would like to thank you for your time and attention. By participating, you are contributing to a better understanding and care of your disease, which may benefit many people in the future.

Annex 2

INFORMED CONSENT FOR THE CONDUCT OF CLINICAL TRIALS(Version No. 1, May 25, 2025)

Study Title: "*Muscle Injury RTP Design in Football: Effects of Backward Design vs. Forward Design.*" *A Randomized Controlled Trial.*" *PROMOTER CODE:*

Promoter Code: Promoter: Óscar Vicente Rodríguez

Principal Investigator: Óscar Vicente Rodríguez, Physiotherapist, Tel: 699 874 059, Email: oscarvicente90@gmail.com

Center: Ciudad Deportiva Atlético Madrid

I, (name and surname), have read the information sheet given to me.

I was able to ask questions about the study.
I have received sufficient information about the study. I have spoken with Óscar Vicente Rodríguez. I understand that my participation is voluntary.

I understand that I can withdraw from the study and request the destruction of my saliva cortisol, sleep monitoring, and anxiety state (GAD-7) results as long as they have not been anonymized.

-Without having to explain myself.

- Without impacting my medical care.

I understand that if I withdraw from the study, the results obtained up to that point can be used for cortisol in saliva, sleep monitoring, and anxiety state results (GAD-7). However, no new analyses will be carried out on my sample as long as it has not been anonymized.
If the research results provide data that may interest me or my family members, I would like to be informed.
I do not want to be informed, but I agree that my physician may contact my family members if the results affect them.
I understand that I have the rights of access, rectification, deletion, opposition, and limitation of data processing. I also have the right to data portability, which allows me to transfer my data to an authorized third party. These rights are in accordance with the provisions of Organic Law 3/2018 of December 5 on the protection of personal data and the guarantee of digital rights.

I freely give my consent to participate in the study and agree to the access and use of my data under the conditions detailed in the patient information sheet.

At the end of the investigation, mark my sample with an X.

0 Destroyed

Anonymized:

It will be incorporated into a collection for which Óscar Vicente Rodríguez is responsible. The collection is located at Ciudad Deportiva Atlético de Madrid and will continue to be used in the study of "Stress and Muscle Injury." Stored in the Ciudad Deportiva Atlético de Madrid biobank in order to be used in other research, possibly unrelated to the initial study for which I consented.

It may be stored in the Ciudad Deportiva Atlético de Madrid biobank for use in other research, possibly unrelated to the initial study for which I consented.

Patient´s signature:

Name: Date

Researchet´s signature:

Name: Date

Annex 3

DATA COLLECTION NOTEBOOK

ID Patient	Age	Tissue involved	Previous injuries	Estimated forecast	Anxiety Average 3 measures	Cortisol Average 3 measures	Sleep Average 3 measures
1M4L	30	2	1	3	Start 2 Half 1 Final 2	Start 3 Half 2 Final 4	Start 3 Half 2 Final 4

Annex 4 (19)

General Anxiety Disorder Assessment (GAD-7)

Name	Date

Over the last two weeks, how often have you experienced these symptoms?	Not at all	Several days	More than half the days	Nearly every day
Feeling nervous, anxious, or on edge?	☐ 0	☐ 1	☐ 2	☐ 3
Not being able to stop or control worrying?	☐ 0	☐ 1	☐ 2	☐ 3
Worrying too much about different things?	☐ 0	☐ 1	☐ 2	☐ 3
Trouble relaxing?	☐ 0	☐ 1	☐ 2	☐ 3
Being so restless that it is hard to sit still?	☐ 0	☐ 1	☐ 2	☐ 3
Becoming easily annoyed or irritable?	☐ 0	☐ 1	☐ 2	☐ 3
Feeling afraid as if something awful might happen?	☐ 0	☐ 1	☐ 2	☐ 3

Score	Risk level
0-4	Minimal anxiety
5-9	Mild anxiety
10-14	Moderate anxiety
15-21	Severe anxiety

Add the score for each column: + +

Total score:

If you checked any problems, how difficult have they made it for you to do your work, take care of things at home, or get along with other people?

☐ Not difficult at all ☐ Somewhat difficult ☐ Very difficult ☐ Extremely difficult

Notes

Annex 5 (22)

Cortisol
ELISA Kit Instructions

Please read all instructions carefully before beginning this assay

PRODUCT #402710

For Research Use Only

Store kit at 2-8°C at all times

Do not freeze kit components

DESCRIPTION

Cortisol, or hydrocortisone, is the primary corticosteroid secreted by the adrenal cortex. Cortisol is synthesized from cholesterol and may be found in the blood as free Cortisol or bound to corticosteroid-binding globulin. The release of Cortisol is controlled by ACTH, which is produced in the anterior pituitary. Plasma Cortisol levels are highest in the morning and decrease throughout the day. Cortisol concentration in the plasma also elevates in response to stress. Cortisol has an anti-inflammatory effect and aids in carbohydrate metabolism, renal function and the promotion of glucogenesis.

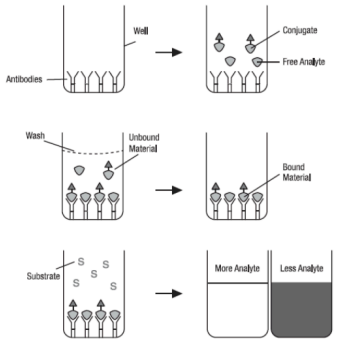
Measurement of plasma Cortisol levels is useful in diagnosing conditions related to functions of the adrenal cortex, including Cushing's syndrome (hypercortisolism), Addison's disease (hypocortisolism) and adrenal tumors. Abnormal Cortisol levels may also possibly be linked to prostate cancer, depression, and schizophrenia.

PRINCIPLE OF ASSAY

This is an ELISA (Enzyme-Linked ImmunoSorbent Assay) for the quantitative analysis of Cortisol levels in biological fluid. This test kit operates on the basis of competition between the enzyme conjugate and the Cortisol in the sample for a limited number of binding sites on the antibody coated plate.

The sample or standard solution is first added to the microplate. Next, the diluted enzyme conjugate is added and the mixture is shaken and incubated at room temperature for one hour. During the incubation, competition for binding sites is taking place. The plate is then washed removing all the unbound material. The bound enzyme conjugate is detected by the addition of substrate which generates an optimal color after 30 minutes. Quantitative test results may be obtained by measuring and comparing the absorbance reading of the wells of the samples against the standards with a microplate reader at 650 nm. The extent of color development is inversely proportional to the amount of Cortisol in the sample or standard. For example, the absence of Cortisol in the sample will result in a bright blue color, whereas the presence of Cortisol will result in decreased or no color development.

PRINCIPLE OF ASSAY (continued)



MATERIALS PROVIDED

1. EIA BUFFER: 30 mL. Provided to dilute enzyme conjugate and Cortisol standards.
2. WASH BUFFER (10X): 20 mL. Dilute 10-fold with deionized water. Diluted wash buffer is used to wash all unbound enzyme conjugate, samples and standards from the plate after the one hour incubation.
3. K-BLUE SUBSTRATE: 20 mL. Stabilized 3,3',5,5' Tetramethylbenzidine (TMB) plus Hydrogen Peroxide (H_2O_2) in a single bottle. It is used to develop the color in the wells after they have been washed. Keep substrate refrigerated. LIGHT SENSITIVE.
4. EXTRACTION BUFFER (5X): 30 mL. Dilute 5-fold with deionized water. This buffer is used for diluting extracted and non-extracted samples.
5. CORTISOL ENZYME CONJUGATE: 150 µL. Cortisol horseradish peroxidase concentrate. Blue capped vial.
6. CORTISOL STANDARD: 100 µL. Cortisol standard provided at the concentration of 1 µg/mL in methanol. Green capped vial.
7. CORTISOL ANTIBODY-COATED MICROPLATE: A 96 well Costar™ microplate with anti-Cortisol rabbit antibody pre-coated on each well. The plate is ready for use as is. DO NOT WASH!

MATERIALS NEEDED BUT NOT PROVIDED

1. 300 mL deionized water to dilute wash buffer and extraction buffer.
2. Precision pipettes that range from 10 µL-1000 µL and disposable tips.

NOTE: If all or several strips are to be used at one time, it is suggested that a multichannel pipette be used.

3. Clean test tubes used to dilute the standards and conjugate.
4. Graduated cylinders to dilute and mix wash buffer and extraction buffer.
5. Microplate reader with 650 nm filter.
6. Plate cover or plastic film to cover plate during incubation.

OPTIONAL MATERIALS:

7. 1 N HCl or Neogen's Red Stop Solution.
8. Microplate shaker.

If performing an extraction on samples, the following will be required:

9. Ethyl ether or ethyl acetate
10. Nitrogen gas
11. Vortex

WARNINGS AND PRECAUTIONS

1. DO NOT use components beyond expiration date.
2. DO NOT mix any reagents or components of this kit with any reagents or components of any other kit. This kit is designed to work properly as provided.
3. DO NOT pipette reagents by mouth.
4. Always pour substrate out of the bottle into a clean test tube - DO NOT pipette out of the bottle. If the pipette tip is unclean this could result in contamination of the substrate.
5. All specimens should be considered potentially infectious. Exercise proper handling precautions.
6. DO NOT smoke, eat or drink in areas where specimens or reagents are being handled.
7. Use aseptic technique when opening and removing reagents from vials and bottles.
8. Keep plate covered except when adding reagents, washing or reading.
9. Kit components should be refrigerated at all times when not in use.

PROCEDURAL NOTES

1. It is not necessary to allow reagents to warm to room temperature before use.
2. Desiccant bag must remain in foil pouch with unused strips. Keep zip-lock pouch sealed when not in use to maintain a dry environment.
3. Always use new pipette tips to pipette buffer, enzyme conjugate, standards and samples.
4. Before pipetting a reagent, rinse the pipette tip three times with that reagent (i.e. fill the tip with the desired amount of reagent and dispense back into the same vial - repeat 2 times). Now the tip is properly rinsed and ready to dispense the reagent into your well or test tube.
5. When pipetting into the wells, DO NOT allow the pipette tip to touch the inside of the well, or any of the reagents already in the well. This can result in cross contamination.
6. Standards and samples should be assayed in duplicate.
7. To quantitate, always run samples alongside a standard curve. If testing a sample that is not extracted, standards should be diluted in the same type of medium being tested. This medium should be known to be negative.
8. Gently mix specimens and reagents before use. Avoid vigorous agitation.
9. When using only partial amounts of a kit, it is recommended to transfer the appropriate volume of each reagent to a clean vessel for repeated dispensing. This will reduce reagent contamination caused by repeated sampling from the original container.
10. The enzyme conjugate is most stable in its concentrated form. Dilute only the volume necessary for the amount of strips currently being used.
11. Before taking an absorbance reading wipe the outside bottom of the wells with a lint-free wiper to remove dust and fingerprints.
12. Before opening the enzyme conjugate and standard vial, tap vial in an upright position to remove any liquid in the cap.

SAMPLE PREPARATION

This assay is non-species specific. Usually, urine, oral fluid and tissue culture supernatant can be assayed directly by diluting them with the diluted extraction buffer. Plasma and most other mediums will need to be extracted.

EXTRACTION OF CORTISOL

1. Pipette 100 µL of plasma into a glass tube (10x75 mm) and add 1 mL of ethyl ether.
2. Vortex the tube for 30 seconds and then allow the phases to separate.
3. Transfer the organic phase into a clean glass tube and evaporate the solvent with a stream of N_2.
4. Dissolve the residue in 100 µL of diluted extraction buffer.
5. Dilute the extract 100 fold by adding 10 µL of the above extract into 990 µL of diluted extraction buffer.
6. Vortex and assay 50 µL in duplicates.
7. The values obtained are multiplied by 100 to give final ng/mL concentrations. If additional dilution is necessary, values must be multiplied by the additional dilution factor in order to calculate final ng/mL concentration.
8. If the concentration is higher than the high range of the standard curve, the samples in #6 need to be further diluted and reassayed.

NOTE: Extraction buffer must be diluted 5-fold with deionized water before use. Any precipitant present must be brought into solution before dilution.

TEST PROCEDURES

1. Prepare standards as follows:

Standard	Preparation
A	stock solution 1 µg/mL (Provided in green capped vial)
B	take 20 µL of A, add to 980 µL of EIA buffer and mix=20 ng/mL
C	take 200 µL of B, add to 1.8 mL of EIA buffer and mix=2 ng/mL
D	take 200 µL of C, add to 1.8 mL of EIA buffer and mix=0.2 ng/mL

Continue standard preparation following Scheme I.

SCHEME I

Standards	ng/mL	EIA buffer (µL added)	B standard µL	C standard µL	D standard µL
S_0	0	as is	-	-	-
S_1	0.04	800	-	-	200
S_2	0.1	500	-	-	500
S_3	0.2	-	-	-	as is
S_4	0.4	800	-	200	-
S_5	1	500	-	500	-
S_6	2	-	-	as is	-
S_7	10	500	500	-	-

2. Determine the number of wells to be used.
3. Dilute the Cortisol enzyme conjugate. Add 1µL of enzyme conjugate into 50 µL total volume of EIA buffer for each we assayed. For the whole plate, add 110 µL of the enzyme conjugate into 5.5 mL total volume of EIA buffer. Mix th

4. Add 50 µL of standards (S) or unknown (U) (some samples may require diluting) to the appropriate wells in duplicate. See Scheme II for suggested template design.
5. Add 50 µL of the diluted enzyme conjugate to each well. Use 8-channel pipette or 12-channel pipette for rapid addition.
6. Mix by shaking plate gently. A microplate shaker may be used.
7. Cover plate with plastic film or plate cover and incubate at room temperature for one hour. NOTE: Keep plate away from drafts and temperature fluctuations.
8. Dilute concentrated wash buffer with deionized water (i.e. 20 mL of wash buffer plus 180 mL of deionized water). Mix thoroughly.
9. After incubation, dump out the contents of the plate. Tap out contents thoroughly on a clean lint-free towel.
10. Wash each well with 300 µL of the diluted wash buffer. Repeat for a total of three washings. An automated plate washer can be used, however, increase wash cycles from three to five.
11. Add 150 µL of substrate to each well. Use multichannel pipette for best results. Mix by shaking plate gently.
12. Incubate at room temperature for 30 minutes.
13. Gently shake plate before taking a reading to ensure uniform color throughout each well.
14. Plate is read in a microplate reader at 650 nm. If a dual wavelength is used, set W_1 at 650 nm and W_2 at 490 nm.
15. If accounting for substrate background, use 2 to 8 wells as blanks with only substrate in the wells (150 µL/well). Subtract the average of these absorbance values from the absorbance values of the wells being assayed.

NOTE: Some microplate readers can be programmed to do these subtractions automatically when reading the plate. Consult your instrument manual.

OPTIONAL TEST PROCEDURES

16. Add 50-100 µL of 1 N HCl or Neogen's Red Stop Solution to each well to stop enzyme reaction.
17. Read plate at 450 nm, if 1N HCl solution was used. Read plate at 650 nm, if Neogen's Red Stop Solution was used.
18. Plot the standard curve and estimate the concentrations of the samples from the curve. See "CALCULATIONS."

NOTE: Absorbance readings will approximately double when stopped with acid. If absorbance readings are too high for measuring with your microplate reader, decrease the substrate incubation by approximately 10 minutes but no more than 15 minutes.

SCHEME II

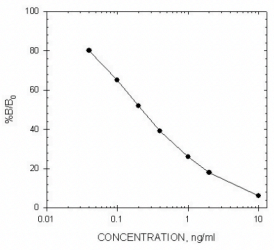
	1	2	3	4	5	6	7	8	9	10	11	12
A	$^{S}0$	$^{S}0$	$^{U}1$	$^{U}1$	$^{U}9$	$^{U}9$	$^{U}17$	$^{U}17$	$^{U}25$	$^{U}25$	$^{U}33$	$^{U}33$
B	$^{S}1$	$^{S}1$	$^{U}2$	$^{U}2$	$^{U}10$	$^{U}10$	$^{U}18$	$^{U}18$	$^{U}26$	$^{U}26$	$^{U}34$	$^{U}34$
C	$^{S}2$	$^{S}2$	$^{U}3$	$^{U}3$	$^{U}11$	$^{U}11$	$^{U}19$	$^{U}19$	$^{U}27$	$^{U}27$	$^{U}35$	$^{U}35$
D	$^{S}3$	$^{S}3$	$^{U}4$	$^{U}4$	$^{U}12$	$^{U}12$	$^{U}20$	$^{U}20$	$^{U}28$	$^{U}28$	$^{U}36$	$^{U}36$
E	$^{S}4$	$^{S}4$	$^{U}5$	$^{U}5$	$^{U}13$	$^{U}13$	$^{U}21$	$^{U}21$	$^{U}29$	$^{U}29$	$^{U}37$	$^{U}37$
F	$^{S}5$	$^{S}5$	$^{U}6$	$^{U}6$	$^{U}14$	$^{U}14$	$^{U}22$	$^{U}22$	$^{U}30$	$^{U}30$	$^{U}38$	$^{U}38$
G	$^{S}6$	$^{S}6$	$^{U}7$	$^{U}7$	$^{U}15$	$^{U}15$	$^{U}23$	$^{U}23$	$^{U}31$	$^{U}31$	$^{U}39$	$^{U}39$
H	$^{S}7$	$^{S}7$	$^{U}8$	$^{U}8$	$^{U}16$	$^{U}16$	$^{U}24$	$^{U}24$	$^{U}32$	$^{U}32$	$^{U}40$	$^{U}40$

CALCULATIONS

1. After the substrate background has been subracted from all absorbance values, average all of your duplicate well absorbance values.
2. The average of your two S_0 values is now your B_0 value. (S_1 now becomes B_1, etc.)
3. Next, find the percent of maximal binding (%B/B_0 value). To do this, divide the averages of each standard absorbance value (now known as B_1 through B_7) by the B_0 absorbance value and multiply by 100 to achieve percentages.
4. Graph your standard curve by plotting the %B/B_0 for each standard concentration on the ordinate (y) axis against
5. Divide the averages of each sample absorbance value by the B_0 value and multiply by 100 to achieve percentages.
6. Using the standard curve, the concentration of each sample can be determined by comparing the %B/B_0 of each sample to the corresponding concentration of Cortisol standard.
7. If the samples were diluted, the concentration determined from the standard curve must be multiplied by the dilution factor.

TYPICAL STANDARD CURVE

Cortisol in EIA Buffer



TYPICAL DATA

NOTE: "Typical data" is a representation. Variances in data will occur. Optical density readings may fluctuate during the shelf-life of the kit, but the %B/B_0 should remain comparable. Measuring wavelength: 650 nm

Standard	Standard Concentration (ng/mL)	Optical Density (Absorbance Value)	%B/B_0
S_0 (B_0)	0	1.235	100
S_1 (B_1)	0 .04	0.984	80
S_2 (B_2)	0.1	0.808	65
S_3 (B_3)	0.2	0.642	52
S_4 (B_4)	0.4	0.486	39
S_5 (B_5)	1	0.318	26
S_6 (B_6)	2	0.217	18
S_7 (B_7)	10	0.080	6

CROSS REACTIVITY

CORTISOL	100.0%
PREDNISOLONE	47.4%
CORTISONE	15.7%
11-DEOXYCORTISOL	15.0%
PREDNISONE	7.83%
CORTICOSTERONE	4.81%
6ß-HYDROXYCORTISOL	1.37%
DEOXYCORTICOSTERONE	0.94%
PROGESTERONE	0.06%
BETAMETHASONE	0.05%
DEHYDROEPIANDROSTERONE	0.03%
DEXAMETHASONE	0.03%
BECLOMETHASONE	0.01%
d-ALDOSTERONE	0.01%
TESTOSTERONE	0.01%
17 -HYDROXYPREGNENOLONE	<0.01%
ANDROSTENEDIONE	<0.01%
CHOLESTEROL	<0.01%
ESTRADIOL	<0.01%
ESTRIOL	<0.01%
ESTRONE	<0.01%
PREGNENOLONE	<0.01%

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TECHNICAL ASSISTANCE

Technical assistance is available Monday-Friday, between 8:00 a.m. and 6:00 p.m. EST.

Annex 6 (21)

The Oura Ring's validated sleep quality scale.

Table 5. Sensitivity, specificity, positive predictive values, negative predictive values, and accuracy of epoch-by-epoch sleep stage classification by the Oura Ring Generation 3 with Oura Sleep Staging Algorithm 2.0 worn on the non-dominant and dominant hand, respectively, compared to polysomnography.

Oura Ring Gen3 non-dominant hand	Sensitivity	Specificity	PVS	PVW	Accuracy	Prevalence- and bias adjusted Kappa
Sleep vs wake	94.5%	73.0%	95.9%	67.0%	91.7%	0.83
Light sleep vs remaining epochs	76.7%	74.4%	75.4%	75.7%	75.5%	0.51
Deep sleep vs remaining epochs	64.0%	93.7%	67.6%	92.7%	88.6%	0.77
R sleep vs remaining epochs	72.6%	94.9%	77.2%	93.6%	90.6%	0.81
Oura Ring Gen3 dominant hand						
Sleep vs wake	94.4%	74.6%	96.1%	66.6%	91.8%	0.84
Light sleep vs remaining epochs	76.8%	74.5%	75.5%	75.8%	75.6%	0.51
Deep sleep vs remaining epochs	64.5%	93.8%	68.1%	92.8%	88.9%	0.78
R sleep vs remaining epochs	71.9%	95.1%	78.1%	93.3%	90.6%	0.81

Abbreviations: PVS=predictive value for sleep; PVW=predictive value for wake.

Annex 6 (24)

BAMIC muscle injury classification

BAMIC	
Gradel 0 (a/b)	Imaging normal/patchy edema
Grade 1a (myofascial), 1b (myotendinous)	<10% CSA; <5 cm of length
Grade 2a (myofascial), 2b (myotendinous)	10%-50% CSA; 5-15 cm of length; fiber disruption 1-5 cm
Grade 2c (tendinous)	<50% tendinous CSA; <5 cm of length
Grade 3a (myofascial), 3b (myotendinous)	>50% CSA; >15 cm of length; fiber disruption >5 cm
Grade 3c (tendinous)	>50% tendinous CSA; <5 cm of length
Grade 4c	Complete tear

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