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Vitamin D supplementation in chronic spinal cord injury (VitD-SCI): study protocol for a randomized controlled trial

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Abstract

Introduction: Vitamin D insufficiency, a vitamin D status or serum 25(OH)D concentration of ≤ 75 nmol/L, is highly prevalent in individuals with a spinal cord injury (SCI). Vitamin D is important for the functioning of the musculoskeletal, immune, and respiratory systems, which are relevant determinants of secondary health conditions in SCI. An insufficiency should be treated with vitamin D supplementation. However, there is a lack of evidence regarding the optimal dosage and duration of vitamin D supplementation for individualized and long-term management of the vitamin D status in the context of SCI. This paper presents the protocol for the vitamin D supplementation in chronic spinal cord injury (VitD-SCI) trial that aims to investigate the effect of a 12-month intake of vitamin D supplementation on vitamin D status as well as several secondary parameters among individuals with a chronic SCI.

Methods and analyses: The VitD-SCI trial is a randomized, placebo-controlled, double-blinded, parallel-group, superiority trial, conducted at the Swiss Paraplegic Center. A total of 45 participants living with an SCI for at least three years (chronic SCI) and a verified vitamin D insufficiency at the first study visit, will be randomly assigned to one of three intervention groups. Participants receive either a monthly dosage of 24'000 IU or 48'000 IU vitamin D or a placebo for 12 months. Measurements taking place every three months include the assessment of vitamin D status (primary outcome) as well as bone mineral density, handgrip strength, fatigue, mood, pain, and pressure injuries (secondary outcomes). Safety and tolerance of vitamin D supplementation will also be evaluated.

Ethics and dissemination: The Swiss Ethics Committee for Northwest/Central Switzerland (EKNZ, 2020-01493) and the Swiss Agency for Therapeutic Products (Swissmedic, 2020DR3150) approved this study. Findings will be disseminated through peer-reviewed publications.

Trial registration: ClinicalTrials.gov (NCT04652544) and Swiss National Clinical Trials Portal (SNCTP000004032).

Article Summary

Strengths and limitations of this study

- The protocol presented here describes the first study to evaluate the effect of different dosages of 12-month vitamin D supplementation on serum 25(OH)D concentration, as well as several secondary functional and subjective outcomes among individuals with a chronic spinal cord injury (SCI).
- The design, a single-center, randomized, placebo-controlled, double-blinded, parallel-group, superiority study, together with rigorous inclusion/exclusion criteria and strict study procedures, allows for the acquirement of robust evidence.
- The adherence of participants to the protocol cannot be objectively assessed, because of the home-based setting.
- The evidence acquired during this study will provide valuable input for supplementation guidelines that will be transferable to individuals with chronic SCI living at similar latitudes.

Introduction

A suboptimal vitamin D status is prevalent in up to 93% of individuals with spinal cord injury (SCI) which is excessive compared to up to 40% among the general population.[1 2] This excessive prevalence can be explained by the adverse impact of SCI on physiological functioning, including altered metabolism and gastrointestinal functioning, and lifestyle behaviors, such as reduced physical exercise, outdoor activity, and sun exposure.[1 3] Vitamin D is important for the optimal functioning of the musculoskeletal and respiratory system as well as the regulation of innate and adaptive immune responses.[4-9] Particularly in the context of SCI, a lower vitamin D status has been associated with an elevated risk of respiratory illness, pressure injuries, and depression, as well as poor physical function and bone mineral density.[10-14] Therefore, the prevention of a vitamin D insufficiency, commonly defined as a vitamin D status of 75 nmol/L or less,[15] is of great concern regarding secondary health conditions in SCI.

Vitamin D supplementation is a promising intervention to reduce and prevent a vitamin D insufficiency as well as secondary complications,[2 4 16] yet the provision of such clinical guidelines in the context of SCI is currently hampered by a lack of evidence regarding the efficacy, as well as the optimal dosage and duration of the supplementation.[1 3] For the general non-SCI population (adults aged 19 – 70 years) a dosage of 600 IU – 800 IU/day has been recommended,[17-19] although other experts consider this dosage as suboptimal.[20 21] Among individuals with chronic SCI, a dosage of 800 IU/day for 12 months

failed to raise vitamin D status to sufficient levels.[22] Higher dosages of 2000 IU/day[23] or 6000 IU/day[24] during three months appeared more successful, but the respective studies did not investigate the long-term efficacy regarding vitamin D status or the lasting consequences for musculoskeletal and subjective health parameters. Though recommended,[25] vitamin D status is not regularly monitored among the chronic SCI population.

To close this evidence gap, we present the protocol for the vitamin D supplementation in chronic spinal cord injury (VitD-SCI) trial: a placebo-controlled randomized controlled trial that investigates the efficacy of a moderate (24'000 IU/month) and a high (48'000 IU/month) dosage of vitamin D supplementation for 12 months among individuals living with an SCI for at least three years (chronic SCI). Besides vitamin D status (primary objective), further assessments include bone mineral density, fatigue, pain, mood, performance of daily activities, and handgrip strength (secondary objectives). We hypothesize a dose-response effect of vitamin D supplementation on vitamin D status and anticipate that the evidence acquired during this study will effectively inform community-based policy regarding vitamin D supplementation in chronic SCI.

Methods and analyses

Study design and setting

The VitD-SCI trial is a placebo-controlled randomized double-blinded superiority study, evaluating the effect of 12 months of vitamin D supplementation on vitamin D status and several secondary outcomes among individuals with a chronic SCI (Figure 1). This protocol was designed according to the recommendations of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement (Supplement 1).[26] The study is planned to run from May 2021 until May 2023. Study visits take place at the Swiss Paraplegic Centre and participants will receive compensation for travel expenses. The VitD-SCI trial is a nested project of the population-based Swiss Spinal Cord Injury (SwiSCI) cohort study.[27]

Patient and public involvement statement

Patient and public organizations (e.g. SwiSCI), as well as clinicians from several specialized SCI centers, have been involved in the design of the study protocol. Study procedures, including the intervention and assessments, have been discussed and tested together with individuals with SCI.

Participants

The inception cohort of the SwiSCI cohort study (2013-present[28]) provides the sampling frame for participant recruitment for the VitD-SCI trial. Eligible are individuals who provided consent to be

contacted for future scientific studies and who fulfill the key VitD-SCI trial inclusion criteria, including a vertebral lesion level of C4 or below and time since SCI of at least 3 years. At present (May 2021), SwiSCI data indicate a sample of over 300 eligible individuals. Among individuals interested in participating, the remaining eligibility criteria (Table 1) will be checked. Women of childbearing age must show a negative pregnancy test at the start of the experimental supplementation and must use adequate contraception during the 12-month treatment phase of the study. Participants are not allowed to take additional vitamin D supplements (> 400 IU/day) or travel to countries with increased sun exposure (below the 37th parallel north) during the study. Informed consent will be obtained from all participants by qualified study employees. A blood sample will be taken to determine vitamin D status at the first visit (Month 0). Only individuals with an insufficient vitamin D status (≤ 75 nmol/L) will be randomized into one of the intervention groups.

Intervention

The trial consists of a three-armed intervention that applies a moderate or generally recommended dosage (24'000 IU vitamin D/month), and a high dosage (48'000 IU vitamin D/month) for comparison to placebo. Both dosages are prescribed in clinical practice and are within safe tolerable upper intake levels of 10'000 IU/day.[17 18 20] Previous studies among individuals with SCI implementing even higher dosages of vitamin D supplementation (up to 50'000 IU/week) did not report any safety issues.[23 24 29 30] The present study will further use a biweekly supplementation procedure, which showed superior adherence and accompanying efficacy over daily administration in achieving a sufficient vitamin D status.[31] The biweekly supplementation schedule is supported by vitamin D pharmacokinetics, which indicates a half-life of serum 25(OH)D of up to three weeks.[32]

As vitamin D supplement, the commercially available Vi-De 3® Monthly Dose (Dr. Wild & Co. AG (Muttenz, Switzerland) will be utilized. One vial (5 mL) contains an ethanol solution (65% alcohol by volume) with 600 µg cholecalciferol, which corresponds to 24'000 IU vitamin D_3. The similar ethanol solution without cholecalciferol will be utilized as a placebo. Both the vitamin D_3 supplement as well as the placebo will be filled in identical vials. An independent and specialized pharmacy will label the vials with a number that is indicative of the order of intake but indiscriminate regarding content, making the vials indistinguishable in odor, taste, and visual appearance. The first vial is to be taken within seven days after the first study visit. Participants are instructed to ingest one single vial every two weeks by emptying the vial in a glass of water and immediately drinking the solution. Participants of the high dosage group will take one vial with 24'000 IU vitamin D_3 every two weeks. Similarly, participants of the placebo group will take one vial with placebo every two weeks. Participants of the moderate dosage group will alternately take one vial with 24'000 IU vitamin D_3 or one vial with placebo every two weeks. Thus, an identical number of vials is assured across all intervention groups. To

promote compliance with the study protocol, participants will receive a reminder every two weeks to take the vials. Participants will also be requested to keep track of the intake of each vial in a study diary and return all (un)used vials to the study center.

Randomization and blinding

Participants will be randomly allocated on a 1:1:1 ratio into one of the three intervention groups, according to a permuted block randomization list with randomly varying block sizes (3 or 6) created using the module "ralloc" (version 3.7.6[33]) within Stata ([Computer program]. Version 16, College Station, Texas, USA: StataCorp, 2019). The allocation sequence will be securely stored and only accessible to an employee, who is not directly involved in the study. Participants and all study employees directly involved in the recruitment and measurements will be blinded to the assignment of the intervention until the end of the study ("last participant out"). Parameters, such as blood and bone mineral density parameters, which may reveal the allocation across the intervention groups, will only be available to employees who have no direct involvement in the study.

Outcomes and assessments

Assessment periods and details are specified in Table 2. The primary outcome is the differential change in vitamin D status from 0 to 12 months. Transitional vitamin D status will also be evaluated every three months.[21] To evaluate the secondary effects of vitamin D supplementation on the musculoskeletal system, differential changes in the following secondary outcomes will be assessed: relevant blood parameters (calcium, parathyroid hormone, ionized calcium, phosphate, cystatin, estimated glomerular filtration rate, testosterone), bone mineral density, functional independence, pressure injuries, handgrip strength, and falls. Differential changes in fatigue, mood, and pain will provide insight into the effect of vitamin D supplementation on subjective parameters. Individual parameters, including demographics, SCI characteristics, skin phototype, and sun exposure will also be collected. Assessments are performed during screening or each of the three-monthly visits, except for bone mineral density, which is measured at 0 and 12 months only to reduce radiation exposure. Serious adverse events will be documented throughout the participant's enrollment to evaluate the safety of the supplementation.

Sample size

We defined the minimal sample size as the sample size needed to detect a statistically meaningful difference in the time course of the primary outcome vitamin D status across the three intervention groups. For this, we estimated the sample size needed to detect an interaction between treatment and time across the three intervention groups using the power analysis package for repeated measures in STATA software, version 16.0 (College Station, TX, USA: StataCorp, 2019). The expected mean vitamin D status at each time point was calculated for each intervention group using the generalized

pharmacokinetic curve equation of Heaney, et al. (2001),[34] which we parametrized for the purpose of this study using the available data for vitamin D supplementation in chronic SCI.[23 35]

Assuming a significance level of 5% and a power of 0.80, minimal sample sizes were calculated for a range of between-group variances (i.e., 1000 to 3500, with 500 incremental steps) and correlations between repeated measures (i.e., 0.1 to 0.9, with 0.1 incremental steps; Supplement 2). Based on this power analysis for sample size, we conservatively plan for 45 participants with a full dataset, implying 15 participants in each of the three intervention groups. In the case of dropouts or a large amount of missing data for a given participant, recruitment will be continued until the minimal sample size of 15 participants per intervention groups is effectively achieved.

Data management and analyses

Data management

The web-browser-based system secuTrial® (interActive Systems, Berlin, Germany), which fulfills the Good Clinical Practice requirements, will be used for data capturing and management. This database allows for individualized accounts with pre-defined roles for each study employee and will be hosted by a study-independent data manager. Built-in quality control mechanisms and notification of missing data will reduce errors during data entry. Participants will be assigned a unique identification code and no directly identifiable information is stored in the database.

Analyses of primary and secondary outcomes

An intention-to-treat analysis will be performed to prevent potential bias resulting from the distortion of baseline equivalence after randomization due to the withdrawal of participants, non-adherence to the study protocol, or an unwarranted level of missing data. Participants will only be included in the analyses for which they have data available. Protocol non-adherence, early withdrawals, and loss to follow-up will be characterized and examined. Sensitivity analyses using different populations or participant groupings may be used to examine the robustness of the estimator generated by the intention-to-treat analysis. Any sensitivity analyses added after the breaking of the blind (post-hoc sensitivity analyses), including per-protocol analysis that will contain any participants recruited as a replacement for withdrawals or dropouts, will be clearly identified as such in the trial reporting. Basic univariable statistical analysis techniques will be used to describe the study population as well as the primary and secondary outcomes at the different measurement points. To evaluate the longitudinal variation in the primary outcome and secondary outcomes, multilevel mixed-effects models that appropriately account for the within-and between-individual sources of variance in outcome variation will be used. In these models, participants are treated as random effects, while the treatment group is used as a fixed parameter. The choice of regression model will depend on the error distribution function of the respective outcome parameter. Time-updated covariates will also be used

in regression modeling, for instance, to evaluate the impact of time-varying vitamin D status on the secondary outcomes. Time lags in time-updated covariates will also be evaluated to further detail temporal associations. Non-linear regression modeling will be used to evaluate pharmacokinetic curves for each of the intervention groups as described above. Thus, estimates are derived for the parameters *a* (i.e., change is constant at equilibrium), and *k* (i.e., the rate constant for the proportion of the total mass of 25(OH)D used or metabolized per day) for mutual comparison as well as with estimates from other populations (other SCI populations, general population, or other health-condition groups).

No interim analyses are planned. If severe clinical deterioration is detected in more than one participant, or on the recommendation of the monitoring committee following a serious adverse event, the study will be suspended until a comprehensive safety review has been completed. If the trial is suspended or halted, an interim analysis will be performed.

Handling of missing data and dropouts

When appropriate, multiple imputation will be used to account for missing data.[36] In case the number of dropouts is substantial and systematically related to baseline values of the primary outcome variable, logistic regression modeling will be used to derive inverse probability weights for use in regression modeling to statistically account for potential longitudinal selection bias. Participants who are withdrawn or drop out will be replaced. Sensitivity analysis will be used to address the robustness of the estimators to changes in the assumptions underlying the chosen imputation strategy.

Quality assurance and safety provisions

Minimizing bias and contamination

Trained study employees will execute all of the measurements following a study manual. Measurement devices will be appropriately serviced and calibrated throughout the study. Questionnaires that have been validated among or adapted for the SCI population will be used. The collection of several possible confounders, including sun exposure, season, and SCI level, allows for the correction of these factors. Participants will be asked to express their belief regarding the assigned intervention every three months, which will be used to compute a measure for the extent of successful blinding of the trial.

Potential risks

There are no guidelines regarding upper limits of serum 25(OH)D concentration among the SCI population,[3] although vitamin D toxicity has been reported with levels exceeding 375-750 nmol/L among the general population.[37] Side effects of vitamin D supplementation, resulting from an overdose, are not expected with the selected dosages in this study. Nevertheless, participants are asked about potential side effects and tolerance of the supplement, and relevant blood parameters

will be monitored. Due to the 65% volume alcohol solution, the intake of the supplement and/or placebo could have a minor influence on the ability to drive or operate machines, but similar solutions have been proven harmless.[38] The sum of the radiation exposure for the two bone mineral density measurements in this study is less than the average yearly radiation exposure due to radon in Switzerland and falls well within the dose guidance value for Swiss research projects.[39 40] Serious Adverse Events will be documented and reported to the local authorities for the entire study duration, which encompasses the signing of the informed consent until the completion of the last protocol-specific procedure including a safety follow-up period. A risked-adapted monitoring[41] will be applied and executed by the Clinical Trial Unit of the study center.

Withdrawal criteria

Participants can withdraw from the study at any time, without providing reasoning. Participants might be redrawn from the study in case of protocol non-adherence, the eligibility criteria are no longer fulfilled, or health problems related to the intake of the vitamin D_3 supplement or placebo, including a vitamin D intoxication (serum 25(OH)D concentration > 375 nmol/L) or hypercalcemia (ionized calcium concentration > 3.5 mmol/L).

Unblinding Procedures

The study physician together with the study employees will make study termination and unblinding decisions. Unblinding will only be allowed in the following circumstances; upon study termination, in the case of premature study termination, or in the case of emergencies or complications. An employee not directly involved in the measurements will perform the unblinding of individual participants during the study. Since each participant receives an individual batch of vials, revealing the blinding for one participant will not unblind the entire cohort.

Ethics and dissemination

Ethics approval

This study will be conducted in compliance with the current version of the Declaration of Helsinki[42] and the International Conference on Harmonization Good Clinical Practice guidelines,[43] as well as all national legal and regulatory requirements.[44 45] Both the Swiss Ethics Committee for Northwest/Central Switzerland (EKNZ, 2020-01493) and the Swiss Agency for Therapeutic Products (Swissmedic, 2020DR3150) have approved the study. The study has been registered at ClinicalTrials.gov (NCT04652544). The regulatory authorities will receive safety and interim reports and will be informed about protocol changes and the study end.

Dissemination policy

Results will be published in peer-reviewed journals and presented at scientific conferences. When desired, individual study results will be shared with the participants after the study end. Dissemination among persons with SCI in Switzerland will be achieved through the newsletters "Paraplegie" and "Paracontact" as well as through online media. Data and statistical code will be made available upon request.

Trial status

This publication is based on version 3 of the VitD-SCI trial protocol dated November 9, 2020. The official start of recruitment was on May 19, 2021 and data collection is estimated to end on May 31, 2023. As of the time of submission, temporary interruptions due to the COVID-19 pandemic are a possibility and in case of extended disruption, a schedule adjustment may be required.

Discussion

This is the first study to investigate a 12-month vitamin D supplementation among individuals with a chronic SCI. The existing studies lack the combination of long-term vitamin D supplementation with different dosages, while not only assessing vitamin D status but also secondary outcomes.

The VitD-SCI trial, for which the protocol is presented here, will provide valuable insights to optimize individual vitamin D supplementation. If a positive relation between a sufficient vitamin D status and secondary outcomes can be established, this could lead the way for standardized clinical recommendations for long-term management of vitamin D status and vitamin D supplementation among the chronic SCI population.

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Funding statement

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Author contributions

JF is responsible for overseeing the trial. JF, CP, and MB were responsible for the study conception and obtained funding. JF, CP, MB, AS, and AH designed the protocol. AS provided clinical expertise is the study physician and principal investigator. PW provided expertise on bone mineral density. MB provided statistical expertise. AJ provided clinical expertise on blood parameters and analyses. GL provided clinical expertise on pain outcomes. AH, MB and JF prepared the first draft of the manuscript. All authors reviewed and revised the manuscript before submission and approved its content.

Disclosure statement

All authors declare that there are no conflicts of interest, intellectual, financial, or proprietary conflicts.

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References

1. Flueck JL, Perret C. Vitamin D deficiency in individuals with a spinal cord injury: a literature review. *Spinal Cord* 2017;55(5):428-34. doi: 10.1038/sc.2016.155
2. Amrein K, Scherkl M, Hoffmann M, et al. Vitamin D deficiency 2.0: an update on the current status worldwide. *Eur J Clin Nutr* 2020;74(11):1498-513. doi: 10.1038/s41430-020-0558-y
3. Lamarche J, Mailhot G. Vitamin D and spinal cord injury: should we care? *Spinal cord* 2016;54(12):1060-75. doi: 10.1038/sc.2016.131
4. Cranney A, Horsley T, O'Donnell S, et al. Effectiveness and safety of vitamin D in relation to bone health. *Evid Rep Technol Assess* 2007(158):1-235.
5. Ceglia L, Harris SS. Vitamin D and its role in skeletal muscle. *Calcif Tissue Int* 2013;92(2):151-62. doi: 10.1007/s00223-012-9645-y
6. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr* 2008;87(4):1080S-6S. doi: 10.1093/ajcn/87.4.1080S
7. Beard JA, Bearden A, Striker R. Vitamin D and the anti-viral state. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology* 2011;50(3):194-200. doi: 10.1016/j.jcv.2010.12.006 [published Online First: 2011/01/19]
8. Jolliffe DA, Camargo CA, Sluyter JD, et al. Vitamin D supplementation to prevent acute respiratory infections: systematic review and meta-analysis of aggregate data from randomised controlled trials. *medRxiv : the preprint server for health sciences* 2020 doi: 10.1101/2020.07.14.20152728 [published Online First: 2020/12/04]
9. Peterlik M, Cross HS. Vitamin D and calcium insufficiency-related chronic diseases: molecular and cellular pathophysiology. *European Journal of Clinical Nutrition* 2009;63(12):1377-86. doi: 10.1038/ejcn.2009.105
10. Zhou XJ, Vaziri ND, Segal JL, et al. Effects of chronic spinal cord injury and pressure ulcer on 25(OH)-vitamin D levels. *J Am Paraplegia Soc* 1993;16(1):9-13. doi: 10.1080/01952307.1993.11735877
11. Barbonetti A, Sperandio A, Micillo A, et al. Independent association of vitamin D with physical function in people with chronic spinal cord injury. *Arch Phys Med Rehabil* 2016;97(5):726-32. doi: 10.1016/j.apmr.2016.01.002 [published Online First: 2016/01/26]
12. Barbonetti A, Cavallo F, D'Andrea S, et al. Lower vitamin D levels are associated with depression in people with chronic spinal cord injury. *Arch Phys Med Rehabil* 2017;98(5):940-46. doi: 10.1016/j.apmr.2016.11.006 [published Online First: 2016/12/18]
13. Lussi C, Frotzler A, Jenny A, et al. Nutritional blood parameters and nutritional risk screening in patients with spinal cord injury and deep pressure ulcer-a retrospective chart analysis. *Spinal cord* 2018;56(2):168-75. doi: 10.1038/s41393-017-0016-4 [published Online First: 2017/10/23]
14. Clark K, Goldstein RL, Hart JE, et al. Plasma vitamin D, past chest illness, and risk of future chest illness in chronic spinal cord injury (SCI): a longitudinal observational study. *Spinal Cord* 2020;58(4):504-12. doi: 10.1038/s41393-019-0409-7 [published Online First: 2020/01/18]
15. Vieth R. Why the minimum desirable serum 25-hydroxyvitamin D level should be 75 nmol/L (30 ng/ml). *Best Practice & Research: Clinical Endocrinology & Metabolism* 2011;25(4):681-91. doi: 10.1016/j.beem.2011.06.009
16. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2009;169(6):551-61. doi: 10.1001/archinternmed.2008.600 [published Online First: 2009/03/25]
17. Institute of Medicine (IOM). Dietary Reference Intakes for Calcium and Vitamin D. Washington (DC): The National Academies Press 2011.
18. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *The Journal of clinical*

endocrinology and metabolism 2011;96(7):1911-30. doi: 10.1210/jc.2011-0385 [published Online First: 2011/06/08]
19. Deutsche Gesellschaft für Ernährung ÖGfE, Schweizerische Gesellschaft für Ernährungsforschung, Schweizerische Vereinigung für Ernährung (Hrsg.). Referenzwerte für die Nährstoffzufuhr Vitamin D. Neustadt a. d. Weinstraße: Neuer Umschau Buchverlag, 2012:1. Auflage, 4., korrigierter Nachdruck.
20. Hathcock JN, Shao A, Vieth R, et al. Risk assessment for vitamin D. *Am J Clin Nutr* 2007;85(1):6-18. doi: 10.1093/ajcn/85.1.6 [published Online First: 2007/01/09]
21. Vieth R, Chan PC, MacFarlane GD. Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. *Am J Clin Nutr* 2001;73(2):288-94. doi: 10.1093/ajcn/73.2.288 [published Online First: 2001/02/07]
22. Bauman WA, Morrison NG, Spungen AM. Vitamin D replacement therapy in persons with spinal cord injury. *The journal of spinal cord medicine* 2005;28(3):203-7. doi: 10.1080/10790268.2005.11753813 [published Online First: 2005/07/29]
23. Bauman WA, Emmons RR, Cirnigliaro CM, et al. An effective oral vitamin D replacement therapy in persons with spinal cord injury. *The journal of spinal cord medicine* 2011;34(5):455-60. doi: 10.1179/2045772311y.0000000032 [published Online First: 2011/11/29]
24. Flueck JL, Schlaepfer MW, Perret C. Effect of 12-week vitamin D supplementation on 25(OH)D status and performance in athletes with a spinal cord injury. *Nutrients* 2016;8(10) doi: 10.3390/nu8100586 [published Online First: 2016/09/27]
25. Oleson CV, Patel PH, Wuermser LA. Influence of season, ethnicity, and chronicity on vitamin D deficiency in traumatic spinal cord injury. *The journal of spinal cord medicine* 2010;33(3):202-13. doi: 10.1080/10790268.2010.11689697 [published Online First: 2010/08/27]
26. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Annals of internal medicine* 2013;158(3):200-7. doi: 10.7326/0003-4819-158-3-201302050-00583 [published Online First: 2013/01/09]
27. Post MWM, Brinkhof MWG, von Elm E, et al. Design of the Swiss Spinal Cord Injury Cohort Study. *Am J Phys Med Rehabil* 2011;90(11 Suppl 2):S5-S16. doi: 10.1097/PHM.0b013e318230fd41
28. Fekete C, Gurtner B, Kunz S, et al. Inception cohort of the Swiss Spinal Cord Injury Cohort Study (SwiSCI): Design, participant characteristics, response rates and non-response. *J Rehabil Med* 2021;53(2):jrm00159. doi: 10.2340/16501977-2795 [published Online First: 2021/02/12]
29. Amorim S, Teixeira VH, Corredeira R, et al. Creatine or vitamin D supplementation in individuals with a spinal cord injury undergoing resistance training: A double-blinded, randomized pilot trial. *The journal of spinal cord medicine* 2018;41(4):471-78. doi: 10.1080/10790268.2017.1372058 [published Online First: 2017/09/14]
30. Pritchett K, Pritchett RC, Stark L, et al. Effect of Vitamin D Supplementation on 25(OH)D Status in Elite Athletes With Spinal Cord Injury. *Int J Sport Nutr Exerc Metab* 2019;29(1):18-23. doi: 10.1123/ijsnem.2017-0233 [published Online First: 2018/05/15]
31. Dalle Carbonare L, Valenti MT, Del Forno F, et al. Vitamin D: daily vs. monthly use in children and elderly - what is going on? *Nutrients* 2017;9(7) doi: 10.3390/nu9070652 [published Online First: 2017/07/05]
32. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocrine reviews* 2001;22(4):477-501. doi: 10.1210/edrv.22.4.0437 [published Online First: 2001/08/09]
33. RALLOC: Stata module to design randomized controlled trials [program], 2018.
34. Heaney RP, Davies KM, Chen TC, et al. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr* 2003;77(1):204-10. doi: 10.1093/ajcn/77.1.204
35. Bauman WA, Zhong YG, Schwartz E. Vitamin D deficiency in veterans with chronic spinal cord injury. *Metabolism* 1995;44(12):1612-6. doi: 10.1016/0026-0495(95)90083-7 [published Online First: 1995/12/01]

36. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393. doi: 10.1136/bmj.b2393 [published Online First: 2009/07/01]
37. Jones G. Pharmacokinetics of vitamin D toxicity. *Am J Clin Nutr* 2008;88(2):582S-86S. doi: 10.1093/ajcn/88.2.582S [published Online First: 2008/08/12]
38. Franz E. Vitamin D im Säuglingsalter-alkoholische oder ölige Tropfen? *Pharmajournal* 2007;12:5-7.
39. The Swiss Federal Council. Radiological Protection Ordinance (RPO), 2017.
40. Bundesamt für Gesundheit (BAG). Strahlenexposition der Schweizer Bevölkerung 2018 [updated 28.08.2018. Available from: https://www.bag.admin.ch/bag/de/home/gesund-leben/umwelt-und-gesundheit/strahlung-radioaktivitaet-schall/strahlung-gesundheit/strahlenexposition-der-schweizer-bevoelkerung.html# accessed 29.01.2020.
41. Brosteanu O, Schwarz G, Houben P, et al. Risk-adapted monitoring is not inferior to extensive on-site monitoring: Results of the ADAMON cluster-randomised study. *Clin Trials* 2017;14(6):584-96. doi: 10.1177/1740774517724165 [published Online First: 2017/08/08]
42. World Medical Association (WMA). Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects 1964.
43. Dixon JR. International conference on harmonization good clinical practice guideline. *Quality Assurance* 1999;6(2):65-74. doi: 10.1080/105294199277860
44. The Federal Assembly of the Swiss Confederation. Federal Act on Research involving Human Beings (Human Research Act, HRA), 2011.
45. The Swiss Federal Council. Ordinance on Clinical Trials in Human Research (Clinical Trials Ordinance, ClinO), 2013.
46. Hanwell HEC, Vieth R, Cole DEC, et al. Sun exposure questionnaire predicts circulating 25-hydroxyvitamin D concentrations in Caucasian hospital workers in southern Italy. *J Steroid Biochem Mol Biol* 2010;121(1-2):334-37. doi: 10.1016/j.jsbmb.2010.03.023 [published Online First: 2010/03/16]
47. Fitzpatrick TB. "Soleil et peau" [Sun and skin]. *Journal de Me´decine Esthe´tique (in French),* 1975;2:33–34.
48. Kirshblum SC, Burns SP, Biering-Sorensen F, et al. International standards for neurological classification of spinal cord injury (revised 2011). *The journal of spinal cord medicine* 2011;34(6):535-46. doi: 10.1179/204577211X13207446293695 [published Online First: 2012/02/15]
49. Itzkovich M, Gelernter I, Biering-Sorensen F, et al. The Spinal Cord Independence Measure (SCIM) version III: reliability and validity in a multi-center international study. *Disabil Rehabil* 2007;29(24):1926-33. doi: 10.1080/09638280601046302 [published Online First: 2007/09/14]
50. Brinkhof MWG, Fekete C, Chamberlain JD, et al. Swiss national community survey on functioning after spinal cord injury: Protocol, characteristics of participants and determinants of non-response. *J Rehabil Med* 2016;48(2):120-30. doi: 10.2340/16501977-2050
51. National Pressure Ulcer Advisory Panel EPUAPaPP, Alliance. PI. Prevention and Treatment of Pressure Ulcers: Quick Reference Guide. In: Haesler E, ed. 2019 ed. Osborne Park, Australia: Cambridge Media, 2014.
52. Widerström-Noga E, Biering-Sørensen F, Bryce T, et al. The international spinal cord injury pain basic data set. *Spinal cord* 2008;46(12):818-23. doi: 10.1038/sc.2008.64 [published Online First: 2008/06/03]
53. Kalpakjian CZ, Scelza WM, Forchheimer MB, et al. Preliminary reliability and validity of a Spinal Cord Injury Secondary Conditions Scale. *The journal of spinal cord medicine* 2007;30(2):131-39. doi: 10.1080/10790268.2007.11753924
54. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67(6):361-70. doi: 10.1111/j.1600-0447.1983.tb09716.x [published Online First: 1983/06/01]

55. Krupp LB, LaRocca NG, Muir-Nash J, et al. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;46(10):1121-3. doi: 10.1001/archneur.1989.00520460115022 [published Online First: 1989/10/01]

Figures

Figure 1: Schematic overview of the study flow. The timeline of the study including the assessments is displayed starting from the screening (top of the figure) to the last study visit (bottom of the figure).

A: Study flow.

B: Legend.

Tables

Table 1: Eligibility criteria

Inclusion criteria	Exclusion criteria
• Informed Consent to the study as documented by a signature. • Chronic (> 3 years) traumatic or non-traumatic SCI a vertebral lesion level of C4 or below. • Between 18 - 60 years old. • Wheelchair dependency during activities of daily living, defined by a score of 0-2 in the Spinal Cord Independence Measure (SCIM-III), subsection "Mobility in the house". • An insufficient vitamin D status (≤ 75 nmol/L) at the first visit.	• Contraindications to the investigational product, including known hypersensitivity or allergy to the cholecalciferol or alcohol solution. • Clinically relevant disorders, including renal dysfunction, hepatic dysfunction, cardiovascular disease, lung disease, diabetes, blood disease, parathyroid disease, cancer, depression, alcohol abuse, and/or the intake of significant concomitant medication (including osteoporosis treatment and benzothiadiazide derivatives). This will be assessed on an individual basis. • Grade 3 or 4 pressure injuries. • Women who are pregnant or planning to become pregnant during the study period. • Women who are breastfeeding. • Fractures in both arms and/or both legs within the last five years. • Intake of > 400 IU/day vitamin D supplementation during the last 12 months before recruitment or during the study. • Visiting a country with increased sun exposure (below the 37th parallel north, i.e. the southern hemisphere) within one month before enrollment or during the study. • Inability to understand or decide on study participation (i.e. make an informed consent) and to adhere to the study protocol, for example, due to language or psychological problems.

Table 2: Tools, parameters, and timing of the study measurements.

Assessment tool	Parameter	Assessment periods
Differential changes in blood parameters (sample taken from the antecubital vein)		
Electrochemiluminescence immunoassay (ECLIA)	25(OH)D (nmol/L)	0M, 3M, 6M, 12M
Photometry - NM-BAPTA	Calcium (mmol/L)	0M, 3M, 6M, 12M
Potentiometry with ion-selective electrodes	Ionized calcium (mmol/L)	0M, 3M, 6M, 12M
Chemiluminescence immunoassay (CLIA)	Parathyroid hormone (ng/L)	0M, 3M, 6M, 12M
Photometry - Molybdate UV	Phosphate (mmol/L)	0M, 3M, 6M, 12M
Photometry - particle-enhanced turbidimetric immunoassay	Cystatin C (mg/L)	0M, 3M, 6M, 12M
Estimated from cystatin C following CKD-EPI and Grubb	Estimated glomerular filtration rate (eGFR) (mL/min)	0M, 3M, 6M, 12M
Chemiluminescent immunoassay (CLIA)	Testosterone (ng/dL)	0M, 3M, 6M, 12M
Differential changes in personal characteristics		
Body mass index (BMI)	From weight and height (kg/m²)	0M, 3M, 6M, 12M
Sun exposure based on Hanwell et al (2010)[46]	Time spent outdoors (min) with level of exposed skin[1]	0M, 3M, 6M, 12M
Physical activity	Sport per week (hours and frequency)	0M, 3M, 6M, 12M
Medication and supplements	Sort and dosage (supplements only)	0M, 3M, 6M, 12M
Further illnesses	Incidence since last measurement	0M, 3M, 6M, 12M
Skin phototype on the posterior forearm based on Fitzpatrick (1975)[47]	Six categories ranging from light to very dark skin types	Screening
SCI characteristics	Time since SCI (years), neurological level of injury (NLI),[48] the degree of impairment following the American Spinal Injury Association (ASIA) Impairment Scale (AIS)[48]	Screening
Differential changes in bone mineral density		
X-ray densitometry (DXA), Lunar iDXA Serie with enCORE v17 Software	T-scores for the forearm (radius), hip (femoral neck), and knee (distal femur and proximal tibia)	0M, 12M
Differential changes in functional independence		
Spinal Cord Independence Measure (SCIM) III[49]	Self-care subscore (0-20), respiration and sphincter management subscore (0-40), indoor mobility subscore (0-10), outdoor mobility subscore (0-30), total score (0-100)	0M, 3M, 6M, 12M
Differential changes in urinary tract infections		
Exact questions of the first-wave questionnaire of the Swiss Spinal Cord Injury (SwiSCI) survey[27 50]	Incidence since the last measurement, medical care required	0M, 3M, 6M, 12M
Differential changes in pressure injuries		
Exact questions of the first-wave questionnaire of the SwiSCI survey[27 50]	Localization and grade following the European and United States National Pressure Ulcer Advisory panels (EPUAP and NPUAP) classification[51]	0M, 3M, 6M, 12M
Differential changes in pain		
Exact questions of the first- and second-wave questionnaire of the SwisSCI survey,[27 50] based on the International SCI Pain Basic Data Set[52] as well as the SCI Secondary Conditions Scale[53]	The occurrence, kind, location, and influence of pain during the last week as well as chronic pain (> 3 months)	0M, 3M, 6M, 12M
Differential changes in strength		
Jamar Smart Hand Dynamometer (Patterson Medical, Warrenville, IL)	Three measurements of the left and right hand (mean kg)	0M, 3M, 6M, 12M
Differential changes in mood		

Hospital Anxiety and Depression Scale (HADS)[54]	Total score (14-56)	0M, 3M, 6M, 12M
Differential changes in fatigue		
Fatigue Severity Scale (FSS)[55]	Total score (9-63)	0M, 3M, 6M, 12M
Differential changes in falls		
Occurrence	Incidence since last measurement, reason daily activity, sport or accident) and medical care required	0M, 3M, 6M, 12M
Safety of the Investigational Medical Products		
Serious adverse events	The occurrence of life-threatening medical complications, the requirement of hospitalization.	Any time
Side-effects, tolerability, and adherence	Number of and reason for missed intake, side-effects	0M, 3M, 6M, 12M

Assessment periods are referenced to the date of the first visit (0M) and include screening (Screening; max 30 days before 0M), 3-month follow-up (3M; 90 ± 7 days), 6-month follow-up (6M; 180 ± 7 days) and 12-month follow-up (12M; 365 ± 7 days). Serious adverse events are continuously evaluated.

[1] Level of exposed skin: 1) hands and face, 2) hands, face, and arms, 3) hands, face, and legs, 4) entire body (bathing suit).

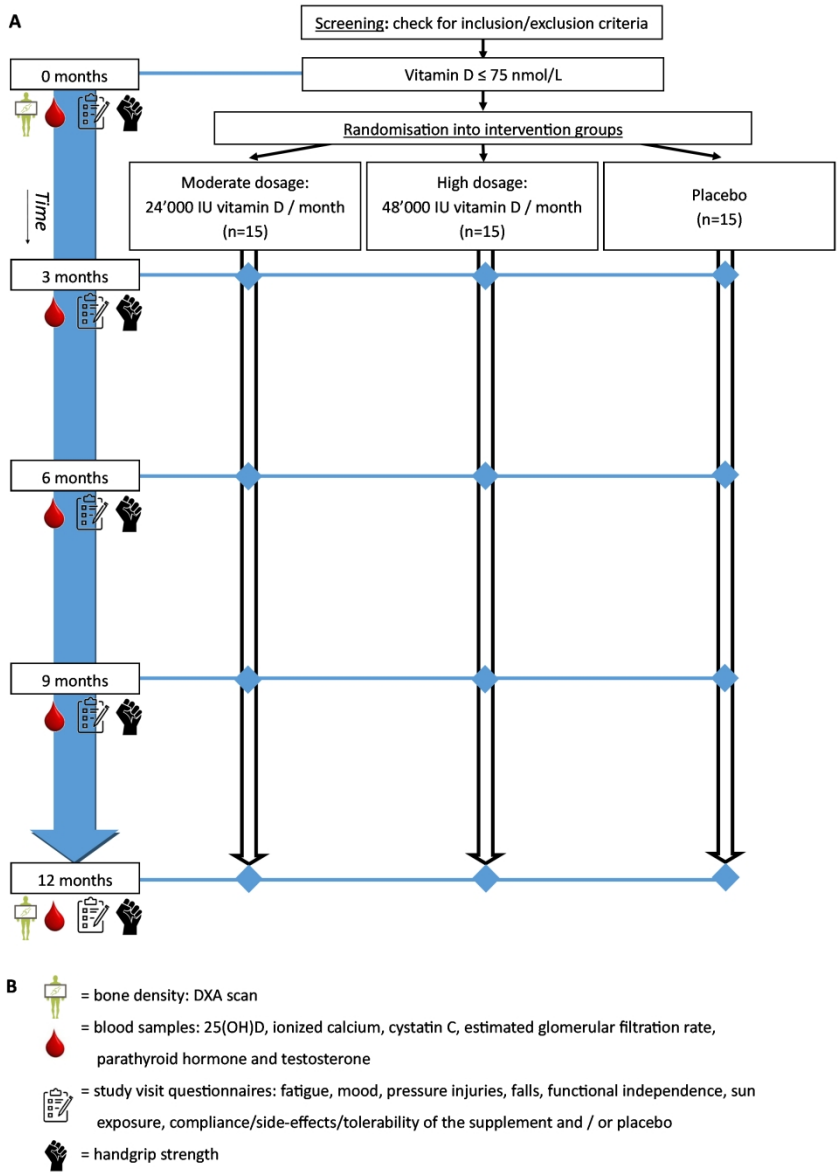


Figure 1: Schematic overview of the study flow. The timeline of the study including the assessments is displayed starting from the screening (top of the figure) to the last study visit (bottom of the figure). A: Study flow. B: Legend.

Supplement 1: SPIRIT Checklist for the Vitamin D Supplementation in Chronic Spinal Cord Injury (VitD-SCI) trial protocol

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section / item	Item No	Description, addressed	Addressed in section
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract - Trial registration; Ethics and dissemination - Ethics approval
	2b	All items from the World Health Organization Trial Registration Data Set	Throughout the paper; publicly accessible information on ClinicalTrials.gov (NCT04652544)
Protocol version	3	Date and version identifier	Ethics and dissemination - Trial Status
Funding	4	Sources and types of financial, material, and other support	Funding statement
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page; Author contributions
	5b	Name and contact information for the trial sponsor	Title page - Corresponding author
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Funding statement; Author contributions
	5d	Composition, roles, and responsibilities of the coordinating center, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Methods and analyses - Potential risks; Author contributions
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Introduction; Methods and analyses - Intervention
	6b	Explanation for choice of comparators	Introduction; Methods and analyses - Intervention

Objectives	7	Specific objectives or hypotheses	Introduction
Trial design	8	Description of trial design including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, non-inferiority, exploratory)	Methods and analyses - Study design and setting, Randomization and blinding
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Methods and analyses - Study design and setting
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (e.g., surgeons, psychotherapists)	Methods and analyses - Participants; Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Methods and analyses - Intervention
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)	Methods and analyses - Intervention, Withdrawal criteria
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)	Methods and analyses - Intervention
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Methods and analyses - Participants; Table 1
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Methods and analyses - Outcomes and assessments; Table 2
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Methods and analyses - Study design and setting, Intervention, Outcomes and assessments; Figure 1; Table 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Methods and analyses - Sample Size; Supplement 2
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Methods and analyses - Participants
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	Methods and analyses - Randomization and blinding
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Methods and analyses - Randomization and blinding

Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions	Methods and analyses - Participants, Randomization and blinding
Blinding (masking)	17a	Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how	Methods and analyses - Intervention, Randomization and blinding
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Methods and analyses - Unblinding procedures
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Methods and analyses - Outcomes and assessments, Data management and analyses, Minimizing bias and contamination; Table 2
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Methods and analyses - Intervention, Analyses of primary and secondary outcomes
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Methods and analyses - Data management
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Methods and analyses - Analyses of primary and secondary outcomes
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	Methods and analyses - Analyses of primary and secondary outcomes
	20c	Definition of analysis population relating to protocol non-adherence (e.g., as randomized analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	Methods and analyses - Analyses of primary and secondary outcomes, Handling of missing data and dropouts
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	There is a monitoring committee responsible for general trial conduct as well as data concerns. Methods and analyses - Potential risks
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Methods and analyses - Analyses of primary and secondary outcomes, Unblinding procedures
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Methods and analyses - Outcomes and assessments, Minimizing bias and contamination, Potential risks

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Methods and analyses - Potential risks
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Abstract - Trial registration; Ethics and dissemination - Ethics approval
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Ethics and dissemination - Ethics approval. Study participants will receive a letter with updates.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32)	Methods and analyses - Participants
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Methods and analyses - Data management, Ethics and dissemination - Dissemination policy
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Disclosure statement
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Ethics and dissemination - Dissemination policy; Funding statement
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Due to the low-risks, the need to compensate for suffered harm is not foreseen (Methods and analyses - Potential risks). Though study insurance is in place in case any care needs to be covered.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Ethics and dissemination - Dissemination policy
	31b	Authorship eligibility guidelines and any intended use of professional writers	Ethics and dissemination - Dissemination policy
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Ethics and dissemination - Dissemination policy
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	Available upon request.
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Methods and analyses - Outcomes and assessments; Table 2

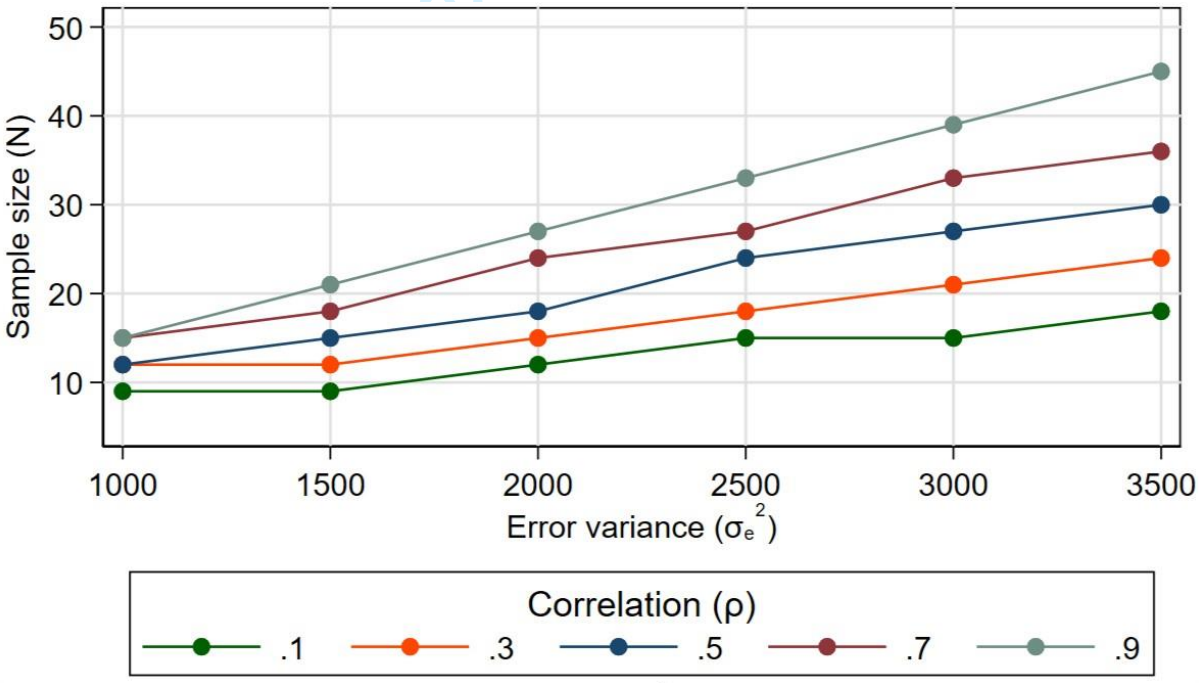
*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Supplement 2: Sample size calculation

A: Expected time course of mean vitamin D status (nmol/L) during the study.

	Baseline	3 months	6 months	9 months	12 months
Placebo	31	31	31	31	31
Moderate dosage	31	49	56	59	60
High dosage	31	91	115	125	129

B: Estimated sample size for repeated-measures ANOVA. F-test for between subjects with H_0: $\delta = 0$ versus H_a: $\delta \neq 0$. Estimated minimal sample size as a function of the error variance and the within-individual correlation of repeated vitamin D status measurements, specifying a power ($1-\beta$) of 0.8 and a significance level (α) of 0.05. Reading example: Presuming an error variance (σ_e^2) of 3500, a between-subject variance (σ_b^2) of 794 and a high within-individual correlation (ρ) of 0.9 for repeated vitamin D status measurements (N_{rep}=5), the estimated minimal overall sample needed is 45 participants, implying 15 participants in each of the three intervention groups (N_g=3).



Schweizer Paraplegiker Zentrum | Centre suisse des paraplégiques | Centro svizzero per paraplegici | Swiss Paraplegic Centre

Clinical Study Protocol

Vitamin D supplementation in individuals with a chronic spinal cord injury – a placebo-controlled randomized double-blinded study

Vitamin-D-Supplementierung bei Personen mit einer chronischen Querschnittlähmung

Study Type:	Clinical trial with an Investigational Medicinal Product
Study Categorization:	ClinO - Category B
Study Registration:	Clinicaltrials.gov and kofam.ch *(will be registered after ethics approval)*
Study Identifier:	2020-06
Sponsor-Investigator:	Dr. sc. nat. Joëlle Flück Sports medicine, Schweizer Paraplegiker-Zentrum Guido A. Zäch Strasse 1 6207 Nottwil, Switzerland Phone: +41 41 939 66 17 Email: joelle.flueck@paraplegie.ch
Investigational Product:	Vitamin D3 (cholecalciferol), Vi-De 3® Monthly Dose, Dr. Wild & Co. AG
Protocol Version and Date:	Version 3.0, 09.11.2020

SIGNATURE PAGE

Study number	2020-06
Study Title	Vitamin D supplementation in individuals with a chronic spinal cord injury – a placebo-controlled randomized double-blinded study

The Sponsor-Investigator and trial statistician have approved the protocol version (3.0, dated 09.11.2020), and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki (World Medical Association (WMA) 1964), ICH-GCP guidelines (Dixon 1999) and the local legally applicable requirements (The Federal Assembly of the Swiss Confederation 2011, The Swiss Federal Council 2013).

Sponsor-Investigator: Dr. sc. nat. Joëlle Flück

Nottwil, 09.11.2020	
Place/Date	**Signature**

Principal Investigator: Dr. med. Anke Scheel-Sailer

Nottwil, 09.11.2020	
Place/Date	**Signature**

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STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	Schweizer Paraplegiker-Zentrum (SPZ) / Dr. sc. nat. Joëlle Flück
Study Title:	Vitamin D supplementation in individuals with a chronic spinal cord injury – a placebo-controlled randomized double-blinded study
Short Title / Study ID:	Vitamin-D-Supplementierung bei Personen mit einer chronischen Querschnittlähmung / 2020-06
Protocol Version and Date:	Version 3.0, 09.11.2020
Trial registration:	clinicaltrials.gov and kofam.ch *(registration will follow after ethics approval)*
Study category and Rationale	Clinical Trial with a medicinal product and a placebo – Category B
Clinical Phase:	Phase 3
Background and Rationale:	Vitamin D plays an important role in the calcium uptake in the gut, but also regarding muscle strength and bone health. A lower vitamin D status is related to an increased risk of cancer, neurodegenerative diseases and cardiovascular diseases as well as reduced bone mass. While vitamin D insufficiency (25(OH)D ≤ 75 nmol/L) is common in the general population, with an estimated prevalence of nearly 75% in Switzerland, available studies in individuals with spinal cord injury (SCI) indicate an even higher prevalence of vitamin D insufficiency in this population. Due to factors specific to SCI, including physiological processes and common use of multiple medications, current evidence provides unreliable clinical guidance regarding the optimal dosage and duration of vitamin D supplementation to secure an optimal vitamin D status (> 75 nmol/L) in this population.
Objective(s):	The main objective of this study is to investigate the effect of vitamin D supplementation on vitamin D status (25(OH)D concentration in the blood) among individuals with a chronic SCI. Further, the effects of vitamin D supplementation on several other parameters (e.g. bone density and mood) are investigated, which could reveal positive secondary effects of supplementation that are especially relevant for clinical practice.
Outcome(s):	The primary outcome is vitamin D status among participants. The main other outcomes are: bone density, handgrip strength, fatigue, mood, pain and pressure ulcers.
Study design:	Placebo-controlled randomized double-blinded study
Inclusion / Exclusion criteria:	Participants will be mainly recruited from the population-based Swiss Spinal Cord Injury Cohort Study (SwiSCI) database. Only individuals who agreed to be contacted for future scientific studies will be approached. The main inclusion criteria are: Informed Consent to the present study as documented by a signature, chronic (> 3 years) traumatic or non-traumatic SCI with a sub-C4-level lesion, 18 – 60 years old and wheelchair dependency during activities of daily living. The main exclusion criteria are: contraindications to the investigational product, clinically relevant disorders, pressure ulcer grade 3 or 4, pregnancy, breastfeeding, vitamin D supplementation within the last 12 months, visiting a country with increased sun exposure (below the 37th parallel north) within the last month before study enrolment or during the study, fractures in both arms and/or both legs within the last five years, inability to understand or decide on study participation and to understand or adhere to the study protocol.

Measurements and procedures:	At study visit #1 (baseline), vitamin D status will be measured. Participants with an insufficient vitamin D status (≤ 75 nmol/L) will be randomly assigned to one of three intervention groups receiving either a placebo, 24'000 IU or 48'000 IU vitamin D per month for 12 months. The main measurements in these groups will be performed at 0, 3, 6, 9, and 12 months, except for bone density which will only be measured at 0 and 12 months. Participants with a sufficient vitamin D status (> 75 nmol/L) will be allocated to the natural time course group, and will not receive any intervention. The measurements in this group will be performed at 0, 6 and 12 months, except for bone density which will only be measured at 0 and 12 months. The following measurements will be performed: -concentration of vitamin D (25(OH)D), ionized calcium, cystatin C, estimated glomerular filtration rate, parathyroid hormone and testosterone from blood samples. -bone density measurements of the forearm, hip and knee using dual-energy X-ray absorptiometry (DXA) scans. -handgrip strength using a Jamar hand dynamometer. -other relevant parameters using questionnaires including sun exposure, mood, fatigue, pressure ulcers, pain and falls.	
Study Product / Intervention:	"Vi-De 3® Monthly Dose" from Dr. Wild & Co. AG (Muttenz, Switzerland) is a commercially available vitamin D3 supplement. One vial (5 mL) contains an ethanol solution (65% alcohol by volume) with 600 µg cholecalciferol, corresponding to 24'000 IU vitamin D3. Depending on the allocated intervention group, participants will take either one vial (24'000 IU, "low" dosage') or two vials (48'000 IU, "high" dosage) with the vitamin D supplement every month.	
Control Intervention (if applicable):	As a placebo, the same solution as Vi-De 3® Monthly Dose (65% alcohol by volume) but without cholecalciferol will be provided, filled in identical 5 mL vials as the biologically active product. The placebo will be indistinguishable from the biologically active product in odor, taste as well as appearance. The participants in the natural time course group will be followed without any intervention.	
Number of Participants with Rationale:	Assuming a significance level of 5% and a power of 80%, the minimal estimated sample size is 15 participants per group. Since we have four groups (3x intervention and 1x control), we aim to include 60 participants with a full dataset. Participants who withdraw or dropout from the study, or for whom data collection is characterized by a large amount of missing data, will be replaced so as to reach the targeted sample sizes of 15 participants per group with a complete dataset for the evaluation of treatment effects. Up to 68 participants might be recruited to account for dropouts.	
Study Duration:	36 months	
Study Schedule:	First-Participant-In (planned): November 2020 Last-Participant-Out (planned): December 2023	
Investigators:	Dr. sc. nat. Joëlle Flück Sportmedizin, SPZ Guido A. Zäch Strasse 1 6207 Nottwil, Switzerland Phone: +41 41 939 66 17 Email: joelle.flueck@paraplegie.ch	Dr. med. Anke Scheel-Sailer Paraplegiology, SPZ Guido A. Zäch Strasse 1 6207 Nottwil, Switzerland Phone: +41 41 939 52 49 Email: anke.scheel-sailer@paraplegie.ch
Study Centre(s):	Single-center study at the SPZ	

Statistical Considerations:	Expected mean effect sizes for 25(OH)D concentration at baseline and four successive follow-ups were derived by visually fitting a pharmacokinetic curve for the expected time course for 25(OH)D concentration to the limited mean empirical data available for vitamin D supplementation in SCI. Assuming a significance level of 5% and a power of 80%, we conservatively plan with up to 60 individuals with a full dataset, which is 15 individuals per group. In case of dropouts or a large amount of missing data for a participant, recruitment will continue until we reach the 15 participants per group with a complete dataset (up to 68 participants might be recruited). Basic univariate statistical analysis techniques will be used to describe baseline values from primary and secondary outcomes. Multilevel mixed-effects models will be used to evaluate the longitudinal variation in primary and secondary outcomes. Non-linear regression modeling will be used to evaluate pharmacokinetic curves for each of the study groups.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki (World Medical Association (WMA) 1964), the ICH-GCP (Dixon 1999) as well as all national legal and regulatory requirements (The Federal Assembly of the Swiss Confederation 2011, The Swiss Federal Council 2013).

ACRONYMS

AE	Adverse Event
BASEC	Business Administration System for Ethical Committees
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CRF	Case Report Form
CTU	Clinical Trial Unit
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GMP	Good Manufacturing Process
H_0	Null hypothesis
H_A	Alternative hypothesis
IMP	Investigational Medicinal Product (Vi-De 3® Monthly Dose and placebo)
pCRF	Paper Case Report Form
PP	Per Protocol (analysis)
PQD	Pharmaceutical Quality Documentation
ISF	Investigator Study Files
ITT	Intention to treat (analysis)
SAE	Serious Adverse Event
RCT	Randomized Controlled Trial
SCI	Spinal Cord Injury
SPS	Schweizer Paraplegiker-Stiftung
SPZ	Schweizer Paraplegiker-Zentrum
SUSAR	Serious Unexpected Serious Adverse Event
TMF	Trial Master Files

STUDY SCHEDULE

Figure 1: Graphical overview of the study flow. The legend of the figure is displayed below (Figure 1a). The timeline of the study including the assessments is displayed on the see next page (Figure 1b), starting from the screening (top of the figure) to the last study visit (bottom of the figure).

***Figure 1a**: Study flow legend.*

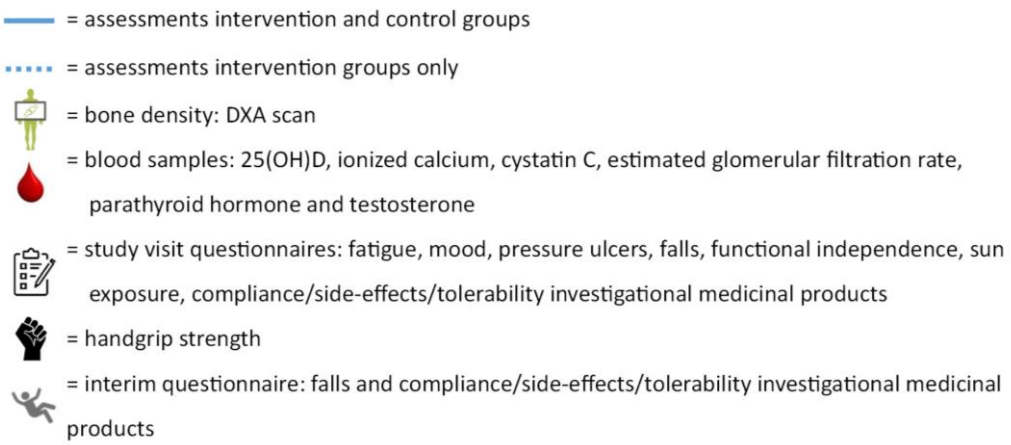

***Figure 1b**: Study flow.*

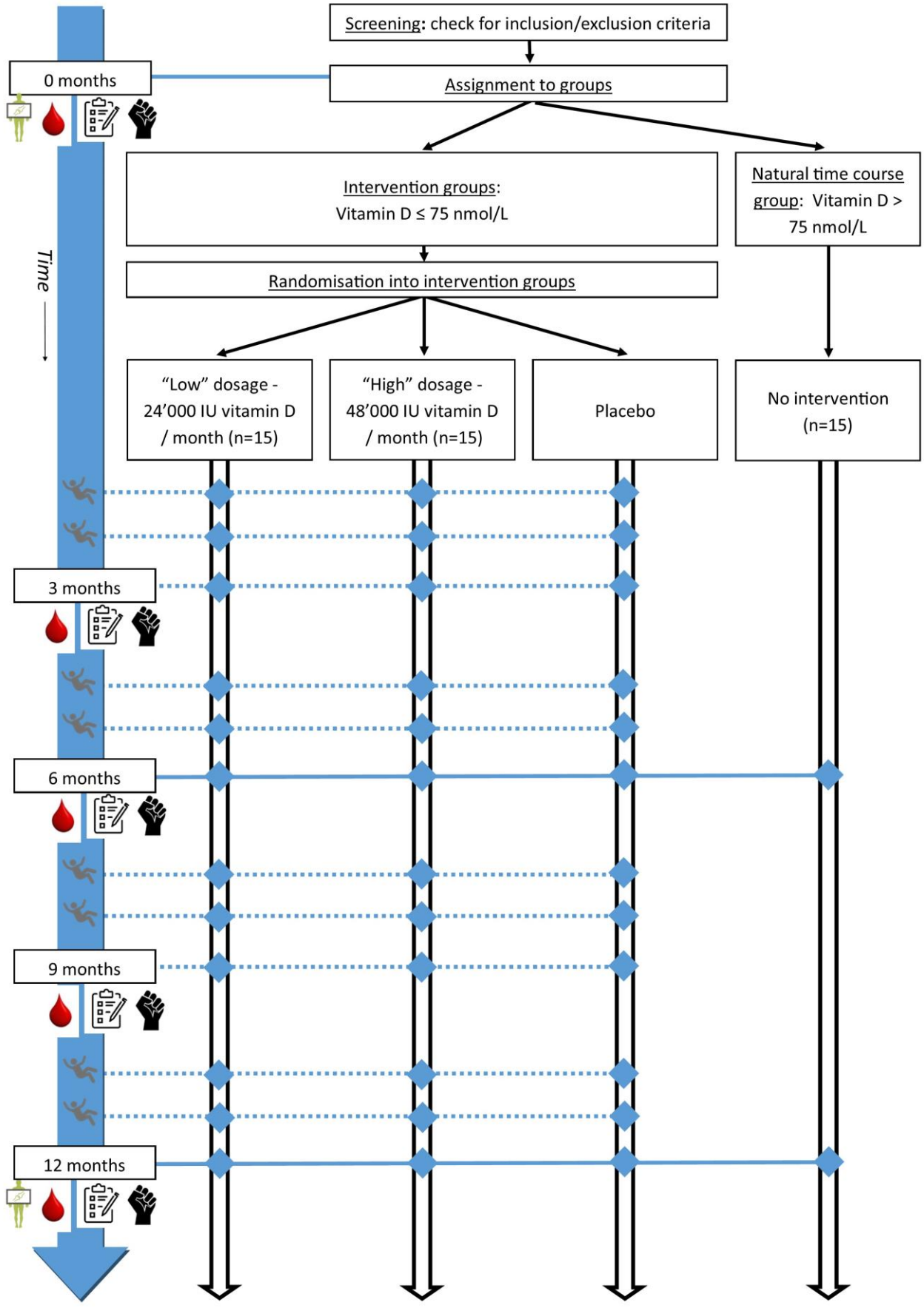

Table 1: Tabular overview of the study assessments, including a specification of the timing, duration and composition of the different assessments.

		Screening	Intervention Period				
Visit number	**Intervention groups (I)**	0	1 (baseline)	2, 3, 5, 6, 8, 9, 11, 12	4, 10	7	13
	Natural time course group (II)	0	1 (baseline)			2	3
Timing of the visit		Between 24 hours to 4 weeks before visit #1	0 (± 7 days)	1, 2, 4, 5, 7, 8, 10, 11 months (± 7 days)	3, 9 months (± 7 days)	6 months (± 7 days)	12 months (± 7 days)
Setting of the visit		SPZ or phone	SPZ	Phone or email	SPZ	SPZ	SPZ
Duration of the visit (minutes)		15-30	120	15	90	120	120
Screening procedure		I & II					
Patient Information and Informed Consent		I & II					
Blood samples, handgrip strength, study visit questionnaires			I & II		I	I & II	I & II
Bone density (DXA)			I & II				I & II
Assignment to the intervention group or natural time course based on vitamin D status			I & II				
Randomization into one of the three intervention groups			I				
Compliance, side-effects and tolerability investigational product				I	I	I	I

SPZ = Schweizer Paraplegiker-Zentrum

I = intervention groups: individuals who have an insufficient vitamin D status (≤ 75 nmol/L) at baseline will be randomly assigned to the "low" dosage (24'000 IU vitamin D/month), "high" dosage (48'000 IU vitamin D/month), or placebo group.

II = natural time course group: individuals who have a sufficient vitamin D status (> 75 nmol/L) at baseline will become neither a supplement nor a placebo.

Table 2: Tabular overview of the administration of the Investigational Medicinal Product (IMP) for each of the study groups.

Group	**Monthly administration of the IMP during 12 months***
"Low" dosage	One vial with Vi-De 3® Monthly Dose (24'000 IU vitamin D) and one vial with placebo
"High" dosage	Two vials with Vi-De 3® Monthly Dose (24'000 IU vitamin D)
Placebo (control)	Two vials with placebo
Natural time course	None

** The administration will take place every two weeks, i.e. the content of one vial will be taken by the participants of the intervention groups every two weeks.*

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor, Sponsor-Investigator

Sponsor: Schweizer Paraplegiker-Zentrum (SPZ), Guido A. Zäch-Strasse 1, 6207 Nottwil.

Sponsor-Investigator: Dr. sc. nat. Joëlle Flück, sports medicine, SPZ, Guido A. Zäch-Strasse 4, 6207 Nottwil, joelle.flueck@paraplegie.ch, +41 41 939 66 17.

The CV as well as proof of Good Clinical Practice (GCP) training can be found in the appendices ("06a_CV_Publication_List_Joëlle_Flück" and "07a_GCP_Certificates_Joëlle_Flück").

1.2 Principal Investigator

Dr. med. Anke Scheel-Sailer, study physician, paraplegiology SPZ, Guido A. Zäch Strasse-1, 6207 Nottwil, anke.scheel@paraplegie.ch, +41 41 939 52 49

The CV as well as proof of Good Clinical Practice (GCP) training can be found in the appendices ("06b_CV_Publication_List_Anke Scheel-Sailer" and "07b_GCP_Certificates_Anke Scheel-Sailer").

1.3 Statistician ("Biostatistician")

Dr. Martin Brinkhof, Swiss Paraplegic Research, Guido A. Zäch-Strasse 4, 6207 Nottwil, martin.brinkhof@paraplegie.ch, +41 41 939 65 97

1.4 Laboratory

Dr. med. Andreas Jenny, paraplegiology SPZ, Guido A. Zäch-Strasse 1, 6207 Nottwil, andreas.jenny@paraplegie.ch, +41 41 939 52 47

1.5 Monitoring institution

Clinical Trial Unit (CTU) SPZ, Guido A. Zäch-Strasse 4, 6207 Nottwil

1.6 Data Safety Monitoring Committee

CTU SPZ, Guido A. Zäch-Strasse 4, 6207 Nottwil, clinical.trial.unit@paraplegie.ch

The CTU of the SPZ is independent of the sports medicine department of the SPZ. The CTU supports us with monitoring, web-based data acquisition software (SecuTrial®, iAS, Berlin, Germany) and managing of access, input and storage of data.

1.7 Any other relevant Committee, Person, Organization, Institution

Dr. rer. nat. biol. Angela Frotzler, CTU SPZ, Guido A. Zäch-Strasse 4, 6207 Nottwil, angela.frotzler@paraplegie.ch, +41 41 939 55 61

Valentin Habermacher, pharmacy SPZ, Guido A. Zäch-Strasse 1, 6207 Nottwil, valentin.habermacher@paraplegie.ch, +41 41 939 59 56

Dr. Anneke Hertig-Godeschalk, study coordinator and main researcher at trial site, sports medicine SPZ, Guido A. Zäch-Strasse 1, 6207 Nottwil, anneke.hertig@paraplegie.ch, +41 41 939 66 03

Dr. med. Gunther Landmann, pain medicine SPZ, Guido A. Zäch-Strasse 1, 6207 Nottwil, gunther.landmann@paraplegie.ch, +41 41 939 49 25

PD Dr. sc. nat. Claudio Perret, sports medicine SPZ, Guido A. Zäch-Strasse 1, 6207 Nottwil, claudio.perret@paraplegie.ch, +41 41 939 66 21

Dr. Inge-Marie Velstra, monitor, CTU SPZ, Guido A. Zäch-Strasse 4, 6207 Nottwil, inge-marie.velstra@paraplegie.ch, +41 41 939 59 45

Dr. sc. ETH Patrik Wyss, radiology SPZ, Guido A. Zäch-Strasse 1, 6207 Nottwil, patrik.wyss@paraplegie.ch, +41 41 939 55 86

2. ETHICAL AND REGULATORY ASPECTS

Before the study will be conducted, the protocol, the proposed patient information and consent form as well as other study-specific documents shall be submitted to the Competent Ethics Committee (CEC) and Competent Authority (CA, Swissmedic) in agreement with local legal requirements, for formal approval. Any amendment to the protocol must as well be approved (if legally required) by these institutions. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study registration

After approval by the CEC, this study will be registered on clinicaltrials.gov as well on the Swiss National Clinical Trials Portal (SNCTP) of the Federal Office of Public Health (FOPH) via the portal of the Business Administration System for Ethical Committees (BASEC).

2.2 Categorization of study

This is an investigator-initiated clinical trial with a medicinal product and a placebo. The product under investigation, "Vi-De 3® Monthly Dose" (600 µg cholecalciferol or 24'000 IU vitamin D3) from Dr. Wild & Co. AG, is commercially available (appendix "16_Product_Information_Vi-De3_Monthly_Dose"). One intervention group will receive a "low" dosage (24'000 IU/month, corresponding to ~ 800 IU/day) while another intervention group will receive a "high" dosage (48'000 IU/month, corresponding to ~ 1600 IU/day) vitamin D supplementation. This is a higher dosage than prescribed in the product information, which is 24'000 IU/month. However, higher dosages are regularly prescribed in clinical practice and have already been studied rather abundantly among the general population (Dawson-Hughes, Heaney et al. 2005, Bischoff-Ferrari, Shao et al. 2010, Bischoff-Ferrari, Dawson-Hughes et al. 2016, Pettersen 2017, Burt, Billington et al. 2019). Even though we will exclude pregnant women, vitamin D is recommended among this sub-population and previously investigated in multiple studies with even higher dosages than the current study (De-Regil, Palacios et al. 2016, Pilz, Zittermann et al. 2018, National Health Service (NHS) 2020). The assigned dosages in this study will not exceed the highest tolerated daily limit (10'000 IU/day) as advised by both the Food Nutrition Board as well as the Endocrine Society (Hathcock, Shao et al. 2007, Holick, Binkley et al. 2011). In addition, several blood parameters will be monitored to check for vitamin D overdose. For example, serum ionized calcium concentration will be measured to monitor possible hypercalcemia. Hypercalcemia is not expected in this study, as in the study by Flück et al. (2016), no hypercalcemia was found among paralyzed athletes with a dosage of 6000 IU/day for 12 weeks. As a placebo, the same solution as Vi-De 3® Monthly Dose, but without cholecalciferol, will be produced for and used in this study. Therefore, this is a category B clinical trial.

2.3 Competent Ethics Committee

The Sponsor-Investigator will obtain approval for this study from the CEC before the start of the clinical trial. No changes will be made in the protocol without the approval of the responsible CEC (Ethics Committee Northwest and Central Switzerland, EKNZ) and the sponsor, except where necessary to eliminate apparent immediate hazards to study participants. This study has already been presented to and approved by the internal clinical study committee (Entscheidungsgremium Klinische Forschung, EGKF) of the SPZ. Unanticipated problems involving risks to humans, premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.10.

2.4 Competent Authority

The Sponsor-Investigator will obtain approval from the CA (Swissmedic) before the start of the clinical trial. Premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the CA within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.10.

2.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki (World Medical Association (WMA) 1964), the guidelines of Good Clinical Practice (GCP) issued by the International Conference on Harmonization (ICH) (Dixon 1999), the Swiss Law and Swiss regulatory authority's requirements (The Federal Assembly of the Swiss Confederation 2011, The Swiss Federal Council 2013). The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study termination in agreement with local requirements.

2.6 Declaration of interest

The Sponsor-Investigator declares that there are no conflicts of interest, intellectual, financial or proprietary conflicts. The supplements, as well as the placebo, are sponsored by Dr. Wild & Co. AG. An agreement can be found in the appendices ("09b_Collaboration_Agreement_Wild").

2.7 Patient Information and Informed Consent

A qualified study employee will explain the study to each participant, including its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time, without providing a reason, and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment. The participant will be informed that his/her medical records may be examined by authorized individuals other than their treating physician.

All participants will be provided with a participant information sheet and a consent form describing the study (appendix "03_ClinO_Participant_Info_Informed_Consent"). This document will provide sufficient information for the participant to make an informed decision about their participation in the study. Enough time (at least 24 hours) will be given to the participant to decide whether to participate or not. The participant should read and consider the statement before signing and dating the informed consent form. The consent form must also be signed and dated by a qualified study employee. The participant will be given a copy of the signed document and the document will be retained as part of the study records (Investigator Study Files (ISF)). The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure. Participants will receive a compensation for travel expenses (CHF50 for each study visit, appendix "11a_Participant_Compensation_Form").

2.8 Participant privacy and confidentiality

The Sponsor-Investigator affirms and upholds the principle of the participants' right to privacy and that they shall comply with applicable privacy laws. Especially, the anonymity of the participants shall be guaranteed when presenting findings/data at scientific meetings or publishing findings/data in scientific journals.

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Participant confidentiality will be further ensured by utilizing identification codes to correspond to study data in the computer files.

For data verification purposes, authorized representatives of the Sponsor (-Investigator), a CA (Swissmedic), or a CEC may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.9 Early termination of the study

The Sponsor-Investigator (and any competent authority) may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns
- insufficient participant recruitment
- when the safety of the participants is doubtful or at risk, respectively
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise
- early evidence of benefit or harm of the experimental intervention

2.10 Protocol amendments

Substantial amendments are only implemented after approval of the CEC and CA, respectively.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of participants may proceed without prior approval of the sponsor and the CEC and CA. Such deviations shall be documented and reported to the sponsor and the CEC and CA as soon as possible.

All non-substantial amendments are communicated to the CA as soon as possible if applicable and to the CEC within the Annual Safety Report.

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

Vitamin D plays an important role in the calcium uptake in the gut, but also in muscle strength and bone health (Cranney, Horsley et al. 2007, Holick and Chen 2008, Reid, Bolland et al. 2014). A lower vitamin D status is related to an increased risk of cancer, neurodegenerative diseases as well as cardiovascular diseases (Garland, Gorham et al. 2007, Annweiler, Rolland et al. 2012, Berridge 2015, Mandarino, Junior et al. 2015, Wong, Lim et al. 2015). An association between vitamin D status and musculoskeletal performance (i.e. strength) as well as with falls has been reported among older individuals (Bischoff, Stahelin et al. 2003, Ceglia and Harris 2013). A double blind placebo-controlled trial reported a significant positive effect of vitamin D supplementation on muscle recovery among ultra-runners, measured by resting and eccentric exercise–induced skeletal biomarker levels and pro-inflammatory cytokines (Zebrowska, Sadowska-Krepa et al. 2020). A meta-analysis reported significantly reduced pain scores among individuals receiving vitamin D compared to those receiving a placebo (Wu, Malihi et al. 2016). A relation between vitamin D supplementation and fatigue as well as cognition has also been suggested (Han, Wu et al. 2017, Pettersen 2017, Sousa, Rosa et al. 2017). To summarize, vitamin D status seems to influence several different body functions as well as subjective perception.

Approximately 80-90% of circulating vitamin D is synthesized from cholesterol following exposure to sunlight (i.e. ultraviolet B), the remainder comes from food or supplementation intake (Holick 1999, Macdonald 2013). As little as 5-30 minutes of sun exposure of the face, arms and legs twice per week could provide an adequate amount of vitamin D (Holick 2007). Even though vitamin D status depends on the season and geographic latitude (Kimlin 2008, Oleson, Patel et al. 2010), the majority of the global general population has an undesirable or insufficient vitamin D status (25(OH)D concentration ≤ 75nmol/L) (Forrest and Stuhldreher 2011, Alkerwi, Sauvageot et al. 2015, Liu, Baylin et al. 2018, Roth, Abrams et al. 2018). A vitamin D insufficiency was found among 74.7% of the general Swiss population (Guessous, Dudler et al. 2012). Due to factors that are specifically present among individuals with a spinal cord injury (SCI), including reduced sun exposure, vitamin D insufficiency is even higher in this population (up to 96%) (Zhou, Vaziri et al. 1993, Vaziri, Pandian et al. 1994, Flueck and Perret 2017, Walia, Goldstein et al. 2018). In a study among Swiss wheelchair athletes, vitamin D insufficiency was found among all of the 20 participants at study initiation (Flueck, Hartmann et al. 2016).

After the occurrence of a SCI, several significant physiological adaptations in body composition occur, not only in the muscles (i.e. decreased muscle mass and changes in muscle fiber type composition) but also within the bones (i.e. reduced bone mineral density and bone stiffness) (Kocina 1997, Schantz, Sjöberg et al. 1997, Haider, Lobos et al. 2018). Especially below the lesion level, osteoporosis is highly prevalent (Morse, Biering-Soerensen et al. 2019) and accompanied by an increased risk of fractures that are often coincided with high complication rates (Edwards and Schnitzer 2015). Falls are also rather prevalent among individuals with SCI, regularly with significant consequences including high expenses, hospitalization and complications during the recovery process (Brotherton, Krause et al. 2007).

Especially among the SCI population, vitamin D insufficiency has detrimental effects. It can further affect bone density, causing osteopenia, osteoporosis and osteomalacia, thereby increasing the risk of fractures even more (Holick 2007). Presence of pressure ulcers, depression and poor physical function have been associated with vitamin D insufficiency among this population (Zhou, Vaziri et al. 1993, Barbonetti, Sperandio et al. 2016, Barbonetti, Cavallo et al. 2017, Lussi, Frotzler et al. 2018), but causality has not been reported.

A sufficient vitamin D status (25(OH)D concentration > 75 nmol/L) (Vieth 2011) can be reached with adequate supplementation. A daily dosage of 600 IU vitamin D has been recommended for adults aged 19 – 70 years (Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin and Calcium 2011), though this dosage has been considered too low (Hathcock, Shao et al. 2007). Among individuals with chronic SCI, dosages of 800 IU/day for 12 months failed to successfully raise vitamin D status to sufficient levels (Bauman, Morrison et al. 2005). Higher dosages of 2000 IU/day (Bauman, Emmons et al. 2011) or 6000 IU/day (Flueck, Schlaepfer et al. 2016) during three months were more successful. However, the body of research regarding vitamin D supplementation among the SCI population is limited and studies tend to have only small numbers of participants. Therefore it is still unclear what dosage should be supplemented and for how long, to achieve a sufficient vitamin D status among individuals with SCI.

Furthermore, there is only limited evidence regarding the effect of vitamin D supplementation on secondary outcomes (e.g. muscle strength and mood) among the chronic SCI population (Flueck, Schlaepfer et al. 2016, Amorim, Teixeira et al. 2018, Pritchett, Pritchett et al. 2019). The main objective of this study is to investigate the effect of two different 12-month vitamin D supplementation dosages, "low" (24'000 IU/month, corresponding to ~ 800 IU/day) and "high" (48'000 IU/month, corresponding to ~ 1600 IU/day), on vitamin D status among individuals with a chronic SCI. The rationale for the dosage and intake can be found in section 3.5. To allow for a reference of habitual current treatment (i.e. no supplementation in case of sufficient vitamin D status), a natural time course group has been included in the study. A further rationale for the inclusion of a placebo as well as a natural time course group can be found in section 3.6. Besides vitamin D status, this study will investigate the effects of vitamin D supplementation on several other parameters (e.g. bone density and mood), which could reveal positive secondary effects of supplementation. The evidence acquired during this study will provide valuable insights regarding vitamin D supplementation among the chronic SCI population.

3.2 Investigational Product and Indication

Vi-De 3® Monthly Dose from Dr. Wild & Co. AG (Muttenz, Switzerland) is a commercially available vitamin D3 supplement. One vial (5 mL) of the monthly dosage contains an ethanol solution (65% alcohol by volume) with 600 µg cholecalciferol, which corresponds to 24'000 IU vitamin D3. Further product information from Swissmedic can be found in the appendices ("16_Product_Information_Vi-De3_Monthly_Dose"). As a placebo, the same ethanol solution (65% alcohol by volume) as Vi-De 3® Monthly Dose will be used, but without cholecalciferol. The Pharmaceutical Quality Documentation (PQD) of the placebo can be found in the appendices ("39a_PQD_Placebo"). The placebo will be indistinguishable from the biologically active product in odor, taste as well as appearance. Both Investigational Medicinal Products (IMPs, Vi-De 3® Monthly Dose and placebo) will be provided by Dr. Wild & Co. AG. A copy of the Good Manufacturing Process (GMP) Certificates can be found in the appendices ("39b_GMP_Wild" and "39c_GMP_Mipharm").

3.3 Preclinical Evidence

Not applicable.

3.4 Clinical Evidence to Date

Regular testing for and supplementation of vitamin D has been recommended among the SCI population (Lussi, Frotzler et al. 2018). However, the number of experimental studies among individuals with SCI looking into vitamin D supplementation and its potential secondary outcomes (Flueck, Schlaepfer et al. 2016, Amorim, Teixeira et al. 2018, Pritchett, Pritchett et al. 2019) is limited (see also section 3.1)

3.5 Dosage Rationale

Evidence about the optimal dosage as well as the duration of vitamin D supplementation among individuals with chronic SCI is scarce. Dosages exceeding the generally recommended dosage of 600 IU/day, are expected to be most successful in reaching a sufficient vitamin D status (Bauman, Morrison et al. 2005, Hathcock, Shao et al. 2007, Bauman, Emmons et al. 2011, Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin and Calcium 2011, Flueck, Schlaepfer et al. 2016). Therefore, besides the "low" dosage (24'000 IU vitamin D/month) it was decided to also include the "high" dosage (48'000 IU vitamin D/month) in this study. Both dosages are prescribed in clinical practice and even the highest dosage vitamin D (48'000 IU/month, corresponding to ~ 1600 IU/day) administered in this study does not exceed the highest tolerated daily limit (10'000 IU/day) as advised by both the Food Nutrition Board as well as the Endocrine Society (Hathcock, Shao et al. 2007, Holick, Binkley et al. 2011). Previous studies among individuals with SCI implementing even higher dosages of vitamin D supplementation (up to 50'000 IU/week) did not report any safety issues among their participants (Bauman, Emmons et al. 2011, Flueck, Schlaepfer et al. 2016, Amorim, Teixeira et al. 2018, Pritchett, Pritchett et al. 2019). There are no guidelines regarding upper limits of vitamin D concentration among the SCI population (Lamarche and Mailhot 2016), though vitamin D toxicity occurs with 25(OH)D serum levels exceeding 375-750 nmol/l among the general population (Jones 2008, Gröber and Holick 2013, Galior, Grebe et al. 2018).
To improve adherence among participants and thereby the efficacy of achieving a sufficient vitamin D status (Dalle Carbonare, Valenti et al. 2017), this study will use the monthly instead of the daily vitamin D supplementation dosage of Dr. Wild & Co. AG.

3.6 Explanation for the choice of the comparator or placebo

As a placebo the same solution as Vi-De 3® Monthly Dose without cholecalciferol will be produced and filled in identical vials (appendix "39a_PQD_Placebo"). This will make the IMPs indistinguishable regarding odor, appearance and taste. Participants with a vitamin D status > 75 nmol/L will be allocated to the natural time course group, and receive neither a vitamin D supplement nor a placebo.

Having a placebo (or control) as well as a natural time course group is ethically justified since participants will not have used any vitamin D supplementation before partaking in this study, which implies that their vitamin D status will remain similar to that before study participation. Hence, partaking in this study involves no additional risk for the participants ("non-maleficence"). The use of a placebo group implies the most rigorous test of the efficacy of vitamin D supplementation in individuals with SCI while minimizing the number of participants needed for maximal treatment separation of outcomes as well as for detecting potential harmful treatment-related effects. The true added benefit (or risk) of treatment can thus be estimated against the background level of care. Finally, the study outcomes include patient-reported outcomes (e.g., pain, mood, and fatigue) that are subject to individual perception or expectation of treatment efficacy. The natural time course group serves as an additional background reference group of habitual current treatment (i.e. no supplementation in case of sufficient vitamin D status) and will allow us to capture as well as facilitate the control of seasonal variation in vitamin D status and other study outcomes (time-updated co-variable adjustment (Lammertse, Tuszynski et al. 2007)). Hence, including a placebo as well as a natural time course group in this study is ethically justifiable (World Medical Association (WMA) 1964).

3.7 Risks / Benefits

Potential risks

All participants will receive a detailed description of the most important information regarding the study on paper (appendix "03_ClinO_Participant_Info_Informed_Consent"). In addition, all participants will be verbally informed about the test procedure, the various measurements, their purpose and the potential risks. Participants can cancel a test or stop participating in the study at any time and without providing a reason to do so. In the event of illness, participants might not be admitted to the study visit. In such a case, the study team decides, whether the missed study visit is postponed to a later date or if the participant is excluded from the study altogether. The inclusion/exclusion criteria that are checked during the screening procedure will further minimize risks in this study (appendix "05a_CRF_Screening_Questionnaire").

Due to the high prevalence of vitamin D insufficiency, vitamin D supplementation is a widely used treatment method. The mono-vitamin D3 product (Vi-De 3® Monthly Dose) used in this study is commercially available in Switzerland (appendix "16_Product_Information_Vi-De3_Monthly_Dose"). In this study, participants will be supplemented with a maximum of 48'000 IU vitamin D/month (corresponding to ~ 1600 IU vitamin D/day). The assigned dosages in this study do not exceed the highest tolerated daily limit (10'000 IU/day) as advised by both the Food Nutrition Board as well as the Endocrine Society (Hathcock, Shao et al. 2007, Holick, Binkley et al. 2011). Previous studies with even higher vitamin D supplementation dosages (up to 50'000 IU/week) did not report any safety or overdose issues among their participants with SCI (Bauman, Emmons et al. 2011, Flueck, Schlaepfer et al. 2016, Amorim, Teixeira et al. 2018, Pritchett, Pritchett et al. 2019). Therefore, the side effects of vitamin D supplementation, which are only known as a result of an overdose, are not expected with the selected dosages in this study. Still, participants will be informed about possible signs of vitamin D overdose, which include: nausea, vomiting, diarrhea, constipation, anorexia, fatigue, headache, muscle and joint pain, muscle weakness and sleepiness. Participants are asked about potential side effects and tolerance of the IMPs during each study visit (appendices "05b_CRF_Visit_Questionnaire" and "05c_CRF_Interim_Questionnaire"). Furthermore, blood samples will be taken to monitor possible overdosing.

According to an independent expert report, there is no evidence that therapeutic dosages of Vi-De 3® Monthly Dose, containing the same alcohol solution as the placebo, have any health effects on infants or toddlers (Franz 2007). Therefore, there is no known risk of taking an ethanol 65% volume percent solution as a placebo among our adult study population. Participants will be informed that, due to the alcohol content, the intake of the supplement and/or placebo could have a minor influence on the ability to drive or the ability to operate machines. Participants receiving a placebo will most likely be vitamin D insufficient (≤ 75 nmol/L) until the end of the study. Nevertheless, this situation resembles that before study enrolment and therefore involves no additional risk for the participants ("non-maleficence"). See also section 3.6 for the more detailed rationale of including the placebo group.

During the bone density measurements, the dual-energy X-ray absorptiometry (DXA) scans expose participants to the following radiation: 0.010 mSv for the forearm, 0.146 mSv for the hip and 0.034

mSv for the knee measurement (appendix "34_Radiation_Exposure_Overview"). The sum of the radiation exposure for the two measurements in this study (2 x 0.190 = 0.380 mSv) is less than the average yearly radiation exposure due to Radon (3.200 mSv) in Switzerland (Bundesamt für Gesundheit (BAG) 2018). The radiation exposure during this study is also well below the dose guidance value (5 mSv) for research projects with no expected direct benefits (The Swiss Federal Council 2017). Before each measurement, the "11b_Questionnaire_DXA" will be filled out, to assure safety and determine the optional measurement side (i.e. no recent fractures or metal). During the examinations, strict guidelines are followed. Hence no additional risks or side effects are to be expected.

During the venous blood collection, the small prick in the elbow can cause a small local inflammation and minor pain.
General emergency measures are in place. In the event of an emergency during study visits, the physician on duty and the in-house resuscitation team of the SPZ will be alerted. The study staff has also recently completed a BLS-AED course. For all other emergencies, participants are instructed to contact the regular emergency authorities

Benefits
In case of a vitamin D insufficiency (25(OH)D ≤ 75 nmol/L) at visit #1, participants will be allocated to the intervention groups and could receive 24'000 IU vitamin D/month or 48'000 IU vitamin /month. Vitamin D status among participants receiving vitamin D supplements will most likely improve, which would also reduce the risk of secondary diseases. In addition to blood parameters, several cognitive and physical outcomes related to vitamin D status are measured and analyzed regularly among the intervention groups as well as the natural time course group. This could provide helpful insights to optimize individual vitamin D supplementation after the end of the study. When a positive relation between a sufficient vitamin D status and secondary outcomes can be established, this could lead the way for standardized recommendations for vitamin D supplementation among the chronic SCI population for daily as well as in clinical practice.

3.8 Justification of choice of the study population

Although research has shown that the prevalence of vitamin D insufficiency is high among individuals with SCI, little is known about optimal dosages as well as potential secondary benefits of supplementation among this population (Flueck, Schlaepfer et al. 2016, Amorim, Teixeira et al. 2018, Pritchett, Pritchett et al. 2019). The age cohort of 18-60 years was chosen, to create a population as coherent as possible. A sub-C4-lesion level was chosen to not restrict the eligibility criteria too much and create a broad SCI population.
Study participants will be mainly recruited from the population-based Swiss Spinal Cord Injury Cohort Study (SwiSCI) database. Only individuals who agreed to be contacted for future scientific studies will be approached. The nesting of the randomized-controlled trial (RCT) in SwiSCI thus supports, conditional on the inclusion and exclusion criteria (see also section 7.1), the establishment of a study population that is representative of the Swiss population of individuals with chronic SCI.

4. STUDY OBJECTIVES

4.1 Overall Objective

The purpose of this study is to evaluate the influence of vitamin D supplementation among individuals with chronic SCI. We aim to study whether different dosages (24'000 IU/month or 48'000 IU/month) of vitamin D supplementation over 12 months will lead to differences in vitamin D status as well as differences in several other outcomes. The use of both a placebo group and a natural time course group as reference groups supports the evaluation of dose-response effects of vitamin D supplementation on the primary outcome (vitamin D status) and secondary outcomes (including bone density and mood) that are not only supported by RCT standards, but also informative in clinical practice.

4.2 Primary Objective

The primary objective is to investigate the effect of vitamin D supplementation on vitamin D status of individuals with a chronic SCI.

4.3 Secondary Objectives

The effect of vitamin D supplementation among participants will also be assessed by measuring several secondary parameters (including bone density and mood). These results could reveal clinically relevant and valuable secondary effects of vitamin D supplementation.

4.4 Safety Objectives

Among the general population, vitamin D toxicity occurs with 25(OH)D serum levels exceeding 375-750 nmol/l (Jones 2008, Gröber and Holick 2013, Galior, Grebe et al. 2018). Vitamin D overdose shows clinical manifestation in the form of hypercalcemia (Jones 2008). There are no guidelines regarding safe upper serum levels of vitamin D among the SCI population (Lamarche and Mailhot 2016). To monitor possible vitamin D overdose as well as hypercalcemia, several blood parameters including 25(OH)D and ionized calcium, will be assessed every three months. Previous studies among individuals with SCI investigating higher dosages of vitamin D supplementation (up to 50'000 IU/week) did not report any safety or overdose issues (Bauman, Emmons et al. 2011, Flueck, Schlaepfer et al. 2016, Amorim, Teixeira et al. 2018, Pritchett, Pritchett et al. 2019). Hence, we expect that the participants of this study will tolerate the vitamin D supplementation well. Furthermore, side-effects and subjective tolerability of the IMPs will be checked monthly.

5. STUDY OUTCOMES

A rationale for the choice of study outcomes can be found in the Background (section 3.1). A description of the different study parameters including measurements will also be documented in a manual. Taking of blood samples, handgrip strength measurements and bone density measurements will be performed by qualified employees, following regular clinical procedures. Questionnaires will be filled out by the participants together with and/or under the supervision of qualified employees.

5.1 Primary Outcome

Vitamin D status, measured by 25(OH)D concentration, will be determined by taking blood samples from the elbow vein at 0-3-6-9-12 months for the three intervention groups and at 0-6-12 months for the natural time course group (appendix "05d_eCRF_Visit").

5.2 Secondary Outcomes

Bone density: Measurements will take place at 0 and 12 months for all groups. Before each measurement, a questionnaire (appendix "11b_Questionnaire_DXA") will be filled out, to assure safety and determine the optimal measurement side (i.e. no recent fractures or metal). Measurements of the forearm (radius), hip (femoral neck) and knee (distal femur and proximal tibia) will be performed using DXA scans (X-ray densitometer with enCORE v17 Software, Lunar iDXA Serie) (appendix "05d_eCRF_Visit"). The DXA apparatus is regularly calibrated following standard protocol. Only one side of each body position will be measured, e.g. only the left forearm. When possible, the non-dominant side (based on the hand) of the body will be measured, i.e. when a participant is right-handed, the left forearm, left hip and left knee will be measured).

The following secondary outcomes will be measured at 0-3-6-9-12 months for the three intervention groups and at 0-6-12 months for the natural time course group:
Fatigue will be assessed by the Fatigue Severity Scale (FSS). This questionnaire is used to measure fatigue and the effects of fatigue on functioning (Krupp, LaRocca et al. 1989). It has been validated among the SCI population (Anton, Miller et al. 2008) as well as among a Swiss German-speaking cohort of healthy and sleep-disordered individuals (Valko, Bassetti et al. 2008) (appendix "11c_Questionnaire_FSS").
Mood will be assessed by the Hospital Anxiety and Depression Scale (HADS) (appendix "11d_Questionnaire_HADS"). This questionnaire reliably detects anxiety and depression (Zigmond and Snaith 1983), has been validated in German (Herrmann and Buss 1994) and its use has been supported among individuals with SCI (Müller, Cieza et al. 2012).
Pain will be assessed using questions of the adapted version of the International SCI Pain Basic Data Set (Widerström-Noga, Biering-Sørensen et al. 2008) as well as the SCI Secondary Conditions Scale (Kalpakjian, Scelza et al. 2007) (appendix "05b_CRF_Visit_Questionnaire"). The occurrence, kind, location and influence of pain during the last week as well as chronic pain (> 3 months) will be evaluated. The exact questions of the first- and second-wave questionnaire of the SwiSCI survey will be used (Post, Brinkhof et al. 2011, Brinkhof, Fekete et al. 2016).
Pressure ulcers will be assessed by the exact questions of the first-wave questionnaire of the SwiSCI survey (Post, Brinkhof et al. 2011, Brinkhof, Fekete et al. 2016). When participants had pressure ulcers, the localization as well as grade using the EPUAP/NPUAP classification (National Pressure Ulcer Advisory Panel and Alliance. 2014), will also be assessed (appendix "05b_CRF_Visit_Questionnaire").

5.3 Other Outcomes of Interest

Other outcomes of interest are assessed during study visits at the SPZ at 0-3-6-9-12 months among the intervention groups and at 0-6-12 months for the natural time course group (appendices "05b_CRF_Visit_Questionnaire" and "05d_eCRF_Visit"), or are assessed monthly via phone or email among the intervention groups (appendix "05c_CRF_Interim_Questionnaire"). Parameters might also be subtracted from participant charts (e.g. MedFolio):
Handgrip strength will be assessed using the Jamar Handgrip Dynamometer. The Dynamometer is regularly calibrated following standard protocol. Participants will be asked to sit up straight, grab the Dynamometer with one hand while holding the respective arm unsupported and close to the body with a 90-degree angle. Both hands will be measured, starting with the left hand (3x) followed by the right hand (3x). The average strength of the three maximum handgrip measurements of both hands will be calculated (appendix "05b_CRF_Visit_Questionnaire").

This measurement will be only be performed among participants who can successfully execute it, i.e. most likely participants with level C4-C7 complete lesions will not be able to execute this. Since handgrip strength is not a primary outcome, this missing data is of no concern for the main results of this study.
Several personal characteristics will be assessed including age, height, weight, skin type, date of the lesion, lesion level, American Spinal Injury Association (ASIA) Impairment Scale (AIS), diseases, intake of medication and/or supplements.
Recent falls will be assessed by asking participants about the incidence, reason (recreation or daily activity), possible injuries and care needed resulting from each fall (appendices "05b_CRF_Visit_Questionnaire" and "05c_CRF_Interim_Questionnaire"). A fall will be defined as an unexpected event in which an individual comes to rest on the ground, the floor, or a lower level (Lamb, Jorstad-Stein et al. 2005).
Functional independence during daily living will be assessed by the Spinal Cord Independence Measure (SCIM, 3rd version) (appendix "11e_SCIM"). The SCIM addresses the ability to perform basic activities of daily living independently among individuals with SCI (Itzkovich, Gelernter et al. 2007).
Sun exposure will be assessed using the questionnaire from Hanwell et al. (2010) (appendix "05b_CRF_Visit_Questionnaire"). Furthermore, the seasons of study participation will be taken into account.

5.4 Safety Outcomes

Blood samples from the elbow vein will be taken and analyzed by the SPZ laboratory at 0-3-6-9-12 months for the three intervention groups and at 0-6-12 months for the natural time course group following standard clinical procedures (appendix "05d_eCRF_Visit"). A total of 45 mL of blood will be taken, of which 30 mL will be stored in the Biobank of the SPZ in case participants provided explicit consent for this. A 25(OH)D level > 375 nmol/L might lead to the exclusion of the participant. The following parameters are related to vitamin D status as well as bone health, and will also be assessed during this study:
Ionized calcium: to monitor hypercalcemia. A concentration > 3.5 mmol/L might lead to the exclusion of the participant.
Cystatin C and estimated glomerular filtration rate (eGFR): to monitor kidney function.
Parathyroid hormone and testosterone are directly related to the vitamin D status and are therefore measured for monitoring this primary outcome.

Side-effects and the general tolerability of the IMPs will be monitored monthly using questionnaires (appendices "05b_CRF_Visit_Questionnaire" and "05c_CRF_Interim_Questionnaire).

6. STUDY DESIGN

6.1 General study design and justification of design

This is a placebo-controlled randomized double-blinded superiority study, evaluating the effect of 12 months of vitamin D supplementation on vitamin D status (blood samples) and several secondary outcomes (e.g. bone density and mood). An overview of the study design can be found in the Study Schedule (pages 9-11).

Potential participants will be mainly recruited from the population-based SwiSCI database. Only individuals who agreed to be contacted for future scientific studies will be approached. When not enough participants can be recruited in this way, recruitment will also be performed among ambulatory patients of the SPZ. An information flyer (appendix "11f_Recruitment_Flyer") will be distributed. During screening (around 15-30 minutes), the inclusion/exclusion criteria will be checked. In case a participant is eligible, the informed consent will be signed. Participants with an insufficient vitamin D status (≤ 75 nmol/L) at study visit #1 will be randomly allocated into one of the three intervention groups receiving either 24'000 IU vitamin D/month, 48'000 IU vitamin D/month or a placebo (ethanol solution without the active ingredient) for 12 months. A permuted block randomization procedure with varying block sizes (3 or 6) will be used for the concealed allocation of the participants in the intervention groups. Participants with a sufficient vitamin D status (> 75 nmol/L) at study visit #1 will be allocated to the natural time course group. Based on a power analysis, we aim to include 60 participants with a full dataset, i.e. 15 participants per group (appendix "39d_Sample_Size_Estimation_Table"). In case of dropouts or a large amount of missing data for a participant, recruitment will be continued until we reach the 15 participants per group with a complete dataset and hence up to 68 participants might be recruited. Participants replacing dropouts who are allocated to the intervention groups, will be assigned to the same intervention group as the participant who dropped out. Several measurements will be performed during the 1.5 to 2 hours study visits at the SPZ, which will take place every three months (intervention groups) or every six months (natural time course group). Further information about the study assessments and data collection procedures can be found in sections 5 and 9.

All study employees involved in the recruitment and measurements, as well as the participants, will be blinded to the assignment of the IMPs until the end of the study ("last participant out"). The key to the blinding of the IMPs will be sealed and stored in a locked room which is only accessible to employees who are not involved in the study measurements. Only in case of emergencies or upon study termination, will the key be opened.

6.2 Methods of minimizing bias

6.2.1 Randomization

A permuted block randomization list with varying block sizes (3 or 6) will be prepared by the statistician (MB), using the statistical software Stata (Stata [Computer program]. Version 16. College Station, TX, USA: StataCorp, 2019. Available from www.stata.com) and the program "ralloc" (Ryan 2018). The allocation of the three intervention groups (for example: "low" dosage = A, "high" dosage = B, and placebo = C) will be documented in a blinding key. The randomization sequence and blinding key will be securely stored in a locked room.

6.2.2 Blinding procedures

Both Vi-De 3® Monthly Dose and the placebo will be provided by Dr. Wild & Co. AG. The IMPs will be filled into identical commercially-available vials, but will initially be labeled differently to allow for the identification of either the biologically active solution or the placebo. For each participant, all vials will be (re)labeled by the pharmacy of the University Hospital Basel following Good Manufacturing Practice (appendix "39e_GMP_Basel"), as well as the randomization list and the blinding key (see section 6.2.1). Each vial will receive an individual (unique) label. Participants will receive vials for the next three months during visits. Furthermore, the vials will be numbered successively (1-6) to indicate the order in which the vials have to be taken. Identification of the vials will be impossible for anyone without access to the binding key. The key to the blinding will be sealed and stored in a locked room which is only accessible to employees who are not involved in the study measurements.

6.2.3 Other methods of minimizing bias

Several methods for reducing bias will be implemented. Sufficiently trained employees will execute all of the measurements. Measurement devices and equipment (e.g. Jamar Handgrip Dynamometer) will be appropriately serviced and calibrated. Furthermore, questionnaires that have been validated among the SCI population will be used, e.g. HADS and SCIM. Furthermore, the assessment of several outcomes allows us to correct for possible confounders in our analyses, e.g. season and SCI level. Participants will be asked to express their belief concerning the assigned intervention every three months (appendix "05b_CRF_Visit_Questionnaire"), which will be used to compute a measure of the extent of successful blinding of the trial.

6.3 Unblinding Procedures (Code break)

Unblinding will only be allowed in the following circumstances; upon study termination, in the case of a suspension of the study or premature study termination, or in the case of emergencies or complications. Whenever possible, only the allocated intervention of the affected participant(s) will be revealed.

7. STUDY POPULATION

7.1 Eligibility criteria

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Informed Consent as documented by a signature (appendix "03_ClinO_Participant_Info_Informed_Consent").
- Between 18 – 60 years old.
- Chronic (> 3 years) traumatic or non-traumatic SCI, with a sub-C4-level lesion.
- Wheelchair-dependency during activities of daily living, defined by a score of 0-2 in the SCIM-III subsection about "Mobility in the house".

The presence of any one of the following criteria will lead to exclusion of the participant:

- Intake of > 400 IU/day of vitamin D during the last 12 months before recruitment or during the study.
- Contraindications to the IMPs, e.g. known hypersensitivity or allergy to the cholecalciferol or alcohol solution.
- Women who are pregnant or planning to become pregnant during the study period. Vitamin D supplementation among pregnant women has been previously investigated in multiple studies using even higher dosages than the current study, while reporting no complications (De-Regil, Palacios et al. 2016, Pilz, Zittermann et al. 2018, National Health Service (NHS) 2020). Hence, vitamin D is recommend to pregnant women in clinical practice (National Institute for Health and Clinical Excellence (NICE) 2008, Chief Medical Officers for the United Kingdom Cardiff and Social Services and Public Safety 2012). It was decided to exclude pregnant women since the experimental supplementation could lead to a high vitamin D status and this factor also adds another bias to the study. For women of childbearing age, a urine pregnancy test was added to the screening procedure. In case these women are sexually active, they will be requested to use birth control during the study.
- Women who are breastfeeding.
- Clinically relevant disorders, including renal dysfunction, hepatic dysfunction, cardiovascular disease, lung disease, diabetes, blood disease, parathyroid disease, cancer, depression) and/or the intake of significant concomitant medication (e.g. osteoporosis treatment and benzothiadiazide derivatives. This will be assessed on an individual basis, potentially with the help of chart review.
- Grade 3 or 4 pressure ulcers.
- Fractures in both arms and/or both legs within the last five years.
- Visiting a country with increased sun exposure (below the 37th parallel north, i.e. the southern hemisphere) within one month before enrollment or during the study.
- Inability to understand or decide on study participation (i.e. make an informed consent) and to adhere to the study protocol, e.g. due to language or psychological problems.
- Participation in another study with an investigational drug within the 30 days preceding and during the present study.

7.2 Recruitment and screening

Potential participants will be mainly recruited from the population-based SwiSCI database. Only individuals who fulfill the criteria and have agreed to be contacted for future scientific studies will be approached (n=343). When not enough participants can be recruited in this way, recruitment will also be performed among ambulatory patients of the SPZ. An information flyer (appendix "11f_Recruitment_Flyer") will be distributed. A screening will take place with interested individuals, either in person at the SPZ or by a phone call (duration 15-30 min). During the screening, a qualified study employee will explain the study and its procedures and any questions from the individuals will be answered. Moreover, the screening questionnaire (appendix "05a_CRF_Screening_Questionnaire") will be filled out together. Women of childbearing age will have a urine pregnancy test during screening and are requested to use birth control during entire the study duration in case they are sexually active. Further chart review might be performed. The study physician will make the final decision regarding the inclusion or exclusion of each individual. The individual will receive the Patient Information and Informed Consent document (appendix "03_ClinO_Participant_Info_Informed_Consent"), and at least 24 hours will be given to decide on participation. The informed consent form will be signed by both the participant and a qualified study employee. If all criteria are satisfied, the first study visit will be planned.
All participants will receive compensation for travel expenses (CHF50 for each study visit, appendix

"11a_Participant_Compensation_Form").

7.3 Assignment to study groups

Based on the vitamin D status at study visit #1 (baseline), participants will be assigned to either one of the three intervention groups (≤ 75 nmol/L; "low" dose, "high" dose or placebo) or the natural time course group (> 75 nmol/L). Participants replacing dropouts who are allocated to the intervention groups, will be assigned to the same intervention group as the participant who dropped out. See section 6.2 for the randomization and blinding protocol. The unblinding procedure is described in section 6.3.

7.4 Criteria for withdrawal/discontinuation of participants

In case of any safety concerns, the study might be discontinued. Participants might be redrawn from the study when:

- They experience illness, side effects, or other health problems related to the intake of the IMP.
- They don't fulfill the inclusion/exclusion criteria anymore. For example, participants redraw their consent, start taking certain medications or visit countries with increased sun exposure (below the 37th parallel north).
- Serum levels indicating a vitamin D intoxication (25(OH)D > 375 nmol/L) or hypercalcemia (ionized calcium concentration > 3.5 mmol/L).

Follow-up procedures for withdrawn participants are described in section 8.5. Participants who withdraw or dropout from the study, or for whom data collection is characterized by a large amount of missing data, will be replaced to reach the targeted sample sizes of 15 participants per group with a complete dataset.

8. STUDY INTERVENTION

See also Table 2 (page 11) for an overview of the IMP administration for all of the study groups.

8.1 Identity of Investigational Products

8.1.1 Experimental Intervention

Vi-De 3® Monthly Dose from Dr. Wild & Co. AG (Muttenz, Switzerland) is a commercially available vitamin D3 supplement. One vial (5 mL) of the monthly dosage contains an ethanol solution (65% alcohol by volume) with 600 µg cholecalciferol, which corresponds to 24'000 IU vitamin D3. One vial of Vi-De 3® Monthly Dose contains 2.6 gram alcohol. In comparison, one glass (250 mL) of apple juice can contain up to 0.165 gram alcohol (Gorgus, Hittinger et al. 2016). Further product information from Swissmedic can be found in the appendices ("16_Product_Information_Vi-De3_Monthly_Dose"). The content of a vial is to be put in a glass of water and taken orally.

8.1.2 Control Intervention (standard/routine/comparator treatment)

A placebo will be produced, consisting of the same ethanol solution (65% alcohol by volume) as Vi-De 3® Monthly Dose, but without cholecalciferol (appendix "39a_PQD_Placebo"). The placebo will be indistinguishable from the biologically active product in odor, taste as well as appearance. The content of a vial is to be put in a glass of water and taken orally.

8.1.3 Packaging, Labelling and Supply (re-supply)

See also the Good Manufacturing Practice (GMP) for IMPs (appendix "39e_GMP_Basel"). All of the vials with both the supplement (5 mL with cholecalciferol or 24'000 IU vitamin D3,") as well as the placebo (5 mL without cholecalciferol) will be provided by Dr. Wild & Co. AG. A copy of the GMP Certificates can be found in the appendices ("39b_GMP_Wild" and "39c_GMP_Mipharm"). All vials will be relabeled by the pharmacy of the University Hospital Basel (appendix "39e_GMP_Basel"). Each vial will receive an individual (unique) label. All vials will be labeled with the required information, an example of the labels can be found in the attachments (appendix "39g_Label_Vials_and_Package"). The vials will be packed in a light-protective package, for example, a carton box. All handling of the vials will be logged (appendix "39f_Accountability_Log_IMP").

8.1.4 Storage Conditions

The vials must be preserved at room temperature (15-30°C), kept out of light and out of the reach of children. The stored vials are only accessible to eligible study employees. The IMPs should only be used until the date marked «EXP» on the vial. When handing the supplement over to the participants, they will be informed about the correct storage and intake. Used and unused vials are to be returned by the participants. The handling of the vials will be logged (appendix "39f_Accountability_Log_IMP").

8.2 Administration of experimental and control interventions

8.2.1 Experimental Intervention

The six vials for the upcoming three months will be handed out to the participants of the intervention groups during the study visits:

-"low" dosage group: 24'000 IU vitamin D/month (corresponding to ~ 800 IU/day). Participants in this group will take one vial with Vi-De 3® Monthly Dose and one vial with placebo every month (i.e. one vial every two weeks) for 12 months.

-"high" dosage group: 48'000 IU vitamin D/month (corresponding to ~ 1600 IU/day). Participants in this group will take two vials with Vi-De 3® Monthly Dose every month (i.e. one vial every two weeks) for 12 months.

Participants are instructed to put the content of the vial in a glass, add some water and drink the solution directly. The handling of the IMP (appendix "39f_Accountability_Log_IMP"), as well as the intake of the IMP (appendix "11g_Diary_IMP"), will be logged. See section 3.5 for the dosage rationale.

8.2.2 Control Intervention

The six vials for the upcoming three months will be handed out to the participants of the placebo group during the study visits:

- Participants in this group will take two vials with placebo every month (e.g. one vial every two weeks) for 12 months.

Participants are instructed to put the content of the vial in a glass, add some water and drink the solution directly. The handling of the IMP (appendix "39f_Accountability_Log_IMP"), as well as the intake of the IMP (appendix "11g_Diary_IMP"), will be logged.

8.3 Dosage modifications

The supplementation dosage will not be modified during the study. In case a participant is subject to any of the withdrawal or discontinuation criteria described in section 7.4, the respective participant might be excluded from the study.

8.4 Compliance with the study intervention

Participants will be asked to log the intake of the IMPs in a diary (appendix "11g_Diary_IMP"). Participants will be reminded (e.g. a phone call or e-mail) every month to take the IMP (appendix "05c_CRF_Interim_Questionnaire"). Participants will be requested to return empty vials (appendix "39f_Accountability_Log_IMP"). During all study visits, compliance will be assessed (appendices "05b_CRF_Visit_Questionnaire" and "05c_CRF_Interim_Questionnaire"). New vials will be handed out every three months. Non-compliant participants, e.g. not taking the IMP or missing study visits, might be removed from the study.

8.5 Data Collection and Follow-up for withdrawn participants

If participants are excluded or withdrawn from the study for any reason, the data collected up to this point will be still be included in the analyses. Among participants that terminate the study due to a serious adverse event (SAE), medical care will be reinsured until laboratory values and/or vital parameters are within normal. No follow-up is planned for participants who otherwise terminate the study regularly or prematurely.

8.6 Trial specific preventive measures

Concomitant interventions, including medication and treatments, defined in the exclusion criteria (section 7.1), might influence the study outcomes and are not permitted during the study. Several blood parameters are monitored every three months among the intervention groups. Potentially relevant changes throughout the study, e.g. new medications or illness of a participant, will be assessed and discussed within the study team to decide on removing the participant from the study or not.

8.7 Concomitant Interventions (treatments)

Concomitant interventions, including medication and treatments, defined in the exclusion criteria (section 7.1), might influence the study outcomes and are not permitted during the study. Concomitant interventions that occur during the study, will be discussed within the study team to decide on removing the participant from the study or not.

8.8 Study Drug Accountability

All vials with either Vi-De 3® Monthly Dose or the placebo needed for the study will be provided by Dr. Wild & Co. AG and, after being relabeled by the pharmacy of the University Hospital Basel, shipped to the SPZ. Delivery of all shipments will be logged. All vials will be stored in a secured room. All handling of the vials will be logged (appendix "39f_Accountability_Log_IMP"). Participants will be asked to log the intake of the IMPs in a diary (appendix "11g_Diary_IMP").

8.9 Return or Destruction of Study Drug

Participants are asked to bring (used and unused) vials back to the SPZ during each visit. The vials will be destroyed by the SPZ pharmacy following routine procedures. All handling of the vials will be logged (appendix "39f_Accountability_Log_IMP").

9. STUDY ASSESSMENTS

9.1 Study flow chart(s) / table of study procedures and assessments

A graphical as well as a tabular overview of the study can be found in the Study Schedule (pages 9-11). Further information about the study assessments and data collection procedures can be found in sections 5 and 9.3.

9.2 Assessments of outcomes

9.2.1 Assessment of primary outcome

A graphical as well as a tabular overview of the study can be found in the Study Schedule (pages 9-11). Further information about the study assessments and data collection procedures can be found in sections 5 and 9.3.

9.2.2 Assessment of secondary outcomes

A graphical as well as a tabular overview of the study can be found in the Study Schedule (pages 9-11). Further information about the study assessments and data collection procedures can be found in sections 5 and 9.3.

9.2.3 Assessment of other outcomes of interest

A graphical as well as a tabular overview of the study can be found in the Study Schedule (pages 9-11). Further information about the study assessments and data collection procedures can be found in sections 5 and 9.3.

9.2.4 Assessment of safety outcomes

9.2.4.1 Adverse events

The participants will be questioned monthly about possible side effects or other problems with the IMPs. In case of any questions, the participants can contact a member of the study team. Participants are instructed to contact regular authorities in case of emergencies. A more detailed description of the handling of adverse events (AE's) is described in section 10.

9.2.4.2 Laboratory parameters

Blood samples will be taken and analyzed by the SPZ laboratory every three months (intervention groups) or every 6 months (natural time course group) following standard clinical procedures. When certain parameters are out of the normal range, the participant might be excluded from the study. For example: 25(OH)D > 375 nmol/L or ionized calcium > 3.5 mmol/L.

9.2.4.3 Vital signs

Not applicable.

9.2.5 Assessments in participants who prematurely stop the study

See section 8.5 for procedures for participants who for any reason prematurely stop the study.

9.3 Procedures at each visit

9.3.1 Screening

See section 7.2 for a detailed description of the recruitment and screening procedures.

9.3.2 Visit 1 (baseline)

During study visit #1 (baseline), venous blood samples are taken (up to 44 mL) from the elbow. Based on their vitamin D status, participants will be assigned to one of the study groups (natural time course group or one of the three intervention groups). Participants assigned to the intervention group will next be randomly allocated to one of the three groups ("low" dosage vitamin D, "high" dosage vitamin D or placebo) and will receive the respective six vials with IMP for the next three months. All further measurements following the Study Schedule (see pages 9-11, and section 5) will be performed. The subsequent visit is planned. The entire visit will have a duration of approximately two hours.

9.3.3 Visits 2-13

Each visit will take place within seven days of the scheduled time frame. Measurements following the Study Schedule (see pages 9-11, and section 5) will be performed. When assigned to one of the intervention groups, participants will receive the respective six vials for the next three months. The subsequent visit is planned. Visits will have a duration of 15 minutes ("interim" visits by phone or email) or 1.5 to 2 hours ("regular" visits at the SPZ).

10. SAFETY

10.1 Drug studies

During the entire duration of the study, all SAEs are collected, fully investigated and documented in source documents and case report forms (CRF) (appendix "05e_CRF_SAE_Form"). Study duration encompasses the time from when the participant signs the informed consent until the last protocol-specific procedure has been completed, including a safety follow-up period. AEs will not be documented.

10.1.1 Definition and assessment of (serious) adverse events and other safety-related events

An AE is any untoward medical occurrence in which a clinical investigation participant is administered a pharmaceutical product and which does not necessarily have a causal relationship with the study procedure. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (Dixon 1999).

An SAE is classified 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.

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious (Dixon 1999). Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. SAEs should be followed until resolution or stabilization. Participants with ongoing SAEs at study termination (including safety visits) will be further followed up until recovery or until stabilization of the disease after termination.

Assessment of Causality

The Sponsor-Investigator makes a causality assessment of the event to the study drug, based on the criteria listed in the ICH E2A guidelines (Dixon 1999):

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfill the above conditions
Not related	A causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to a reaction	

Unexpected Adverse Drug Reaction

An “unexpected” adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (Dixon 1999).

Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Sponsor-Investigator evaluates any SAE that has been reported regarding seriousness, causality and expectedness. If the event is related to the IMP and is both serious and unexpected, it is classified as a SUSAR. Unblinding is needed to determine a SUSAR. When possible, treatment allocation will not be disclosed to the Sponsor-Investigator, nor to the study staff, in order not to make the participant ineligible.

Assessment of Severity

For the severity assessment of AEs, the “Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0” will be used as a severity grading scale (National Cancer Institute 2017).

10.1.2 Reporting of serious adverse events and other safety-related events

Reporting of SAEs

For the reporting of all SAEs, a standardized form (appendix "05e_CRF_SAE_Form") will be used. All SAEs will be reported 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 site. SAEs resulting in death are reported to the CEC via BASEC within seven days.

Reporting of SUSARs

A SUSAR will be reported by the Sponsor-Investigator to the CEC via BASEC and to Swissmedic within seven days (if the event is fatal), or within 15 days (all other events).

Reporting of Safety Signals

All suspected new risks and relevant new aspects of known adverse reactions that require safety-related measures, i.e. so-called safety signals, will be reported to the Sponsor-Investigator within 24 hours. The Sponsor-Investigator must report the safety signals within seven days to the CEC via BASEC and to Swissmedic.

Reporting and Handling of Pregnancies

Participants who become pregnant during the study will have to contact the study team immediately and will, after consulting with the study physician, be withdrawn from the study. Any pregnancy during the treatment phase of the study and within 30 days after discontinuation of the IMP will be reported to the Sponsor-Investigator within 24 hours. The course and outcome of the pregnancy should be followed up carefully, and any abnormal outcome regarding the mother or the child should be documented and reported.

Periodic reporting of safety

An annual safety report is submitted once a year to the local CEC and to Swissmedic by the Sponsor-Investigator.

10.1.3 Follow up of (Serious) Adverse Events

Among participants that terminate the study due to an SAE, medical care will be reinsured until laboratory values and/or vital parameters are within normal. No follow-up is planned for participants who otherwise terminate the study regularly or prematurely.

10.2 Medical Device Category C studies

Not applicable.

10.3 Medical Device Category A studies

Not applicable.

10.4 Assessment, notification and reporting on the use of radiation sources

The DXA scans expose participants to the following radiation: 0.010 mSv for the forearm, 0.146 mSv for the hip measurement and 0.034 mSv for the knee (appendix "34_Radiation_Exposure_Overview"). The sum of the radiation exposure for the two measurements in this study (2 x 0.190 = 0.380 mSv) is less than the average yearly radiation exposure due to Radon (3.200 mSv) in Switzerland (Bundesamt für Gesundheit (BAG) 2018). The radiation exposure during this study is also well below the dose guidance value (5 mSv) for research projects with no expected direct benefits (The Swiss Federal Council 2017). During the measurements, strict guidelines are followed. Hence no additional risks or side-effects are to be expected. If the permitted dose guidance value is exceeded at any time, the Sponsor-Investigator notifies the CEC via BASEC within seven working days of it becoming known.

11. STATISTICAL METHODS

11.1 Hypothesis

H_0: $\bar{x}_1 = \bar{x}_2 = \bar{x}_3 \rightarrow$ Vitamin D supplementation during 12 months has no effect on 25(OH)D concentration

H_A: $\bar{x}_1 < \bar{x}_2 < \bar{x}_3 \rightarrow$ Vitamin D supplementation during 12 months has an dose-response effect on 25(OH)D concentration

With:

$\bar{x}_1$ = mean difference in 25(OH)D concentration from baseline to the last visit in the placebo group

$\bar{x}_2$ = mean difference in 25(OH)D concentration from baseline to the last visit in the "low" dosage group (i.e. 24'000 IU vitamin D/month)

$\bar{x}_3$ = mean difference in 25(OH)D concentration from baseline to the last visit in the "high" dosage group (i.e. 48'000 IU vitamin D/month)

11.2 Determination of Sample Size

We used the power analysis package for repeated measures in Stata (Stata [Computer program]. Version 14.1. College Station, TX, USA: StataCorp, 2015. Available from www.stata.com) to estimate the sample size needed to detect an interaction between treatment and time across the three treatment groups (appendix "39d_Sample_Size_Estimation_Table"). Expected mean effect sizes for the primary outcome (25(OH)D concentration) at baseline and the four successive follow-up time points were derived by visually fitting a pharmacokinetic curve for the expected time course for serum concentration to the limited, mean empirical data that were available for vitamin D supplementation in chronic SCI (Bauman, Zhong et al. 1995, Bauman, Emmons et al. 2011). Unavailability of individual data precluded statistical fitting. Moreover, the previous studies provided limited information on between-group variances, while within-participant variance was not reported.

The expected time course of 25(OH)D concentration was modeled as a negative exponential growth curve (Heaney, Davies et al. 2003) with the equation C(t)=C(0)+a*(1-e^(-kt)), in which C(t) is the 25(OH)D concentration at time t (in days); C(0) is the baseline serum concentration; a is the change (increment or decrement) at equilibrium produced by a given constant input; k is the rate constant representing the proportion of the total mass of 25(OH)D used (or metabolized) per day. C(t), C(0) and a are all expressed in nmol/L.

We thus anticipate a common mean baseline concentration of 31 nmol/L across groups and, presuming no effect of placebo treatment, further derived the following matrix for the expected time course of mean 25(OH)D concentration for the experimental groups at the successive time points:

Table 3: Expected time course of mean 25(OH)D concentration (nmol/L) during the study.

	Baseline	**3 months**	**6 months**	**9 months**	**12 months**
Placebo	31	31	31	31	31
"Low" dosage	31	49	56	59	60
"High" dosage	31	91	115	125	129

Assuming a significance level 5% and a power of 0.80, minimal sample sizes were calculated for a range of between-group variances (i.e., 1000 to 3500, with 500 incremental steps) and correlations between repeated measures (i.e., 0.1 to 0.9, with 0.1 incremental steps). The estimated minimal sample sizes are provided in the appendices ("39d_Sample_Size_Estimation_Table"). We conservatively plan for 60 participants with a full dataset, that is, 15 participants in each of the three intervention groups and 15 in the natural time course group. In the case of dropouts or a large amount of missing data for a participant, recruitment will continue recruitment until we reach the 15 participants per group with a complete dataset. Up to 68 participants may be recruited to account for dropouts.

11.3 Statistical criteria of termination of the trial

The study will be temporarily postponed as to implement a comprehensive safety review that evaluates potential arguments for premature study termination, if one of the following situations arises among participants during the study period:

- Severe clinical or neurological deterioration in more than one participant.
- Any other SAE determined by the Data Safety Monitoring Committee to be a reason to suspend the study.

11.4 Planned Analyses

11.4.1 Datasets to be analyzed, analysis populations

We will implement an intention-to-treat (ITT) analysis to prevent potential bias that may result from the distortion of baseline equivalence after randomization due to the withdrawal of participants, non-adherence to the study protocol or an unwarranted level of missing data. Participants will only be included in the analyses for which they have available data. Conforming to the ITT principle, all randomized participants will be included in the primary analyses in the group that they were randomized to. Protocol non-adherence, early withdrawals, and loss to follow-up will be characterized and examined. Sensitivity analyses using different populations or participant's groupings may be used to examine the robustness of the estimator generated by the ITT analysis and will be further elaborated in the statistical analysis plan before the blind has been broken. Any sensitivity analyses added after the breaking of the blind (post-hoc sensitivity analyses), including per protocol (PP) analysis that will include any participants recruited as a replacement for withdrawals or dropouts, will be clearly identified as such in the trial reporting.

11.4.2 Primary Analysis

Basic univariable statistical analysis techniques will be used to describe the study population as well as the primary and secondary outcomes at the different measurement points.

To evaluate the longitudinal variation in the primary outcome and secondary outcomes we will use multilevel mixed-effects models that appropriately account for the within-and between-individual sources of variance in outcome variation. In these models, individuals are treated as random effects, while the treatment group is used as a fixed parameter. Choice of regression model will depend on the error distribution function of the respective outcome parameter, using normal regression for continuous outcomes (e.g., 25(OH)D concentration), probit regression for censored scales (e.g., pain questionnaire), and ordinal or stereotype regression for ordered responses (e.g., HADS), and logistic regression for binomial outcomes (e.g., any falls). Time-updated covariates will also be used in regression modeling, for instance, to evaluate the impact of time-varying 25(OH)D concentration on secondary outcomes such as bone density, mood, handgrip strength or pain. Time lags in time-updated covariates will also be evaluated as to further detail temporal associations.

A detailed statistical analysis plan is currently under development. The data will be released for analysis after the last participant visit takes place, and the database has been cleaned. Deviations from the statistical analysis plan that occur after the group assignment has been revealed, will be recorded and included in the trial report.

11.4.3 Secondary Analyses

We will further use non-linear regression modeling to evaluate pharmacokinetic curves for each of the treatment groups as described above (section 11.2). Thus estimates are derived for the parameters a (i.e., change is constant at equilibrium), and k (i.e., the rate constant for the proportion of the total mass of 25(OH)D used or metabolized per day) for mutual comparison as well as with estimates from other populations (other SCI populations, general population, or other health-condition groups).

11.4.4 Interim analyses

Interim analyses have not been planned. In the case that the Data Safety Monitoring Committee advises us to suspend or stop the trial, an interim analysis will be performed. The reasons for implementing an interim analysis as part of a safety review are indicated in section 11.3.

11.4.5 Safety analysis

Blood samples will be analyzed by the laboratory of the SPZ. When large, abnormal deviations are found (e.g. hypercalcemia, ionized calcium concentration > 3.5 mmol/L) the Sponsor-Investigator will be informed.

11.4.6 Deviation(s) from the original statistical plan

Any deviation from the specified statistical analysis plan will be reported as such. A full list of deviations from the analysis plan will be recorded in a separate file. Modifications to the analysis plan will be discussed and validated within the study team breaking breaking the blind.

11.5 Handling of missing data and dropouts

Multiple imputation will be used to appropriately account for missing data in the predictor variables (Sterne, White et al. 2009). In case that the number of dropouts is substantial and systematically related to baseline values of the primary outcome variable, logistic regression modeling will be used to derive inverse probability weights for use in regression modeling as to statistically account for potential longitudinal selection bias. Withdrawn / dropped-out participants will be replaced. Sensitivity analysis will be used to address the robustness of the estimators to changes in the assumptions underlying the chosen imputation strategy.

12. QUALITY ASSURANCE AND CONTROL

12.1 Data handling and record keeping / archiving

12.1.1 Case Report Forms

Upon admittance to the study, a study ID will be assigned to each participant and noted on each relevant study document. The key will be saved on a secured electronic server of the SPZ. Participants will not be identified on the CRFs by name or initials or birth date. CRFs will be kept current to reflect participant status during the study. For each enrolled participant, an Electronic Case Report Form (eCRF) is maintained. No data will be recorded directly in eCRFs. Study data will be transferred from the source documents to the eCRF. The data management system SecuTrial® (iAS, Berlin, Germany) will be used to create eCRFs and data will be entered through a data capture tool. Study personnel will be appointed and authorized to enter data into the eCRF.

12.1.2 Specification of source documents

Paper source documents (pCRFs) will be saved in the Trial Master Files (TMF) and/or ISF. Files will be stored in a secured room, which is only accessible to members of the study team. The following table represents what are considered source documents, as well as the way they are recorded and saved:

Table 4: Source data list.

Data	**Source document**	**Location of source documents**
Informed Consent form	Informed consent form: "03_ClinO_Participant_Info_Informed_Consent"	ISF
Inclusion / exclusion criteria	pCRF "05a_CRF_Screening_Questionnaire"	ISF
Participant characteristics	pCRF "05a_CRF_Screening_Questionnaire" pCRF "05b_CRF_Visit_Questionnaire" Participants' chart from Medfolio (e.g. medical history, ASIA Score)	ISF
Screened and eligible participants	Screening list	ISF
Enrolled participants	SecuTrial® (copy printed)	ISF
Randomization Sequence and Blinding key of IP	pCRF	TMF
IMP logs	pCRF "39f_Accountability_Log_IMP"	TMF ISF
Primary outcome	Participants' chart from Medfolio "05d_eCRF_Visit"	ISF
Secondary outcomes	pCRF "05b_CRF_Visit_Questionnaire" pCRF "05c_CRF_Interim_Questionnaire" Participants' chart from Medfolio - "05d_eCRF_Visit"	ISF
SAEs	pCRF "05e_CRF_SAE_Form"	ISF

12.1.3 Record keeping and archiving

All study data will be archived in a lockable room and/or secured servers with restricted access at the SPZ, for a minimum of 10 years after study termination or premature termination of the study.

12.2 Data management

12.2.1 Data Management System

The SecuTrial® (iAS, Berlin, Germany) web-based data capture and management system will be used. The system is hosted on a secured server maintained by the IT department of the SPZ.

The data management system allows defining roles for data entry, verification, validation and management. An audit trail documents all entries and changes made in the system and by whom. Relevant study data will be transferred into the data management system SecuTrial® (iAS, Berlin, Germany).

The project set-up and eCRFs will be tested by the data manager of the SPZ CTU and at least one member of the study team before the release into the production environment using a custom testing protocol

Only coded data will be stored in the electronic data capture and management system. Personal data, which allows identifying an individual, will not be stored on a server or personal computer. The identification document containing both name, birth year and participant identification number will be printed from the data management system at the time of patient entry and kept in the study documentation. The study documentation will be stored in a locked data storage room with limited access at the SPZ.

12.2.2 Data security, access and back-up

Data is only accessible to the study employees according to their level of authorization and the data manager of the CTU. The data manager will only have access to the encrypted data.

A back-up system is in place. It is maintained and controlled by the IT department of the SPZ.

12.2.3 Analysis and archiving

Encrypted data will be exported from the data management system by the CTU data manager for analysis in statistic software.

Electronic data will be stored in an electronic archive maintained and controlled by the IT department of the SPZ. Electronic data will not be deleted. Only coded data will be stored and analyzed. Source data and identification data will be stored in a locked archive room with limited access for a minimum of 10 years.

12.2.4 Electronic and central data validation

Data quality will be enforced through a variety of mechanisms. Referential data rules, valid values, range checks, and consistency checks will be applied. Furthermore, data will be reviewed and verified before data entry completion.

12.3 Monitoring

The CTU of the SPZ will perform the study-specific monitoring. The monitoring plan can be found in the appendices ("04a_Monitoring_Plan"). The monitoring plan is based on the risked based approach described in the ADAMON project (Brosteanu, Schwarz et al. 2017). All source data and documents are accessible to monitors and questions will be answered during monitoring visits.

12.4 Audits and Inspections

All study documents and data will be accessible for audits or inspections to qualified personal (e.g. of the SPZ CTU, the CEC and CA). All questions will be answered during regular inspections.

12.5 Confidentiality, Data Protection

Direct access to source documents will be permitted for purposes of monitoring (see also section 12.3), audits and inspections (see also section 12.4). Members of the study team will at all times have access to the protocol, dataset, statistical code and other study-related documents during and after the study (publication, dissemination).

12.6 Storage of biological material and related health data

Blood samples will be analyzed in the laboratory if the SPZ and destroyed afterward. Only in case of the participants' explicit consent, will a coded sample of each blood sample (30 mL) be stored in the Biobank of the SPZ for a minimum of five years. In case a participant withdraws consent, the blood samples will be fully anonymized.

13. PUBLICATION AND DISSEMINATION POLICY

Study results might be presented within the SPZ as well as during (inter)national congresses and meetings. We intend to publish the protocol and results of this study in peer-reviewed journals. Individual study results might also be discussed with the participants. The publication policy is also described in the collaboration agreement with Wild & Co. AG (appendix "09b_Collaboration_Agreement_Wild ").

14. FUNDING AND SUPPORT

14.1 Funding

This study is mainly funded by the SPZ. Being a SwiSCI-nested project, this study is also funded by the Schweizer-Paraplegiker Stiftung (SPS). A funding confirmation can be found in the appendices ("09a_Funding_Confirmation_SPS").

14.2 Other Support

Dr. Wild & Co. AG will provide both the Vi-De 3® Monthly Dose as well as the placebo free of charge. The collaboration agreement can be found in the appendices ("09b_Collaboration_Agreement_Wild ").

15. INSURANCE

Insurance will be provided by the Sponsor. The proof of insurance can be found in the appendices ("10_Insurance_Proof"). A copy will be filed in the TMF.

16. REFERENCES

Alkerwi, A., N. Sauvageot, G. Gilson and S. Stranges (2015). "Prevalence and correlates of vitamin D deficiency and insufficiency in Luxembourg adults: evidence from the observation of cardiovascular risk factors (ORISCAV-LUX) study." Nutrients **7**(8): 6780-6796.

Amorim, S., V. H. Teixeira, R. Corredeira, M. Cunha, B. Maia, P. Margalho and J. Pires (2018). "Creatine or vitamin D supplementation in individuals with a spinal cord injury undergoing resistance training: A double-blinded, randomized pilot trial." J Spinal Cord Med **41**(4): 471-478.

Annweiler, C., Y. Rolland, A. M. Schott, H. Blain, B. Vellas, F. R. Herrmann and O. Beauchet (2012). "Higher vitamin D dietary intake is associated with lower risk of Alzheimer's disease: a 7-year follow-up." J Gerontol A Biol Sci Med Sci **67**(11): 1205-1211.

Anton, H. A., W. C. Miller and A. F. Townson (2008). "Measuring fatigue in persons with spinal cord injury." Archives of Physical Medicine and Rehabilitation **89**(3): 538-542.

Barbonetti, A., F. Cavallo, S. D'Andrea, M. Muselli, G. Felzani, S. Francavilla and F. Francavilla (2017). "Lower vitamin D levels are associated with depression in people with chronic spinal cord injury." Arch Phys Med Rehabil **98**(5): 940-946.

Barbonetti, A., A. Sperandio, A. Micillo, S. D'Andrea, F. Pacca, G. Felzani, S. Francavilla and F. Francavilla (2016). "Independent association of vitamin D with physical function in people with chronic spinal cord injury." Arch Phys Med Rehabil **97**(5): 726-732.

Bauman, W. A., R. R. Emmons, C. M. Cirnigliaro, S. C. Kirshblum and A. M. Spungen (2011). "An effective oral vitamin D replacement therapy in persons with spinal cord injury." J Spinal Cord Med **34**(5): 455-460.

Bauman, W. A., N. G. Morrison and A. M. Spungen (2005). "Vitamin D replacement therapy in persons with spinal cord injury." J Spinal Cord Med **28**(3): 203-207.

Bauman, W. A., Y. G. Zhong and E. Schwartz (1995). "Vitamin D deficiency in veterans with chronic spinal cord injury." Metabolism **44**(12): 1612-1616.

Berridge, M. J. (2015). "Vitamin D cell signalling in health and disease." Biochem Biophys Res Commun **460**(1): 53-71.

Bischoff-Ferrari, H. A., B. Dawson-Hughes, E. J. Orav, H. B. Staehelin, O. W. Meyer, R. Theiler, W. Dick, W. C. Willett and A. Egli (2016). "Monthly high-dose vitamin D treatment for the prevention of functional decline: a randomized clinical trial." JAMA Internal Medicine **176**(2): 175-183.

Bischoff-Ferrari, H. A., A. Shao, B. Dawson-Hughes, J. Hathcock, E. Giovannucci and W. C. Willett (2010). "Benefit-risk assessment of vitamin D supplementation." Osteoporos Int **21**(7): 1121-1132.

Bischoff, H. A., H. B. Stahelin, W. Dick, R. Akos, M. Knecht, C. Salis, M. Nebiker, R. Theiler, M. Pfeifer, B. Begerow, R. A. Lew and M. Conzelmann (2003). "Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial." J Bone Miner Res **18**(2): 343-351.

Brinkhof, M. W. G., C. Fekete, J. D. Chamberlain, M. W. M. Post, A. Gemperli and SwiSCI Study Group (2016). "Swiss national community survey on functioning after spinal cord injury: Protocol, characteristics of participants and determinants of non-response." J Rehabil Med **48**(2): 120-130.

Brosteanu, O., G. Schwarz, P. Houben, U. Paulus, A. Strenge-Hesse, U. Zettelmeyer, A. Schneider and D. Hasenclever (2017). "Risk-adapted monitoring is not inferior to extensive on-site monitoring: Results of the ADAMON cluster-randomised study." Clinical Trials (London, England) **14**(6): 584-596.

Brotherton, S. S., J. S. Krause and P. J. Nietert (2007). "Falls in individuals with incomplete spinal cord injury." Spinal Cord **45**(1): 37-40.

Bundesamt für Gesundheit (BAG). (2018, 28.08.2018). "Strahlenexposition der Schweizer Bevölkerung." Retrieved 29.01, 2020, from https://www.bag.admin.ch/bag/de/home/gesund-leben/umwelt-und-gesundheit/strahlung-radioaktivitaet-schall/strahlung-gesundheit/strahlenexposition-der-schweizer-bevoelkerung.html#.

Burt, L. A., E. O. Billington, M. S. Rose, D. A. Raymond, D. A. Hanley and S. K. Boyd (2019). "Effect of high-dose vitamin D supplementation on volumetric bone density and bone strength: a randomized clinical trial." JAMA **322**(8): 736-745.

Ceglia, L. and S. S. Harris (2013). "Vitamin D and its role in skeletal muscle." Calcif Tissue Int **92**(2): 151-162.

Chief Medical Officers for the United Kingdom Cardiff, B., Edinburgh, London: Welsh Government, Department of Health, and T. S. G. Social Services and Public Safety, Department of Health; 2012

(2012). Vitamin D - advice on supplements for at risk groups.

Cranney, A., T. Horsley, S. O'Donnell, H. Weiler, L. Puil, D. Ooi, S. Atkinson, L. Ward, D. Moher, D. Hanley, M. Fang, F. Yazdi, C. Garritty, M. Sampson, N. Barrowman, A. Tsertsvadze and V. Mamaladze (2007). "Effectiveness and safety of vitamin D in relation to bone health." Evid Rep Technol Assess(158): 1-235.

Dalle Carbonare, L., M. T. Valenti, F. Del Forno, E. Caneva and A. Pietrobelli (2017). "Vitamin D: daily vs. monthly use in children and elderly - what is going on?" Nutrients **9**(7).

Dawson-Hughes, B., R. P. Heaney, M. F. Holick, P. Lips, P. J. Meunier and R. Vieth (2005). "Estimates of optimal vitamin D status." Osteoporosis International **16**(7): 713-716.

De-Regil, L. M., C. Palacios, L. K. Lombardo and J. P. Peña-Rosas (2016). "Vitamin D supplementation for women during pregnancy." Cochrane Database Syst Rev(1): CD008873-CD008873.

Dixon, J. R. (1999). "International conference on harmonization good clinical practice guideline." Quality Assurance **6**(2): 65-74.

Edwards, W. B. and T. J. Schnitzer (2015). "Bone imaging and fracture risk after spinal cord injury." Curr Osteoporos Rep **13**(5): 310-317.

Flueck, J. L., K. Hartmann, M. Strupler and C. Perret (2016). "Vitamin D deficiency in Swiss elite wheelchair athletes." Spinal Cord **54**(11): 991-995.

Flueck, J. L. and C. Perret (2017). "Vitamin D deficiency in individuals with a spinal cord injury: a literature review." Spinal Cord **55**(5): 428-434.

Flueck, J. L., M. W. Schlaepfer and C. Perret (2016). "Effect of 12-week vitamin D supplementation on 25(OH)D status and performance in athletes with a spinal cord injury." Nutrients **8**(10).

Forrest, K. Y. Z. and W. L. Stuhldreher (2011). "Prevalence and correlates of vitamin D deficiency in US adults." Nutrition Research (New York, N.Y.) **31**(1): 48-54.

Franz, E. (2007). "Vitamin D im Säuglingsalter-alkoholische oder ölige Tropfen?" Pharmajournal **12**: 5-7.

Galior, K., S. Grebe and R. Singh (2018). "Development of Vitamin D Toxicity from Overcorrection of Vitamin D Deficiency: A Review of Case Reports." Nutrients **10**(8).

Garland, C. F., E. D. Gorham, S. B. Mohr, W. B. Grant, E. L. Giovannucci, M. Lipkin, H. Newmark, M. F. Holick and F. C. Garland (2007). "Vitamin D and prevention of breast cancer: pooled analysis." J Steroid Biochem Mol Biol **103**(3-5): 708-711.

Gorgus, E., M. Hittinger and D. Schrenk (2016). "Estimates of ethanol exposure in children from food not labeled as alcohol-containing." J Anal Toxicol **40**(7): 537-542.

Gröber, U. and M. F. Holick (2013). Vitamin D - Die Heilkraft des Sonnenvitamins, Wissenschaftliche Verlagsgesellschaft mbH.

Guessous, I., V. Dudler, N. Glatz, J. M. Theler, O. Zoller, F. Paccaud, M. Burnier, M. Bochud and Swiss Survey on Salt Group (2012). "Vitamin D levels and associated factors: a population-based study in Switzerland." Swiss Medical Weekly **142**: 0-0.

Haider, I. T., S. M. Lobos, N. Simonian, T. J. Schnitzer and W. B. Edwards (2018). "Bone fragility after spinal cord injury: reductions in stiffness and bone mineral at the distal femur and proximal tibia as a function of time." Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA **29**(12): 2703-2715.

Han, B., X. Wu and Y. Guo (2017). "Improvement of fatigue after vitamin D supplementation in kidney transplant recipients." Medicine **96**(21): e6918-e6918.

Hanwell, H. E. C., R. Vieth, D. E. C. Cole, A. Scillitani, S. Modoni, V. Frusciante, G. Ritrovato, I. Chiodini, S. Minisola and V. Carnevale (2010). "Sun exposure questionnaire predicts circulating 25-hydroxyvitamin D concentrations in Caucasian hospital workers in southern Italy." The Journal of Steroid Biochemistry and Molecular Biology **121**(1-2): 334-337.

Hathcock, J. N., A. Shao, R. Vieth and R. Heaney (2007). "Risk assessment for vitamin D." Am J Clin Nutr **85**(1): 6-18.

Heaney, R. P., K. M. Davies, T. C. Chen, M. F. Holick and M. J. Barger-Lux (2003). "Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol." The American Journal of Clinical Nutrition **77**(1): 204-210.

Herrmann, C. and U. Buss (1994). "Description and validation of a German version of the Hospital Anxiety and Depression Scale (HADS): A questionnaire for identifying emotional disorders in physically ill patients." Diagnostica **40**: 143–154.

Holick, M. F. (1999). Evolution, biologic functions, and recommended dietary allowances for vitamin D. Vitamin D: Molecular Biology, Physiology, and Clinical Applications. M. F. Holick. Totowa, NJ, Humana Press**:** 1-16.

Holick, M. F. (2007). "Optimal vitamin D status for the prevention and treatment of osteoporosis." Drugs Aging **24**(12): 1017-1029.

Holick, M. F. (2007). "Vitamin D deficiency." N Engl J Med **357**(3): 266-281.

Holick, M. F., N. C. Binkley, H. A. Bischoff-Ferrari, C. M. Gordon, D. A. Hanley, R. P. Heaney, M. H. Murad and C. M. Weaver (2011). "Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline." J Clin Endocrinol Metab **96**(7): 1911-1930.

Holick, M. F. and T. C. Chen (2008). "Vitamin D deficiency: a worldwide problem with health consequences." Am J Clin Nutr **87**(4): 1080S-1086S.

Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin, D. and Calcium (2011). Dietary Reference Intakes for Calcium and Vitamin D. Washington (DC), National Academies Press (US).

Itzkovich, M., I. Gelernter, F. Biering-Sorensen, C. Weeks, M. T. Laramee, B. C. Craven, M. Tonack, S. L. Hitzig, E. Glaser, G. Zeilig, S. Aito, G. Scivoletto, M. Mecci, R. J. Chadwick, W. S. El Masry, A. Osman, C. A. Glass, P. Silva, B. M. Soni, B. P. Gardner, G. Savic, E. M. Bergstrom, V. Bluvshtein, J. Ronen and A. Catz (2007). "The Spinal Cord Independence Measure (SCIM) version III: reliability and validity in a multi-center international study." Disabil Rehabil **29**(24): 1926-1933.

Jones, G. (2008). "Pharmacokinetics of vitamin D toxicity." Am J Clin Nutr **88**(2): 582S-586S.

Kalpakjian, C. Z., W. M. Scelza, M. B. Forchheimer and L. L. Toussaint (2007). "Preliminary reliability and validity of a Spinal Cord Injury Secondary Conditions Scale." The Journal of Spinal Cord Medicine **30**(2): 131-139.

Kimlin, M. G. (2008). "Geographic location and vitamin D synthesis." Molecular Aspects of Medicine **29**(6): 453-461.

Kocina, P. (1997). "Body composition of spinal cord injured adults." Sports Med **23**(1): 48-60.

Krupp, L. B., N. G. LaRocca, J. Muir-Nash and A. D. Steinberg (1989). "The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus." Arch Neurol **46**(10): 1121-1123.

Lamarche, J. and G. Mailhot (2016). "Vitamin D and spinal cord injury: should we care?" Spinal cord **54**(12): 1060-1075.

Lamb, S. E., E. C. Jorstad-Stein, K. Hauer, C. Becker and Prevention of Falls Network Europe and Outcomes Consensus Group (2005). "Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe consensus." J Am Geriatr Soc **53**(9): 1618-1622.

Lammertse, D., M. H. Tuszynski, J. D. Steeves, A. Curt, J. W. Fawcett, C. Rask, J. F. Ditunno, M. G. Fehlings, J. D. Guest, P. H. Ellaway, N. Kleitman, A. R. Blight, B. H. Dobkin, R. Grossman, H. Katoh, A. Privat, M. Kalichman and P. International Campaign for Cures of Spinal Cord Injury (2007). "Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: clinical trial design." Spinal cord **45**(3): 232-242.

Liu, X., A. Baylin and P. D. Levy (2018). "Vitamin D deficiency and insufficiency among US adults: prevalence, predictors and clinical implications." The British journal of nutrition **119**(8): 928-936.

Lussi, C., A. Frotzler, A. Jenny, D. J. Schaefer, R. W. Kressig and A. Scheel-Sailer (2018). "Nutritional blood parameters and nutritional risk screening in patients with spinal cord injury and deep pressure ulcer-a retrospective chart analysis." Spinal cord **56**(2): 168-175.

Macdonald, H. M. (2013). "Contributions of sunlight and diet to vitamin D status." Calcified tissue international **92**(2): 163-176.

Mandarino, N. R., F. Junior, J. V. Salgado, J. S. Lages and N. S. Filho (2015). "Is vitamin d deficiency a new risk factor for cardiovascular disease?" Open Cardiovasc Med J **9**: 40-49.

Morse, L. R., F. Biering-Soerensen, L. D. Carbone, T. Cervinka, C. M. Cirnigliaro, T. E. Johnston, N. Liu, K. L. Troy, F. M. Weaver, C. Shuhart and B. C. Craven (2019). "Bone mineral density testing in spinal cord injury: 2019 ISCD official position." J Clin Densitom **22**(4): 554-566.

Müller, R., A. Cieza and S. Geyh (2012). "Rasch analysis of the Hospital Anxiety and Depression Scale in spinal cord injury." Rehabilitation psychology **57**(3): 214-223.

National Cancer Institute (2017). Common Terminology Criteria for Adverse Events (CTCAE).

National Health Service (NHS). (2020, 14.02.2020). "Vitamins, supplements and nutrition in pregnancy - Your pregnancy and baby guide." Retrieved 05.03, 2020, from https://www.nhs.uk/conditions/pregnancy-and-baby/vitamins-minerals-supplements-pregnant/.

National Institute for Health and Clinical Excellence (NICE) (2008). NICE clinical guideline 62. A. care. Manchester.

National Pressure Ulcer Advisory Panel, E. P. U. A. P. a. P. P. and P. I. Alliance. (2014). Prevention and Treatment of Pressure Ulcers: Quick Reference Guide. E. Haesler. Osborne Park, Australia, Cambridge Media.

Oleson, C. V., P. H. Patel and L. A. Wuermser (2010). "Influence of season, ethnicity, and chronicity on vitamin D deficiency in traumatic spinal cord injury." J Spinal Cord Med **33**(3): 202-213.

Pettersen, J. A. (2017). "Does high dose vitamin D supplementation enhance cognition?: A randomized trial in healthy adults." Experimental Gerontology **90**: 90-97.

Pilz, S., A. Zittermann, R. Obeid, A. Hahn, P. Pludowski, C. Trummer, E. Lerchbaum, F. R. Pérez-López, S. N. Karras and W. März (2018). "The role of vitamin D in fertility and during pregnancy and lactation: A review of clinical data." International journal of environmental research and public health **15**(10): 2241.

Post, M. W. M., M. W. G. Brinkhof, E. von Elm, C. Boldt, M. Brach, C. Fekete, I. Eriks-Hoogland, A. Curt, G. Stucki and SwiSCI study group (2011). "Design of the Swiss Spinal Cord Injury Cohort Study." American Journal of Physical Medicine & Rehabilitation **90**(11 Suppl 2): S5-S16.

Pritchett, K., R. C. Pritchett, L. Stark, E. Broad and M. LaCroix (2019). "Effect of Vitamin D Supplementation on 25(OH)D Status in Elite Athletes With Spinal Cord Injury." Int J Sport Nutr Exerc Metab **29**(1): 18-23.

Reid, I. R., M. J. Bolland and A. Grey (2014). "Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis." Lancet (London, England) **383**(9912): 146-155.

Roth, D. E., S. A. Abrams, J. Aloia, G. Bergeron, M. W. Bourassa, K. H. Brown, M. S. Calvo, K. D. Cashman, G. Combs, L. M. De-Regil, M. E. Jefferds, K. S. Jones, H. Kapner, A. R. Martineau, L. M. Neufeld, R. L. Schleicher, T. D. Thacher and S. J. Whiting (2018). "Global prevalence and disease burden of vitamin D deficiency: a roadmap for action in low- and middle-income countries." Annals of the New York Academy of Sciences **1430**(1): 44-79.

Ryan, P. (2018). RALLOC: Stata module to design randomized controlled trials.

Schantz, P., B. Sjöberg, A. M. Widebeck and B. Ekblom (1997). "Skeletal muscle of trained and untrained paraplegics and tetraplegics." Acta Physiologica Scandinavica **161**(1): 31-39.

Sousa, J. R., É. P. C. Rosa, I. F. d. O. C. Nunes and C. M. R. G. d. Carvalho (2017). "Effect of vitamin D supplementation on patients with systemic lupus erythematosus: a systematic review." Revista Brasileira de Reumatologia **57**(5): 466-471.

Sterne, J. A., I. R. White, J. B. Carlin, M. Spratt, P. Royston, M. G. Kenward, A. M. Wood and J. R. Carpenter (2009). "Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls." BMJ **338**: b2393.

The Federal Assembly of the Swiss Confederation (2011). Federal Act on Research involving Human Beings (Human Research Act, HRA).

The Swiss Federal Council (2013). Ordinance on Clinical Trials in Human Research (Clinical Trials Ordinance, ClinO).

The Swiss Federal Council (2017). Radiological Protection Ordinance (RPO).

Valko, P. O., C. L. Bassetti, K. E. Bloch, U. Held and C. R. Baumann (2008). "Validation of the fatigue severity scale in a Swiss cohort." Sleep **31**(11): 1601-1607.

Vaziri, N. D., M. R. Pandian, J. L. Segal, R. L. Winer, I. Eltorai and S. Brunnemann (1994). "Vitamin D, parathormone, and calcitonin profiles in persons with long-standing spinal cord injury." Arch Phys Med Rehabil **75**(7): 766-769.

Vieth, R. (2011). "Why the minimum desirable serum 25-hydroxyvitamin D level should be 75 nmol/L (30 ng/ml)." Best Practice & Research: Clinical Endocrinology & Metabolism **25**(4): 681-691.

Walia, P., R. L. Goldstein, M. Teylan, A. A. Lazzari, J. E. Hart, C. G. Tun and E. Garshick (2018).

"Associations between vitamin D, adiposity, and respiratory symptoms in chronic spinal cord injury." J Spinal Cord Med **41**(6): 667-675.

Widerström-Noga, E., F. Biering-Sørensen, T. Bryce, D. D. Cardenas, N. B. Finnerup, M. P. Jensen, J. S. Richards and P. J. Siddall (2008). "The international spinal cord injury pain basic data set." Spinal cord **46**(12): 818-823.

Wong, G., W. H. Lim, J. Lewis, J. C. Craig, R. Turner, K. Zhu, E. M. Lim and R. Prince (2015). "Vitamin D and cancer mortality in elderly women." BMC Cancer **15**: 106.

World Medical Association (WMA) (1964). Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects

Wu, Z., Z. Malihi, A. W. Stewart, C. M. Lawes and R. Scragg (2016). "Effect of vitamin D supplementation on pain: A systematic review and meta-analysis." Pain Physician **19**(7): 415-427.

Zebrowska, A., E. Sadowska-Krepa, A. Stanula, Z. Waskiewicz, O. Lakomy, E. Bezuglov, P. T. Nikolaidis, T. Rosemann and B. Knechtle (2020). "The effect of vitamin D supplementation on serum total 25(OH) levels and biochemical markers of skeletal muscles in runners." J Int Soc Sports Nutr **17**(1): 18.

Zhou, X. J., N. D. Vaziri, J. L. Segal, R. L. Winer, I. Eltorai and S. R. Brunnemann (1993). "Effects of chronic spinal cord injury and pressure ulcer on 25(OH)-vitamin D levels." The Journal of the American Paraplegia Society **16**(1): 9-13.

Zigmond, A. S. and R. P. Snaith (1983). "The hospital anxiety and depression scale." Acta Psychiatr Scand **67**(6): 361-370.

17. APPENDICES

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Vitamin D supplementation in chronic spinal cord injury (VitD-SCI): study protocol for a randomized controlled trial

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Abstract

Introduction: Vitamin D insufficiency, a vitamin D status or serum 25(OH)D concentration of ≤ 75 nmol/L, is highly prevalent in individuals with a spinal cord injury (SCI). Vitamin D is important for the functioning of the musculoskeletal, immune, and respiratory systems, which are relevant determinants of secondary health conditions in SCI. An insufficiency should be treated with vitamin D supplementation. However, there is a lack of evidence regarding the optimal dosage and duration of vitamin D supplementation for individualized and long-term management of the vitamin D status in the context of SCI. This paper presents the protocol for the vitamin D supplementation in chronic spinal cord injury (VitD-SCI) trial that aims to investigate the effect of a 12-month intake of vitamin D supplementation on vitamin D status as well as on several secondary parameters among individuals with a chronic SCI.

Methods and analyses: The VitD-SCI trial is a randomized, placebo-controlled, double-blinded, parallel-group, superiority trial, conducted at the Swiss Paraplegic Center. A total of 45 participants living with an SCI for at least three years (chronic SCI) and a vitamin D insufficiency at the first study visit, will be randomly assigned to one of three intervention groups. Participants receive either a monthly dosage of 24'000 IU or 48'000 IU vitamin D or a placebo for 12 months. Measurements taking place every three months include the assessment of vitamin D status (primary outcome) as well as bone mineral density, handgrip strength, fatigue, mood, pain, and pressure injuries (secondary outcomes). Safety and tolerance of vitamin D supplementation will also be evaluated.

Ethics and dissemination: The Swiss Ethics Committee for Northwest/Central Switzerland (EKNZ, 2020-01493) and the Swiss Agency for Therapeutic Products (Swissmedic, 2020DR3150) approved this study. Findings will be disseminated through peer-reviewed publications.

Trial registration: ClinicalTrials.gov (NCT04652544) and Swiss National Clinical Trials Portal (SNCTP000004032).

Article Summary

Strengths and limitations of this study

- The longitudinal study design facilitates control for within- and between-person variation in investigating the temporal efficacy of vitamin D supplementation on vitamin D dynamics.
- The recurrent assessment of contextual parameters, including sun exposure and secondary health conditions, for use as time-updated covariates in the data analysis, will further support unbiased inference of the efficacy of vitamin D supplementation.
- The adherence of participants to the protocol cannot be objectively assessed, because of the home-based setting.
- Dietary vitamin D will not be assessed over the study period, which precludes scaling of vitamin D efficacy to between- and within-person variation in nutrition intake.
- For reasons of feasibility, not all supposedly relevant clinical outcomes can be assessed, including respiratory and immune function.

Introduction

A suboptimal vitamin D status is prevalent in up to 93% of individuals with spinal cord injury (SCI) which is excessive compared to up to 40% among the general population.[1 2] This excessive prevalence can be explained by the adverse impact of SCI on physiological functioning, including altered metabolism and gastrointestinal functioning, and lifestyle behaviors, such as reduced physical exercise, outdoor activity, and sun exposure.[1 3] Vitamin D is important for the optimal functioning of the musculoskeletal and respiratory system as well as the regulation of innate and adaptive immune responses.[4-9] Particularly in the context of SCI, a lower vitamin D status has been associated with an elevated risk of respiratory illness, pressure injuries, and depression, as well as poor physical function and bone mineral density.[10-14] Therefore, the prevention of a vitamin D insufficiency, commonly defined as a vitamin D status of 75 nmol/L or less,[15] is of great concern regarding secondary health conditions in SCI.

Vitamin D supplementation is a promising intervention to reduce and prevent a vitamin D insufficiency as well as secondary complications,[2 4 16] yet the provision of such clinical guidelines in the context of SCI is currently hampered by a lack of evidence regarding the efficacy, as well as the optimal dosage and duration of the supplementation.[1 3] For the general non-SCI population (adults aged 19 – 70 years) a dosage of 600 IU – 800 IU/day has been recommended,[17-19] although other experts consider this dosage as suboptimal.[20 21] Among individuals with chronic SCI, a dosage of 800 IU/day for 12 months failed to raise vitamin D status to sufficient levels.[22] Higher dosages of 2000 IU/day[23] or 6000 IU/day[24] during three months appeared more successful, but the respective studies did not investigate the long-term efficacy regarding vitamin D status or the lasting consequences for musculoskeletal and subjective health parameters. Though recommended,[25] vitamin D status is not regularly monitored among the chronic SCI population.

To close this evidence gap, we present the protocol for the vitamin D supplementation in chronic spinal cord injury (VitD-SCI) trial: a placebo-controlled randomized controlled trial that investigates the efficacy of a moderate (24'000 IU/month) and a high (48'000 IU/month) dosage of vitamin D supplementation for 12 months among individuals living with an SCI for at least three years (chronic SCI). Besides vitamin D status (primary objective), further assessments include bone mineral density, fatigue, pain, mood, performance of daily activities, and handgrip strength (secondary objectives). We hypothesize a dose-response effect of vitamin D supplementation on vitamin D status and anticipate that the evidence acquired during this study will effectively inform community-based policy regarding vitamin D supplementation in chronic SCI.

Methods and analyses

Study design and setting

The VitD-SCI trial is a placebo-controlled randomized double-blinded superiority study, evaluating the effect of 12 months of vitamin D supplementation on vitamin D status and several secondary outcomes among individuals with a chronic SCI (Figure 1). This protocol was designed according to the recommendations of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement (Supplement 1).[26] The study is planned to run from May 2021 until May 2023. Study visits take place at the Swiss Paraplegic Centre and participants will receive compensation for travel expenses. The VitD-SCI trial is a nested project of the population-based Swiss Spinal Cord Injury (SwiSCI) cohort study.[27]

Patient and public involvement statement

Patient and public organizations (e.g. SwiSCI), as well as clinicians from several specialized SCI centers, have been involved in the design of the study protocol. Study procedures, including the intervention and assessments, have been discussed and tested together with individuals with SCI.

Participants

The inception cohort of the SwiSCI cohort study (2013-present[28]) provides the sampling frame for participant recruitment for the VitD-SCI trial. Eligible are individuals who provided consent to be contacted for future scientific studies and who fulfill the key VitD-SCI trial inclusion criteria, including a vertebral lesion level of C4 or below and time since SCI of at least 3 years. At present (May 2021), SwiSCI data indicate a sample of over 300 eligible individuals. Among individuals interested in participating, the remaining eligibility criteria (Table 1) will be checked. Women of childbearing age must show a negative pregnancy test at the start of the experimental supplementation and must use adequate contraception during the 12-month treatment phase of the study. Participants are not allowed to take additional vitamin D supplements (> 400 IU/day) or travel to countries with increased sun exposure (below the 37th parallel north) during the study. No further eligibility criteria, such as the completeness or the lesion level, were set, to allow a generalization of the study results as well as to increase the feasibility. The recurrent assessment of contextual parameters for use as time-updated covariates in the data analysis will further support unbiased inference of the temporal efficacy of vitamin D supplementation. Informed consent will be obtained from all participants by qualified study employees (Supplement 2). A blood sample will be taken to determine vitamin D status at the first visit (Month 0). Only individuals with an insufficient vitamin D status (≤ 75 nmol/L) will be randomized into one of the intervention groups.

Intervention

The trial consists of a three-armed intervention that applies a moderate or generally recommended dosage (24'000 IU vitamin D/month), and a high dosage (48'000 IU vitamin D/month) for comparison to placebo. Both dosages are prescribed in clinical practice and are within safe tolerable upper intake levels of 10'000 IU/day.[17 18 20] Previous studies among individuals with SCI implementing even higher dosages of vitamin D supplementation (up to 50'000 IU/week) did not report any safety issues.[23 24 29 30] The present study will further use a biweekly supplementation procedure, which showed superior adherence and accompanying efficacy over daily administration in achieving a sufficient vitamin D status.[31] The biweekly supplementation schedule is supported by vitamin D pharmacokinetics, which indicates a half-life of serum 25(OH)D of up to three weeks.[32]

As vitamin D supplement, the commercially available Vi-De 3® Monthly Dose (Dr. Wild & Co. AG (Muttenz, Switzerland) will be utilized. One vial (5 mL) contains an ethanol solution (65% alcohol by volume) with 600 µg cholecalciferol, which corresponds to 24'000 IU vitamin D_3. The similar ethanol solution without cholecalciferol will be utilized as a placebo. Both the vitamin D_3 supplement as well as the placebo will be filled in identical vials. An independent and specialized pharmacy will label the vials with a number that is indicative of the order of intake but indiscriminate regarding content, making the vials indistinguishable in odor, taste, and visual appearance. The first vial is to be taken within seven days after the first study visit. Participants are instructed to ingest one single vial every two weeks by emptying the vial in a glass of water and immediately drinking the solution. Participants of the high dosage group will take one vial with 24'000 IU vitamin D_3 every two weeks. Similarly, participants of the placebo group will take one vial with placebo every two weeks. Participants of the moderate dosage group will alternately take one vial with 24'000 IU vitamin D_3 or one vial with placebo every two weeks. Thus, an identical number of vials is assured across all intervention groups. The adherence of participants to the protocol cannot be objectively assessed, because the supplement intake occurs at home. To promote compliance with the study protocol, participants will receive a reminder every two weeks to take the vials. Participants will also be requested to keep track of the intake of each vial in a study diary and return all (un)used vials to the study center.

Randomization and blinding

Participants will be randomly allocated on a 1:1:1 ratio into one of the three intervention groups, according to a permuted block randomization list with randomly varying block sizes (3 or 6) created using the module "ralloc" (version 3.7.6[33]) within Stata ([Computer program]. Version 16, College Station, Texas, USA: StataCorp, 2019). The allocation sequence will be securely stored and only accessible to an employee, who is not directly involved in the study. Participants and all study employees directly involved in the recruitment and measurements will be blinded to the assignment

of the intervention until the end of the study ("last participant out"). Parameters, such as blood and bone mineral density parameters, which may reveal the allocation across the intervention groups, will only be available to employees who have no direct involvement in the study.

Outcomes and assessments

Assessment periods and details are specified in Table 2. Assessments are performed during screening or each of the three-monthly visits, except for bone mineral density, which is measured at 0 and 12 months only to reduce radiation exposure. The primary outcome is the differential change in vitamin D status from 0 to 12 months. Transitional vitamin D status will also be evaluated every three months.[21] The recurrent assessment of contributory parameters, including sun exposure and secondary health conditions, provide time-updated information to statistically control for within- and between-person variation in investigating the efficacy of vitamin D supplementation on vitamin D dynamics. To evaluate the secondary effects of vitamin D supplementation on the musculoskeletal system, differential changes in the following secondary outcomes will be assessed: relevant blood parameters (calcium, parathyroid hormone, ionized calcium, phosphate, cystatin, estimated glomerular filtration rate, testosterone), bone mineral density, functional independence, pressure injuries, handgrip strength, and falls. Differential changes in fatigue, mood, and pain will provide insight into the effect of vitamin D supplementation on subjective parameters. Individual parameters, including demographics, SCI characteristics, skin phototype, and sun exposure will also be collected. Furthermore, the occurrence of any new illness, injury or disease together with newly taken medication and supplements will be assessed at each visit. Since nutritional intake of vitamin D only accounts for a limited intake and vitamin D fortification of nutrition in Switzerland is rare,[34] no dietary assessments are planned, which precludes scaling of vitamin D efficacy to between- and within-person variation in nutrition intake. Due to feasibility reasons, no direct measurements of respiratory or immune function will be assessed.

Serious adverse events will be documented throughout the participant's enrollment to evaluate the safety of the supplementation.

Sample size

We defined the minimal sample size as the sample size needed to detect a statistically meaningful difference in the time course of the primary outcome vitamin D status across the three intervention groups. For this, we estimated the sample size needed to detect an interaction between treatment and time across the three intervention groups using the power analysis package for repeated measures in STATA software, version 16.0 (College Station, TX, USA: StataCorp, 2019). The expected mean vitamin D status at each time point was calculated for each intervention group using the generalized pharmacokinetic curve equation of Heaney, et al. (2001),[35] which we parametrized for the purpose of this study using the available data for vitamin D supplementation in chronic SCI.[23 36]

Assuming a significance level of 5% and a power of 0.80, minimal sample sizes were calculated for a range of between-group variances (i.e., 1000 to 3500, with 500 incremental steps) and correlations between repeated measures (i.e., 0.1 to 0.9, with 0.1 incremental steps; Supplement 3). Based on this power analysis for sample size, we conservatively plan for 45 participants with a full dataset, implying 15 participants in each of the three intervention groups. In the case of dropouts or a large amount of missing data for a given participant, recruitment will be continued until the minimal sample size of 15 participants per intervention groups is effectively achieved. Sample size calculation did not take secondary outcome parameters into account. Since long-term studies among the chronic SCI population are rare, this study may inform the minimal sample size needed for future studies targeting the dynamics of secondary outcome parameters in response to vitamin D supplementation.

Data management and analyses

Data management

The web-browser-based system secuTrial® (interActive Systems, Berlin, Germany), which fulfills the Good Clinical Practice requirements, will be used for data capturing and management. This database allows for individualized accounts with pre-defined roles for each study employee and will be hosted by a study-independent data manager. Built-in quality control mechanisms and notification of missing data will reduce errors during data entry. Participants will be assigned a unique identification code and no directly identifiable information is stored in the database.

Analyses of primary and secondary outcomes

An intention-to-treat analysis will be performed to prevent potential bias resulting from the distortion of baseline equivalence after randomization due to the withdrawal of participants, non-adherence to the study protocol, or an unwarranted level of missing data. Participants will only be included in the analyses for which they have data available. Protocol non-adherence, early withdrawals, and loss to follow-up will be characterized and examined. Sensitivity analyses using different populations or participant groupings may be used to examine the robustness of the estimator generated by the intention-to-treat analysis. Any sensitivity analyses added after the breaking of the blind (post-hoc sensitivity analyses), including per-protocol analysis that will contain any participants recruited as a replacement for withdrawals or dropouts, will be clearly identified as such in the trial reporting. Basic univariable statistical analysis techniques will be used to describe the study population as well as the primary and secondary outcomes at the different measurement points. To evaluate the longitudinal variation in the primary outcome and secondary outcomes, multilevel mixed-effects models that appropriately account for the within-and between-individual sources of variance in outcome variation will be used. In these models, participants are treated as random effects, while the treatment group is used as a fixed parameter. The choice of regression model will depend on the error distribution function of the respective outcome parameter. Time-updated covariates will also be used

in regression modeling, for instance, to evaluate the impact of time-varying vitamin D status on the secondary outcomes. Time lags in time-updated covariates will also be evaluated to further detail temporal associations. Non-linear regression modeling will be used to evaluate pharmacokinetic curves for each of the intervention groups as described above. Thus, estimates are derived for the parameters *a* (i.e., change is constant at equilibrium), and *k* (i.e., the rate constant for the proportion of the total mass of 25(OH)D used or metabolized per day) for mutual comparison as well as with estimates from other populations (other SCI populations, general population, or other health-condition groups).

No interim analyses are planned. If severe clinical deterioration is detected in more than one participant, or on the recommendation of the monitoring committee following a serious adverse event, the study will be suspended until a comprehensive safety review has been completed. If the trial is suspended or halted, an interim analysis will be performed.

Handling of missing data and dropouts

When appropriate, multiple imputation will be used to account for missing data.[37] In case the number of dropouts is substantial and systematically related to baseline values of the primary outcome variable, logistic regression modeling will be used to derive inverse probability weights for use in regression modeling to statistically account for potential longitudinal selection bias. Participants who are withdrawn or drop out will be replaced. Sensitivity analysis will be used to address the robustness of the estimators to changes in the assumptions underlying the chosen imputation strategy.

Quality assurance and safety provisions

Minimizing bias and contamination

Trained study employees will execute all of the measurements following a study manual. Measurement devices will be appropriately serviced and calibrated throughout the study. Questionnaires that have been validated among or adapted for the SCI population will be used. The collection of several possible confounders, including sun exposure, season, and SCI level, allows for the correction of these factors. Participants will be asked to express their belief regarding the assigned intervention every three months, which will be used to compute a measure for the extent of successful blinding of the trial.

Potential risks

There are no guidelines regarding upper limits of serum 25(OH)D concentration among the SCI population,[3] although vitamin D toxicity has been reported with levels exceeding 375-750 nmol/L among the general population.[38] Side effects of vitamin D supplementation, resulting from an overdose, are not expected with the selected dosages in this study. Nevertheless, participants are asked about potential side effects and tolerance of the supplement, and relevant blood parameters

will be monitored. Due to the 65% volume alcohol solution, the intake of the supplement and/or placebo could have a minor influence on the ability to drive or operate machines, but similar solutions have been proven harmless.[39] The sum of the radiation exposure for the two bone mineral density measurements in this study is less than the average yearly radiation exposure due to radon in Switzerland and falls well within the dose guidance value for Swiss research projects.[40 41] Serious Adverse Events will be documented and reported to the local authorities for the entire study duration, which encompasses the signing of the informed consent until the completion of the last protocol-specific procedure including a safety follow-up period. A risked-adapted monitoring[42] will be applied and executed by the Clinical Trial Unit of the study center.

Withdrawal criteria

Participants can withdraw from the study at any time, without providing reasoning. Participants might be redrawn from the study in case of protocol non-adherence, the eligibility criteria are no longer fulfilled, or health problems related to the intake of the vitamin D_3 supplement or placebo, including a vitamin D intoxication (serum 25(OH)D concentration > 375 nmol/L) or hypercalcemia (ionized calcium concentration > 3.5 mmol/L).

Unblinding Procedures

The study physician together with the study employees will make study termination and unblinding decisions. Unblinding will only be allowed in the following circumstances; upon study termination, in the case of premature study termination, or in the case of emergencies or complications. An employee not directly involved in the measurements will perform the unblinding of individual participants during the study. Since each participant receives an individual batch of vials, revealing the blinding for one participant will not unblind the entire cohort.

Ethics and dissemination

Ethics approval

This study will be conducted in compliance with the current version of the Declaration of Helsinki[43] and the International Conference on Harmonization Good Clinical Practice guidelines,[44] as well as all national legal and regulatory requirements.[45 46] Both the Swiss Ethics Committee for Northwest/Central Switzerland (EKNZ, 2020-01493) and the Swiss Agency for Therapeutic Products (Swissmedic, 2020DR3150) have approved the study. The study has been registered at ClinicalTrials.gov (NCT04652544). The regulatory authorities will receive safety and interim reports and will be informed about protocol changes and the study end.

Dissemination policy

Results will be published in peer-reviewed journals and presented at scientific conferences. When desired, individual study results will be shared with the participants after the study end. Dissemination among persons with SCI in Switzerland will be achieved through the newsletters "Paraplegie" and "Paracontact" as well as through online media. Data and statistical code will be made available upon request.

Trial status

This publication is based on version 3 of the VitD-SCI trial protocol dated November 9, 2020. The official start of recruitment was on May 19, 2021 and data collection is estimated to end on May 31, 2023. As of the time of submission, temporary interruptions due to the COVID-19 pandemic are a possibility and in case of extended disruption, a schedule adjustment may be required.

Discussion

This is the first study to investigate a 12-month vitamin D supplementation among individuals with a chronic SCI. The existing studies lack the combination of long-term vitamin D supplementation with different dosages, while not only assessing vitamin D status but also secondary outcomes.

The VitD-SCI trial, for which the protocol is presented here, will provide valuable insights to optimize individual vitamin D supplementation. If a positive relation between a sufficient vitamin D status and secondary outcomes can be established, this could lead the way for standardized clinical recommendations for long-term management of vitamin D status and vitamin D supplementation among the chronic SCI population.

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Author contributions

JF is responsible for overseeing the trial. JF, CP, and MB were responsible for the study conception and obtained funding. JF, CP, MB, AS, and AH designed the protocol. AS provided clinical expertise is the study physician and principal investigator. PW provided expertise on bone mineral density. MB provided statistical expertise. AJ provided clinical expertise on blood parameters and analyses. GL provided clinical expertise on pain outcomes. AH, MB and JF prepared the first draft of the manuscript. All authors reviewed and revised the manuscript before submission and approved its content.

Disclosure statement

All authors declare that there are no conflicts of interest, intellectual, financial, or proprietary conflicts.

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References

1. Flueck JL, Perret C. Vitamin D deficiency in individuals with a spinal cord injury: a literature review. *Spinal Cord* 2017;55(5):428-34. doi: 10.1038/sc.2016.155
2. Amrein K, Scherkl M, Hoffmann M, et al. Vitamin D deficiency 2.0: an update on the current status worldwide. *Eur J Clin Nutr* 2020;74(11):1498-513. doi: 10.1038/s41430-020-0558-y
3. Lamarche J, Mailhot G. Vitamin D and spinal cord injury: should we care? *Spinal cord* 2016;54(12):1060-75. doi: 10.1038/sc.2016.131
4. Cranney A, Horsley T, O'Donnell S, et al. Effectiveness and safety of vitamin D in relation to bone health. *Evid Rep Technol Assess* 2007(158):1-235.
5. Ceglia L, Harris SS. Vitamin D and its role in skeletal muscle. *Calcif Tissue Int* 2013;92(2):151-62. doi: 10.1007/s00223-012-9645-y
6. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr* 2008;87(4):1080S-6S. doi: 10.1093/ajcn/87.4.1080S
7. Beard JA, Bearden A, Striker R. Vitamin D and the anti-viral state. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology* 2011;50(3):194-200. doi: 10.1016/j.jcv.2010.12.006 [published Online First: 2011/01/19]
8. Jolliffe DA, Camargo CA, Sluyter JD, et al. Vitamin D supplementation to prevent acute respiratory infections: systematic review and meta-analysis of aggregate data from randomised controlled trials. *medRxiv : the preprint server for health sciences* 2020 doi: 10.1101/2020.07.14.20152728 [published Online First: 2020/12/04]
9. Peterlik M, Cross HS. Vitamin D and calcium insufficiency-related chronic diseases: molecular and cellular pathophysiology. *European Journal of Clinical Nutrition* 2009;63(12):1377-86. doi: 10.1038/ejcn.2009.105
10. Zhou XJ, Vaziri ND, Segal JL, et al. Effects of chronic spinal cord injury and pressure ulcer on 25(OH)-vitamin D levels. *J Am Paraplegia Soc* 1993;16(1):9-13. doi: 10.1080/01952307.1993.11735877
11. Barbonetti A, Sperandio A, Micillo A, et al. Independent association of vitamin D with physical function in people with chronic spinal cord injury. *Arch Phys Med Rehabil* 2016;97(5):726-32. doi: 10.1016/j.apmr.2016.01.002 [published Online First: 2016/01/26]
12. Barbonetti A, Cavallo F, D'Andrea S, et al. Lower vitamin D levels are associated with depression in people with chronic spinal cord injury. *Arch Phys Med Rehabil* 2017;98(5):940-46. doi: 10.1016/j.apmr.2016.11.006 [published Online First: 2016/12/18]
13. Lussi C, Frotzler A, Jenny A, et al. Nutritional blood parameters and nutritional risk screening in patients with spinal cord injury and deep pressure ulcer-a retrospective chart analysis. *Spinal cord* 2018;56(2):168-75. doi: 10.1038/s41393-017-0016-4 [published Online First: 2017/10/23]
14. Clark K, Goldstein RL, Hart JE, et al. Plasma vitamin D, past chest illness, and risk of future chest illness in chronic spinal cord injury (SCI): a longitudinal observational study. *Spinal Cord* 2020;58(4):504-12. doi: 10.1038/s41393-019-0409-7 [published Online First: 2020/01/18]
15. Vieth R. Why the minimum desirable serum 25-hydroxyvitamin D level should be 75 nmol/L (30 ng/ml). *Best Practice & Research: Clinical Endocrinology & Metabolism* 2011;25(4):681-91. doi: 10.1016/j.beem.2011.06.009
16. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2009;169(6):551-61. doi: 10.1001/archinternmed.2008.600 [published Online First: 2009/03/25]
17. Institute of Medicine (IOM). Dietary Reference Intakes for Calcium and Vitamin D. Washington (DC): The National Academies Press 2011.
18. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *The Journal of clinical*

endocrinology and metabolism 2011;96(7):1911-30. doi: 10.1210/jc.2011-0385 [published Online First: 2011/06/08]
19. Deutsche Gesellschaft für Ernährung ÖGfE, Schweizerische Gesellschaft für Ernährungsforschung, Schweizerische Vereinigung für Ernährung (Hrsg.). Referenzwerte für die Nährstoffzufuhr Vitamin D. Neustadt a. d. Weinstraße: Neuer Umschau Buchverlag, 2012:1. Auflage, 4., korrigierter Nachdruck.
20. Hathcock JN, Shao A, Vieth R, et al. Risk assessment for vitamin D. *Am J Clin Nutr* 2007;85(1):6-18. doi: 10.1093/ajcn/85.1.6 [published Online First: 2007/01/09]
21. Vieth R, Chan PC, MacFarlane GD. Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. *Am J Clin Nutr* 2001;73(2):288-94. doi: 10.1093/ajcn/73.2.288 [published Online First: 2001/02/07]
22. Bauman WA, Morrison NG, Spungen AM. Vitamin D replacement therapy in persons with spinal cord injury. *The journal of spinal cord medicine* 2005;28(3):203-7. doi: 10.1080/10790268.2005.11753813 [published Online First: 2005/07/29]
23. Bauman WA, Emmons RR, Cirnigliaro CM, et al. An effective oral vitamin D replacement therapy in persons with spinal cord injury. *The journal of spinal cord medicine* 2011;34(5):455-60. doi: 10.1179/2045772311y.0000000032 [published Online First: 2011/11/29]
24. Flueck JL, Schlaepfer MW, Perret C. Effect of 12-week vitamin D supplementation on 25(OH)D status and performance in athletes with a spinal cord injury. *Nutrients* 2016;8(10) doi: 10.3390/nu8100586 [published Online First: 2016/09/27]
25. Oleson CV, Patel PH, Wuermser LA. Influence of season, ethnicity, and chronicity on vitamin D deficiency in traumatic spinal cord injury. *The journal of spinal cord medicine* 2010;33(3):202-13. doi: 10.1080/10790268.2010.11689697 [published Online First: 2010/08/27]
26. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Annals of internal medicine* 2013;158(3):200-7. doi: 10.7326/0003-4819-158-3-201302050-00583 [published Online First: 2013/01/09]
27. Post MWM, Brinkhof MWG, von Elm E, et al. Design of the Swiss Spinal Cord Injury Cohort Study. *Am J Phys Med Rehabil* 2011;90(11 Suppl 2):S5-S16. doi: 10.1097/PHM.0b013e318230fd41
28. Fekete C, Gurtner B, Kunz S, et al. Inception cohort of the Swiss Spinal Cord Injury Cohort Study (SwiSCI): Design, participant characteristics, response rates and non-response. *J Rehabil Med* 2021;53(2):jrm00159. doi: 10.2340/16501977-2795 [published Online First: 2021/02/12]
29. Amorim S, Teixeira VH, Corredeira R, et al. Creatine or vitamin D supplementation in individuals with a spinal cord injury undergoing resistance training: A double-blinded, randomized pilot trial. *The journal of spinal cord medicine* 2018;41(4):471-78. doi: 10.1080/10790268.2017.1372058 [published Online First: 2017/09/14]
30. Pritchett K, Pritchett RC, Stark L, et al. Effect of Vitamin D Supplementation on 25(OH)D Status in Elite Athletes With Spinal Cord Injury. *Int J Sport Nutr Exerc Metab* 2019;29(1):18-23. doi: 10.1123/ijsnem.2017-0233 [published Online First: 2018/05/15]
31. Dalle Carbonare L, Valenti MT, Del Forno F, et al. Vitamin D: daily vs. monthly use in children and elderly - what is going on? *Nutrients* 2017;9(7) doi: 10.3390/nu9070652 [published Online First: 2017/07/05]
32. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocrine reviews* 2001;22(4):477-501. doi: 10.1210/edrv.22.4.0437 [published Online First: 2001/08/09]
33. RALLOC: Stata module to design randomized controlled trials [program], 2018.
34. Bundesamt für Lebensmittelsicherheit und Veterinärwesen. Fachinformation zu Vitamin D. Bern, 2017.
35. Heaney RP, Davies KM, Chen TC, et al. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr* 2003;77(1):204-10. doi: 10.1093/ajcn/77.1.204

36. Bauman WA, Zhong YG, Schwartz E. Vitamin D deficiency in veterans with chronic spinal cord injury. *Metabolism* 1995;44(12):1612-6. doi: 10.1016/0026-0495(95)90083-7 [published Online First: 1995/12/01]
37. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393. doi: 10.1136/bmj.b2393 [published Online First: 2009/07/01]
38. Jones G. Pharmacokinetics of vitamin D toxicity. *Am J Clin Nutr* 2008;88(2):582S-86S. doi: 10.1093/ajcn/88.2.582S [published Online First: 2008/08/12]
39. Franz E. Vitamin D im Säuglingsalter-alkoholische oder ölige Tropfen? *Pharmajournal* 2007;12:5-7.
40. The Swiss Federal Council. Radiological Protection Ordinance (RPO), 2017.
41. Bundesamt für Gesundheit (BAG). Strahlenexposition der Schweizer Bevölkerung 2018 [updated 28.08.2018. Available from: https://www.bag.admin.ch/bag/de/home/gesund-leben/umwelt-und-gesundheit/strahlung-radioaktivitaet-schall/strahlung-gesundheit/strahlenexposition-der-schweizer-bevoelkerung.html# accessed 29.01.2020.
42. Brosteanu O, Schwarz G, Houben P, et al. Risk-adapted monitoring is not inferior to extensive on-site monitoring: Results of the ADAMON cluster-randomised study. *Clin Trials* 2017;14(6):584-96. doi: 10.1177/1740774517724165 [published Online First: 2017/08/08]
43. World Medical Association (WMA). Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects 1964.
44. Dixon JR. International conference on harmonization good clinical practice guideline. *Quality Assurance* 1999;6(2):65-74. doi: 10.1080/105294199277860
45. The Federal Assembly of the Swiss Confederation. Federal Act on Research involving Human Beings (Human Research Act, HRA), 2011.
46. The Swiss Federal Council. Ordinance on Clinical Trials in Human Research (Clinical Trials Ordinance, ClinO), 2013.
47. Hanwell HEC, Vieth R, Cole DEC, et al. Sun exposure questionnaire predicts circulating 25-hydroxyvitamin D concentrations in Caucasian hospital workers in southern Italy. *J Steroid Biochem Mol Biol* 2010;121(1-2):334-37. doi: 10.1016/j.jsbmb.2010.03.023 [published Online First: 2010/03/16]
48. Fitzpatrick TB. "Soleil et peau" [Sun and skin]. *Journal de Me´decine Esthe´tique (in French),* 1975;2:33–34.
49. Kirshblum SC, Burns SP, Biering-Sorensen F, et al. International standards for neurological classification of spinal cord injury (revised 2011). *The journal of spinal cord medicine* 2011;34(6):535-46. doi: 10.1179/204577211X13207446293695 [published Online First: 2012/02/15]
50. Itzkovich M, Gelernter I, Biering-Sorensen F, et al. The Spinal Cord Independence Measure (SCIM) version III: reliability and validity in a multi-center international study. *Disabil Rehabil* 2007;29(24):1926-33. doi: 10.1080/09638280601046302 [published Online First: 2007/09/14]
51. Brinkhof MWG, Fekete C, Chamberlain JD, et al. Swiss national community survey on functioning after spinal cord injury: Protocol, characteristics of participants and determinants of non-response. *J Rehabil Med* 2016;48(2):120-30. doi: 10.2340/16501977-2050
52. National Pressure Ulcer Advisory Panel EPUAPaPP, Alliance. PI. Prevention and Treatment of Pressure Ulcers: Quick Reference Guide. In: Haesler E, ed. 2019 ed. Osborne Park, Australia: Cambridge Media, 2014.
53. Widerström-Noga E, Biering-Sørensen F, Bryce T, et al. The international spinal cord injury pain basic data set. *Spinal cord* 2008;46(12):818-23. doi: 10.1038/sc.2008.64 [published Online First: 2008/06/03]
54. Kalpakjian CZ, Scelza WM, Forchheimer MB, et al. Preliminary reliability and validity of a Spinal Cord Injury Secondary Conditions Scale. *The journal of spinal cord medicine* 2007;30(2):131-39. doi: 10.1080/10790268.2007.11753924

55. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67(6):361-70. doi: 10.1111/j.1600-0447.1983.tb09716.x [published Online First: 1983/06/01]
56. Krupp LB, LaRocca NG, Muir-Nash J, et al. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;46(10):1121-3. doi: 10.1001/archneur.1989.00520460115022 [published Online First: 1989/10/01]

Figures

Figure 1: Schematic overview of the study flow. The timeline of the study including the assessments is displayed starting from the screening (top of the figure) to the last study visit (bottom of the figure).

A: Study flow.

B: Legend.

Tables

Table 1: Eligibility criteria

Inclusion criteria	Exclusion criteria
• Informed Consent to the study as documented by a signature. • Chronic (> 3 years) traumatic or non-traumatic SCI a vertebral lesion level of C4 or below. • Between 18 - 60 years old. • Wheelchair dependency during activities of daily living, defined by a score of 0-2 in the Spinal Cord Independence Measure (SCIM-III), subsection "Mobility in the house". • An insufficient vitamin D status (≤ 75 nmol/L) at the first visit.	• Contraindications to the investigational product, including known hypersensitivity or allergy to the cholecalciferol or alcohol solution. • Clinically relevant disorders, including renal dysfunction, hepatic dysfunction, cardiovascular disease, lung disease, diabetes, blood disease, parathyroid disease, cancer, depression, alcohol abuse, and/or the intake of significant concomitant medication (including osteoporosis treatment and benzothiadiazide derivatives). This will be assessed on an individual basis. • Grade 3 or 4 pressure injuries. • Women who are pregnant or planning to become pregnant during the study period. • Women who are breastfeeding. • Fractures in both arms and/or both legs within the last five years. • Intake of > 400 IU/day vitamin D supplementation during the last 12 months before recruitment or during the study. • Visiting a country with increased sun exposure (below the 37th parallel north, i.e. the southern hemisphere) within one month before enrollment or during the study. • Inability to understand or decide on study participation (i.e. make an informed consent) and to adhere to the study protocol, for example, due to language or psychological problems.

Table 2: Tools, parameters, and timing of the study measurements.

Assessment tool	Parameter	Assessment periods
Differential changes in blood parameters (sample taken from the antecubital vein)		
Electrochemiluminescence immunoassay (ECLIA)	25(OH)D (nmol/L)	0M, 3M, 6M, 12M
Photometry - NM-BAPTA	Calcium (mmol/L)	0M, 3M, 6M, 12M
Potentiometry with ion-selective electrodes	Ionized calcium (mmol/L)	0M, 3M, 6M, 12M
Chemiluminescence immunoassay (CLIA)	Parathyroid hormone (ng/L)	0M, 3M, 6M, 12M
Photometry - Molybdate UV	Phosphate (mmol/L)	0M, 3M, 6M, 12M
Photometry - particle-enhanced turbidimetric immunoassay	Cystatin C (mg/L)	0M, 3M, 6M, 12M
Estimated from cystatin C following CKD-EPI and Grubb	Estimated glomerular filtration rate (eGFR) (mL/min)	0M, 3M, 6M, 12M
Chemiluminescent immunoassay (CLIA)	Testosterone (ng/dL)	0M, 3M, 6M, 12M
Differential changes in personal characteristics		
Body mass index (BMI)	From weight and height (kg/m²)	0M, 3M, 6M, 12M
Sun exposure based on Hanwell et al (2010)[47]	Time spent outdoors (min) with level of exposed skin*	0M, 3M, 6M, 12M
Physical activity	Sport per week (hours and frequency)	0M, 3M, 6M, 12M
Medication and supplements	Sort and dosage (supplements only)	0M, 3M, 6M, 12M
Further illnesses	Incidence since last measurement	0M, 3M, 6M, 12M
Skin phototype on the posterior forearm based on Fitzpatrick (1975)[48]	Six categories ranging from light to very dark skin types	Screening
SCI characteristics	Time since SCI (years), neurological level of injury (NLI),[49] the degree of impairment following the American Spinal Injury Association (ASIA) Impairment Scale (AIS)[49]	Screening
Differential changes in bone mineral density		
X-ray densitometry (DXA), Lunar iDXA Serie with enCORE v17 Software	T-scores for the forearm (radius), hip (femoral neck), and knee (distal femur and proximal tibia)	0M, 12M
Differential changes in functional independence		
Spinal Cord Independence Measure (SCIM) III[50]	Self-care subscore (0-20), respiration and sphincter management subscore (0-40), indoor mobility subscore (0-10), outdoor mobility subscore (0-30), total score (0-100)	0M, 3M, 6M, 12M
Differential changes in urinary tract infections		
Exact questions of the first-wave questionnaire of the Swiss Spinal Cord Injury (SwiSCI) survey[27 51]	Incidence since the last measurement, medical care required	0M, 3M, 6M, 12M
Differential changes in pressure injuries		
Exact questions of the first-wave questionnaire of the SwiSCI survey[27 51]	Localization and grade following the European and United States National Pressure Ulcer Advisory panels (EPUAP and NPUAP) classification[52]	0M, 3M, 6M, 12M
Differential changes in pain		
Exact questions of the first- and second-wave questionnaire of the SwisSCI survey,[27 51] based on the International SCI Pain Basic Data Set[53] as well as the SCI Secondary Conditions Scale[54]	The occurrence, kind, location, and influence of pain during the last week as well as chronic pain (> 3 months)	0M, 3M, 6M, 12M
Differential changes in strength		
Jamar Smart Hand Dynamometer (Patterson Medical, Warrenville, IL)	Three measurements of the left and right hand (mean kg)	0M, 3M, 6M, 12M
Differential changes in mood		

Hospital Anxiety and Depression Scale (HADS)[55]	Total score (14-56)	0M, 3M, 6M, 12M
Differential changes in fatigue		
Fatigue Severity Scale (FSS)[56]	Total score (9-63)	0M, 3M, 6M, 12M
Differential changes in falls		
Occurrence	Incidence since last measurement, reason daily activity, sport or accident) and medical care required	0M, 3M, 6M, 12M
Safety of the Investigational Medical Products		
Serious adverse events	The occurrence of life-threatening medical complications, the requirement of hospitalization.	Any time
Side-effects, tolerability, and adherence	Number of and reason for missed intake, side-effects	0M, 3M, 6M, 12M

Assessment periods are referenced to the date of the first visit (0M) and include screening (Screening; max 30 days before 0M), 3-month follow-up (3M; 90 ± 7 days), 6-month follow-up (6M; 180 ± 7 days) and 12-month follow-up (12M; 365 ± 7 days). Serious adverse events are continuously evaluated.

* Level of exposed skin: 1) hands and face, 2) hands, face, and arms, 3) hands, face, and legs, 4) entire body (bathing suit).

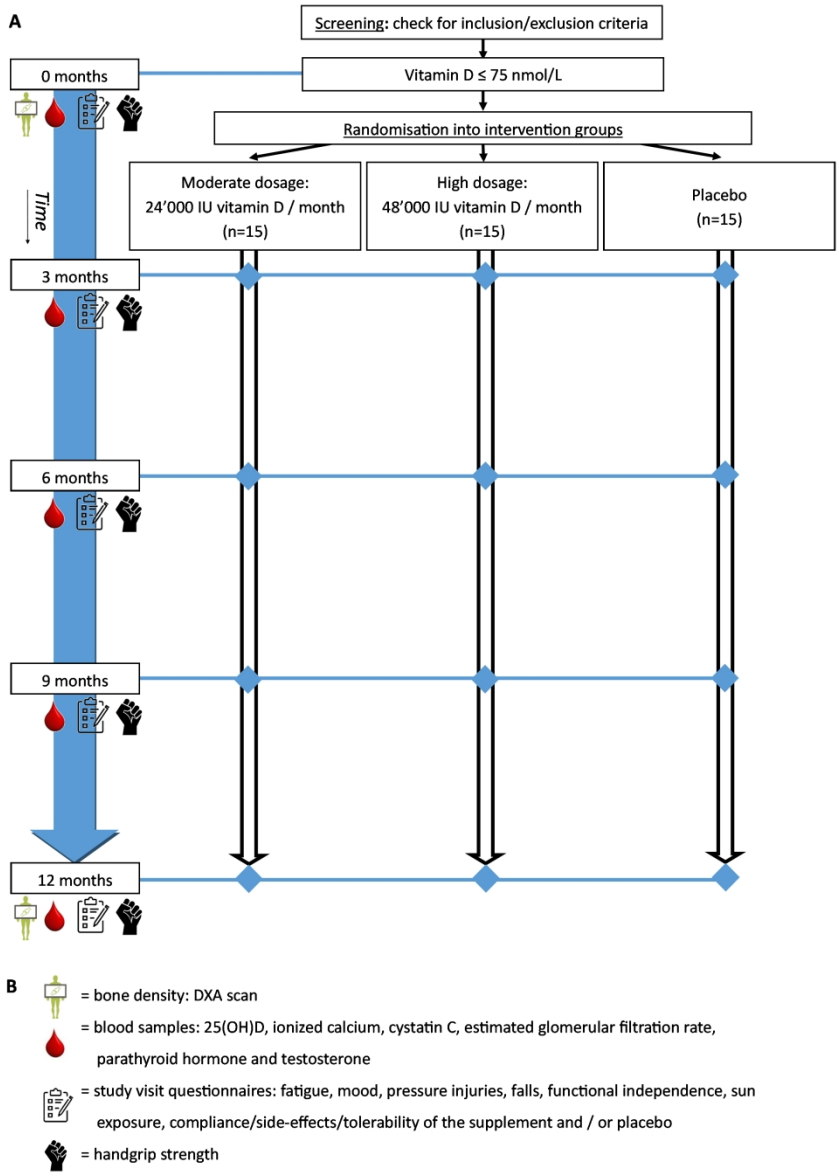

Figure 1: Schematic overview of the study flow. The timeline of the study including the assessments is displayed starting from the screening (top of the figure) to the last study visit (bottom of the figure). A: Study flow. B: Legend.

Supplement 1: SPIRIT Checklist for the Vitamin D Supplementation in Chronic Spinal Cord Injury (VitD-SCI) trial protocol

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section / item	Item No	Description, addressed	Addressed in section
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title, page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract - Trial registration, page 2; Ethics and dissemination - Ethics approval, page 10
	2b	All items from the World Health Organization Trial Registration Data Set	Throughout the paper, pages 1-20; publicly accessible information on ClinicalTrials.gov (NCT04652544)
Protocol version	3	Date and version identifier	Ethics and dissemination - Trial Status, page 11
Funding	4	Sources and types of financial, material, and other support	Funding statement, page 12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page, page 1; Author contributions, page 12
	5b	Name and contact information for the trial sponsor	Title page - Corresponding author, page 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Funding statement, page 12; Author contributions, page 12
	5d	Composition, roles, and responsibilities of the coordinating center, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Methods and analyses - Potential risks, page 9; Author contributions, page 12
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Introduction, page 4; Methods and analyses - Intervention, page 6

	6b	Explanation for choice of comparators	Introduction, page 4; Methods and analyses - Intervention, page 6
Objectives	7	Specific objectives or hypotheses	Introduction, page 4
Trial design	8	Description of trial design including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, non-inferiority, exploratory)	Methods and analyses - Study design and setting, page 5; Randomization and blinding, page 6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Methods and analyses - Study design and setting, page 5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (e.g., surgeons, psychotherapists)	Methods and analyses - Participants, page 5; Table 1, page 18
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Methods and analyses - Intervention, page 6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)	Methods and analyses - Intervention, page 6; Withdrawal criteria, page 10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)	Methods and analyses - Intervention, page 6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Methods and analyses - Participants, page 5; Table 1, page 18
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Methods and analyses - Outcomes and assessments, page 7; Table 2, page 19
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Methods and analyses - Study design and setting, page 5; Intervention, page 6; Outcomes and assessments, page 7; Figure 1; Table 2, page 19
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Methods and analyses - Sample Size, page 7; Supplement 2
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Methods and analyses - Participants, page 5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	Methods and analyses - Randomization and blinding, page 6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Methods and analyses - Randomization and blinding, page 6
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions	Methods and analyses - Participants, page 5; Randomization and blinding, page 6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how	Methods and analyses - Intervention, page 6; Randomization and blinding, page 6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Methods and analyses - Unblinding procedures, page 10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Methods and analyses - Outcomes and assessments, page 7; Data management and analyses, page 8; Minimizing bias and contamination, page 9; Table 2, page 19
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Methods and analyses - Intervention, page 6; Analyses of primary and secondary outcomes, page 8
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Methods and analyses - Data management, page 8
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Methods and analyses - Analyses of primary and secondary outcomes, page 8
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	Methods and analyses - Analyses of primary and secondary outcomes, page 8
	20c	Definition of analysis population relating to protocol non-adherence (e.g., as randomized analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	Methods and analyses - Analyses of primary and secondary outcomes, page 8; Handling of missing data and dropouts, page 9
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	There is a monitoring committee responsible for general trial conduct as well as data concerns. Methods and analyses - Potential risks, page 9
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Methods and analyses - Analyses of primary and secondary outcomes, page 8; Unblinding procedures, page 10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Methods and analyses - Outcomes and assessments, page 7; Minimizing bias and contamination; page 9, Potential risks, page 9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Methods and analyses - Potential risks, page 9
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Abstract - Trial registration, page 2; Ethics and dissemination - Ethics approval, page 10
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Ethics and dissemination - Ethics approval, page 10. Study participants will receive a letter with updates.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32)	Methods and analyses - Participants, page 5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Methods and analyses - Data management, page 8; Ethics and dissemination - Dissemination policy, page 11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Disclosure statement, page 12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Ethics and dissemination - Dissemination policy, page 11; Funding statement, page 12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Due to the low-risks, the need to compensate for suffered harm is not foreseen (Methods and analyses - Potential risks, page 9). Though study insurance is in place in case any care needs to be covered.

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Ethics and dissemination - Dissemination policy, page 11
	31b	Authorship eligibility guidelines and any intended use of professional writers	Ethics and dissemination - Dissemination policy, page 11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Ethics and dissemination - Dissemination policy, page 11
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	Supplement 3
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Methods and analyses - Outcomes and assessments, page 7; Table 2, page 19

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Supplement 2: Participant information and informed consent form.

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Vitamin-D-Supplementierung bei Personen mit einer chronischen Querschnittlähmung *(Vitamin D supplementation in individuals with a chronic spinal cord injury – a placebo-controlled randomized double-blinded study)*

Sehr geehrte Dame, sehr geehrter Herr,

Wir möchten Sie anfragen, ob Sie an einer klinischen Studie teilnehmen wollen. Im Folgenden wird Ihnen dieses Studienvorhaben dargestellt: Zunächst in einer kurzen Zusammenfassung, damit Sie wissen, um was es geht, anschliessend in einer detaillierten Beschreibung.

Zusammenfassung

1	**Ziel der Studie** Diese Studie untersucht den Einfluss einer zwölfmonatigen Vitamin-D-Supplementierung (Glossar, Seite 8) auf den Vitamin-D-Spiegel von Personen mit einer chronischen Querschnittlähmung.
2	**Auswahl** Wir suchen Personen im Alter von 18 bis 60 Jahren mit einer chronischen sub-C4 Querschnittlähmung (d.h. drei oder mehr Jahre sind seit der Diagnose vergangen und die Läsionshöhe ist unterhalb C4), die im Alltag auf einen Rollstuhl angewiesen sind.
3	**Allgemeine Informationen zur Studie** Dies ist eine doppelblinde, randomisierte, Placebo-kontrollierte, klinische Studie (Glossar, Seite 8). Diese Studie wird organisiert durch das Schweizer Paraplegiker-Zentrum (SPZ), mit Dr. sc. nat. Joëlle Flück als Studienleiterin (Sponsor-Investigator). Studienteilnehmende mit einem ausreichenden Vitamin-D-Spiegel zu Beginn der Studie werden der natürliche Zeitverlaufgruppe zugeordnet und erhalten keine Supplementierung. Studienteilnehmende, bei welchen zu Beginn der Studie ein Vitamin-D-Mangel diagnostiziert wurde, werden zufällig ("randomisiert") einer der drei Interventionsgruppen zugeordnet. Diese Studienteilnehmenden bekommen entweder eine "niedrige" Vitamin-D-Dosierung (24'000 IE/Monat), eine "hohe" Vitamin-D-Dosierung (48'000 IE/Monat) oder ein Placebo. Als Supplement wird das handelsübliche Vi-De 3® Monatsdosis (Glossar, Seite 8) von Dr. Wild & Co. AG abgegeben. Das Placebo enthält die gleiche alkoholische Lösung (5 mL) wie das Supplement, aber ohne Wirkstoff. Pro Gruppe haben wir geplant 15 Studienteilnehmende zu untersuchen, was zu einer Gesamtzahl von 60 Studienteilnehmenden führt.
4	**Ablauf** Mittels einer Blutanalyse während der ersten Studienvisite wird Ihr Vitamin-D-Spiegel bestimmt. Studienteilnehmende mit einem ausreichenden Vitamin-D-Spiegel werden der natürliche Zeitverlaufgruppe zugeordnet und erhalten keine Supplementierung. Studienteilnehmende mit einem Vitamin-D-Mangel werden zufällig einer der drei Interventionsgruppen zugeordnet. Das Supplement bzw. das Placebo sollen alle zwei Wochen über 12 Monate eingenommen werden. Erst nach Studienabschluss werden Sie, sowie auch die Studienmitarbeiter, herausfinden, in welche der Interventionsgruppen Sie zugeordnet waren. Abhängig von der Gruppe, in der Sie sich befinden, umfasst die Studie drei (natürliche Zeitverlaufgruppe) oder fünf (Interventionsgruppen) Studienvisiten von 1.5 bis 2.0 Stunden im SPZ. Während den Studienvisiten werden folgende Messungen durchgeführt: Knochendichte, Blutentnahme, Handkraft sowie Ausfüllen verschiedener Fragebögen.

5	**Nutzen** Bei allen Studienteilnehmenden werden der Vitamin-D-Spiegel sowie alle weiteren Messwerte regelmässig überprüft. Werden Sie in einer der Interventionsgruppen eingeteilt und bekommen Sie das Vitamin-D-Supplement, wird Ihr Vitamin-D-Mangel mit grosser Wahrscheinlichkeit während der Studie behoben. Sofern Studienteilnehmende dies wünschen, werden die individuellen Studienresultate nach Beendigung der gesamten Studie zusammengestellt und besprochen. Dies könnte genutzt werden, um später die Vitamin-D-Supplementation individuell zu optimieren und auf die eigenen Bedürfnisse anzupassen. Wir erhoffen uns, dass wir anhand der gewonnen Erkenntnisse dieser Studie, die Richtlinien zur Verabreichung von Vitamin D bei Querschnittgelähmten verbessern können.
6	**Rechte** Sie entscheiden freiwillig, ob Sie an der Studie teilnehmen wollen oder nicht. Ihre Entscheidung hat keinen Einfluss auf Ihre medizinische Behandlung und Sie müssen diese Entscheidung nicht begründen.
7	**Pflichten** Wenn Sie bei der Studie mitmachen, müssen Sie bestimmte Regeln beachten. Dies ist notwendig für Ihre Sicherheit und Gesundheit. Wir werden Sie dabei so gut wie möglich unterstützen. Als Studienteilnehmende sind Sie unter anderem verpflichtet, den (medizinischen) Anweisungen der Studienmitarbeiter zu folgen und sich an den Studienplan (z.B. Einnahme des Supplements) zu halten.
8	**Risiken** Das Risiko dieser Studie ist minimal. Die Messungen werden von spezialisierten Mitarbeitern durchgeführt. Ausserdem sind im SPZ sind alle notwendigen Sicherheitsmassnahmen vorhanden.
9	**Andere Behandlungsmöglichkeiten** Sie müssen bei dieser Studie nicht teilnehmen. Neben Vitamin-D-Supplementen, welche rezeptfreigekauft werden können, könnte auch Sonnenexposition dazu beitragen, Ihren Vitamin-D-Spiegel zu verbessern.
10	**Ergebnisse** Bei Studienergebnissen und Zufallsbefunden während der Studie werden Sie informiert, wenn diese Ergebnisse für Sie gesundheitlich wichtig sind. Falls Sie dies nicht möchten, informieren Sie bitte einen Studienmitarbeiter.
11	**Vertraulichkeit von Daten und Proben** Wir halten alle gesetzlichen Regeln des Datenschutzes ein und alle Beteiligten unterliegen der Schweigepflicht. Ihre persönlichen und medizinischen Daten sowie Ihre Proben werden verschlüsselt verwendet. Die Daten und Proben werden nur für andere Forschungsprojekte weiter verwendet, wenn Sie Ihr separates Einverständnis dafür geben.
12	**Rücktritt** Sie können jederzeit von der Studie zurücktreten und nicht mehr teilnehmen. Die bis dahin erhobenen Daten und Proben werden noch ausgewertet, weil das ganze Projekt sonst seinen Wert verliert.
13	**Entschädigung** Alle Studienteilnehmenden bekommen eine Reisespesenentschädigung. Sie erhalten zusätzlich keine weitere finanzielle Entschädigung.
14	**Haftung** Die Studienversicherung des SPZ (Basler Versicherungen) kommt für Schäden im Rahmen der Studie auf.

15	**Finanzierung** Die Studie wird von der SPZ und Schweizer Paraplegiker-Stiftung bezahlt.
16	**Kontaktperson** Dr. Anneke Hertig-Godeschalk Studienkoordinatorin anneke.hertig@paraplegie.ch +41 41 939 66 03 Sportmedizin, SPZ Guido A. Zäch-Strasse 1 6207 Nottwil

Studieninformation

1. Ziel der Studie

Wir wollen mit dieser Studie den Einfluss einer zwölfmonatigen Vitamin-D-Supplementierung (Glossar, Seite 8) auf den Vitamin-D-Spiegel von Personen mit einer chronischen Querschnittlähmung untersuchen. Nebst dem Vitamin-D-Spiegel im Blut, werden auch diverse weitere physische und psychische Messwerte untersucht. Diese Studie soll dazu beitragen, Querschnittgelähmte optimal bezüglich einer Vitamin-D-Supplementation zu beraten.

2. Auswahl

Es können alle Personen teilnehmen, die eine chronische sub-C4 Querschnittlähmung haben (d.h. drei oder mehr Jahre sind seit der Diagnose vergangen und die Läsionshöhe ist unterhalb C4) und im Alltag auf einen Rollstuhl angewiesen sind. Ausserdem müssen Sie zwischen 18 und 60 Jahre alt und ansonsten gesund sein. Falls Sie an einer bekannten Resorptionsstörung, Erkrankung der Schilddrüse oder Niereninsuffizienz leiden, dürfen Sie nicht an der Studie teilnehmen. Sie sollten in den letzten 12 Monaten vor Einschluss in die Studie keine Vitamin-D-Supplemente zu sich genommen haben. Sollten Sie sich im letzten Monat auf der südlichen Halbkugel aufgehalten haben, also z.B. in Süd-Afrika, Australien, Mittel- oder Südamerika, oder sollten Sie einen solchen Aufenthalt im Zeitraum der Studie geplant haben, können Sie nicht teilnehmen. Frauen, die schwanger sind oder stillen, werden aus Sicherheitsgründen von einer Teilnahme ausgeschlossen.

3. Allgemeine Informationen

Ein Vitamin-D-Mangel wird mit verschiedenen gesundheitlichen Risiken, unter anderem einer verminderten Muskelfunktion sowie einem vermehrten Auftreten von Depressionen in Verbindung gebracht. Unter Querschnittgelähmten ist ein Vitamin-D-Mangel sehr stark verbreitet. Eine Supplementierung mit Vitamin D kann zu einem optimalen Vitamin-D-Spiegel führen, doch nur wenn eine ausreichende Dosierung verabreicht wird. Erkenntnisse zu diesem Thema liegen bis jetzt nur aus Studien mit Fussgängern vor, welche aufgrund verschiedener körperlicher Unterschiede, beispielsweise bei der Verdauung und der Körperzusammensetzung, nicht immer eins zu eins auf Querschnittgelähmte übertragen werden können. Ausserdem sind die wenigen Studien, die es im Bereich Querschnittlähmung dazu gibt, in ihre Aussagekraft eingeschränkt: Sie laufen meistens nur über eine kurze Zeit und beziehen sich auf eine begrenzte Anzahl von Messwerten.

In der aktuellen Studie werden wir den Effekt einer Vitamin-D-Supplementierung über 12 Monate untersuchen. Dies ist eine doppelblinde, randomisierte, Placebo-kontrollierte, klinische Studie (Glossar, Seite 8), die im SPZ durchgeführt wird. Studienteilnehmende mit einem ausreichenden Vitamin-D-Spiegel zu Beginn der Studie werden der natürliche Zeitverlaufgruppe zugeordnet und erhalten keine Supplementierung. Studienteilnehmende, bei welchen zu Beginn der Studie ein Mangel an Vitamin D diagnostiziert wurde, werden zufällig ("randomisiert") auf die drei Interventionsgruppen verteilt. Diese Studienteilnehmenden bekommen entweder eine "niedrige" Vitamin-D-Dosierung (24'000 IE/Monat), eine "hohe" Vitamin-D-Dosierung (48'000 IE/Monat) oder ein Placebo. Als Supplement wird das handelsübliche Vi-De 3® Monatsdosis (Glossar, Seite 8) von Dr. Wild & Co. AG abgegeben. Vi-De 3® Monatsdosis ist eine 5 mL alkoholische Lösung mit Mono-Vitamin D3. Die vorgeschlagenen Dosierungen sind im Rahmen der Supplementierungs-Richtlinien (600 bis 2000 IE/Tag), übersteigen die höchst tolerierte Tagesdosis (10‘000 IE/Tag) nicht und sind weit unter der Schwelle, welche zu einer Vergiftung führen kann (40’000 bis 100’000 IE/Tag über 1-2 Monate). Die Placebo-Gruppe erhält die gleiche alkoholische Lösung (5 mL) wie die Interventionsgruppen, aber ohne Wirkstoff.

Das Vitamin D bzw. das Placebo soll alle zwei Wochen über 12 Monate, aufgelöst in einem Glas Wasser, eingenommen werden. Pro Gruppe haben wir geplant, 15 Studienteilnehmende zu untersuchen, was zu einer Gesamtzahl von 60 Studienteilnehmenden führt.
Wir machen diese Studie so, wie es die Gesetze in der Schweiz vorschreiben. Ausserdem beachten wir alle international anerkannten Richtlinien. Die zuständige Kantonale Ethikkommission und Swissmedic haben die Studie geprüft und bewilligt. Eine Beschreibung dieser Studie finden Sie auch auf der Internetseite des Bundesamtes für Gesundheit (www.kofam.ch, Registriernummer: SNCTP000004032) sowie unter www.clinicaltrials.gov (Registriernummer: NCT04652544).

4. Ablauf

Im Rahmen des Screening-Termins (telefonisch oder im SPZ) werden wir überprüfen, ob Sie die Ein- und Ausschlusskriterien erfüllen. Bei gebärfähigen Frauen wird ein Urin-Schwangerschaftstest durchgeführt und während der Studie eine Schwangerschaftsverhütung verlangt. Falls Sie alle Kriterien erfüllen und Sie sich zu einer Studienteilnahme entscheiden, werden wir Ihnen weitere Studieninformationen und die Einverständniserklärung zustellen, welche Sie bei der ersten Studienvisite unterschrieben zurückbringen müssen. Mittels einer Blutanalyse während der erste Studienvisite wird Ihr Vitamin-D-Spiegel bestimmt. Bei einem ausreichenden Vitamin-D-Spiegel zu Beginn der Studie werden Sie der natürliche Zeitverlaufflgruppe zugeordnet und erhalten keine Supplementierung. Bei einem Vitamin-D-Mangel zu Beginn der Studie werden Sie zufällig einer der drei Interventionsgruppen zugeordnet und erhalten entweder eine "niedrige" Vitamin-D-Dosierung, eine "hohe" Vitamin-D-Dosierung oder ein Placebo. Erst nach Studienabschluss werden Sie, sowie auch die Studienmitarbeiter, herausfinden, in welche der Interventionsgruppen Sie zugeordnet waren. Die Einnahme des Supplements, müssen Sie mittels einem Tagebuch dokumentieren.
Abhängig von der Gruppe, in der Sie sich befinden, umfasst die Studie drei (natürliche Zeitverlaufgruppe) oder fünf (Interventionsgruppen) Studienvisiten von 1.5 bis 2.0 Stunden im SPZ, während denen die folgenden Messungen durchgeführt werden:

- Knochendichte mittels DXA ("dual energy X-ray absorptiometry"). DXA ist eine spezielle Art der Röntgenuntersuchung. Die Messung dauert nur wenige Minuten, ist absolut schmerzfrei und nur mit einer sehr geringen Strahlenbelastung verbunden. Messungen des Unterarms, der Hüfte und des Knies werden nur bei der ersten und letzten Visite durchgeführt.
- Blutentnahme (15 mL venös in Armbeuge) zur Bestimmung von u.a. Vitamin-D- und Kalzium- Werten.
- Handkraft wird an beiden Händen mit einem Dynamometer (Handkraftmesser) gemessen.
  Das Messgerät besteht aus einem Griff und einem Belastungsmesser, der während der Messung so kräftig wie möglich zusammenzugedrückt werden sollte. Diese Messung wird nur unter Studienteilnehmende durchgeführt, die sie erfolgreich machen können, also unter Studienteilnehmende die von der Lähmungshöhe her über eine entsprechende Handfunktion verfügen.
- Verschiedene weiteren Messwerte (Stürze, Schmerzen, Stimmung, Sonneneinstrahlung) werden mittels Fragebögen erhoben.

Daneben wird unter den Studienteilnehmenden der Interventionsgruppen jeden Monat telefonisch oder via E-Mail eine 15-minütige Befragung zur Überprüfung der Einnahme und der Verträglichkeit des Supplements durchgeführt.
Es kann sein, dass wir Sie von der Studie vorzeitig ausschliessen müssen. Das kann zum Beispiel geschehen, wenn Ihr Vitamin-D-Spiegel eine Obergrenze (> 375 nmol/L) überschreitet. In diesem Fall werden Sie zu Ihrer Sicherheit abschliessend noch einmal untersucht. Bitte bringen Sie dann alle Produkte, die wir Ihnen gegeben haben, zu uns zurück.

5. Nutzen

Bei allen Studienteilnehmenden werden der Vitamin-D-Spiegel sowie weitere Messwerte regelmässig überprüft. Nach Abschluss der Studie kann man Rückschlüsse ziehen, ob bei einer Supplementation die gemessenen Werte besser sind. Werden Sie in eine der Interventionsgruppen eingeteilt und bekommen Sie das Vitamin-D-Supplement, wird Ihr Vitamin-D-Mangel mit grosser Wahrscheinlichkeit während der Studie behoben. Sofern Studienteilnehmende dies wünschen, werden die individuellen Studienresultate nach Beendigung der gesamten Studie zusammengestellt und besprochen. Dies könnte genutzt werden, um später die Vitamin-D-Supplementation individuell zu optimieren und auf die eigenen Bedürfnisse anzupassen.
Wir erhoffen uns, dass wir anhand der gewonnen Erkenntnisse dieser Studie, die Richtlinien zur Verabreichung von Vitamin D bei Querschnittgelähmten verbessern können.

6. Rechte

Sie nehmen freiwillig teil. Wenn Sie nicht mitmachen oder später Ihre Teilnahme zurückziehen wollen, müssen Sie dies nicht begründen. Ihre medizinische Behandlung/Betreuung ist unabhängig von Ihrem Entscheid gewährleistet. Sie dürfen jederzeit Fragen zur Studienteilnahme sowie zur Studie selber stellen. Wenden Sie sich dazu bitte an eine der Personen, die am Ende dieser Information genannt ist.

7. Pflichten

Wenn Sie bei der Studie mitmachen, müssen Sie bestimmte Regeln beachten. Dies ist notwendig für Ihre Sicherheit und Gesundheit. Wir werden Sie dabei so gut wie möglich unterstützen. Als Studienteilnehmende sind Sie verpflichtet:

- den (medizinischen) Anweisungen der Studienmitarbeiter zu folgen und sich an den Studienplan (z.B. Einnahme des Supplements) zu halten.
- uns mitzuteilen, wenn sich ihre Pläne bezüglich eines Auslandaufenthalts auf der südlichen Halbkugel (z. B: Mittel- oder Südafrika, Mittel- oder Südamerika, Australien) während der Studienzeit ändern.
- uns über das Vorhandensein/den Verlauf einer allfälligen Erkrankung und über neue Symptome, neue Beschwerden und Änderungen im Befinden (auch nach Studienende/-abbruch, bis die unerwünschte Wirkung abklingt) zu informieren.
- uns über die gleichzeitige Behandlung und Therapien bei einem anderen Arzt und über die Einnahme von Medikamenten zu informieren. Nennen Sie dabei bitte alle Medikamente, d. h. auch solche, die Sie selbst gekauft haben, für die Sie kein Rezept brauchen sowie Medikamente der Alternativmedizin.
- uns mitzuteilen, wenn Sie während der Studie oder innerhalb von 30 Tage nach Studienende Schwanger wurden.

Bitte bringen Sie, wenn Sie zu einer Studienvisite ins SPZ kommen, alle Packungen des Supplements mit, die wir Ihnen gegeben haben. Damit gemeint sind einerseits die leeren, andererseits aber auch die eventuell noch vollen Packungen.
Wenn Sie die Pflichten nicht beachten, können Sie Haftungsansprüche verlieren.

8. Risiken und Belastungen für die Studienteilnehmende

Die Messungen werden von spezialisierten Mitarbeitern durchgeführt. Ausserdem sind im SPZ alle notwendigen Sicherheitsmassnahmen vorhanden.
Das Vitamin-D-Supplement sowie das Placebo enthalten eine alkoholische Lösung (65 Volumenprozent Ethanol), was einen geringen Einfluss auf die Fahrtüchtigkeit oder die Fähigkeit, Maschinen zu bedienen, haben kann. Vitamin D ist in grossen Mengen giftig. Die höchste Dosierung in unserer Studie übersteigt die höchste tolerierte Tagesdosis nicht und ist weit unter der Schwelle, welche zu einer Vergiftung führen kann. Bei unserer Dosierung sind somit keinerlei Nebenwirkungen zu erwarten. Mittels der Blutuntersuchung werden wir Ihren Vitamin-D-Spiegel während der ganzen Studie beobachten. Bitte wenden Sie sich an einen Studienmitarbeiter, falls Sie eines der folgenden Anzeichen einer Vitamin-D-Überdosierung bemerken: Übelkeit, Erbrechen, Durchfall, Verstopfung, Anorexie, Müdigkeit, Kopfschmerzen, Muskel- und Gelenkschmerzen, Muskelschwäche oder Schläfrigkeit. Wenn Sie in die Placebo-Gruppe zugeordnet werden, wird Ihr Vitamin-D-Mangel mit
grosser Wahrscheinlichkeit bis am Ende der Studie weiterexistieren. Dies birgt aber keine zusätzlichen Risiken im Vergleich zur Situation vor der Studienteilnahme.
Durch die Blutentnahme in der Armbeuge können lokal leichte Entzündungen auftreten. Durch die Messung der Knochendichte am Unterarm (0.010 mSv), an der Hüfte (0.146 mSv) und am Knie (0.034 mSv) werden Sie einer minimalen Röntgenstrahlung ausgesetzt (2 Messungen x 0.190 = 0.380 mSv). Im Vergleich dazu beträgt die jährlichen radioaktiven Strahlenlast für die Schweizer Bevölkerung durch Radon durchschnittlich 3.200 mSv. Sollten Sie während der Studie schwanger werden, müssen Sie die Studienmitarbeiter sofort informieren und dürfen nicht weiter an der Studie teilnehmen.

9. Andere Behandlungsmöglichkeiten

Sie müssen bei dieser Studie nicht teilnehmen. Neben Vitamin-D-Supplementen, welche rezeptfrei gekauft werden können, könnte auch Sonnenexposition dazu beitragen, Ihren Vitamin-D-Spiegel zu verbessern.

10. Ergebnisse aus der Studie

Die Studienmitarbeiter werden Sie während der Studie über alle neuen Erkenntnisse informieren, die den Nutzen der Studie oder Ihre Sicherheit und somit Ihr Einwilligung zur Teilnahme an der Studie beeinflussen können. Sie werden die Informationen mündlich und schriftlich erhalten.
Bei Zufallsbefunden, die bei Ihnen zur Verhinderung, Feststellung und Behandlung bestehender oder künftig zu erwartender Krankheiten beitragen können, werden Sie informiert. Wenn Sie nicht informiert werden wollen, sprechen Sie bitte mit einem Studienmitarbeiter.

11. Vertraulichkeit der Daten und Proben

Für diese Studie werden Ihre persönlichen und medizinischen Daten erfasst. Nur sehr wenige Fachpersonen werden Ihre unverschlüsselten Daten sehen, und zwar ausschliesslich, um Aufgaben im Rahmen der Studie zu erfüllen. Bei der Datenerhebung zu Studienzwecken werden die Daten verschlüsselt. Verschlüsselung bedeutet, dass alle Bezugsdaten, die Sie identifizieren könnten (Name, Geburtsjahr), gelöscht und durch einen Schlüssel ersetzt werden. Die Schlüssel-Liste bleibt immer im SPZ. Diejenigen Personen, die den Schlüssel nicht kennen, können daher keine Rückschlüsse auf Ihre Person ziehen. Ihr Name taucht niemals im Internet oder einer Publikation auf. Manchmal gibt es die Vorgabe bei einer Zeitschrift zur Publikation, dass Einzel-Daten (sogenannte Roh-Daten) übermittelt werden müssen. Wenn Einzel-Daten übermittelt werden müssen, dann sind die Daten immer verschlüsselt und somit ebenfalls nicht zu Ihnen als Person rückverfolgbar. Bei einer Publikation sind die zusammengefassten Daten daher auch nicht auf Sie als Einzelperson rückverfolgbar. Alle Personen, die im Rahmen der Studie Einsicht in Ihre Daten haben, unterliegen der Schweigepflicht. Die Vorgaben des Datenschutzes werden eingehalten und Sie als teilnehmende Person haben jederzeit das Recht auf Einsicht in Ihre Daten.
Möglicherweise wird diese Studie durch die zuständige Ethikkommission, die Arzneimittelbehörde Swissmedic oder durch die Institution, die die Studie veranlasst hat, überprüft. Die Studienmitarbeiter müssen eventuell Ihre persönlichen und medizinischen Daten für solche Kontrollen offenlegen. Ebenso kann es sein, dass bei Schäden ausnahmsweise auch ein Vertreter der Versicherung Ihre Daten ansehen muss. Alle Personen müssen absolute Vertraulichkeit wahren.
Im Rahmen dieses Projektes werden Daten erhoben bzw. Messungen durchgeführt, welche auch für Ihren behandelnden Arzt und damit Ihre persönliche, medizinische Betreuung im SPZ von Interesse sein können. Deshalb werden diese Daten (z.B. Blutwerte) auch in Ihrer elektronischen Krankenakte gespeichert. Dies dient in erster Linie dazu, doppelte Untersuchungen und damit auch Ihre Belastung durch Untersuchungen zu verringern.

12. Rücktritt

Sie können jederzeit aufhören und von der Studie zurücktreten, wenn Sie das wünschen. Die bis dahin erhobenen Daten und Proben werden noch verschlüsselt ausgewertet, weil das ganze Projekt sonst seinen Wert verliert. Prüfen Sie bitte, ob Sie damit einverstanden sind, bevor Sie bei der Studie mitmachen.

13. Entschädigung für die Studienteilnehmende

Die in dieser Studieninformation erwähnten studienspezifischen Untersuchungen sind kostenlos. Weder Ihnen noch Ihrer Krankenkasse entstehen im Zusammenhang mit Ihrer Teilnahme Kosten. Das Vitamin-D-Supplement sowie Placebo werden kostenlos zu Verfügung gestellt. Alle Studienteilnehmende bekommen eine Reisespesenentschädigung (CHF50 pro Studienvisite). Sie erhalten zusätzlich keine weitere finanzielle Entschädigung.

14. Haftung

Die Institution (SPZ), die die Studie veranlasst hat und für die Durchführung verantwortlich ist, haftet für Schäden, welche Ihnen im Zusammenhang mit der getesteten Substanz oder Forschungshandlungen (z.B. Untersuchungen) entstehen könnten. Die Voraussetzungen und das Vorgehen dazu sind gesetzlich geregelt. Die SPZ hat dazu eine Versicherung bei der Basler Versicherungen (Aeschengraben 21, 4002 Basel) abgeschlossen, um in einem möglichen Schadenfall für die Haftung aufkommen zu können. Bei Schäden, die auf ein zugelassenes und gemäss dem medizinischen Standard angewendetes Heilmittel zurückzuführen sind oder welche im Rahmen der Placebo-Verwendung auftraten, greifen dieselben Haftungsregelungen wie bei einer Behandlung ausserhalb einer Studie. Falls Sie einen Schaden erlitten haben, so wenden Sie sich bitte an einen Studienmitarbeiter.

15. Finanzierung der Studie

Die Studie wird von der SPZ und Schweizer Paraplegiker-Stiftung bezahlt.

16. Kontaktpersonen

Bei Fragen, Unsicherheiten oder Notfällen, die während der Studie oder danach auftreten, können Sie sich jederzeit an eine dieser Kontaktpersonen wenden:

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6207 Nottwil

Bitte kontaktieren Sie in Notfällen Ihre örtlichen Notfalldienste.

17. Glossar; was heisst….

- *Was heisst "doppelblind"?*
  Eine Studie zu "verblinden" dient dazu, bessere und genauere Ergebnisse zu erhalten. "Doppelblind" ist eine Studie dann, wenn weder die Studienteilnehmenden noch die Forschenden wissen, ob Studienteilnehmende das echte Medikament oder das Placebo erhalten. Nur die unabhängige Person, die diese Zuordnung ausgelost hat, weiss, wer was erhält. Wenn der Test zu Ende ist, wird die "Verblindung" aufgelöst. In einem Notfall kann die "Verblindung" jederzeit auch früher aufgehoben werden. Ein Studienteilnehmer, der weiss, dass er das echte Medikament und nicht das Placebo erhält, achtet ganz anders auf Reaktionen des Körpers als jemand, der weiss, dass er nur das Placebo erhält. Dies kann dazu führen, dass Studienteilnehmende, die das echte Medikament erhalten, die Wirkung des Medikaments im Vergleich zu denjenigen, die nur das Placebo erhalten, überschätzen.
- *Was heisst "randomisiert“?*
  Bei vielen Studien werden zwei oder mehrere unterschiedliche Arten der Behandlung verglichen. Zum Beispiel vergleicht man ein echtes Medikament mit einem Placebo. Man bildet dann zwei Gruppen von Studienteilnehmenden, die einen bekommen das echte Medikament und die anderen das Placebo. „Randomisieren“ bedeutet, dass ausgelost wird, wer in welche Gruppe kommt. Es ist bei einem solchen Test also Zufall, ob man das echte Medikament erhält oder das Placebo.
- *Was heisst "Placebo“?*
  Ein Scheinmedikament, das so aussieht wie ein echtes und auch gleich verpackt ist, wie jenes das der Arzt verschreibt und zu dem es einen Beipackzettel gibt. Es ist aber kein Wirkstoff drin, sondern es besteht nur aus Wasser oder Zucker oder ähnlichem. Manchmal behandelt man einen Teil der Studienteilnehmenden an einem Medikamententest mit dem richtigen Medikament (mit dem Wirkstoff) und den anderen Teil mit einem solchen Placebo (ohne Wirkstoff). Dann kann man im Vergleich besser abschätzen, wie gut das Medikament tatsächlich wirkt. In dieser Studie besteht das Placebo aus der gleichen alkoholischen Lösung (5 mL, 65 Volumenprozent Ethanol) wie das Vitamin-D-Supplement, aber ohne Wirkstoff.
- *Was ist "Vitamin-D-Supplementierung"?*
  Unter Supplementation versteht man die gezielte und ergänzende Versorgung mit einzelnen Nährstoffen, zusätzlich zur gewöhnlichen Nahrung. Die entsprechenden Produkte bezeichnet man als Supplement. Bei Vitamin-D-Supplementierung wird Vitamin D als Supplement eingenommen, zum Beispiel in Form einer Flüssigkeit oder einer Tablette.
- *Was ist "Vi-De 3® - Monatsdosis"?*
  Dies ist ein handelsübliches Vitamin-D-Supplement mit Wirkstoff Cholecalciferol (Mono-Vitamin D3), fabriziert von der Firma Dr. Wild & Co. AG. Vi-De 3® Monatsdosis ist eine 5 mL alkoholische Lösung (65 Volumenprozent Ethanol), was 2.600 g Alkohol pro Flasche entspricht. Zum Vergleich: 250 mL Apfelsaft enthaltet 0.165 g Alkohol.

Einwilligungserklärung

Schriftliche Einwilligungserklärung zur Teilnahme an einem Studienprojekt

Bitte lesen Sie dieses Formular sorgfältig durch. Bitte fragen Sie, wenn Sie etwas nicht verstehen oder wissen möchten. Für die Teilnahme ist Ihre schriftliche Einwilligung notwendig.

BASEC-Nummer:	2020-01493
Titel der Studie:	Vitamin-D-Supplementierung bei Personen mit einer chronischen Querschnittlähmung
Verantwortliche Institution:	Schweizer Paraplegiker-Zentrum Guido A. Zäch-Strasse 1 6207 Nottwil
Ort der Durchführung:	Schweizer Paraplegiker-Zentrum Guido A. Zäch-Strasse 1 6207 Nottwil
Verantwortliche Studienmitarbeiterin am Studienort:	Dr. sc. nat. Joëlle Flück
Studienteilnehmende:	☐ weiblich ☐ männlich
Name und Vorname in Druckbuchstaben:	
Geburtsdatum:	

- Ich wurde vom unterzeichnenden Studienmitarbeiter mündlich und schriftlich über den Zweck, den Ablauf der Studie, über mögliche Vor- und Nachteile sowie über eventuelle Risiken informiert.
- Ich nehme an dieser Studie freiwillig teil und akzeptiere den Inhalt der abgegebenen schriftlichen Information. Ich hatte genügend Zeit, meine Entscheidung zu treffen.
- Meine Fragen im Zusammenhang mit der Teilnahme an dieser Studie sind mir beantwortet worden. Ich behalte die schriftliche Information und erhalte eine Kopie meiner schriftlichen Einwilligungserklärung.
- Ich wurde über mögliche andere Behandlungen und Behandlungsverfahren aufgeklärt.
- Ich bin einverstanden, dass die zuständigen Fachleute des Sponsors, der zuständigen Ethikkommission und der Arzneimittelbehörde Swissmedic zu Prüf- und Kontrollzwecken in meine unverschlüsselten Daten Einsicht nehmen dürfen, jedoch unter strikter Einhaltung der Vertraulichkeit.
- Bei Studienergebnissen oder Zufallsbefunden, die direkt meine Gesundheit betreffen, werde ich informiert. Wenn ich das nicht wünsche, informiere ich einen Studienmitarbeiter.
- Ich weiss, dass meine gesundheitsbezogenen und persönlichen Daten (und Proben) nur in verschlüsselter Form zu Forschungszwecken für diese Studie weitergegeben werden können, eventuell auch ins Ausland.
- Im Fall einer Weiterbehandlung ausserhalb des Studienzentrums ermächtige ich meinen/meine nachbehandelnden Arzt/Ärzte, meine für die Studie relevanten Nachbehandlungsdaten dem Studienmitarbeiter zu übermitteln.
- Ich kann jederzeit und ohne Angabe von Gründen von der Studienteilnahme zurücktreten. Meine weitere medizinische Behandlung ist unabhängig von der Studienteilnahme immer gewährleistet. Die bis zum Rücktritt erhobenen Daten und Proben werden für die Auswertung zur Studie verwendet.
- Ich bin darüber informiert, dass eine Versicherung Schäden deckt, die auf die Studie zurückzuführen sind.
- Ich bin mir bewusst, dass die in der Studieninformation genannten Pflichten einzuhalten sind. Im Interesse meiner Gesundheit kann mich ein Studienmitarbeiter jederzeit von der Studie ausschliessen.

Ort, Datum	Unterschrift Studienteilnehmende

Bestätigung des Studienmitarbeiters: Hiermit bestätige ich, dass ich dieser Studienteilnehmerin/diesem Studienteilnehmer Wesen, Bedeutung und Tragweite der Studie erläutert habe. Ich versichere, alle im Zusammenhang mit dieser Studie stehenden Verpflichtungen gemäss dem geltenden Recht zu erfüllen. Sollte ich zu irgendeinem Zeitpunkt während der Durchführung der Studie von Aspekten erfahren, welche die Bereitschaft der Studienteilnehmerin/des Studienteilnehmers zur Teilnahme an der Studie beeinflussen könnten, werde ich sie/ ihn umgehend darüber informieren.

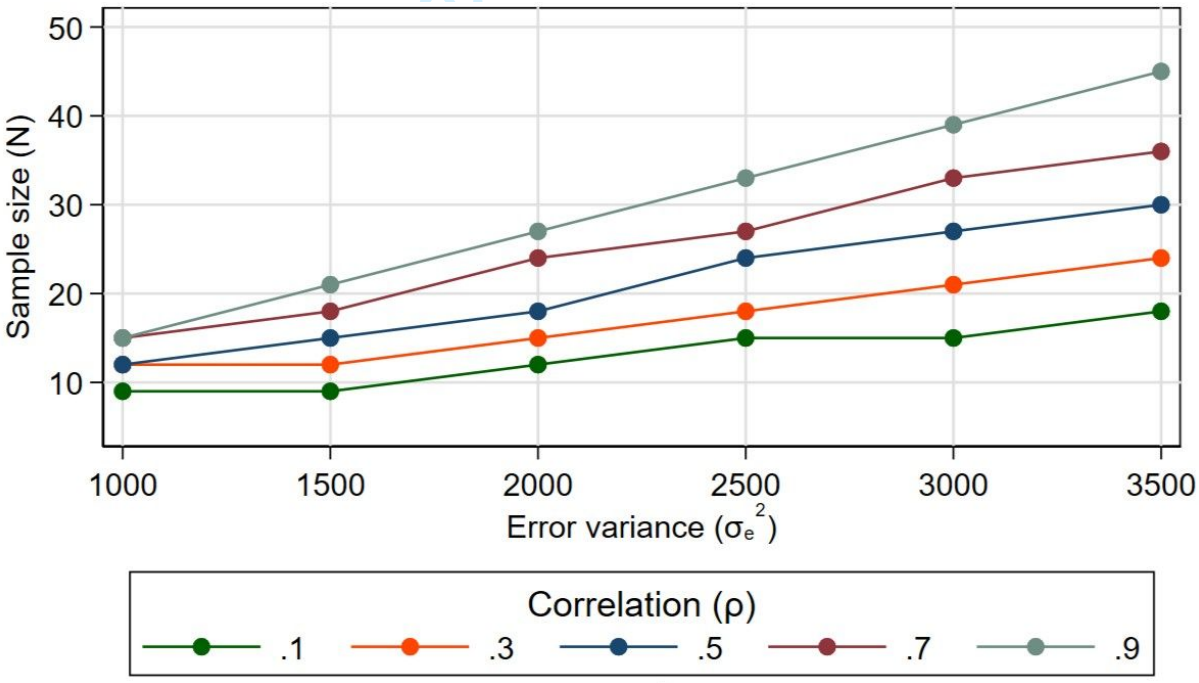
Ort, Datum	Name und Vorname des Studienmitarbeiters in Druckbuchstaben Unterschrift des Studienmitarbeiters

Supplement 3: Sample size calculation

A: Expected time course of mean vitamin D status (nmol/L) during the study.

	Baseline	3 months	6 months	9 months	12 months
Placebo	31	31	31	31	31
Moderate dosage	31	49	56	59	60
High dosage	31	91	115	125	129

B: Estimated sample size for repeated-measures ANOVA. F-test for between subjects with H_0: $\delta = 0$ versus H_a: $\delta \neq 0$. Estimated minimal sample size as a function of the error variance and the within-individual correlation of repeated vitamin D status measurements, specifying a power ($1-\beta$) of 0.8 and a significance level (α) of 0.05. Reading example: Presuming an error variance (σ_e^2) of 3500, a between-subject variance (σ_b^2) of 794 and a high within-individual correlation (ρ) of 0.9 for repeated vitamin D status measurements (N_{rep}=5), the estimated minimal overall sample needed is 45 participants, implying 15 participants in each of the three intervention groups (N_g=3).



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Vitamin D supplementation in chronic spinal cord injury (VitD-SCI): study protocol for a randomized controlled trial

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Vitamin D supplementation in chronic spinal cord injury (VitD-SCI): study protocol for a randomized controlled trial

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Keywords: vitamin D insufficiency, vitamin D status, cholecalciferol, paraplegia, tetraplegia, bone health, handgrip strength

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Abstract

Introduction: Vitamin D insufficiency, a vitamin D status or serum 25(OH)D concentration of ≤ 75 nmol/L, is highly prevalent in individuals with a spinal cord injury (SCI). Vitamin D is important for the functioning of the musculoskeletal, immune, and respiratory systems, which are relevant determinants of secondary health conditions in SCI. An insufficiency should be treated with vitamin D supplementation. However, there is a lack of evidence regarding the optimal dosage and duration of vitamin D supplementation for individualized and long-term management of the vitamin D status in the context of SCI. This paper presents the protocol for the vitamin D supplementation in chronic spinal cord injury (VitD-SCI) trial that aims to investigate the effect of a 12-month intake of vitamin D supplementation on vitamin D status as well as on several secondary parameters among individuals with a chronic SCI.

Methods and analyses: The VitD-SCI trial is a randomized, placebo-controlled, double-blinded, parallel-group, superiority trial, conducted at the Swiss Paraplegic Center. A total of 45 participants living with an SCI for at least three years (chronic SCI) and a vitamin D insufficiency at the first study visit, will be randomly assigned to one of three intervention groups. Participants receive either a monthly dosage of 24'000 IU or 48'000 IU vitamin D or a placebo for 12 months. Measurements taking place every three months include the assessment of vitamin D status (primary outcome) as well as bone mineral density, handgrip strength, fatigue, mood, pain, and pressure injuries (secondary outcomes). Safety and tolerance of vitamin D supplementation will also be evaluated.

Ethics and dissemination: The Swiss Ethics Committee for Northwest/Central Switzerland (EKNZ, 2020-01493) and the Swiss Agency for Therapeutic Products (Swissmedic, 2020DR3150) approved this study. Findings will be disseminated through peer-reviewed publications.

Trial registration: ClinicalTrials.gov (NCT04652544) and Swiss National Clinical Trials Portal (SNCTP000004032).

Article Summary

Strengths and limitations of this study

- The longitudinal study design facilitates control for within- and between-person variation in investigating the temporal efficacy of vitamin D supplementation on vitamin D dynamics.
- The recurrent assessment of contextual parameters, including sun exposure and secondary health conditions, for use as time-updated covariates in the data analysis, will further support unbiased inference of the efficacy of vitamin D supplementation.
- The adherence of participants to the protocol cannot be objectively assessed, because of the home-based setting.
- Dietary vitamin D will not be assessed over the study period, which precludes scaling of vitamin D efficacy to between- and within-person variation in nutrition intake.
- For reasons of feasibility, not all supposedly relevant clinical outcomes can be assessed, including respiratory and immune function.

Introduction

A suboptimal vitamin D status is prevalent in up to 93% of individuals with spinal cord injury (SCI) which is excessive compared to up to 40% among the general population.[1 2] This excessive prevalence can be explained by the adverse impact of SCI on physiological functioning, including altered metabolism and gastrointestinal functioning, and lifestyle behaviors, such as reduced physical exercise, outdoor activity, and sun exposure.[1 3] Vitamin D is important for the optimal functioning of the musculoskeletal and respiratory system as well as the regulation of innate and adaptive immune responses.[4-9] Particularly in the context of SCI, a lower vitamin D status has been associated with an elevated risk of respiratory illness, pressure injuries, and depression, as well as poor physical function and bone mineral density.[10-14] Therefore, the prevention of a vitamin D insufficiency, commonly defined as a vitamin D status of 75 nmol/L or less,[15] is of great concern regarding secondary health conditions in SCI.

Vitamin D supplementation is a promising intervention to reduce and prevent a vitamin D insufficiency as well as secondary complications,[2 4 16] yet the provision of such clinical guidelines in the context of SCI is currently hampered by a lack of evidence regarding the efficacy, as well as the optimal dosage and duration of the supplementation.[1 3] For the general non-SCI population (adults aged 19 – 70 years) a dosage of 600 IU – 800 IU/day has been recommended,[17-19] although other experts consider this dosage as suboptimal.[20 21] Among individuals with chronic SCI, a dosage of 800 IU/day for 12 months failed to raise vitamin D status to sufficient levels.[22] Higher dosages of 2000 IU/day[23] or 6000 IU/day[24] during three months appeared more successful, but the respective studies did not investigate the long-term efficacy regarding vitamin D status or the lasting consequences for musculoskeletal and subjective health parameters. Though recommended,[25] vitamin D status is not regularly monitored among the chronic SCI population.

To close this evidence gap, we present the protocol for the vitamin D supplementation in chronic spinal cord injury (VitD-SCI) trial: a placebo-controlled randomized controlled trial that investigates the efficacy of a moderate (24'000 IU/month) and a high (48'000 IU/month) dosage of vitamin D supplementation for 12 months among individuals living with an SCI for at least three years (chronic SCI). Besides vitamin D status (primary objective), further assessments include bone mineral density, fatigue, pain, mood, performance of daily activities, and handgrip strength (secondary objectives). We hypothesize a dose-response effect of vitamin D supplementation on vitamin D status and anticipate that the evidence acquired during this study will effectively inform community-based policy regarding vitamin D supplementation in chronic SCI.

Methods and analyses

Study design and setting

The VitD-SCI trial is a placebo-controlled randomized double-blinded superiority study, evaluating the effect of 12 months of vitamin D supplementation on vitamin D status and several secondary outcomes among individuals with a chronic SCI (Figure 1). This protocol was designed according to the recommendations of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement (Supplement 1).[26] The study is planned to run from May 2021 until May 2023. Study visits take place at the Swiss Paraplegic Centre and participants will receive compensation for travel expenses. The VitD-SCI trial is a nested project of the population-based Swiss Spinal Cord Injury (SwiSCI) cohort study.[27]

Patient and public involvement statement

Patient and public organizations (e.g. SwiSCI), as well as clinicians from several specialized SCI centers, have been involved in the design of the study protocol. Study procedures, including the intervention and assessments, have been discussed and tested together with individuals with SCI.

Participants

The inception cohort of the SwiSCI cohort study (2013-present[28]) provides the sampling frame for participant recruitment for the VitD-SCI trial. Eligible are individuals who provided consent to be contacted for future scientific studies and who fulfill the key VitD-SCI trial inclusion criteria, including a vertebral lesion level of C4 or below and time since SCI of at least 3 years. At present (May 2021), SwiSCI data indicate a sample of over 300 eligible individuals. Among individuals interested in participating, the remaining eligibility criteria (Table 1) will be checked. Women of childbearing age must show a negative pregnancy test at the start of the experimental supplementation and must use adequate contraception during the 12-month treatment phase of the study. Participants are not allowed to take additional vitamin D supplements (> 400 IU/day) or travel to countries with increased sun exposure (below the 37th parallel north) during the study. No further eligibility criteria, such as the completeness or the lesion level, were set, to allow a generalization of the study results as well as to increase the feasibility. The recurrent assessment of contextual parameters for use as time-updated covariates in the data analysis will further support unbiased inference of the temporal efficacy of vitamin D supplementation. Informed consent will be obtained from all participants by qualified study employees (Supplement 2). A blood sample will be taken to determine vitamin D status at the first visit (Month 0). Only individuals with an insufficient vitamin D status (≤ 75 nmol/L) will be randomized into one of the intervention groups.

Intervention

The trial consists of a three-armed intervention that applies a moderate or generally recommended dosage (24'000 IU vitamin D/month), and a high dosage (48'000 IU vitamin D/month) for comparison to placebo. Both dosages are prescribed in clinical practice and are within safe tolerable upper intake levels of 10'000 IU/day.[17 18 20] Previous studies among individuals with SCI implementing even higher dosages of vitamin D supplementation (up to 50'000 IU/week) did not report any safety issues.[23 24 29 30] The present study will further use a biweekly supplementation procedure, which showed superior adherence and accompanying efficacy over daily administration in achieving a sufficient vitamin D status.[31] The biweekly supplementation schedule is supported by vitamin D pharmacokinetics, which indicates a half-life of serum 25(OH)D of up to three weeks.[32]

As vitamin D supplement, the commercially available Vi-De 3® Monthly Dose (Dr. Wild & Co. AG (Muttenz, Switzerland) will be utilized. One vial (5 mL) contains an ethanol solution (65% alcohol by volume) with 600 µg cholecalciferol, which corresponds to 24'000 IU vitamin D_3. The similar ethanol solution without cholecalciferol will be utilized as a placebo. Both the vitamin D_3 supplement as well as the placebo will be filled in identical vials. An independent and specialized pharmacy will label the vials with a number that is indicative of the order of intake but indiscriminate regarding content, making the vials indistinguishable in odor, taste, and visual appearance. The first vial is to be taken within seven days after the first study visit. Participants are instructed to ingest one single vial every two weeks by emptying the vial in a glass of water and immediately drinking the solution. Participants of the high dosage group will take one vial with 24'000 IU vitamin D_3 every two weeks. Similarly, participants of the placebo group will take one vial with placebo every two weeks. Participants of the moderate dosage group will alternately take one vial with 24'000 IU vitamin D_3 or one vial with placebo every two weeks. Thus, an identical number of vials is assured across all intervention groups. The adherence of participants to the protocol cannot be objectively assessed, because the supplement intake occurs at home. To promote compliance with the study protocol, participants will receive a reminder every two weeks to take the vials. Participants will also be requested to keep track of the intake of each vial in a study diary and return all (un)used vials to the study center.

Randomization and blinding

Participants will be randomly allocated on a 1:1:1 ratio into one of the three intervention groups, according to a permuted block randomization list with randomly varying block sizes (3 or 6) created using the module "ralloc" (version 3.7.6[33]) within Stata ([Computer program]. Version 16, College Station, Texas, USA: StataCorp, 2019). The allocation sequence will be securely stored and only accessible to an employee, who is not directly involved in the study. Participants and all study employees directly involved in the recruitment and measurements will be blinded to the assignment

of the intervention until the end of the study ("last participant out"). Parameters, such as blood and bone mineral density parameters, which may reveal the allocation across the intervention groups, will only be available to employees who have no direct involvement in the study.

Outcomes and assessments

Assessment periods and details are specified in Table 2. Assessments are performed during screening or each of the three-monthly visits, except for bone mineral density, which is measured at 0 and 12 months only to reduce radiation exposure. The primary outcome is the differential change in vitamin D status from 0 to 12 months. Transitional vitamin D status will also be evaluated every three months.[21] The recurrent assessment of contributory parameters, including sun exposure and secondary health conditions, provide time-updated information to statistically control for within- and between-person variation in investigating the efficacy of vitamin D supplementation on vitamin D dynamics. To evaluate the secondary effects of vitamin D supplementation on the musculoskeletal system, differential changes in the following secondary outcomes will be assessed: relevant blood parameters (calcium, parathyroid hormone, ionized calcium, phosphate, cystatin, estimated glomerular filtration rate, testosterone), bone mineral density, functional independence, pressure injuries, handgrip strength, and falls. Differential changes in fatigue, mood, and pain will provide insight into the effect of vitamin D supplementation on subjective parameters. Individual parameters, including demographics, SCI characteristics, skin phototype, and sun exposure will also be collected. Furthermore, the occurrence of any new illness, injury or disease together with newly taken medication and supplements will be assessed at each visit. Since nutritional intake of vitamin D only accounts for a limited intake and vitamin D fortification of nutrition in Switzerland is rare,[34] no dietary assessments are planned, which precludes scaling of vitamin D efficacy to between- and within-person variation in nutrition intake. Due to feasibility reasons, no direct measurements of respiratory or immune function will be assessed.

Serious adverse events will be documented throughout the participant's enrollment to evaluate the safety of the supplementation.

Sample size

We defined the minimal sample size as the sample size needed to detect a statistically meaningful difference in the time course of the primary outcome vitamin D status across the three intervention groups. For this, we estimated the sample size needed to detect an interaction between treatment and time across the three intervention groups using the power analysis package for repeated measures in STATA software, version 16.0 (College Station, TX, USA: StataCorp, 2019). The expected mean vitamin D status at each time point was calculated for each intervention group using the generalized pharmacokinetic curve equation of Heaney, et al. (2001),[35] which we parametrized for the purpose of this study using the available data for vitamin D supplementation in chronic SCI.[23 36]

Assuming a significance level of 5% and a power of 0.80, minimal sample sizes were calculated for a range of between-group variances (i.e., 1000 to 3500, with 500 incremental steps) and correlations between repeated measures (i.e., 0.1 to 0.9, with 0.1 incremental steps; Supplement 3). Based on this power analysis for sample size, we conservatively plan for 45 participants with a full dataset, implying 15 participants in each of the three intervention groups. In the case of dropouts or a large amount of missing data for a given participant, recruitment will be continued until the minimal sample size of 15 participants per intervention groups is effectively achieved. Sample size calculation did not take secondary outcome parameters into account. Since long-term studies among the chronic SCI population are rare, this study may inform the minimal sample size needed for future studies targeting the dynamics of secondary outcome parameters in response to vitamin D supplementation.

Data management and analyses

Data management

The web-browser-based system secuTrial® (interActive Systems, Berlin, Germany), which fulfills the Good Clinical Practice requirements, will be used for data capturing and management. This database allows for individualized accounts with pre-defined roles for each study employee and will be hosted by a study-independent data manager. Built-in quality control mechanisms and notification of missing data will reduce errors during data entry. Participants will be assigned a unique identification code and no directly identifiable information is stored in the database.

Analyses of primary and secondary outcomes

An intention-to-treat analysis will be performed to prevent potential bias resulting from the distortion of baseline equivalence after randomization due to the withdrawal of participants, non-adherence to the study protocol, or an unwarranted level of missing data. Participants will only be included in the analyses for which they have data available. Protocol non-adherence, early withdrawals, and loss to follow-up will be characterized and examined. Sensitivity analyses using different populations or participant groupings may be used to examine the robustness of the estimator generated by the intention-to-treat analysis. Any sensitivity analyses added after the breaking of the blind (post-hoc sensitivity analyses), including per-protocol analysis that will contain any participants recruited as a replacement for withdrawals or dropouts, will be clearly identified as such in the trial reporting. Basic univariable statistical analysis techniques will be used to describe the study population as well as the primary and secondary outcomes at the different measurement points. To evaluate the longitudinal variation in the primary outcome and secondary outcomes, multilevel mixed-effects models that appropriately account for the within-and between-individual sources of variance in outcome variation will be used. In these models, participants are treated as random effects, while the treatment group is used as a fixed parameter. The choice of regression model will depend on the error distribution function of the respective outcome parameter. Time-updated covariates will also be used

in regression modeling, for instance, to evaluate the impact of time-varying vitamin D status on the secondary outcomes. Time lags in time-updated covariates will also be evaluated to further detail temporal associations. Non-linear regression modeling will be used to evaluate pharmacokinetic curves for each of the intervention groups as described above. Thus, estimates are derived for the parameters *a* (i.e., change is constant at equilibrium), and *k* (i.e., the rate constant for the proportion of the total mass of 25(OH)D used or metabolized per day) for mutual comparison as well as with estimates from other populations (other SCI populations, general population, or other health-condition groups).

No interim analyses are planned. If severe clinical deterioration is detected in more than one participant, or on the recommendation of the monitoring committee following a serious adverse event, the study will be suspended until a comprehensive safety review has been completed. If the trial is suspended or halted, an interim analysis will be performed.

Handling of missing data and dropouts

When appropriate, multiple imputation will be used to account for missing data.[37] In case the number of dropouts is substantial and systematically related to baseline values of the primary outcome variable, logistic regression modeling will be used to derive inverse probability weights for use in regression modeling to statistically account for potential longitudinal selection bias. Participants who are withdrawn or drop out will be replaced. Sensitivity analysis will be used to address the robustness of the estimators to changes in the assumptions underlying the chosen imputation strategy.

Quality assurance and safety provisions

Minimizing bias and contamination

Trained study employees will execute all of the measurements following a study manual. Measurement devices will be appropriately serviced and calibrated throughout the study. Questionnaires that have been validated among or adapted for the SCI population will be used. The collection of several possible confounders, including sun exposure, season, and SCI level, allows for the correction of these factors. Participants will be asked to express their belief regarding the assigned intervention every three months, which will be used to compute a measure for the extent of successful blinding of the trial.

Potential risks

There are no guidelines regarding upper limits of serum 25(OH)D concentration among the SCI population,[3] although vitamin D toxicity has been reported with levels exceeding 375-750 nmol/L among the general population.[38] Side effects of vitamin D supplementation, resulting from an overdose, are not expected with the selected dosages in this study. Nevertheless, participants are asked about potential side effects and tolerance of the supplement, and relevant blood parameters

will be monitored. Due to the 65% volume alcohol solution, the intake of the supplement and/or placebo could have a minor influence on the ability to drive or operate machines, but similar solutions have been proven harmless.[39] The sum of the radiation exposure for the two bone mineral density measurements in this study is less than the average yearly radiation exposure due to radon in Switzerland and falls well within the dose guidance value for Swiss research projects.[40 41] Serious Adverse Events will be documented and reported to the local authorities for the entire study duration, which encompasses the signing of the informed consent until the completion of the last protocol-specific procedure including a safety follow-up period. A risked-adapted monitoring[42] will be applied and executed by the Clinical Trial Unit of the study center.

Withdrawal criteria

Participants can withdraw from the study at any time, without providing reasoning. Participants might be redrawn from the study in case of protocol non-adherence, the eligibility criteria are no longer fulfilled, or health problems related to the intake of the vitamin D_3 supplement or placebo, including a vitamin D intoxication (serum 25(OH)D concentration > 375 nmol/L) or hypercalcemia (ionized calcium concentration > 3.5 mmol/L).

Unblinding Procedures

The study physician together with the study employees will make study termination and unblinding decisions. Unblinding will only be allowed in the following circumstances; upon study termination, in the case of premature study termination, or in the case of emergencies or complications. An employee not directly involved in the measurements will perform the unblinding of individual participants during the study. Since each participant receives an individual batch of vials, revealing the blinding for one participant will not unblind the entire cohort.

Ethics and dissemination

Ethics approval

This study will be conducted in compliance with the current version of the Declaration of Helsinki[43] and the International Conference on Harmonization Good Clinical Practice guidelines,[44] as well as all national legal and regulatory requirements.[45 46] Both the Swiss Ethics Committee for Northwest/Central Switzerland (EKNZ, 2020-01493) and the Swiss Agency for Therapeutic Products (Swissmedic, 2020DR3150) have approved the study. The study has been registered at ClinicalTrials.gov (NCT04652544). After trial registration, we discovered not all of the secondary and further outcome parameters were mentioned in the registry, the missing outcome parameters were added subsequently. The regulatory authorities will receive safety and interim reports and will be informed about protocol changes and the study end.

Dissemination policy

Results will be published in peer-reviewed journals and presented at scientific conferences. When desired, individual study results will be shared with the participants after the study end. Dissemination among persons with SCI in Switzerland will be achieved through the newsletters "Paraplegie" and "Paracontact" as well as through online media. Data and statistical code will be made available upon request.

Trial status

This publication is based on version 3 of the VitD-SCI trial protocol dated November 9, 2020. The official start of recruitment was on May 19, 2021 and data collection is estimated to end on May 31, 2023. As of the time of submission, temporary interruptions due to the COVID-19 pandemic are a possibility and in case of extended disruption, a schedule adjustment may be required.

Discussion

This is the first study to investigate a 12-month vitamin D supplementation among individuals with a chronic SCI. The existing studies lack the combination of long-term vitamin D supplementation with different dosages, while not only assessing vitamin D status but also secondary outcomes.

The VitD-SCI trial, for which the protocol is presented here, will provide valuable insights to optimize individual vitamin D supplementation. If a positive relation between a sufficient vitamin D status and secondary outcomes can be established, this could lead the way for standardized clinical recommendations for long-term management of vitamin D status and vitamin D supplementation among the chronic SCI population.

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Author contributions

JF is responsible for overseeing the trial. JF, CP, and MB were responsible for the study conception and obtained funding. JF, CP, MB, AS, and AH designed the protocol. AS provided clinical expertise is the study physician and principal investigator. PW provided expertise on bone mineral density. MB provided statistical expertise. AJ provided clinical expertise on blood parameters and analyses. GL provided clinical expertise on pain outcomes. AH, MB and JF prepared the first draft of the manuscript. All authors reviewed and revised the manuscript before submission and approved its content.

Disclosure statement

All authors declare that there are no conflicts of interest, intellectual, financial, or proprietary conflicts.

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References

1. Flueck JL, Perret C. Vitamin D deficiency in individuals with a spinal cord injury: a literature review. *Spinal Cord* 2017;55(5):428-34. doi: 10.1038/sc.2016.155
2. Amrein K, Scherkl M, Hoffmann M, et al. Vitamin D deficiency 2.0: an update on the current status worldwide. *Eur J Clin Nutr* 2020;74(11):1498-513. doi: 10.1038/s41430-020-0558-y
3. Lamarche J, Mailhot G. Vitamin D and spinal cord injury: should we care? *Spinal cord* 2016;54(12):1060-75. doi: 10.1038/sc.2016.131
4. Cranney A, Horsley T, O'Donnell S, et al. Effectiveness and safety of vitamin D in relation to bone health. *Evid Rep Technol Assess* 2007(158):1-235.
5. Ceglia L, Harris SS. Vitamin D and its role in skeletal muscle. *Calcif Tissue Int* 2013;92(2):151-62. doi: 10.1007/s00223-012-9645-y
6. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr* 2008;87(4):1080S-6S. doi: 10.1093/ajcn/87.4.1080S
7. Beard JA, Bearden A, Striker R. Vitamin D and the anti-viral state. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology* 2011;50(3):194-200. doi: 10.1016/j.jcv.2010.12.006 [published Online First: 2011/01/19]
8. Jolliffe DA, Camargo CA, Sluyter JD, et al. Vitamin D supplementation to prevent acute respiratory infections: systematic review and meta-analysis of aggregate data from randomised controlled trials. *medRxiv : the preprint server for health sciences* 2020 doi: 10.1101/2020.07.14.20152728 [published Online First: 2020/12/04]
9. Peterlik M, Cross HS. Vitamin D and calcium insufficiency-related chronic diseases: molecular and cellular pathophysiology. *European Journal of Clinical Nutrition* 2009;63(12):1377-86. doi: 10.1038/ejcn.2009.105
10. Zhou XJ, Vaziri ND, Segal JL, et al. Effects of chronic spinal cord injury and pressure ulcer on 25(OH)-vitamin D levels. *J Am Paraplegia Soc* 1993;16(1):9-13. doi: 10.1080/01952307.1993.11735877
11. Barbonetti A, Sperandio A, Micillo A, et al. Independent association of vitamin D with physical function in people with chronic spinal cord injury. *Arch Phys Med Rehabil* 2016;97(5):726-32. doi: 10.1016/j.apmr.2016.01.002 [published Online First: 2016/01/26]
12. Barbonetti A, Cavallo F, D'Andrea S, et al. Lower vitamin D levels are associated with depression in people with chronic spinal cord injury. *Arch Phys Med Rehabil* 2017;98(5):940-46. doi: 10.1016/j.apmr.2016.11.006 [published Online First: 2016/12/18]
13. Lussi C, Frotzler A, Jenny A, et al. Nutritional blood parameters and nutritional risk screening in patients with spinal cord injury and deep pressure ulcer-a retrospective chart analysis. *Spinal cord* 2018;56(2):168-75. doi: 10.1038/s41393-017-0016-4 [published Online First: 2017/10/23]
14. Clark K, Goldstein RL, Hart JE, et al. Plasma vitamin D, past chest illness, and risk of future chest illness in chronic spinal cord injury (SCI): a longitudinal observational study. *Spinal Cord* 2020;58(4):504-12. doi: 10.1038/s41393-019-0409-7 [published Online First: 2020/01/18]
15. Vieth R. Why the minimum desirable serum 25-hydroxyvitamin D level should be 75 nmol/L (30 ng/ml). *Best Practice & Research: Clinical Endocrinology & Metabolism* 2011;25(4):681-91. doi: 10.1016/j.beem.2011.06.009
16. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2009;169(6):551-61. doi: 10.1001/archinternmed.2008.600 [published Online First: 2009/03/25]
17. Institute of Medicine (IOM). Dietary Reference Intakes for Calcium and Vitamin D. Washington (DC): The National Academies Press 2011.
18. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *The Journal of clinical*

endocrinology and metabolism 2011;96(7):1911-30. doi: 10.1210/jc.2011-0385 [published Online First: 2011/06/08]
19. Deutsche Gesellschaft für Ernährung ÖGfE, Schweizerische Gesellschaft für Ernährungsforschung, Schweizerische Vereinigung für Ernährung (Hrsg.). Referenzwerte für die Nährstoffzufuhr Vitamin D. Neustadt a. d. Weinstraße: Neuer Umschau Buchverlag, 2012:1. Auflage, 4., korrigierter Nachdruck.
20. Hathcock JN, Shao A, Vieth R, et al. Risk assessment for vitamin D. *Am J Clin Nutr* 2007;85(1):6-18. doi: 10.1093/ajcn/85.1.6 [published Online First: 2007/01/09]
21. Vieth R, Chan PC, MacFarlane GD. Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. *Am J Clin Nutr* 2001;73(2):288-94. doi: 10.1093/ajcn/73.2.288 [published Online First: 2001/02/07]
22. Bauman WA, Morrison NG, Spungen AM. Vitamin D replacement therapy in persons with spinal cord injury. *The journal of spinal cord medicine* 2005;28(3):203-7. doi: 10.1080/10790268.2005.11753813 [published Online First: 2005/07/29]
23. Bauman WA, Emmons RR, Cirnigliaro CM, et al. An effective oral vitamin D replacement therapy in persons with spinal cord injury. *The journal of spinal cord medicine* 2011;34(5):455-60. doi: 10.1179/2045772311y.0000000032 [published Online First: 2011/11/29]
24. Flueck JL, Schlaepfer MW, Perret C. Effect of 12-week vitamin D supplementation on 25(OH)D status and performance in athletes with a spinal cord injury. *Nutrients* 2016;8(10) doi: 10.3390/nu8100586 [published Online First: 2016/09/27]
25. Oleson CV, Patel PH, Wuermser LA. Influence of season, ethnicity, and chronicity on vitamin D deficiency in traumatic spinal cord injury. *The journal of spinal cord medicine* 2010;33(3):202-13. doi: 10.1080/10790268.2010.11689697 [published Online First: 2010/08/27]
26. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Annals of internal medicine* 2013;158(3):200-7. doi: 10.7326/0003-4819-158-3-201302050-00583 [published Online First: 2013/01/09]
27. Post MWM, Brinkhof MWG, von Elm E, et al. Design of the Swiss Spinal Cord Injury Cohort Study. *Am J Phys Med Rehabil* 2011;90(11 Suppl 2):S5-S16. doi: 10.1097/PHM.0b013e318230fd41
28. Fekete C, Gurtner B, Kunz S, et al. Inception cohort of the Swiss Spinal Cord Injury Cohort Study (SwiSCI): Design, participant characteristics, response rates and non-response. *J Rehabil Med* 2021;53(2):jrm00159. doi: 10.2340/16501977-2795 [published Online First: 2021/02/12]
29. Amorim S, Teixeira VH, Corredeira R, et al. Creatine or vitamin D supplementation in individuals with a spinal cord injury undergoing resistance training: A double-blinded, randomized pilot trial. *The journal of spinal cord medicine* 2018;41(4):471-78. doi: 10.1080/10790268.2017.1372058 [published Online First: 2017/09/14]
30. Pritchett K, Pritchett RC, Stark L, et al. Effect of Vitamin D Supplementation on 25(OH)D Status in Elite Athletes With Spinal Cord Injury. *Int J Sport Nutr Exerc Metab* 2019;29(1):18-23. doi: 10.1123/ijsnem.2017-0233 [published Online First: 2018/05/15]
31. Dalle Carbonare L, Valenti MT, Del Forno F, et al. Vitamin D: daily vs. monthly use in children and elderly - what is going on? *Nutrients* 2017;9(7) doi: 10.3390/nu9070652 [published Online First: 2017/07/05]
32. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocrine reviews* 2001;22(4):477-501. doi: 10.1210/edrv.22.4.0437 [published Online First: 2001/08/09]
33. RALLOC: Stata module to design randomized controlled trials [program], 2018.
34. Bundesamt für Lebensmittelsicherheit und Veterinärwesen. Fachinformation zu Vitamin D. Bern, 2017.
35. Heaney RP, Davies KM, Chen TC, et al. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr* 2003;77(1):204-10. doi: 10.1093/ajcn/77.1.204

36. Bauman WA, Zhong YG, Schwartz E. Vitamin D deficiency in veterans with chronic spinal cord injury. *Metabolism* 1995;44(12):1612-6. doi: 10.1016/0026-0495(95)90083-7 [published Online First: 1995/12/01]
37. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393. doi: 10.1136/bmj.b2393 [published Online First: 2009/07/01]
38. Jones G. Pharmacokinetics of vitamin D toxicity. *Am J Clin Nutr* 2008;88(2):582S-86S. doi: 10.1093/ajcn/88.2.582S [published Online First: 2008/08/12]
39. Franz E. Vitamin D im Säuglingsalter-alkoholische oder ölige Tropfen? *Pharmajournal* 2007;12:5-7.
40. The Swiss Federal Council. Radiological Protection Ordinance (RPO), 2017.
41. Bundesamt für Gesundheit (BAG). Strahlenexposition der Schweizer Bevölkerung 2018 [updated 28.08.2018. Available from: https://www.bag.admin.ch/bag/de/home/gesund-leben/umwelt-und-gesundheit/strahlung-radioaktivitaet-schall/strahlung-gesundheit/strahlenexposition-der-schweizer-bevoelkerung.html# accessed 29.01.2020.
42. Brosteanu O, Schwarz G, Houben P, et al. Risk-adapted monitoring is not inferior to extensive on-site monitoring: Results of the ADAMON cluster-randomised study. *Clin Trials* 2017;14(6):584-96. doi: 10.1177/1740774517724165 [published Online First: 2017/08/08]
43. World Medical Association (WMA). Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects 1964.
44. Dixon JR. International conference on harmonization good clinical practice guideline. *Quality Assurance* 1999;6(2):65-74. doi: 10.1080/105294199277860
45. The Federal Assembly of the Swiss Confederation. Federal Act on Research involving Human Beings (Human Research Act, HRA), 2011.
46. The Swiss Federal Council. Ordinance on Clinical Trials in Human Research (Clinical Trials Ordinance, ClinO), 2013.
47. Hanwell HEC, Vieth R, Cole DEC, et al. Sun exposure questionnaire predicts circulating 25-hydroxyvitamin D concentrations in Caucasian hospital workers in southern Italy. *J Steroid Biochem Mol Biol* 2010;121(1-2):334-37. doi: 10.1016/j.jsbmb.2010.03.023 [published Online First: 2010/03/16]
48. Fitzpatrick TB. "Soleil et peau" [Sun and skin]. *Journal de Me´decine Esthe´tique (in French),* 1975;2:33–34.
49. Kirshblum SC, Burns SP, Biering-Sorensen F, et al. International standards for neurological classification of spinal cord injury (revised 2011). *The journal of spinal cord medicine* 2011;34(6):535-46. doi: 10.1179/204577211X13207446293695 [published Online First: 2012/02/15]
50. Itzkovich M, Gelernter I, Biering-Sorensen F, et al. The Spinal Cord Independence Measure (SCIM) version III: reliability and validity in a multi-center international study. *Disabil Rehabil* 2007;29(24):1926-33. doi: 10.1080/09638280601046302 [published Online First: 2007/09/14]
51. Brinkhof MWG, Fekete C, Chamberlain JD, et al. Swiss national community survey on functioning after spinal cord injury: Protocol, characteristics of participants and determinants of non-response. *J Rehabil Med* 2016;48(2):120-30. doi: 10.2340/16501977-2050
52. National Pressure Ulcer Advisory Panel EPUAPaPP, Alliance. PI. Prevention and Treatment of Pressure Ulcers: Quick Reference Guide. In: Haesler E, ed. 2019 ed. Osborne Park, Australia: Cambridge Media, 2014.
53. Widerström-Noga E, Biering-Sørensen F, Bryce T, et al. The international spinal cord injury pain basic data set. *Spinal cord* 2008;46(12):818-23. doi: 10.1038/sc.2008.64 [published Online First: 2008/06/03]
54. Kalpakjian CZ, Scelza WM, Forchheimer MB, et al. Preliminary reliability and validity of a Spinal Cord Injury Secondary Conditions Scale. *The journal of spinal cord medicine* 2007;30(2):131-39. doi: 10.1080/10790268.2007.11753924

55. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67(6):361-70. doi: 10.1111/j.1600-0447.1983.tb09716.x [published Online First: 1983/06/01]
56. Krupp LB, LaRocca NG, Muir-Nash J, et al. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;46(10):1121-3. doi: 10.1001/archneur.1989.00520460115022 [published Online First: 1989/10/01]

Figures

Figure 1: Schematic overview of the study flow. The timeline of the study including the assessments is displayed starting from the screening (top of the figure) to the last study visit (bottom of the figure).

A: Study flow.

B: Legend.

Tables

Table 1: Eligibility criteria

Inclusion criteria	Exclusion criteria
• Informed Consent to the study as documented by a signature. • Chronic (> 3 years) traumatic or non-traumatic SCI a vertebral lesion level of C4 or below. • Between 18 - 60 years old. • Wheelchair dependency during activities of daily living, defined by a score of 0-2 in the Spinal Cord Independence Measure (SCIM-III), subsection "Mobility in the house". • An insufficient vitamin D status (≤ 75 nmol/L) at the first visit.	• Contraindications to the investigational product, including known hypersensitivity or allergy to the cholecalciferol or alcohol solution. • Clinically relevant disorders, including renal dysfunction, hepatic dysfunction, cardiovascular disease, lung disease, diabetes, blood disease, parathyroid disease, cancer, depression, alcohol abuse, and/or the intake of significant concomitant medication (including osteoporosis treatment and benzothiadiazide derivatives). This will be assessed on an individual basis. • Grade 3 or 4 pressure injuries. • Women who are pregnant or planning to become pregnant during the study period. • Women who are breastfeeding. • Fractures in both arms and/or both legs within the last five years. • Intake of > 400 IU/day vitamin D supplementation during the last 12 months before recruitment or during the study. • Visiting a country with increased sun exposure (below the 37th parallel north, i.e. the southern hemisphere) within one month before enrollment or during the study. • Inability to understand or decide on study participation (i.e. make an informed consent) and to adhere to the study protocol, for example, due to language or psychological problems.

Table 2: Tools, parameters, and timing of the study measurements.

Assessment tool	Parameter	Assessment periods
Differential changes in blood parameters (sample taken from the antecubital vein)		
Electrochemiluminescence immunoassay (ECLIA)	25(OH)D (nmol/L)	0M, 3M, 6M, 12M
Photometry - NM-BAPTA	Calcium (mmol/L)	0M, 3M, 6M, 12M
Potentiometry with ion-selective electrodes	Ionized calcium (mmol/L)	0M, 3M, 6M, 12M
Chemiluminescence immunoassay (CLIA)	Parathyroid hormone (ng/L)	0M, 3M, 6M, 12M
Photometry - Molybdate UV	Phosphate (mmol/L)	0M, 3M, 6M, 12M
Photometry - particle-enhanced turbidimetric immunoassay	Cystatin C (mg/L)	0M, 3M, 6M, 12M
Estimated from cystatin C following CKD-EPI and Grubb	Estimated glomerular filtration rate (eGFR) (mL/min)	0M, 3M, 6M, 12M
Chemiluminescent immunoassay (CLIA)	Testosterone (ng/dL)	0M, 3M, 6M, 12M
Differential changes in personal characteristics		
Body mass index (BMI)	From weight and height (kg/m²)	0M, 3M, 6M, 12M
Sun exposure based on Hanwell et al (2010)[47]	Time spent outdoors (min) with level of exposed skin*	0M, 3M, 6M, 12M
Physical activity	Sport per week (hours and frequency)	0M, 3M, 6M, 12M
Medication and supplements	Sort and dosage (supplements only)	0M, 3M, 6M, 12M
Further illnesses	Incidence since last measurement	0M, 3M, 6M, 12M
Skin phototype on the posterior forearm based on Fitzpatrick (1975)[48]	Six categories ranging from light to very dark skin types	Screening
SCI characteristics	Time since SCI (years), neurological level of injury (NLI),[49] the degree of impairment following the American Spinal Injury Association (ASIA) Impairment Scale (AIS)[49]	Screening
Differential changes in bone mineral density		
X-ray densitometry (DXA), Lunar iDXA Serie with enCORE v17 Software	T-scores for the forearm (radius), hip (femoral neck), and knee (distal femur and proximal tibia)	0M, 12M
Differential changes in functional independence		
Spinal Cord Independence Measure (SCIM) III[50]	Self-care subscore (0-20), respiration and sphincter management subscore (0-40), indoor mobility subscore (0-10), outdoor mobility subscore (0-30), total score (0-100)	0M, 3M, 6M, 12M
Differential changes in urinary tract infections		
Exact questions of the first-wave questionnaire of the Swiss Spinal Cord Injury (SwiSCI) survey[27 51]	Incidence since the last measurement, medical care required	0M, 3M, 6M, 12M
Differential changes in pressure injuries		
Exact questions of the first-wave questionnaire of the SwiSCI survey[27 51]	Localization and grade following the European and United States National Pressure Ulcer Advisory panels (EPUAP and NPUAP) classification[52]	0M, 3M, 6M, 12M
Differential changes in pain		
Exact questions of the first- and second-wave questionnaire of the SwisSCI survey,[27 51] based on the International SCI Pain Basic Data Set[53] as well as the SCI Secondary Conditions Scale[54]	The occurrence, kind, location, and influence of pain during the last week as well as chronic pain (> 3 months)	0M, 3M, 6M, 12M
Differential changes in strength		
Jamar Smart Hand Dynamometer (Patterson Medical, Warrenville, IL)	Three measurements of the left and right hand (mean kg)	0M, 3M, 6M, 12M
Differential changes in mood		

Hospital Anxiety and Depression Scale (HADS)[55]	Total score (14-56)	0M, 3M, 6M, 12M
Differential changes in fatigue		
Fatigue Severity Scale (FSS)[56]	Total score (9-63)	0M, 3M, 6M, 12M
Differential changes in falls		
Occurrence	Incidence since last measurement, reason daily activity, sport or accident) and medical care required	0M, 3M, 6M, 12M
Safety of the Investigational Medical Products		
Serious adverse events	The occurrence of life-threatening medical complications, the requirement of hospitalization.	Any time
Side-effects, tolerability, and adherence	Number of and reason for missed intake, side-effects	0M, 3M, 6M, 12M

Assessment periods are referenced to the date of the first visit (0M) and include screening (Screening; max 30 days before 0M), 3-month follow-up (3M; 90 ± 7 days), 6-month follow-up (6M; 180 ± 7 days) and 12-month follow-up (12M; 365 ± 7 days). Serious adverse events are continuously evaluated.

* Level of exposed skin: 1) hands and face, 2) hands, face, and arms, 3) hands, face, and legs, 4) entire body (bathing suit).

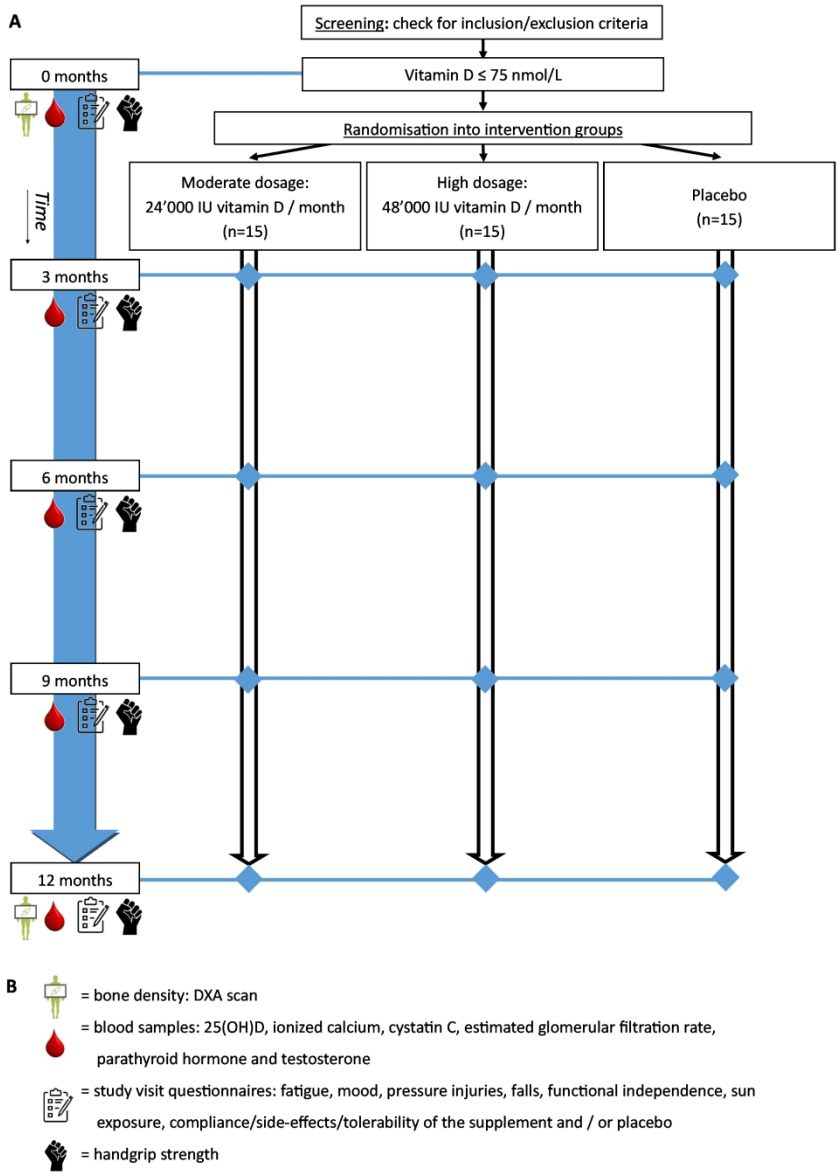

Figure 1: Schematic overview of the study flow. The timeline of the study including the assessments is displayed starting from the screening (top of the figure) to the last study visit (bottom of the figure). A: Study flow. B: Legend.

Supplement 1: SPIRIT Checklist for the Vitamin D Supplementation in Chronic Spinal Cord Injury (VitD-SCI) trial protocol

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section / item	Item No	Description, addressed	Addressed in section
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title, page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract - Trial registration, page 2; Ethics and dissemination - Ethics approval, page 10
	2b	All items from the World Health Organization Trial Registration Data Set	Throughout the paper, pages 1-20; publicly accessible information on ClinicalTrials.gov (NCT04652544)
Protocol version	3	Date and version identifier	Ethics and dissemination - Trial Status, page 11
Funding	4	Sources and types of financial, material, and other support	Funding statement, page 12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page, page 1; Author contributions, page 12
	5b	Name and contact information for the trial sponsor	Title page - Corresponding author, page 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Funding statement, page 12; Author contributions, page 12
	5d	Composition, roles, and responsibilities of the coordinating center, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Methods and analyses - Potential risks, page 9; Author contributions, page 12
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Introduction, page 4; Methods and analyses - Intervention, page 6

	6b	Explanation for choice of comparators	Introduction, page 4; Methods and analyses - Intervention, page 6
Objectives	7	Specific objectives or hypotheses	Introduction, page 4
Trial design	8	Description of trial design including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, non-inferiority, exploratory)	Methods and analyses - Study design and setting, page 5; Randomization and blinding, page 6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Methods and analyses - Study design and setting, page 5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (e.g., surgeons, psychotherapists)	Methods and analyses - Participants, page 5; Table 1, page 18
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Methods and analyses - Intervention, page 6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)	Methods and analyses - Intervention, page 6; Withdrawal criteria, page 10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)	Methods and analyses - Intervention, page 6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Methods and analyses - Participants, page 5; Table 1, page 18
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Methods and analyses - Outcomes and assessments, page 7; Table 2, page 19
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Methods and analyses - Study design and setting, page 5; Intervention, page 6; Outcomes and assessments, page 7; Figure 1; Table 2, page 19
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Methods and analyses - Sample Size, page 7; Supplement 2
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Methods and analyses - Participants, page 5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	Methods and analyses - Randomization and blinding, page 6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Methods and analyses - Randomization and blinding, page 6
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions	Methods and analyses - Participants, page 5; Randomization and blinding, page 6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how	Methods and analyses - Intervention, page 6; Randomization and blinding, page 6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Methods and analyses - Unblinding procedures, page 10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Methods and analyses - Outcomes and assessments, page 7; Data management and analyses, page 8; Minimizing bias and contamination, page 9; Table 2, page 19
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Methods and analyses - Intervention, page 6; Analyses of primary and secondary outcomes, page 8
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Methods and analyses - Data management, page 8
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Methods and analyses - Analyses of primary and secondary outcomes, page 8
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	Methods and analyses - Analyses of primary and secondary outcomes, page 8
	20c	Definition of analysis population relating to protocol non-adherence (e.g., as randomized analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	Methods and analyses - Analyses of primary and secondary outcomes, page 8; Handling of missing data and dropouts, page 9
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	There is a monitoring committee responsible for general trial conduct as well as data concerns. Methods and analyses - Potential risks, page 9
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Methods and analyses - Analyses of primary and secondary outcomes, page 8; Unblinding procedures, page 10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Methods and analyses - Outcomes and assessments, page 7; Minimizing bias and contamination; page 9, Potential risks, page 9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Methods and analyses - Potential risks, page 9
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Abstract - Trial registration, page 2; Ethics and dissemination - Ethics approval, page 10
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Ethics and dissemination - Ethics approval, page 10. Study participants will receive a letter with updates.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32)	Methods and analyses - Participants, page 5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Methods and analyses - Data management, page 8; Ethics and dissemination - Dissemination policy, page 11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Disclosure statement, page 12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Ethics and dissemination - Dissemination policy, page 11; Funding statement, page 12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Due to the low-risks, the need to compensate for suffered harm is not foreseen (Methods and analyses - Potential risks, page 9). Though study insurance is in place in case any care needs to be covered.

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Ethics and dissemination - Dissemination policy, page 11
	31b	Authorship eligibility guidelines and any intended use of professional writers	Ethics and dissemination - Dissemination policy, page 11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Ethics and dissemination - Dissemination policy, page 11
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	Supplement 3
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Methods and analyses - Outcomes and assessments, page 7; Table 2, page 19

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Supplement 2: Participant information and informed consent form.

Schweizer Paraplegiker Zentrum | Centre suisse des paraplégiques | Centro svizzero per paraplegici | Swiss Paraplegic Centre

Vitamin-D-Supplementierung bei Personen mit einer chronischen Querschnittlähmung *(Vitamin D supplementation in individuals with a chronic spinal cord injury – a placebo-controlled randomized double-blinded study)*

Sehr geehrte Dame, sehr geehrter Herr,

Wir möchten Sie anfragen, ob Sie an einer klinischen Studie teilnehmen wollen. Im Folgenden wird Ihnen dieses Studienvorhaben dargestellt: Zunächst in einer kurzen Zusammenfassung, damit Sie wissen, um was es geht, anschliessend in einer detaillierten Beschreibung.

Zusammenfassung

1	**Ziel der Studie** Diese Studie untersucht den Einfluss einer zwölfmonatigen Vitamin-D-Supplementierung (Glossar, Seite 8) auf den Vitamin-D-Spiegel von Personen mit einer chronischen Querschnittlähmung.
2	**Auswahl** Wir suchen Personen im Alter von 18 bis 60 Jahren mit einer chronischen sub-C4 Querschnittlähmung (d.h. drei oder mehr Jahre sind seit der Diagnose vergangen und die Läsionshöhe ist unterhalb C4), die im Alltag auf einen Rollstuhl angewiesen sind.
3	**Allgemeine Informationen zur Studie** Dies ist eine doppelblinde, randomisierte, Placebo-kontrollierte, klinische Studie (Glossar, Seite 8). Diese Studie wird organisiert durch das Schweizer Paraplegiker-Zentrum (SPZ), mit Dr. sc. nat. Joëlle Flück als Studienleiterin (Sponsor-Investigator). Studienteilnehmende mit einem ausreichenden Vitamin-D-Spiegel zu Beginn der Studie werden der natürliche Zeitverlaufgruppe zugeordnet und erhalten keine Supplementierung. Studienteilnehmende, bei welchen zu Beginn der Studie ein Vitamin-D-Mangel diagnostiziert wurde, werden zufällig ("randomisiert") einer der drei Interventionsgruppen zugeordnet. Diese Studienteilnehmenden bekommen entweder eine "niedrige" Vitamin-D-Dosierung (24'000 IE/Monat), eine "hohe" Vitamin-D-Dosierung (48'000 IE/Monat) oder ein Placebo. Als Supplement wird das handelsübliche Vi-De 3® Monatsdosis (Glossar, Seite 8) von Dr. Wild & Co. AG abgegeben. Das Placebo enthält die gleiche alkoholische Lösung (5 mL) wie das Supplement, aber ohne Wirkstoff. Pro Gruppe haben wir geplant 15 Studienteilnehmende zu untersuchen, was zu einer Gesamtzahl von 60 Studienteilnehmenden führt.
4	**Ablauf** Mittels einer Blutanalyse während der ersten Studienvisite wird Ihr Vitamin-D-Spiegel bestimmt. Studienteilnehmende mit einem ausreichenden Vitamin-D-Spiegel werden der natürliche Zeitverlaufgruppe zugeordnet und erhalten keine Supplementierung. Studienteilnehmende mit einem Vitamin-D-Mangel werden zufällig einer der drei Interventionsgruppen zugeordnet. Das Supplement bzw. das Placebo sollen alle zwei Wochen über 12 Monate eingenommen werden. Erst nach Studienabschluss werden Sie, sowie auch die Studienmitarbeiter, herausfinden, in welche der Interventionsgruppen Sie zugeordnet waren. Abhängig von der Gruppe, in der Sie sich befinden, umfasst die Studie drei (natürliche Zeitverlaufgruppe) oder fünf (Interventionsgruppen) Studienvisiten von 1.5 bis 2.0 Stunden im SPZ. Während den Studienvisiten werden folgende Messungen durchgeführt: Knochendichte, Blutentnahme, Handkraft sowie Ausfüllen verschiedener Fragebögen.

5	**Nutzen** Bei allen Studienteilnehmenden werden der Vitamin-D-Spiegel sowie alle weiteren Messwerte regelmässig überprüft. Werden Sie in einer der Interventionsgruppen eingeteilt und bekommen Sie das Vitamin-D-Supplement, wird Ihr Vitamin-D-Mangel mit grosser Wahrscheinlichkeit während der Studie behoben. Sofern Studienteilnehmende dies wünschen, werden die individuellen Studienresultate nach Beendigung der gesamten Studie zusammengestellt und besprochen. Dies könnte genutzt werden, um später die Vitamin-D-Supplementation individuell zu optimieren und auf die eigenen Bedürfnisse anzupassen. Wir erhoffen uns, dass wir anhand der gewonnen Erkenntnisse dieser Studie, die Richtlinien zur Verabreichung von Vitamin D bei Querschnittgelähmten verbessern können.
6	**Rechte** Sie entscheiden freiwillig, ob Sie an der Studie teilnehmen wollen oder nicht. Ihre Entscheidung hat keinen Einfluss auf Ihre medizinische Behandlung und Sie müssen diese Entscheidung nicht begründen.
7	**Pflichten** Wenn Sie bei der Studie mitmachen, müssen Sie bestimmte Regeln beachten. Dies ist notwendig für Ihre Sicherheit und Gesundheit. Wir werden Sie dabei so gut wie möglich unterstützen. Als Studienteilnehmende sind Sie unter anderem verpflichtet, den (medizinischen) Anweisungen der Studienmitarbeiter zu folgen und sich an den Studienplan (z.B. Einnahme des Supplements) zu halten.
8	**Risiken** Das Risiko dieser Studie ist minimal. Die Messungen werden von spezialisierten Mitarbeitern durchgeführt. Ausserdem sind im SPZ sind alle notwendigen Sicherheitsmassnahmen vorhanden.
9	**Andere Behandlungsmöglichkeiten** Sie müssen bei dieser Studie nicht teilnehmen. Neben Vitamin-D-Supplementen, welche rezeptfreigekauft werden können, könnte auch Sonnenexposition dazu beitragen, Ihren Vitamin-D-Spiegel zu verbessern.
10	**Ergebnisse** Bei Studienergebnissen und Zufallsbefunden während der Studie werden Sie informiert, wenn diese Ergebnisse für Sie gesundheitlich wichtig sind. Falls Sie dies nicht möchten, informieren Sie bitte einen Studienmitarbeiter.
11	**Vertraulichkeit von Daten und Proben** Wir halten alle gesetzlichen Regeln des Datenschutzes ein und alle Beteiligten unterliegen der Schweigepflicht. Ihre persönlichen und medizinischen Daten sowie Ihre Proben werden verschlüsselt verwendet. Die Daten und Proben werden nur für andere Forschungsprojekte weiter verwendet, wenn Sie Ihr separates Einverständnis dafür geben.
12	**Rücktritt** Sie können jederzeit von der Studie zurücktreten und nicht mehr teilnehmen. Die bis dahin erhobenen Daten und Proben werden noch ausgewertet, weil das ganze Projekt sonst seinen Wert verliert.
13	**Entschädigung** Alle Studienteilnehmenden bekommen eine Reisespesenentschädigung. Sie erhalten zusätzlich keine weitere finanzielle Entschädigung.
14	**Haftung** Die Studienversicherung des SPZ (Basler Versicherungen) kommt für Schäden im Rahmen der Studie auf.

15	**Finanzierung** Die Studie wird von der SPZ und Schweizer Paraplegiker-Stiftung bezahlt.
16	**Kontaktperson** Dr. Anneke Hertig-Godeschalk Studienkoordinatorin anneke.hertig@paraplegie.ch +41 41 939 66 03 Sportmedizin, SPZ Guido A. Zäch-Strasse 1 6207 Nottwil

Studieninformation

1. Ziel der Studie

Wir wollen mit dieser Studie den Einfluss einer zwölfmonatigen Vitamin-D-Supplementierung (Glossar, Seite 8) auf den Vitamin-D-Spiegel von Personen mit einer chronischen Querschnittlähmung untersuchen. Nebst dem Vitamin-D-Spiegel im Blut, werden auch diverse weitere physische und psychische Messwerte untersucht. Diese Studie soll dazu beitragen, Querschnittgelähmte optimal bezüglich einer Vitamin-D-Supplementation zu beraten.

2. Auswahl

Es können alle Personen teilnehmen, die eine chronische sub-C4 Querschnittlähmung haben (d.h. drei oder mehr Jahre sind seit der Diagnose vergangen und die Läsionshöhe ist unterhalb C4) und im Alltag auf einen Rollstuhl angewiesen sind. Ausserdem müssen Sie zwischen 18 und 60 Jahre alt und ansonsten gesund sein. Falls Sie an einer bekannten Resorptionsstörung, Erkrankung der Schilddrüse oder Niereninsuffizienz leiden, dürfen Sie nicht an der Studie teilnehmen. Sie sollten in den letzten 12 Monaten vor Einschluss in die Studie keine Vitamin-D-Supplemente zu sich genommen haben. Sollten Sie sich im letzten Monat auf der südlichen Halbkugel aufgehalten haben, also z.B. in Süd-Afrika, Australien, Mittel- oder Südamerika, oder sollten Sie einen solchen Aufenthalt im Zeitraum der Studie geplant haben, können Sie nicht teilnehmen. Frauen, die schwanger sind oder stillen, werden aus Sicherheitsgründen von einer Teilnahme ausgeschlossen.

3. Allgemeine Informationen

Ein Vitamin-D-Mangel wird mit verschiedenen gesundheitlichen Risiken, unter anderem einer verminderten Muskelfunktion sowie einem vermehrten Auftreten von Depressionen in Verbindung gebracht. Unter Querschnittgelähmten ist ein Vitamin-D-Mangel sehr stark verbreitet. Eine Supplementierung mit Vitamin D kann zu einem optimalen Vitamin-D-Spiegel führen, doch nur wenn eine ausreichende Dosierung verabreicht wird. Erkenntnisse zu diesem Thema liegen bis jetzt nur aus Studien mit Fussgängern vor, welche aufgrund verschiedener körperlicher Unterschiede, beispielsweise bei der Verdauung und der Körperzusammensetzung, nicht immer eins zu eins auf Querschnittgelähmte übertragen werden können. Ausserdem sind die wenigen Studien, die es im Bereich Querschnittlähmung dazu gibt, in ihre Aussagekraft eingeschränkt: Sie laufen meistens nur über eine kurze Zeit und beziehen sich auf eine begrenzte Anzahl von Messwerten.

In der aktuellen Studie werden wir den Effekt einer Vitamin-D-Supplementierung über 12 Monate untersuchen. Dies ist eine doppelblinde, randomisierte, Placebo-kontrollierte, klinische Studie (Glossar, Seite 8), die im SPZ durchgeführt wird. Studienteilnehmende mit einem ausreichenden Vitamin-D-Spiegel zu Beginn der Studie werden der natürliche Zeitverlaufgruppe zugeordnet und erhalten keine Supplementierung. Studienteilnehmende, bei welchen zu Beginn der Studie ein Mangel an Vitamin D diagnostiziert wurde, werden zufällig ("randomisiert") auf die drei Interventionsgruppen verteilt. Diese Studienteilnehmenden bekommen entweder eine "niedrige" Vitamin-D-Dosierung (24'000 IE/Monat), eine "hohe" Vitamin-D-Dosierung (48'000 IE/Monat) oder ein Placebo. Als Supplement wird das handelsübliche Vi-De 3® Monatsdosis (Glossar, Seite 8) von Dr. Wild & Co. AG abgegeben. Vi-De 3® Monatsdosis ist eine 5 mL alkoholische Lösung mit Mono-Vitamin D3. Die vorgeschlagenen Dosierungen sind im Rahmen der Supplementierungs-Richtlinien (600 bis 2000 IE/Tag), übersteigen die höchst tolerierte Tagesdosis (10‘000 IE/Tag) nicht und sind weit unter der Schwelle, welche zu einer Vergiftung führen kann (40’000 bis 100’000 IE/Tag über 1-2 Monate). Die Placebo-Gruppe erhält die gleiche alkoholische Lösung (5 mL) wie die Interventionsgruppen, aber ohne Wirkstoff.

Das Vitamin D bzw. das Placebo soll alle zwei Wochen über 12 Monate, aufgelöst in einem Glas Wasser, eingenommen werden. Pro Gruppe haben wir geplant, 15 Studienteilnehmende zu untersuchen, was zu einer Gesamtzahl von 60 Studienteilnehmenden führt.
Wir machen diese Studie so, wie es die Gesetze in der Schweiz vorschreiben. Ausserdem beachten wir alle international anerkannten Richtlinien. Die zuständige Kantonale Ethikkommission und Swissmedic haben die Studie geprüft und bewilligt. Eine Beschreibung dieser Studie finden Sie auch auf der Internetseite des Bundesamtes für Gesundheit (www.kofam.ch, Registriernummer: SNCTP000004032) sowie unter www.clinicaltrials.gov (Registriernummer: NCT04652544).

4. Ablauf

Im Rahmen des Screening-Termins (telefonisch oder im SPZ) werden wir überprüfen, ob Sie die Ein- und Ausschlusskriterien erfüllen. Bei gebärfähigen Frauen wird ein Urin-Schwangerschaftstest durchgeführt und während der Studie eine Schwangerschaftsverhütung verlangt. Falls Sie alle Kriterien erfüllen und Sie sich zu einer Studienteilnahme entscheiden, werden wir Ihnen weitere Studieninformationen und die Einverständniserklärung zustellen, welche Sie bei der ersten Studienvisite unterschrieben zurückbringen müssen. Mittels einer Blutanalyse während der erste Studienvisite wird Ihr Vitamin-D-Spiegel bestimmt. Bei einem ausreichenden Vitamin-D-Spiegel zu Beginn der Studie werden Sie der natürliche Zeitverlaufflgruppe zugeordnet und erhalten keine Supplementierung. Bei einem Vitamin-D-Mangel zu Beginn der Studie werden Sie zufällig einer der drei Interventionsgruppen zugeordnet und erhalten entweder eine "niedrige" Vitamin-D-Dosierung, eine "hohe" Vitamin-D-Dosierung oder ein Placebo. Erst nach Studienabschluss werden Sie, sowie auch die Studienmitarbeiter, herausfinden, in welche der Interventionsgruppen Sie zugeordnet waren. Die Einnahme des Supplements, müssen Sie mittels einem Tagebuch dokumentieren. Abhängig von der Gruppe, in der Sie sich befinden, umfasst die Studie drei (natürliche Zeitverlaufgruppe) oder fünf (Interventionsgruppen) Studienvisiten von 1.5 bis 2.0 Stunden im SPZ, während denen die folgenden Messungen durchgeführt werden:

- Knochendichte mittels DXA ("dual energy X-ray absorptiometry"). DXA ist eine spezielle Art der Röntgenuntersuchung. Die Messung dauert nur wenige Minuten, ist absolut schmerzfrei und nur mit einer sehr geringen Strahlenbelastung verbunden. Messungen des Unterarms, der Hüfte und des Knies werden nur bei der ersten und letzten Visite durchgeführt.
- Blutentnahme (15 mL venös in Armbeuge) zur Bestimmung von u.a. Vitamin-D- und Kalzium- Werten.
- Handkraft wird an beiden Händen mit einem Dynamometer (Handkraftmesser) gemessen. Das Messgerät besteht aus einem Griff und einem Belastungsmesser, der während der Messung so kräftig wie möglich zusammenzugedrückt werden sollte. Diese Messung wird nur unter Studienteilnehmende durchgeführt, die sie erfolgreich machen können, also unter Studienteilnehmende die von der Lähmungshöhe her über eine entsprechende Handfunktion verfügen.
- Verschiedene weiteren Messwerte (Stürze, Schmerzen, Stimmung, Sonneneinstrahlung) werden mittels Fragebögen erhoben.

Daneben wird unter den Studienteilnehmenden der Interventionsgruppen jeden Monat telefonisch oder via E-Mail eine 15-minütige Befragung zur Überprüfung der Einnahme und der Verträglichkeit des Supplements durchgeführt.
Es kann sein, dass wir Sie von der Studie vorzeitig ausschliessen müssen. Das kann zum Beispiel geschehen, wenn Ihr Vitamin-D-Spiegel eine Obergrenze (> 375 nmol/L) überschreitet. In diesem Fall werden Sie zu Ihrer Sicherheit abschliessend noch einmal untersucht. Bitte bringen Sie dann alle Produkte, die wir Ihnen gegeben haben, zu uns zurück.

5. Nutzen

Bei allen Studienteilnehmenden werden der Vitamin-D-Spiegel sowie weitere Messwerte regelmässig überprüft. Nach Abschluss der Studie kann man Rückschlüsse ziehen, ob bei einer Supplementation die gemessenen Werte besser sind. Werden Sie in eine der Interventionsgruppen eingeteilt und bekommen Sie das Vitamin-D-Supplement, wird Ihr Vitamin-D-Mangel mit grosser Wahrscheinlichkeit während der Studie behoben. Sofern Studienteilnehmende dies wünschen, werden die individuellen Studienresultate nach Beendigung der gesamten Studie zusammengestellt und besprochen. Dies könnte genutzt werden, um später die Vitamin-D-Supplementation individuell zu optimieren und auf die eigenen Bedürfnisse anzupassen.
Wir erhoffen uns, dass wir anhand der gewonnen Erkenntnisse dieser Studie, die Richtlinien zur Verabreichung von Vitamin D bei Querschnittgelähmten verbessern können.

6. Rechte

Sie nehmen freiwillig teil. Wenn Sie nicht mitmachen oder später Ihre Teilnahme zurückziehen wollen, müssen Sie dies nicht begründen. Ihre medizinische Behandlung/Betreuung ist unabhängig von Ihrem Entscheid gewährleistet. Sie dürfen jederzeit Fragen zur Studienteilnahme sowie zur Studie selber stellen. Wenden Sie sich dazu bitte an eine der Personen, die am Ende dieser Information genannt ist.

7. Pflichten

Wenn Sie bei der Studie mitmachen, müssen Sie bestimmte Regeln beachten. Dies ist notwendig für Ihre Sicherheit und Gesundheit. Wir werden Sie dabei so gut wie möglich unterstützen. Als Studienteilnehmende sind Sie verpflichtet:

- den (medizinischen) Anweisungen der Studienmitarbeiter zu folgen und sich an den Studienplan (z.B. Einnahme des Supplements) zu halten.
- uns mitzuteilen, wenn sich ihre Pläne bezüglich eines Auslandaufenthalts auf der südlichen Halbkugel (z. B: Mittel- oder Südafrika, Mittel- oder Südamerika, Australien) während der Studienzeit ändern.
- uns über das Vorhandensein/den Verlauf einer allfälligen Erkrankung und über neue Symptome, neue Beschwerden und Änderungen im Befinden (auch nach Studienende/-abbruch, bis die unerwünschte Wirkung abklingt) zu informieren.
- uns über die gleichzeitige Behandlung und Therapien bei einem anderen Arzt und über die Einnahme von Medikamenten zu informieren. Nennen Sie dabei bitte alle Medikamente, d. h. auch solche, die Sie selbst gekauft haben, für die Sie kein Rezept brauchen sowie Medikamente der Alternativmedizin.
- uns mitzuteilen, wenn Sie während der Studie oder innerhalb von 30 Tage nach Studienende Schwanger wurden.

Bitte bringen Sie, wenn Sie zu einer Studienvisite ins SPZ kommen, alle Packungen des Supplements mit, die wir Ihnen gegeben haben. Damit gemeint sind einerseits die leeren, andererseits aber auch die eventuell noch vollen Packungen.
Wenn Sie die Pflichten nicht beachten, können Sie Haftungsansprüche verlieren.

8. Risiken und Belastungen für die Studienteilnehmende

Die Messungen werden von spezialisierten Mitarbeitern durchgeführt. Ausserdem sind im SPZ alle notwendigen Sicherheitsmassnahmen vorhanden.
Das Vitamin-D-Supplement sowie das Placebo enthalten eine alkoholische Lösung (65 Volumenprozent Ethanol), was einen geringen Einfluss auf die Fahrtüchtigkeit oder die Fähigkeit, Maschinen zu bedienen, haben kann. Vitamin D ist in grossen Mengen giftig. Die höchste Dosierung in unserer Studie übersteigt die höchste tolerierte Tagesdosis nicht und ist weit unter der Schwelle, welche zu einer Vergiftung führen kann. Bei unserer Dosierung sind somit keinerlei Nebenwirkungen zu erwarten. Mittels der Blutuntersuchung werden wir Ihren Vitamin-D-Spiegel während der ganzen Studie beobachten. Bitte wenden Sie sich an einen Studienmitarbeiter, falls Sie eines der folgenden Anzeichen einer Vitamin-D-Überdosierung bemerken: Übelkeit, Erbrechen, Durchfall, Verstopfung, Anorexie, Müdigkeit, Kopfschmerzen, Muskel- und Gelenkschmerzen, Muskelschwäche oder Schläfrigkeit. Wenn Sie in die Placebo-Gruppe zugeordnet werden, wird Ihr Vitamin-D-Mangel mit
grosser Wahrscheinlichkeit bis am Ende der Studie weiterexistieren. Dies birgt aber keine zusätzlichen Risiken im Vergleich zur Situation vor der Studienteilnahme.
Durch die Blutentnahme in der Armbeuge können lokal leichte Entzündungen auftreten. Durch die Messung der Knochendichte am Unterarm (0.010 mSv), an der Hüfte (0.146 mSv) und am Knie (0.034 mSv) werden Sie einer minimalen Röntgenstrahlung ausgesetzt (2 Messungen x 0.190 = 0.380 mSv). Im Vergleich dazu beträgt die jährlichen radioaktiven Strahlenlast für die Schweizer Bevölkerung durch Radon durchschnittlich 3.200 mSv. Sollten Sie während der Studie schwanger werden, müssen Sie die Studienmitarbeiter sofort informieren und dürfen nicht weiter an der Studie teilnehmen.

9. Andere Behandlungsmöglichkeiten

Sie müssen bei dieser Studie nicht teilnehmen. Neben Vitamin-D-Supplementen, welche rezeptfrei gekauft werden können, könnte auch Sonnenexposition dazu beitragen, Ihren Vitamin-D-Spiegel zu verbessern.

10. Ergebnisse aus der Studie

Die Studienmitarbeiter werden Sie während der Studie über alle neuen Erkenntnisse informieren, die den Nutzen der Studie oder Ihre Sicherheit und somit Ihr Einwilligung zur Teilnahme an der Studie beeinflussen können. Sie werden die Informationen mündlich und schriftlich erhalten.
Bei Zufallsbefunden, die bei Ihnen zur Verhinderung, Feststellung und Behandlung bestehender oder künftig zu erwartender Krankheiten beitragen können, werden Sie informiert. Wenn Sie nicht informiert werden wollen, sprechen Sie bitte mit einem Studienmitarbeiter.

11. Vertraulichkeit der Daten und Proben

Für diese Studie werden Ihre persönlichen und medizinischen Daten erfasst. Nur sehr wenige Fachpersonen werden Ihre unverschlüsselten Daten sehen, und zwar ausschliesslich, um Aufgaben im Rahmen der Studie zu erfüllen. Bei der Datenerhebung zu Studienzwecken werden die Daten verschlüsselt. Verschlüsselung bedeutet, dass alle Bezugsdaten, die Sie identifizieren könnten (Name, Geburtsjahr), gelöscht und durch einen Schlüssel ersetzt werden. Die Schlüssel-Liste bleibt immer im SPZ. Diejenigen Personen, die den Schlüssel nicht kennen, können daher keine Rückschlüsse auf Ihre Person ziehen. Ihr Name taucht niemals im Internet oder einer Publikation auf. Manchmal gibt es die Vorgabe bei einer Zeitschrift zur Publikation, dass Einzel-Daten (sogenannte Roh-Daten) übermittelt werden müssen. Wenn Einzel-Daten übermittelt werden müssen, dann sind die Daten immer verschlüsselt und somit ebenfalls nicht zu Ihnen als Person rückverfolgbar. Bei einer Publikation sind die zusammengefassten Daten daher auch nicht auf Sie als Einzelperson rückverfolgbar. Alle Personen, die im Rahmen der Studie Einsicht in Ihre Daten haben, unterliegen der Schweigepflicht. Die Vorgaben des Datenschutzes werden eingehalten und Sie als teilnehmende Person haben jederzeit das Recht auf Einsicht in Ihre Daten.
Möglicherweise wird diese Studie durch die zuständige Ethikkommission, die Arzneimittelbehörde Swissmedic oder durch die Institution, die die Studie veranlasst hat, überprüft. Die Studienmitarbeiter müssen eventuell Ihre persönlichen und medizinischen Daten für solche Kontrollen offenlegen. Ebenso kann es sein, dass bei Schäden ausnahmsweise auch ein Vertreter der Versicherung Ihre Daten ansehen muss. Alle Personen müssen absolute Vertraulichkeit wahren.
Im Rahmen dieses Projektes werden Daten erhoben bzw. Messungen durchgeführt, welche auch für Ihren behandelnden Arzt und damit Ihre persönliche, medizinische Betreuung im SPZ von Interesse sein können. Deshalb werden diese Daten (z.B. Blutwerte) auch in Ihrer elektronischen Krankenakte gespeichert. Dies dient in erster Linie dazu, doppelte Untersuchungen und damit auch Ihre Belastung durch Untersuchungen zu verringern.

12. Rücktritt

Sie können jederzeit aufhören und von der Studie zurücktreten, wenn Sie das wünschen. Die bis dahin erhobenen Daten und Proben werden noch verschlüsselt ausgewertet, weil das ganze Projekt sonst seinen Wert verliert. Prüfen Sie bitte, ob Sie damit einverstanden sind, bevor Sie bei der Studie mitmachen.

13. Entschädigung für die Studienteilnehmende

Die in dieser Studieninformation erwähnten studienspezifischen Untersuchungen sind kostenlos. Weder Ihnen noch Ihrer Krankenkasse entstehen im Zusammenhang mit Ihrer Teilnahme Kosten. Das Vitamin-D-Supplement sowie Placebo werden kostenlos zu Verfügung gestellt. Alle Studienteilnehmende bekommen eine Reisespesenentschädigung (CHF50 pro Studienvisite). Sie erhalten zusätzlich keine weitere finanzielle Entschädigung.

14. Haftung

Die Institution (SPZ), die die Studie veranlasst hat und für die Durchführung verantwortlich ist, haftet für Schäden, welche Ihnen im Zusammenhang mit der getesteten Substanz oder Forschungshandlungen (z.B. Untersuchungen) entstehen könnten. Die Voraussetzungen und das Vorgehen dazu sind gesetzlich geregelt. Die SPZ hat dazu eine Versicherung bei der Basler Versicherungen (Aeschengraben 21, 4002 Basel) abgeschlossen, um in einem möglichen Schadenfall für die Haftung aufkommen zu können. Bei Schäden, die auf ein zugelassenes und gemäss dem medizinischen Standard angewendetes Heilmittel zurückzuführen sind oder welche im Rahmen der Placebo-Verwendung auftraten, greifen dieselben Haftungsregelungen wie bei einer Behandlung ausserhalb einer Studie. Falls Sie einen Schaden erlitten haben, so wenden Sie sich bitte an einen Studienmitarbeiter.

15. Finanzierung der Studie

Die Studie wird von der SPZ und Schweizer Paraplegiker-Stiftung bezahlt.

16. Kontaktpersonen

Bei Fragen, Unsicherheiten oder Notfällen, die während der Studie oder danach auftreten, können Sie sich jederzeit an eine dieser Kontaktpersonen wenden:

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Sportmedizin
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Guido A. Zäch-Strasse 1
6207 Nottwil

Bitte kontaktieren Sie in Notfällen Ihre örtlichen Notfalldienste.

17. Glossar; was heisst….

- *Was heisst "doppelblind"?*
  Eine Studie zu "verblinden" dient dazu, bessere und genauere Ergebnisse zu erhalten. "Doppelblind" ist eine Studie dann, wenn weder die Studienteilnehmenden noch die Forschenden wissen, ob Studienteilnehmende das echte Medikament oder das Placebo erhalten. Nur die unabhängige Person, die diese Zuordnung ausgelost hat, weiss, wer was erhält. Wenn der Test zu Ende ist, wird die "Verblindung" aufgelöst. In einem Notfall kann die "Verblindung" jederzeit auch früher aufgehoben werden. Ein Studienteilnehmer, der weiss, dass er das echte Medikament und nicht das Placebo erhält, achtet ganz anders auf Reaktionen des Körpers als jemand, der weiss, dass er nur das Placebo erhält. Dies kann dazu führen, dass Studienteilnehmende, die das echte Medikament erhalten, die Wirkung des Medikaments im Vergleich zu denjenigen, die nur das Placebo erhalten, überschätzen.
- *Was heisst "randomisiert"?*
  Bei vielen Studien werden zwei oder mehrere unterschiedliche Arten der Behandlung verglichen. Zum Beispiel vergleicht man ein echtes Medikament mit einem Placebo. Man bildet dann zwei Gruppen von Studienteilnehmenden, die einen bekommen das echte Medikament und die anderen das Placebo. „Randomisieren" bedeutet, dass ausgelost wird, wer in welche Gruppe kommt. Es ist bei einem solchen Test also Zufall, ob man das echte Medikament erhält oder das Placebo.
- *Was heisst "Placebo"?*
  Ein Scheinmedikament, das so aussieht wie ein echtes und auch gleich verpackt ist, wie jenes das der Arzt verschreibt und zu dem es einen Beipackzettel gibt. Es ist aber kein Wirkstoff drin, sondern es besteht nur aus Wasser oder Zucker oder ähnlichem. Manchmal behandelt man einen Teil der Studienteilnehmenden an einem Medikamententest mit dem richtigen Medikament (mit dem Wirkstoff) und den anderen Teil mit einem solchen Placebo (ohne Wirkstoff). Dann kann man im Vergleich besser abschätzen, wie gut das Medikament tatsächlich wirkt. In dieser Studie besteht das Placebo aus der gleichen alkoholischen Lösung (5 mL, 65 Volumenprozent Ethanol) wie das Vitamin-D-Supplement, aber ohne Wirkstoff.
- *Was ist "Vitamin-D-Supplementierung"?*
  Unter Supplementation versteht man die gezielte und ergänzende Versorgung mit einzelnen Nährstoffen, zusätzlich zur gewöhnlichen Nahrung. Die entsprechenden Produkte bezeichnet man als Supplement. Bei Vitamin-D-Supplementierung wird Vitamin D als Supplement eingenommen, zum Beispiel in Form einer Flüssigkeit oder einer Tablette.
- *Was ist "Vi-De 3® - Monatsdosis"?*
  Dies ist ein handelsübliches Vitamin-D-Supplement mit Wirkstoff Cholecalciferol (Mono-Vitamin D3), fabriziert von der Firma Dr. Wild & Co. AG. Vi-De 3® Monatsdosis ist eine 5 mL alkoholische Lösung (65 Volumenprozent Ethanol), was 2.600 g Alkohol pro Flasche entspricht. Zum Vergleich: 250 mL Apfelsaft enthaltet 0.165 g Alkohol.

Einwilligungserklärung

Schriftliche Einwilligungserklärung zur Teilnahme an einem Studienprojekt

Bitte lesen Sie dieses Formular sorgfältig durch. Bitte fragen Sie, wenn Sie etwas nicht verstehen oder wissen möchten. Für die Teilnahme ist Ihre schriftliche Einwilligung notwendig.

BASEC-Nummer:	2020-01493
Titel der Studie:	Vitamin-D-Supplementierung bei Personen mit einer chronischen Querschnittlähmung
Verantwortliche Institution:	Schweizer Paraplegiker-Zentrum Guido A. Zäch-Strasse 1 6207 Nottwil
Ort der Durchführung:	Schweizer Paraplegiker-Zentrum Guido A. Zäch-Strasse 1 6207 Nottwil
Verantwortliche Studienmitarbeiterin am Studienort:	Dr. sc. nat. Joëlle Flück
Studienteilnehmende:	☐ weiblich ☐ männlich
Name und Vorname in Druckbuchstaben:	
Geburtsdatum:	

- Ich wurde vom unterzeichnenden Studienmitarbeiter mündlich und schriftlich über den Zweck, den Ablauf der Studie, über mögliche Vor- und Nachteile sowie über eventuelle Risiken informiert.
- Ich nehme an dieser Studie freiwillig teil und akzeptiere den Inhalt der abgegebenen schriftlichen Information. Ich hatte genügend Zeit, meine Entscheidung zu treffen.
- Meine Fragen im Zusammenhang mit der Teilnahme an dieser Studie sind mir beantwortet worden. Ich behalte die schriftliche Information und erhalte eine Kopie meiner schriftlichen Einwilligungserklärung.
- Ich wurde über mögliche andere Behandlungen und Behandlungsverfahren aufgeklärt.
- Ich bin einverstanden, dass die zuständigen Fachleute des Sponsors, der zuständigen Ethikkommission und der Arzneimittelbehörde Swissmedic zu Prüf- und Kontrollzwecken in meine unverschlüsselten Daten Einsicht nehmen dürfen, jedoch unter strikter Einhaltung der Vertraulichkeit.
- Bei Studienergebnissen oder Zufallsbefunden, die direkt meine Gesundheit betreffen, werde ich informiert. Wenn ich das nicht wünsche, informiere ich einen Studienmitarbeiter.
- Ich weiss, dass meine gesundheitsbezogenen und persönlichen Daten (und Proben) nur in verschlüsselter Form zu Forschungszwecken für diese Studie weitergegeben werden können, eventuell auch ins Ausland.
- Im Fall einer Weiterbehandlung ausserhalb des Studienzentrums ermächtige ich meinen/meine nachbehandelnden Arzt/Ärzte, meine für die Studie relevanten Nachbehandlungsdaten dem Studienmitarbeiter zu übermitteln.
- Ich kann jederzeit und ohne Angabe von Gründen von der Studienteilnahme zurücktreten. Meine weitere medizinische Behandlung ist unabhängig von der Studienteilnahme immer gewährleistet. Die bis zum Rücktritt erhobenen Daten und Proben werden für die Auswertung zur Studie verwendet.
- Ich bin darüber informiert, dass eine Versicherung Schäden deckt, die auf die Studie zurückzuführen sind.
- Ich bin mir bewusst, dass die in der Studieninformation genannten Pflichten einzuhalten sind. Im Interesse meiner Gesundheit kann mich ein Studienmitarbeiter jederzeit von der Studie ausschliessen.

Ort, Datum	Unterschrift Studienteilnehmende

Bestätigung des Studienmitarbeiters: Hiermit bestätige ich, dass ich dieser Studienteilnehmerin/diesem Studienteilnehmer Wesen, Bedeutung und Tragweite der Studie erläutert habe. Ich versichere, alle im Zusammenhang mit dieser Studie stehenden Verpflichtungen gemäss dem geltenden Recht zu erfüllen. Sollte ich zu irgendeinem Zeitpunkt während der Durchführung der Studie von Aspekten erfahren, welche die Bereitschaft der Studienteilnehmerin/des Studienteilnehmers zur Teilnahme an der Studie beeinflussen könnten, werde ich sie/ ihn umgehend darüber informieren.

Ort, Datum	Name und Vorname des Studienmitarbeiters in Druckbuchstaben Unterschrift des Studienmitarbeiters

Supplement 3: Sample size calculation

A: Expected time course of mean vitamin D status (nmol/L) during the study.

	Baseline	3 months	6 months	9 months	12 months
Placebo	31	31	31	31	31
Moderate dosage	31	49	56	59	60
High dosage	31	91	115	125	129

B: Estimated sample size for repeated-measures ANOVA. F-test for between subjects with H_0: $\delta = 0$ versus H_a: $\delta \neq 0$. Estimated minimal sample size as a function of the error variance and the within-individual correlation of repeated vitamin D status measurements, specifying a power ($1-\beta$) of 0.8 and a significance level (α) of 0.05. Reading example: Presuming an error variance (σ_e^2) of 3500, a between-subject variance (σ_b^2) of 794 and a high within-individual correlation (ρ) of 0.9 for repeated vitamin D status measurements (N_{rep}=5), the estimated minimal overall sample needed is 45 participants, implying 15 participants in each of the three intervention groups (N_g=3).