Effectiveness of Stromal Vascular Fraction (SVF) and Platelets Rich Plasma (PRP) in patients with Osteoarthritis: Study protocol for a phase III, prospective, randomized, controlled multi-center study: (SPOST study).

Adrien Schwitzguebel, David Andres Ramirez Cadavid, Charles Benaim, Tamara Da Silva, Pierre Decavel

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Abstract

Background: Available evidence on the conservative treatment of osteoarthritis still leaves the place for questioning on the efficacy of Platelet-Rich Plasma (PRP) and on whether Stromal Vascular Fraction (SVF) offers a superior therapeutic tool.

Objective: To assess the clinical efficacy of SVF as adjuvant therapy to PRP on functionality and tissue regeneration for osteoarthritis.

Methods: In a multi-centric, randomized, triple-blind controlled trial, 130 individuals with osteoarthritis will be block-randomized in a 1:1 ratio. Patients will receive an initial single PRP or PRP + SVF injection, followed by one- and two-months PRP doses. The primary endpoint is the functional improvement measured with the Single Assessment Numeric Evaluation (SANE) scale at 6 months follow-up. The secondary endpoints, gathered at 3, 6, and 12 months follow-up will include clinical outcomes: Low Extremity Functional Scale (LEFS) and Quick Disabilities of the Arm, Shoulder and Hand (quick-DASH) score, Pain Visual Analogue Scale (VAS) during maximal physical activity, SANE, the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) (in knee osteoarthritis cases), return to work and to sports in days; and Magnetic Resonance Imaging (MRI) AMADEUS score at 6 months and at 12 months.

Results: Participants recruitment and data collection is expected to begin in August 2024. Final end-points will be gathered in august 2027.

Conclusions: The study results will provide insight into the clinical efficacy of SVF as adjuvant therapy to PRP on functionality and tissue regeneration in osteoarthritis. This trial is registered on ClinicalTrials.gov (NCT05660824) and SNCTP Clinical Trial: This trial is registered on ClinicalTrials.gov (NCT05660824) and SNCTP.

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Abstract

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Trial Registration: This trial is registered on ClinicalTrials.gov (NCT05660824) and will be registered on the Portal for clinical trials in Switzerland (SNCTP).

Keywords: Stromal Vascular Fraction (SVF); Platelet-Rich Plasma (PRP); osteoarthritis

Introduction

Osteoarthritis, the most common joint disease [1], has a high social and individual impact and the development of therapeutic options is a public health priority. It's multifactorial etiology is still a source of active research[2, 3]. Most common conservative treatments for osteoarthritis treatment include pain killers, active physical therapies, orthotics, infiltrations of corticosteroids, hyaluronic acid (HA), and platelet-rich plasma (PRP) [1][4].
PRP may be beneficial in osteoarthritis by interfering with catabolic and inflammatory events and by subsequently promoting anabolic responses. Activation of PRP releases biologically active components, including platelet-derived growth factor (PDGF), transforming growth factor-β (PGF-β), type I insulin-like growth factor (IGF-1) and vascular endothelial growth factor (VEGF). These proteins are responsible for a range of critical tissue healing roles such as chondrocyte and mesenchymal stem cells proliferation, bone and vessel remodelling, inflammatory modulation and collagen synthesis[5].
For osteoarthritis, an improvement of clinical outcomes has been found in several clinical trials[6] [7], presumably associated with the chondroprotective effect of PRP. Nevertheless, an in-vivo effect

on human cartilage regeneration is not yet demonstrated despite the numerous studies approaching the subject [8].

Preclinical models elucidated how injected Adipose Derived- Mesenchymal Stem Cells (AD-MSC) coordinate the cartilage regeneration process [9-11] through paracrine mechanisms [12], producing cytokines and trophic bioactive factors that stimulate cellular proliferation, reduce inflammation, fibrosis, oxidative stress, and chondrocytes senescence [1].
The choice of AD-MSC instead of Bone Marrow Mesenchymal Stem Cells for the treatment of osteoarthrosis and tendinopathies is supported by a better hypoxic tolerance, less immunologic and inflammatory responses [13], better chondrogenic inductions and gene expressions [14], and a less variable and a more reliable clinical result [13].
Stromal Vascular Fraction (SVF), a product from specific adipose tissue processing, contains mesenchymal stem cells, endothelial precursor cells, T regulatory cells, macrophages, smooth muscle cells, pericytes and preadipocytes. SVF extraction and injection techniques have been recently used as an alternative to harvest AD-MSC due to its logistic simplicity and feasibility in clinical practice.
SVF injections produce a clinically significant effect on the treatment of knee osteoarthritis [15], and a possible improvement in cartilage quality [16, 17].

Objectives
1) To assess the clinical efficacy of SVF as adjuvant therapy to PRP on functionality for osteoarthritis.
2) To assess the clinical efficacy of SVF as adjuvant therapy to PRP on tissue regeneration for osteoarthritis.

Methods

Study design

This multicenter, parallel-group, triple-blind study will enroll 130 patients who will be randomly assigned in a 1:1 ratio to either the intervention or control group using stratified randomization. The study will employ a superiority framework.

The follow-up will last 12 months, with endpoints at 1, 2, 3, 6, and 12 months.

Study setting

In this multicentric study, we aim to recruit all patients between July 2025 and July 2026 in the Sports Medicine Division, La Providence Hospital, and in the Rehabilitation division, Hôpital Fribourgeois, both in Switzerland. The lead center is the Sports Medicine Division of La Providence Hospital where Dr. Adrien Schwitzguébel is the Sponsor- Investigator. All the interventions will be performed in the lead center.

Eligibility criteria

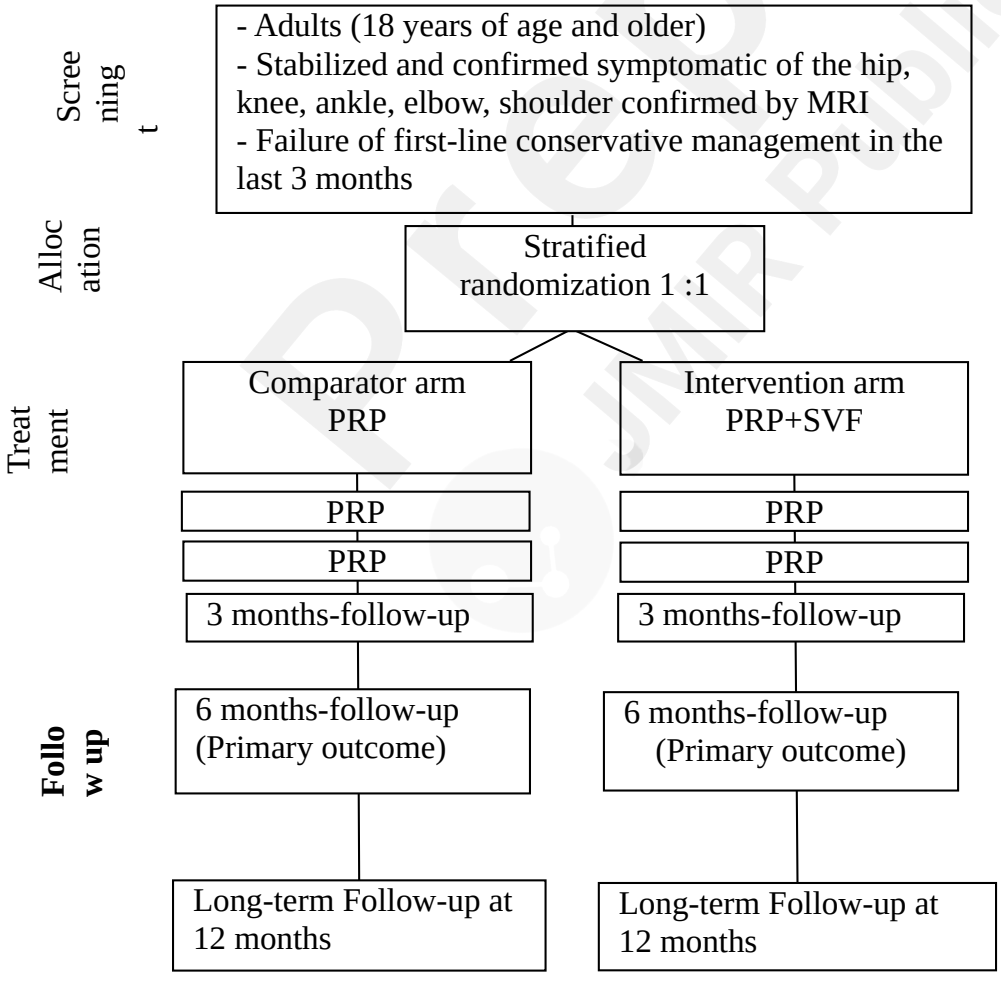
Patients will be recruited if suffering from osteoarthritis with persistent symptoms despite a proper first-line treatment (i.e. active physical therapies, sports and daily activities adaptation, orthotics use, medication), and when a surgical procedure is not indicated or retained.
The main following inclusion criteria will be applied: (i) age older than 16 years old,
(ii) symptomatic osteoarthritis of the hip, knee, ankle, elbow, shoulder confirmed by MRI, (iii) failure of first-line conservative management in the last 3 months including medical or infiltrative treatment, orthotics use, active rehabilitation plan, adaptation of sports and work habits.
The main following exclusion criteria will be applied: (i) patient is familiar with the lipoaspiration process (ii) significant disease of the contralateral member with a function evaluated with SANE score below 80%, (iii) co-existence of microcrystalline disease (i.e. gout, pseudogout), (iv) active inflammatory rheumatic disorders, (v) need of regular anti-inflammatory treatment (either NSAIDs or corticosteroids) or anticoagulants, (vi) patients with decompensated renal failure, hepatic dysfunction, or severe pulmonary or cardiovascular disease, (vii) patients with an immunocompromised status, and (viii) women who are pregnant or intend to become pregnant during the study.
If a bilateral disease is present and both sides require either the experimental or the control intervention, only the most symptomatic side will be studied.
The informed consent will be obtained by the local site investigator. Other physicians in connected structures (i.e., orthopedists, general practitioners, physiotherapists) are informed of the study and will be asked to refer patients to the referent sports medicine departments.

Interventions

In both study groups the intervention will be performed in the operations room under aseptic conditions as follows:
The patient is placed with a surgical drape hiding the interventional zone from patient's sight. The blinded investigator performs a 1.5 mm incision under local anesthesia on each abdomen side in order to introduce the cannula used to extract the SVF. 60 ml of tumescent solution are then injected to each side, after an interval of 20 minutes to allow the tumescent solution to act on the abdominal adipose tissue. At this point, in the experimental arm, the unblinded investigator extracts 30 ml of adipose tissue from the abdomen orifices. In the control arm, the unblinded investigator performs a sham adipose tissue extraction by introducing the extraction cannula and moving it 2 minutes in each side. Then, the venipuncture is performed, and 15 ml of blood is extracted for the PRP preparation. The blinded investigator prepares the SVF-PRP mixture or PRP alone. In parallel, the patient is prepared for the ultrasound-guided injection procedure. With a 18 gauge needle, the SVF-PRP mixture or PRP alone is injected.
Post-intervention care includes (i) partial discharge for 1 month in case of lower extremity osteoarthritis, (ii) active strengthening of the muscles without overloading the affected structures using, if possible, the blood-flow restriction technique and gentle non-weight bearing muscle activation including core stability exercises, (iii) mobility, and (iv) daily activities, work, and sports habits modification.
One- and two-months later, patients in both study arms will receive two additional ultrasound-guided PRP injections in the same joint. A total of 5 follow-up visits are planned for the study. Figure 1 shows study flow chart.
Anticoagulants (e.g aspirin), anti-inflammatory drugs (e.g ibuprofen, naproxen, meloxicam) should not be used 2 weeks before and 2 weeks after each injection as it can potentially interrupt the therapeutic acute inflammatory response and cytokines expected production.
Active physical therapies regimen, orthotics use, sports and daily activities are adapted to the patient,

on a day-by-day basis, during the post-intervention care.

Figure 1. Study Flow Chart.



Outcome measurements and assessments

The primary outcome is the functional improvement measured with the Single Assessment Numeric Evaluation (SANE) (18) scale at 6 months follow-up. A clinically relevant functional improvement is a difference of 10 points out of 100 points. Note: the SANE score is performed after showing the patient the results of the LEFS for inferior member or the QuickDASH score for superior member.
The secondary outcomes will be clinical parameters gathered at 6 months and 12 months follow-up:

- Low Extremity Functional Scale (LEFS) (19) for inferior member and Quick Disabilities of the Arm, Shoulder and Hand (quick-DASH) [20] score for superior member,
- Pain Visual Analogue Scale (VAS) during maximal physical activity performed by the patient according to manageable pain and clinical recommendations,
- Simple Assessment Numeric Evaluation (SANE) score at the different endpoints,
- In knee osteoarthritis cases, the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) [21],
- Return to work and to sports in days.

Assessment of the improvement of the affected cartilage quality using MRI and in the case of knee osteoarthritis the AMADEUS (Area Measurement And Depth & Underlying Structures) score [22] at 6 months and 12 months follow-up (previous MRI should not be dated more than 3 months before the intervention).

These parameters will be measured at every study site visit. It is initially planned to statistically assess the outcomes at 6 months and 12 months. However, assessment of these parameters at other timepoints might be subject to exploratory analysis.
Participant timeline is presented in Table 1.

Study Visits	**Screening**[a]	**Baseline**[b]	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Timing (± visit window) *M: Month(s) d: Days*	-3 weeks (+ 3 weeks)	0	1 M (± 7 d)	2 M (± 7 d)	3 M (± 7 d)	6 M (± 7 d)	12 M (± 7 d)
Informed consent	X						
In-/Exclusion Criteria	X						
Baseline characteristics[b]		X					
Clinical scores[c]		X	X	X	X	X	X
MRI		X				X	X
Randomization		X					
Lipoharvesting or sham lipoharvesting		X					
Intervention[d]		X					
PRP injection			X	X			
Concomitant medication		X	X	X	X	X	X
AEs and SAEs[e]		X	X	X	X	X	X

Table 1: Study assessments and procedures at study visits.

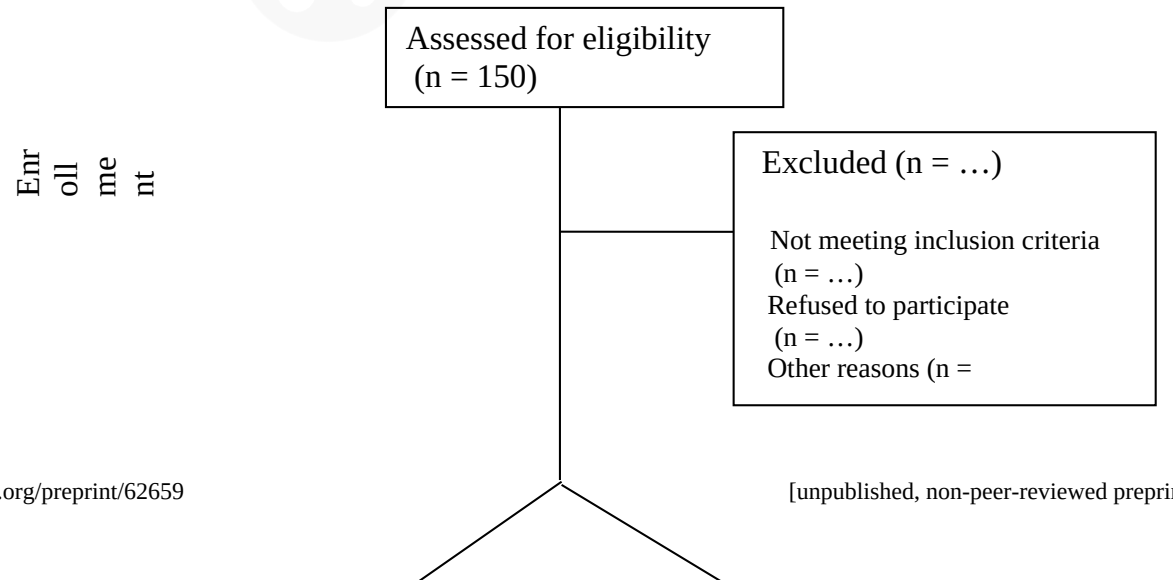
[a]**Screening and baseline visits** can be performed on the same day if patient has been given reasonable time to make a consented decision about participation in the study; [b] **Baseline characteristics**: Age, gender, height, weight, BMI, smoking status, comorbidities, Baseline Kellgren–Lawrence grade (knee osteoarthritis), current and previous treatments, post-traumatic etiology; [c]**Clinical scores collected:** Single Assessment Numeric Evaluation (SANE) score, Low Extremity Functional Scale (LEFS) for inferior member, Quick Disabilities of the Arm, Shoulder and Hand (quick-DASH) score for superior member, Pain Visual Analogue Scale (VAS) during maximal physical activity, Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) in knee osteoarthritis cases, Return to work and to sports in days, AMADEUS score, [d]**Intervention:** Experimental arm: SVF+PRP injection at baseline or Active comparator arm: PRP only injection at baseline; [e]**AEs and SAEs:** pain will be assessed as an AE of interest,

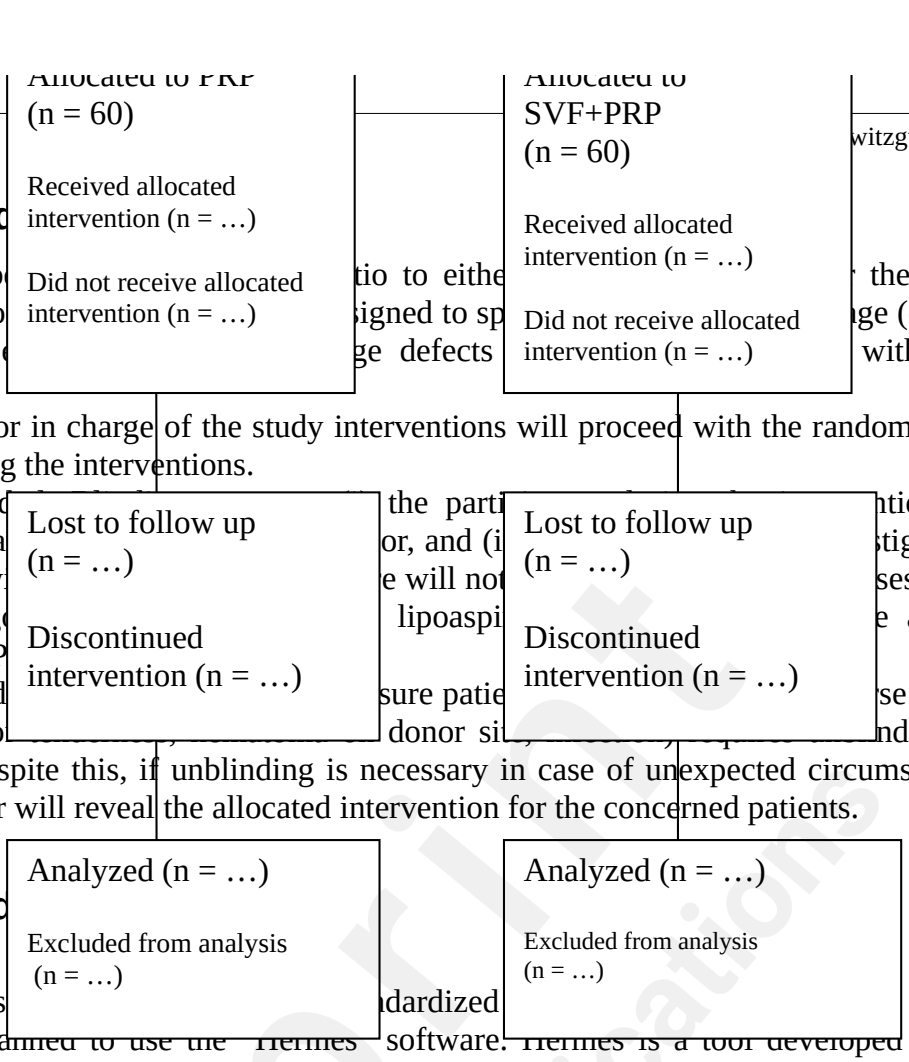
during intervention and 48 hours following the intervention.

Sample size

A sample size of 108 patients was determined using the online calculator “PS” [23].
We considered the SVF intervention as clinically relevant with an observed difference of 10 points out of 100 points of the SANE score. A standard deviation of 16 was evaluated based on preliminary analysis in La Providence Hospital (i.e. 16 for 300 patients treated with PRP for osteoarthritis). A power calculation using the “PS” software, and considering an independent analysis, a sample size of 108 is required to be able to reject the null hypothesis that this response difference is zero with a probability (power) of 0,90. The one-tailed Type I error probability associated with this test of the null hypothesis is 0,05. Considering a drop-out rate of 10% (mainly due to loss to follow-up), we calculated a final sample size of 119 patients. To obtain 119 evaluable participants approximately 150 will be screened (including potential screening failures and dropouts). Figure 2 shows de CONSORT (Consolidated Standards pf reporting Trials) diagram.

Figure 2. CONSORT diagram showing the flow of participants through each stage of the randomized trial.





Randomization and

Study participants will be randomized in a 1:1 ratio to either the active comparator arm. Each block will be assigned to stratify for age (over or under 40), presence of [illegible] defects and/or with bone deformation.
The unblinded investigator in charge of the study interventions will proceed with the randomization shortly prior to performing the interventions.
This study is triple-blinded [illegible] the participants, the outcome assessors and throughout the [illegible] duration, and (iii) the investigator in charge of the interventions will not participate in the assessment.
All patients will undergo [illegible] lipoaspirate and an ultrasonographic guided PRP.
It is expected that unblinding will not compromise patient safety as the adverse effects of the SVF (local pain or discomfort, hematoma at donor site, etc.) require the same standing for clinical management. Despite this, if unblinding is necessary in case of unexpected circumstances, the unblinded investigator will reveal the allocated intervention for the concerned patients.

Data collection and analysis

All data collected in this study will be recorded on standardized case report forms (CRF), see annexes 1-4. It is planned to use the "Hermes" software. Hermes is a tool developed by the Sponsor-Investigator (AS), used for patient registry and validated by the local Ethical Committee board (authorization # CERVD AO_2020-00006). Only data with logical numeric variables within the correct ranges or pre-defined categoric variables can be entered into the electronic CRFs. Data entry for variables of interest is mandatory.

CRFs will be kept current to reflect participant status at each phase during the course of the study. Study-related data will be collected in a coded manner (participants will not be identified in the CRF by name or initials). Identification of patients must be guaranteed at the study site. Patient's identification will be recorded in a sequential list stored in the local investigator's secured server. At the end of the study, when the database has been checked for completeness and validated by the Sponsor-Investigator, it will be locked and used for statistical analyses. All study essential documents (e.g., ICF, CRFs) will be archived for at least 10 years after completion of the clinical trial.
Data sharing is not applicable to this article as to date, no datasets were generated or analysed.

Statistical analysis

The absolute difference in the primary outcome (SANE score at 6 months) will be compared with paired Student or Wilcoxon test, depending on the variable distribution, with an intention-to-treat analysis. The absolute difference in secondary outcomes (changes from baseline to other time points) between the treatment and control groups will be evaluated with the appropriate statistical test (categorical variables: chi-squared, Fisher's exact; continuous variables: Student's or Wilcoxon rank tests). All analyses will be performed with an intention-to-treat and a per-protocol analysis. Estimates of effect, 95% confidence intervals and descriptive p values will be reported whenever possible. In addition, graphs will be presented whenever possible.

Post-hoc analysis will be performed to attempt to identify variables of interest using the appropriate global linear model.
Because the intervention is not considered at risk, no interim analysis is planned. In case of missing data concerning the primary outcome, patients will be withdrawn. Patients with missing data for any of the secondary outcomes will be kept in the study but will be excluded from the corresponding analysis.

Oversight and monitoring

For quality control of the study conduct and data retrieval, all study sites will have regular monitoring activities performed by appropriately trained and qualified monitors, outsourced by the Sponsor-Investigator. Monitoring activities consist of on-site monitoring as well as remote and centralized monitoring.
The objectives of a monitoring visit are:
1) to verify the Informed Consent Form process for each monitored participant;
2) to verify the prompt and accurate recording of all monitored data points, and prompt reporting of all safety events;
3) to compare collected data with participants' source documents; and
4) to ensure investigators are in compliance with the protocol.
The monitors may also inspect the clinical site regulatory files to ensure that regulatory requirements and applicable guidelines (ICH-GCP) are being followed.

Serious Adverse Event (SAEs) will be defined as any untoward medical occurrence that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. SAEs should be followed until resolution or stabilization. Assessment of Causality will be done based on the criteria listed in the ICH E2A guidelines[24] and severity will be graded based on the CTCAE (Common Terminology Criteria for Adverse Events) Version 5 [25]. All SAEs will be reported immediately and within a maximum of 24 hours to the Sponsor-Investigator of the study. The Sponsor-Investigator will re-evaluate the SAE and return the form to the co-investigator. SAEs resulting in death will be reported via Sponsor-Investigator to the Swiss Business Administration System for Ethics Committees (BASEC) and to the other in trial involved Ethics Committees within 7 days.

Regular audits are not planned. For the purpose of onsite inspection or audit, the competent authorities or ethics committee may require access to all source documents and other study-related records. The Sponsor-Investigator and the local investigators must ensure availability of these documents at any time.

Ethics and dissemination

The principal investigator will obtain approval from the competent authority (Swissmedic) before the start of the study. No changes to the protocol are made without prior Sponsor and the competent ethics committee approval, except when necessary to eliminate immediate hazards to participants.

The recruiting investigator explains the study's nature, purpose, procedures, duration, risks, benefits, and discomforts. Participation is voluntary, and subjects can withdraw anytime without affecting

their medical care. Each subject receives an information sheet and consent form to make an informed decision, with time to consult others and ask questions. Consent is obtained before any procedures, and the signed form is kept as part of the records. Participants are informed that authorized individuals may examine their medical records.
The investigator upholds the participant's right to privacy and complies with privacy laws, ensuring anonymity in scientific presentations and publications. Medical information from the study is confidential, and third-party disclosure is prohibited. Subject confidentiality is maintained using identification code numbers. Authorized representatives, such as those from Swissmedic or an ethics committee, may access relevant medical records for data verification.

Results

The current version of the study protocol, as presented in this article, is to be approved by the Switzerland regulatory authorities. Enrollment to the study is expected to begin in August 2024.

Discussion

The present study design allows to assess the potential benefits of SVF injection, an easy-to-use, simple and non-invasive cellular therapy on the most frequent joint disease. With this high-quality randomized controlled trial, SVF is compared to one of the mostly used non-invasive therapy in the field of sports medicine, PRP. Compared to PRP, cellular therapy with SVF needs a better training of the physician, fat lipo-aspiration, it is more time consuming, and therefore engenders higher costs. In other words, it requires more resources. In Authors point of view, patients and caregivers should only invest in the resources mentioned above in case of clearly demonstrated benefits, as to what the present study aims to contribute.

Different techniques have been used to inject or implant cellular therapy with mesenchymal stem cells (MSC) to the required site but there is not yet a consensus about the best use. However, biologically, some elements support the use of AD-MSC for non-bone tissue. AD-MSC would be theoretically more resilient than bone-marrow stem cells (BMSC) to the hypoxic articular cavity because they are less dependent on mitochondrial respiration for energy production. From an immunological perspective, AD-MSC should be preferable to BMSC since these could induce a higher immunological response due to their higher cell-surface human leukocyte antigen class I (HLA1) expression. AD-MSC highly expresses IL-33, which promotes regulatory T cell phenotype proliferation. This would theoretically mean a beneficial effect on anti-inflammatory effects [13].
Han X et al. compared AD-MSC with BMSC for knee osteoarthritis and found a superior therapeutic effect of AD-MSC compared to BMSC on VAS and WOMAC scores (26). Wenyan Zhou et al. performed a meta-analysis comparing AD-MSC and B-MSC therapies [13]. They found no statistical differences in clinical scores between the two therapies but did find a higher variability in BMSC results, suggesting AD-MSC as a more reliable therapeutic option. Ude et al. found better chondrogenic inductions and gene expressions with AD-MSC than with BMSC [14]. The interest of MSC is highlighted for its possible long-term chondroprotective or event chondro-regenerative effect. Indeed, in the 5 relevant meta-analyses assessing this point [27-31], in addition to good clinical outcomes in all cases, a stabilization of the chondral lesions was observed by W. Ma [30] and even a diminution was observed by B. Maheshwer [31]. An even more clear beneficial effect has already been proved on clinical parameters. In a recent meta-analysis including 18 randomized clinical trials (RCT) evaluating AD-MSC and SVF for the treatment of knee osteoarthritis, Agarwal et al. [15] found a statistically significant improvement in WOMAC scores by 62.11% [95% CI -72.68, -51.54, $Q = 93.51$, $p < 0.0001$] after twenty-four-month treatment.
To our knowledge, there are no RCTs directly comparing AD-MSC with SVF injections. A

retrospective observational study comparing AD-MSC and SVF for the treatment of knee osteoarthritis concluded a superiority of SVF [32].
The first main strength of our study design is the elevated sample size. Second, the generalization potential due to the inclusion of all major peripheral joints for osteoarthritis. Third, even if the pathologies and their localizations differ between the participants, our study population is well-designed and reproductible, with standardized diagnosis criteria, and a failure of a first-line standardized rehabilitation plan. Fourth, the multicentric design allows a better reproducibility of the patient selection and management, even if interventions are performed at the main study centre by a single investigator. This is however a study strength, as it will avoid bias related to the intervention techniques.
A sham lipoaspiration procedure with the patient awake is performed to maintain blinding in the control group. Despite all precautions taken to uphold allocation concealment, breaches may occur if the patient diligently questions the procedure. For ethical reasons, if at 6 months the progression is unsatisfactory, the intervention's nature may be disclosed if deemed clinically relevant, allowing the patient to benefit from SVF infiltration. Consequently, the study may be limited, as the initial 12-month secondary outcomes will not be considered in the final analysis. Second, the minimal clinically important difference was chosen as the limit to detect a clinically relevant difference for sample size calculation. From Authors point of view, even in the case of statistically significant positive effects of the treatment, the generalization of the procedure should be balanced by a complementary cost-effectiveness analysis. Indeed, in case of mild benefits, other procedures as strengthening, biomechanics adaptation, medication, annual PRP infiltrations, shockwave therapies, or even slight daily activities adaptation might be options of choice. One should be aware that cellular therapies should not be presented to patients as “magic potion” or “youth elixir”. Especially, Authors warn about the recognized risk of financial benefits based on overemphasized clinical promises. Third, a single-question score is used as primary outcome. One could argue that this method, selected by necessity due to the different pathologies and localizations included into the same statistical analysis, might lead to measurement bias. In order to reduce this risk, before the SANE assessment, the patient will be informed of his result to the QuickDASH score (superior member) or LEFS score (inferior member) before responding to the SANE score. Finally, the patient selection, the clinical follow-up and the rehabilitation plan might differ across the various recruitment centres (multicentric design).

Conclusions

This study will contribute data to establish the clinical relevance of SVF treatment for the most relevant disease of the musculoskeletal system.

Acknowledgements

A request for funding has been presented to the Swiss Medical Foundation.

Data Availability

All data requests should be directed to the corresponding author.

Authors' Contributions

David Ramirez, Adrien Schwitzguébel and Tamara Da Silva established the study design and wrote

the draft of the manuscript; Charles Benaim contributed to the protocol conception and to the statistical analysis, Pierre Decavel participated in the manuscript writing. All authors read and approved the final manuscript. Data management activities will be done by Adrien Schwitzguébel and David Ramirez. David Ramirez and Adrien Schwitzguébel contributed equally

Conflicts of interest

Authors declare that they have no competing interests regarding the present study.

References

1. Agarwal N, Mak C, Bojanic C, To K, Khan W. Meta-Analysis of Adipose Tissue Derived Cell-Based Therapy for the Treatment of Knee Osteoarthritis. *Cells*. Jun 1 2021;10(6)doi:10.3390/cells10061365

2. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*. Dec 1988;15(12):1833-40.

3. Binkley JM, Stratford PW, Lott SA, Riddle DL. The Lower Extremity Functional Scale (LEFS): scale development, measurement properties, and clinical application. North American Orthopaedic Rehabilitation Research Network. *Phys Ther*. Apr 1999;79(4):371-83.

4. Costa LAV, Lenza M, Irrgang JJ, Fu FH, Ferretti M. How Does Platelet-Rich Plasma Compare Clinically to Other Therapies in the Treatment of Knee Osteoarthritis? A Systematic Review and Meta-analysis. *Am J Sports Med*. Mar 2023;51(4):1074-1086. doi:10.1177/03635465211062243

5. Dai W, Leng X, Wang J, et al. Intra-Articular Mesenchymal Stromal Cell Injections Are No Different From Placebo in the Treatment of Knee Osteoarthritis: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Arthroscopy*. Jan 2021;37(1):340-358. doi:10.1016/j.arthro.2020.10.016

6. Emadedin M, Ghorbani Liastani M, Fazeli R, et al. Long-Term Follow-up of Intra-articular Injection of Autologous Mesenchymal Stem Cells in Patients with Knee, Ankle, or Hip Osteoarthritis. *Arch Iran Med*. Jun 2015;18(6):336-44.

7. Filardo G, Previtali D, Napoli F, Candrian C, Zaffagnini S, Grassi A. PRP Injections for the Treatment of Knee Osteoarthritis: A Meta-Analysis of Randomized Controlled Trials. *Cartilage*. Dec 2021;13(1_suppl):364s-375s. doi:10.1177/1947603520931170

8. Giorgino R, Albano D, Fusco S, Peretti GM, Mangiavini L, Messina C. Knee Osteoarthritis: Epidemiology, Pathogenesis, and Mesenchymal Stem Cells: What Else Is New? An Update. *Int J Mol Sci*. Mar 29 2023;24(7)doi:10.3390/ijms24076405

9. Guideline IHT. Clinical safety data management: definitions and standards for expedited reporting E2A. 1994:

10. Han X, Yang B, Zou F, Sun J. Clinical therapeutic efficacy of mesenchymal stem cells derived from adipose or bone marrow for knee osteoarthritis: a meta-analysis of randomized controlled trials. *J Comp Eff Res*. Apr 2020;9(5):361-374. doi:10.2217/cer-2019-0187

11. Hudak PL, Amadio PC, Bombardier C. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. The Upper Extremity Collaborative Group (UECG). *Am J Ind Med*. Jun 1996;29(6):602-8. doi:10.1002/(sici)1097-0274(199606)29:6<602::Aid-ajim4>3.0.Co;2-l

12. Jungmann PM, Welsch GH, Brittberg M, et al. Magnetic Resonance Imaging Score and Classification System (AMADEUS) for Assessment of Preoperative Cartilage Defect Severity. *Cartilage*. Jul 2017;8(3):272-282. doi:10.1177/1947603516665444

13. Kalamegam G, Memic A, Budd E, Abbas M, Mobasheri A. A Comprehensive Review of Stem Cells for Cartilage Regeneration in Osteoarthritis. *Adv Exp Med Biol*. 2018;1089:23-36. doi:10.1007/5584_2018_205

14. Kim SH, Djaja YP, Park YB, Park JG, Ko YB, Ha CW. Intra-articular Injection of Culture-Expanded Mesenchymal Stem Cells Without Adjuvant Surgery in Knee Osteoarthritis: A Systematic Review and Meta-analysis. *Am J Sports Med*. Sep 2020;48(11):2839-2849. doi:10.1177/0363546519892278

15. Kim SH, Ha CW, Park YB, Nam E, Lee JE, Lee HJ. Intra-articular injection of mesenchymal stem cells for clinical outcomes and cartilage repair in osteoarthritis of the knee: a meta-analysis of randomized controlled trials. *Arch Orthop Trauma Surg*. Jul 2019;139(7):971-980. doi:10.1007/s00402-019-03140-8

16. Kim YS, Koh YG. Injection of Mesenchymal Stem Cells as a Supplementary Strategy of Marrow Stimulation Improves Cartilage Regeneration After Lateral Sliding Calcaneal Osteotomy for Varus Ankle Osteoarthritis: Clinical and Second-Look Arthroscopic Results. *Arthroscopy*. May 2016;32(5):878-89. doi:10.1016/j.arthro.2016.01.020

17. Ma W, Liu C, Wang S, Xu H, Sun H, Fan X. Efficacy and safety of intra-articular injection of mesenchymal stem cells in the treatment of knee osteoarthritis: A systematic review and meta-analysis. *Medicine*. 2020;99(49):e23343-e23343. doi:10.1097/MD.0000000000023343

18. Maheshwer B, Polce EM, Paul K, et al. Regenerative Potential of Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis and Chondral Defects: A Systematic Review and Meta-analysis. *Arthroscopy*. Jan 2021;37(1):362-378. doi:10.1016/j.arthro.2020.05.037

19. Medicine VSo. Biostat.app.vum.org. Updated 27 Apr 2022. Accessed 22/10/2022, 2022.

20. Mizuno K, Muneta T, Morito T, et al. Exogenous synovial stem cells adhere to defect of meniscus and differentiate into cartilage cells. *J Med Dent Sci*. Mar 2008;55(1):101-11.

21. Muhammad SA, Nordin N, Mehat MZ, Fakurazi S. Comparative efficacy of stem cells and secretome in articular cartilage regeneration: a systematic review and meta-analysis. *Cell Tissue Res*. Feb 2019;375(2):329-344. doi:10.1007/s00441-018-2884-0

22. O'Connor CM, Ring D. Correlation of Single Assessment Numeric Evaluation (SANE) with other Patient Reported Outcome Measures (PROMs). *Arch Bone Jt Surg*. Jul 2019;7(4):303-306.

23. Park YB, Ha CW, Kim JA, et al. Single-stage cell-based cartilage repair in a rabbit model: cell tracking and in vivo chondrogenesis of human umbilical cord blood-derived mesenchymal stem cells and hyaluronic acid hydrogel composite. *Osteoarthritis Cartilage*. Apr 2017;25(4):570-580. doi:10.1016/j.joca.2016.10.012

24. Singh H, Knapik DM, Polce EM, et al. Relative Efficacy of Intra-articular Injections in the Treatment of Knee Osteoarthritis: A Systematic Review and Network Meta-analysis. *Am J Sports Med*. Sep 2022;50(11):3140-3148. doi:10.1177/03635465211029659

25. U.S. DOHAHS. Common Terminology Criteria for Adverse Events (CTCAE) v5.0. November 27, 2017 ed2017.

26. Ude CC, Sulaiman SB, Min-Hwei N, et al. Cartilage regeneration by chondrogenic induced adult stem cells in osteoarthritic sheep model. *PLoS One*. 2014;9(6):e98770. doi:10.1371/journal.pone.0098770

27. Xie X, Zhang C, Tuan RS. Biology of platelet-rich plasma and its clinical application in cartilage repair. *Arthritis Res Ther*. Feb 25 2014;16(1):204. doi:10.1186/ar4493

28. Yao Q, Wu X, Tao C, et al. Osteoarthritis: pathogenic signaling pathways and therapeutic targets. *Signal Transduct Target Ther*. Feb 3 2023;8(1):56. doi:10.1038/s41392-023-01330-w

29. Yokota N, Hattori M, Ohtsuru T, et al. Comparative Clinical Outcomes After Intra-articular Injection With Adipose-Derived Cultured Stem Cells or Noncultured Stromal Vascular Fraction for the Treatment of Knee Osteoarthritis. *Am J Sports Med*. Sep 2019;47(11):2577-2583. doi:10.1177/0363546519864359

30. Zhang W, Ouyang H, Dass CR, Xu J. Current research on pharmacologic and regenerative therapies for osteoarthritis. *Bone Res*. 2016;4:15040. doi:10.1038/boneres.2015.40

31. Zhou W, Lin J, Zhao K, et al. Single-Cell Profiles and Clinically Useful Properties of Human Mesenchymal Stem Cells of Adipose and Bone Marrow Origin. *Am J Sports Med*. Jun 2019;47(7):1722-1733. doi:10.1177/0363546519848678

32. Zwolanek D, Satué M, Proell V, et al. Tracking mesenchymal stem cell contributions to regeneration in an immunocompetent cartilage regeneration model. *JCI Insight*. Oct 19 2017;2(20)doi:10.1172/jci.insight.87322

Abbreviations

AE	Adverse event
AD-MSC	Adipose derived mesenchymal stem cells
AMADEUS	Area measurement and depth & underlying structures score

B-MSC	Bone marrow derived Mesenchymal stem cells
CRF	Case report form
DASH	Disabilities of the arm, shoulder and hand score
LEFS	Low extremity functional scale
MRI	Magnetic resonance imaging
PRP	Plasma-rich plasma
SANE	Single assessment numeric evaluation
SAE	Serious adverse events
SVF	Stromal vascular fraction
VAS	Visual analog pain scale
WOMAC	Western Ontario McMaster Universities osteoarthritis index

Appendices:

Appendix 1 : Participants Screening Case Report Form (CRF)

Appendix 2: Participants Enrollment Case Report Form (CRF)

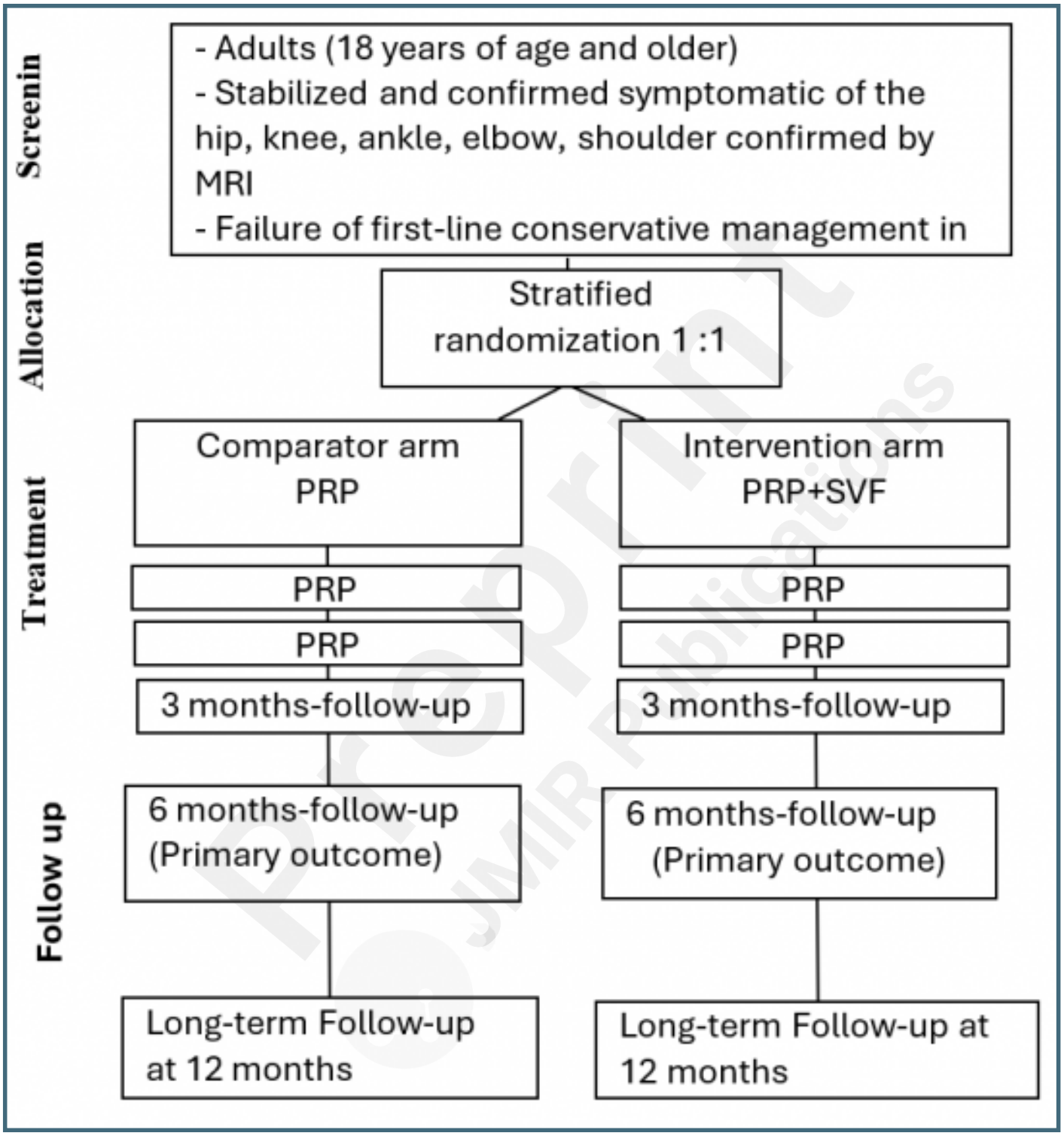
Appendix 3: Participants Follow-up Case Report Form (CRF)

Appendix 4: Averse Events and Serious Adverse Events Case Report Form (CRF)

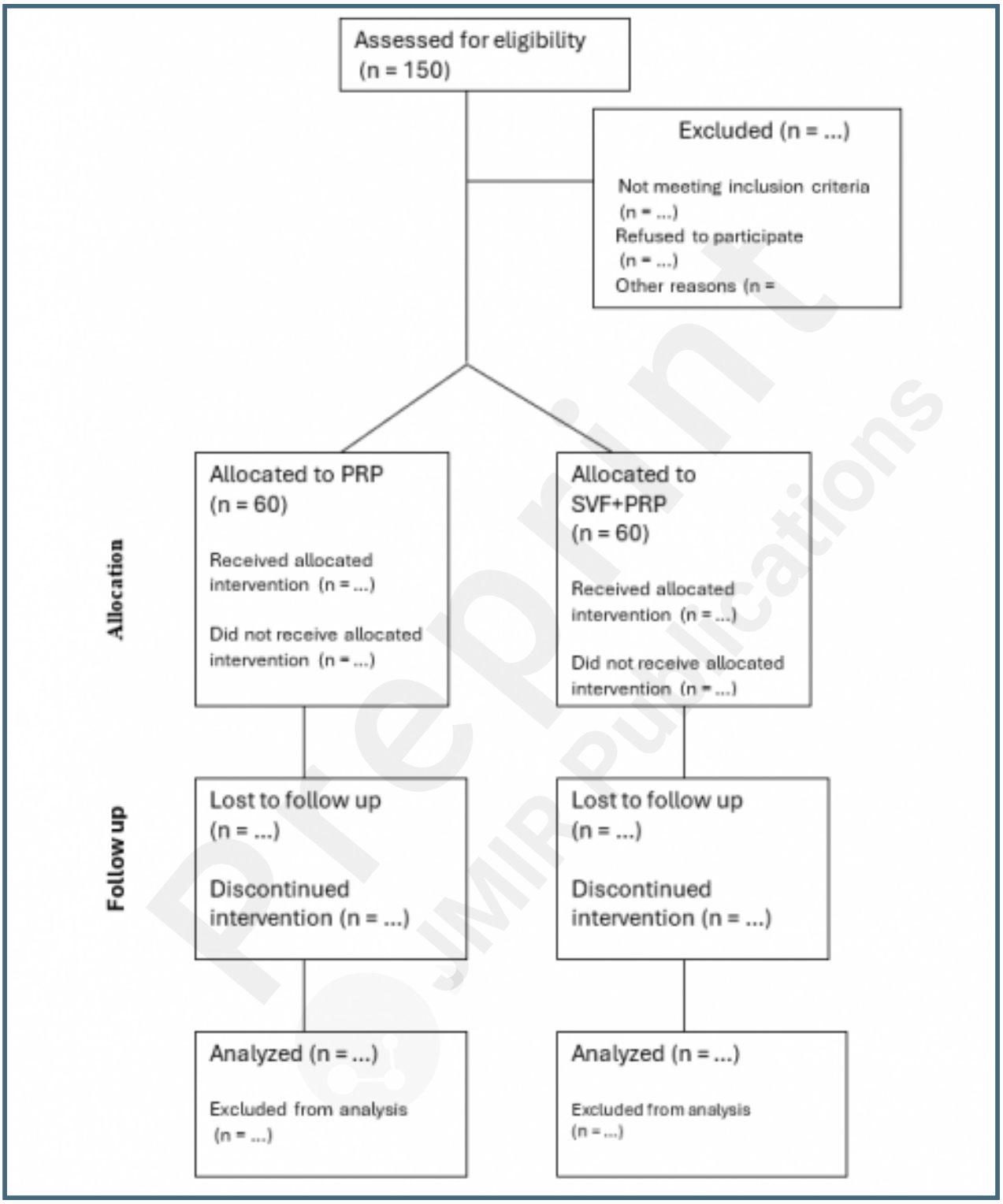
Supplementary Files

Figures

Study Flow Chart.



CONSORT diagram showing the flow of participants through each stage of the randomized trial.



Multimedia Appendixes

Participants Screening Case Report Form (CRF).
URL: http://asset.jmir.pub/assets/803183f3d533481f5a6048565ac12f2b.pdf

Participants Enrollment Case Report Form (CRF).
URL: http://asset.jmir.pub/assets/6a7bd3039a0aa64aa340130475438c5c.pdf

Participants Follow-up Case Report Form (CRF).
URL: http://asset.jmir.pub/assets/8bbaaa572a1b4ea94f3a644afb5f69b5.pdf

Averse Events and Serious Adverse Events Case Report Form (CRF).
URL: http://asset.jmir.pub/assets/c42869d060b14d60884a5e34b757d3b7.pdf