# PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

### Title (Provisional)

Impact of an acute 1-month cannabidiol treatment on pain and inflammation after a long bone fracture: a triple-blind randomized, placebo controlled, clinical trial protocol

### Authors

Brazeau, Daphnée; Deshaies, Amelie A; Williamson, David; Bernard, Francis; Arbour, Caroline; Pinard, Anne Marie; Rouleau, Dominique; De Beaumont, Louis

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## VERSION 1 - REVIEW

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| **Reviewer** | **1** |
| **Name** | **Chilibeck, Philip** |
| **Affiliation** | **University of Saskatchewan** |
| **Date** | **22-Oct-2024** |
| **COI** | **None** |

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This seems like an interesting and potentially impactful study. I have the following comments:

Line 88: Was gender evaluated in these cited studies or did they evaluate sex?

Line 120: change “facilitate” to “facilitates”

Line 133: Define the abbreviation TRP

Line 190: Provide justification for the planned age range (or consider expanding the age range to improve feasibility of recruitment).

Line 201: I would suggest changing “women of childbearing potential” to “sexually active women of childbearing potential”, so that those who are not sexually active and therefore not practicing birth control can be included.

Line 209: In the introduction, it is mentioned that CBD does not impair ability to work and drive. Why then do you have as an exclusion criterion “Transport business drivers and heavy machinery operators”?

Line 210: Will excluding those with osteoporosis exclude too many older adults?

Line 226: What is your block size?

Line 227: what are the age categories for stratification?

Line 238-239: Clarify whether these doses are mg/day or mg/tablet (given twice a day)

Line 257: A period is missing

Are you using an “intent-to-treat” analysis?

How are missing data to be handled?

line 433: “A 10% loss to follow-up is expected based on a 3-month trial with the same patient characteristics.” Is there a reference available for this statement?

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| **Reviewer** | **2** |
| **Name** | **Dehghan, Niloofar** |
| **Affiliation** | **University of Arizona, Banner University Medical Center,** |
| **Date** | **01-Nov-2024** |
| **COI** | **None** |

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The fractures included are too heterogeneous. I don’t think it’s fair to include femur and metacarpal/pharynx fractures, these are not the same, they have different natural history, treatment, pain levels, and functional limitations. Including long bones such as femur, tibia, humerus, radius/ulna is more reasonable. You should exclude the hand/foot.

Define alcohol misuse in your exclusion criteria

Lines 201-203 – The way this is written is way too broad. Basically you are excluding all women under the age of 50. This is a major issue. You need to include women not just men.

Line 210 – why are you excluding those with history of osteoporosis? This excludes the majority of older women who are not going to have children. So now you have excluded all women from your study (young and old).

3 month f/u is too short, you need to f/u for at least one year, that is standard for orthopaedic RCTs. The effect of the treatment needs to be monitored especially its effect one bone union, which won’t be noticed by just a 3 month f/u.

Secondary outcome needs to also look at fracture healing and complications, such as infection, revision surgery, nonunion, etc. Are you capturing these at all?

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## VERSION 1 - AUTHOR RESPONSE

**Reviewer: 1**

Dr. Philip Chilibeck, University of Saskatchewan

Comments to the Author:
This seems like an interesting and potentially impactful study. I have the following comments:

Line 88: Was gender evaluated in these cited studies or did they evaluate sex?
*Author's response:* Thank you for raising this point. Although studies cited have reported gender biases in pain treatment, it is indeed the female sex that is more prone to chronic pain according to these studies, so "gender" has been changed to "sex" in the sentence.

Line 120: change "facilitate" to "facilitates"
*Author's response:* Thank you for pointing that out, we modified accordingly.

Line 133: Define the abbreviation TRP
*Author's response:* Thank you for pointing that out, we modified accordingly.

190: Provide justification for the planned age range (or consider expanding the age range to improve feasibility of recruitment).
*Author's response:* Thank you for raising the relevance of planned age range. The planned age range of 18 to 70 years, targeting a population representative of individuals who frequently experience traumatic fractures, was chosen both for methodological and pathophysiological reasons.

First, recovery mechanisms, chronic pain prevalence and complication rates are welldocumented and better characterized in this age group. It also allows for a more homogenous evaluation of fracture healing and pain recovery, reducing variability caused by confounding factors. Including participants over 70 introduces additional challenges, such as increased comorbidities, chronic diseases, bone fragility, polymedication and increased complications, which could slow the healing process, influence pain perception and complicate result interpretation.

Second, participants safety was a critical consideration. While CBD has an excellent safety profile, data in elderly populations remain limited. Moreover, the increased likelihood of drug interactions with treatments common in this age group introduces potential risks.

Finally, in terms of feasibility, expanding the age range beyond 70 is unlikely to significantly improve recruitment feasibility, as many older individuals would be excluded by other criteria, such as comorbidities, concomitant medications, or fracture location as fractures of the pelvis, vertebrae and rib cage are statistically more common in older population (Farr et al., 2017).

A summarized justification has been added in line 182.

Line 201: I would suggest changing “women of childbearing potential” to “sexually active women of childbearing potential”, so that those who are not sexually active and therefore not practicing birth control can be included.

*Author’s response:* We appreciate the reviewers' suggestion and understand the concern regarding overly strict exclusion criteria. The statement used in the exclusion criteria is standard practice in clinical trials to ensure participants safety and to comply with ethical requirements (Health Canada and CIUSSS du Nord-de-l’Île-de-Montréal ethics board), particularly when a product has not been formally validated for use in pregnant or breastfeeding women. To clarify our criteria, the extensive accepted forms of contraception include:

- Must be post-menopausal and menstruation-free for at least 1 year prior to screening.
- If of childbearing age, must agree to use medically effective contraception (IUDs, oral contraceptives, and barrier methods (e.g., condoms)) from visit 1 until 30 days after visit 2 (1 ovulatory cycle).
- If of childbearing age, must agree to abstain completely from sexual intercourse. - Be surgically sterile

Therefore, women who are not currently sexually active can still be eligible and if their situation changes, they must agree to adopt a contraceptive method. To maintain scientific rigor and safety, we prefer to keep this criterion as it is. However, we keep in mind your argument and we will ensure this criterion is clearly explained, based on the extensive criteria mentioned above, during the initial participant interview to avoid any confusion or unnecessary exclusion. Examples of accepted contraceptive methods have been added to the exclusion criteria.

Line 209: In the introduction, it is mentioned that CBD does not impair ability to work and drive. Why then do you have as an exclusion criterion “Transport business drivers and heavy machinery operators”?

*Author’s response:* Thank you for raising this point. Indeed, several studies support the fact that CBD does not impair driving ability which is why we believe it is safe to consume at the daily doses prescribed in the trial without affecting activities of daily living (Arkell et al., 2020; Egloff et al., 2023; McCartney et al., 2022). However, we have chosen to exclude adults who work several hours a day on the road or with heavy machinery for precautionary reasons since errors in these professions could lead to serious accidents, and in compliance with Health Canada guidelines, which emphasize the importance of mitigating risks. Furthermore, we anticipate that this exclusion will have minimal impact on recruitment, as it concerns a very small proportion of potential participants (<1%). This measure aligns with our commitment to ensuring participant and public safety.

Line 210: Will excluding those with osteoporosis exclude too many older adults? *Author’s response:* Thank you for raising this important question. The decision to exclude participants with osteoporosis was made to reduce variability related to bone fragility, which could impact study outcomes such as pain, healing process, complications and recovery timeline (Giannoudis et al., 2007). In addition, osteoporotic often have a different etiology since they

typically stem from underlying bone fragility rather than from the significant trauma, that characterizes typical fractures targeted by this study.

Furthermore, the exclusion of osteoporotic patients does not mean the systematic exclusion of the majority of older adults. In fact, according to a report from the Public Health Agency of Canada, the prevalence of diagnosed osteoporosis in Canadians aged 40 to 70 is approximately 7% (System, 2024). This exclusion is therefore not substantial, particularly given the overlap with other exclusion criteria, such as fracture type. For instance, in individuals aged 50 to 70 diagnosed with osteoporosis, 40% to 70% of fractures occur in bones that are excluded from the study such as pelvis and spine (Kanis & Diseases, 2008).

The aim of this phase two study is to assess the therapeutic potential of CBD in individuals with traumatic fractures. These findings will provide a foundation for future research involving more complex populations, including those with osteoporosis.

Line 226: What is your block size?
*Author's response:* Thank you for this question. We opted for block randomization with randomly selected block sizes to minimize selection bias and maintain the blinding of investigators and other project members by ensuring the unpredictability of block assignments. This information has been added to the protocol.

Line 227: what are the age categories for stratification?
*Author's response:* Thank you for this question, the stratification will be based on two age groups: participants aged 45 and under, and those over 45. This information has been added to the protocol. This information was added in line 233.

Line 238-239: Clarify whether these doses are mg/day or mg/tablet (given twice a day)
*Author's response:* Thank you for pointing that out, we modified accordingly.

Line 257: A period is missing
*Author's response:* Thank you for pointing that out, we modified accordingly.

Are you using an "intent-to-treat" analysis?
*Author's response:* Thank you for raising that point. Indeed, efficacy analyses will be performed on an intention-to-treat (ITT) dataset. The ITT dataset will include all participants randomized in the analysis, whether or not they have completed treatment in order to limit bias and reflect results under real treatment conditions. This segment has been added to the protocol in line 430.

How are missing data to be handled?
*Author's response:* Missing data will be reported and justified in the results. Furthermore, the multiple imputation method, which has been recognized in clinical studies involving experimental treatment, will be applied. Additionally, a sensitivity analysis will be performed

to assess the impact of missing data on the results. This segment has been added to the protocol in line 416.

line 433: “A 10% loss to follow-up is expected based on a 3-month trial with the same patient characteristics.” Is there a reference available for this statement? *Author’s response*: Thank you for pointing out the missing reference. We based our statement on a study conducted by our team at the same hospital involving patients with isolated fractures who participated in an intervention and returned for assessment three months post-accident (Jodoin et al., 2024). The corresponding reference has now been added to the article.

**Reviewer: 2**

Dr. Niloofar Dehghan, University of Arizona, Banner University Medical Center,

Comments to the Author:

The fractures included are too heterogeneous. I don’t think it’s fair to include femur and metacarpal/pharynx fractures, these are not the same, they have different natural history, treatment, pain levels, and functional limitations. Including long bones such as femur, tibia, humerus, radius/ulna is more reasonable. You should exclude the hand/foot.

*Author’s response:* Thank you for raising this point, the type of fracture selected is indeed a crucial aspect to consider. While we acknowledge the heterogeneity of the fractures included, our primary objective is to evaluate the effect of CBD on acute pain across a broad range of fracture types. This decision was made to maximize the generalizability of the results and their relevance to diverse clinical population knowing that the acute mechanisms of inflammation and pain are similar across fractures.

To ensure the inclusion of fractures with sufficiently severe pain, we established a minimum threshold of 3/10 on the VAS for initial pain. This criterion excludes fractures associated with low pain levels, which may not provide meaningful data for evaluating the effects of CBD on pain. Furthermore, we address concerns about heterogeneity through randomization and stratification by fractured bone, ensuring a balanced distribution of fracture types across study groups.

Additionally, we have included functional limitations at 1 and 3 months, as well as changes in pain from recruitment to 3 months, as secondary measures. These measures will allow us to enable further subgroup analyses if necessary to account for the natural history and functional differences between fracture types. The inclusion of hand and foot fractures also enhances the feasibility of recruitment by broadening the pool of eligible participants.

Define alcohol misuse in your exclusion criteria

Author’s response: Thank you for this comment. To be more specific, we've added to line 205 that alcohol abuse is defined according to DSM-5 criteria.

Lines 201-203 – The way this is written is way too broad. Basically you are excluding all women under the age of 50. This is a major issue. You need to include women not just men.

*Author's response:* Thank you for raising this important point. We understand your concern regarding the inclusion of women in this study and appreciate the opportunity to address it. The statement used in the exclusion criteria is standard practice in clinical trials to ensure participants safety and to comply with ethical requirements (Health Canada and CIUSSS du Nord-de-l'Île-de-Montréal ethics board), particularly when a product has not been formally validated for use in pregnant or breastfeeding women. To clarify our criteria, the extensive accepted forms of contraception include:

- Must be post-menopausal and menstruation-free for at least 1 year prior to screening.
- If of childbearing age, must agree to use medically effective contraception (IUDs, oral contraceptives, and barrier methods (e.g., condoms)) from visit 1 until 30 days after visit 2 (1 ovulatory cycle).
- If of childbearing age, must agree to abstain completely from sexual intercourse. - Be surgically sterile

Therefore, women who are not currently sexually active can still be eligible and if their situation changes, they must agree to adopt a contraceptive method. Moreover, a study highlights that the prevalence of contraception use ranges from 60.9% in women aged 20–29 to 75% in women aged 40–49 which supports the inclusion of the majority of women within the specified age range (Daniels, 2020).

To maintain scientific rigor and safety, we prefer to keep this criterion as it is. However, we keep in mind your argument and we will ensure this criterion is clearly explained, based on the extensive criteria mentioned above, during the initial participant interview to avoid any confusion or unnecessary exclusion. Examples of accepted contraceptive methods have been added to the exclusion criteria.

Line 210 – why are you excluding those with history of osteoporosis? This excludes the majority of older women who are not going to have children. So now you have excluded all women from your study (young and old).

*Author's response:* Thank you for raising this point. The decision to exclude participants with osteoporosis was made to reduce variability related to bone fragility, which could impact study outcomes such as pain, healing process, complications and recovery timeline (Giannoudis et al., 2007). In addition, osteoporotic often have a different etiology since they typically stem from underlying bone fragility rather than from the significant trauma, that characterizes typical fractures targeted by this study.

Furthermore, the exclusion of osteoporotic patients does not mean the systematic exclusion of the majority of older adults. In fact, according to a report from the Public Health Agency of Canada, the prevalence of diagnosed osteoporosis in Canadians aged 40 to 70 is approximately 7% (System, 2024), while among women in this age group, it rises to 11%. This exclusion is therefore not substantial, particularly given the overlap with other exclusion criteria, such as fracture type. For instance, in individuals aged 50 to 70 diagnosed with osteoporosis, 40% to 70% of fractures occur in bones that are excluded from the study such as pelvis and spine (Kanis & Diseases, 2008).

The aim of this phase two study is to assess the therapeutic potential of CBD in individuals with traumatic fractures. These findings will provide a foundation for future research involving more complex populations, including those with osteoporosis.

3 month f/u is too short, you need to f/u for at least one year, that is standard for orthopaedic RCTs. The effect of the treatment needs to be monitored especially its effect one bone union, which won't be noticed by just a 3 month f/u.
*Author's response:* The 3-month follow-up was selected based on the primary objective of the study: evaluating the effect of CBD on acute post-traumatic pain. Three months is a clinically significant timeframe, marking the transition from acute to chronic pain, which is crucial for understanding whether CBD can help prevent chronic pain development.

While we acknowledge that longer follow-ups are standard in orthopedic studies assessing bone healing and complications, this study is focused on short-term outcomes such as pain reduction, opioid consumption, and return to functionality. These parameters can be adequately captured within the 3-month period.

Extending the follow-up to one year would introduce substantial logistical and financial challenges, increase participant attrition, and shift the focus away from the primary aim of the study. However, we recognize the importance of long-term outcomes and emphasize that, if this study demonstrates a beneficial effect of CBD, it will lay the groundwork for future research evaluating its impact on bone healing and long-term recovery.

Secondary outcome needs to also look at fracture healing and complications, such as infection, revision surgery, nonunion, etc. Are you capturing these at all?
*Author's response:* In line with the previous answer, the primary objective of this study is to evaluate the efficacy of CBD in managing acute post-fracture pain and return to functionality. While complications such as non-union, infections, or revision surgery are important considerations, including them as secondary endpoints would require a prolonged follow-up period and a significant increase in sample size, which falls beyond the scope of the current study.

Furthermore, assessing parameters such as bone healing or complications would necessitate additional follow-ups, measurement tools (e.g., X-rays, imaging studies, or surgical follow-ups), and resources, further complicating the study design and participant retention.

That said, while bone healing is not a specific endpoint in this study, all serious adverse events, including infections, reoperations, or complications, will be documented and reported as part of the safety monitoring process. This ensures that any relevant safety signals are captured and addressed.

If CBD demonstrates efficacy in reducing pain and improving functional recovery in this phase two study, it will pave the way for future research investigating its potential impact on long-term outcomes, such as bone consolidation and complications.

**References**

Arkell, T. R., Vinckenbosch, F., Kevin, R. C., Theunissen, E. L., McGregor, I. S., & Ramaekers, J. G. (2020). Effect of Cannabidiol and Δ9-Tetrahydrocannabinol on Driving Performance: A Randomized Clinical Trial. *Jama*, *324*(21), 2177-2186. https://doi.org/10.1001/jama.2020.21218

Daniels, K. A., JC. (2020). *Current contraceptive status among women aged 15–49: United States, 2017–2019.*

Egloff, L., Frei, P., Gerlach, K., Mercer-Chalmers-Bender, K., & Scheurer, E. (2023). Effect of vaporizing cannabis rich in cannabidiol on cannabinoid levels in blood and on driving ability - a randomized clinical trial. *Int J Legal Med*, *137*(6), 1713-1723. https://doi.org/10.1007/s00414-023-03076-0

Farr, J. N., Melton, L. J., 3rd, Achenbach, S. J., Atkinson, E. J., Khosla, S., & Amin, S. (2017). Fracture Incidence and Characteristics in Young Adults Aged 18 to 49 Years: A Population-Based Study. *J Bone Miner Res*, *32*(12), 2347-2354. https://doi.org/10.1002/jbmr.3228

Giannoudis, P., Tzioupis, C., Almalki, T., & Buckley, R. (2007). Fracture healing in osteoporotic fractures: is it really different? A basic science perspective. *Injury*, *38 Suppl 1*, S90-99. https://doi.org/10.1016/j.injury.2007.02.014

Jodoin, M., Herrero Babiloni, A., Provost, C., Blais, H., Bellemare, A., Desjardins, M., Rouleau, D. M., & De Beaumont, L. (2024). 10-Day Theta Burst Stimulation Intervention Facilitates the Clinical Rehabilitation of Patients After an Isolated Limb Fracture: A Longitudinal SHAM-Controlled Pilot Study. *American Journal of Physical Medicine & Rehabilitation*, *103*(11), e152-e161. https://doi.org/10.1097/phm.0000000000002543

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McCartney, D., Suraev, A. S., Doohan, P. T., Irwin, C., Kevin, R. C., Grunstein, R. R., Hoyos, C. M., & McGregor, I. S. (2022). Effects of cannabidiol on simulated driving and cognitive performance: A dose-ranging randomised controlled trial. *J Psychopharmacol*, *36*(12), 1338-1349. https://doi.org/10.1177/02698811221095356

## VERSION 2 - REVIEW

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| **Reviewer** | **1** |
| **Name** | **Chilibeck, Philip** |
| **Affiliation** | **University of Saskatchewan** |
| **Date** | **13-Jan-2025** |

## COI

The authors have addressed all my comments. My only remaining suggestion is to indicate which randomized block sizes you will be using for randomization. Block size should be divisible by your number of groups, so not all block sizes may be appropriate.

## VERSION 2 - AUTHOR RESPONSE

**Reviewer: 1**

Dr. Philip Chilibeck, University of Saskatchewan

Comments to the Author:

The authors have addressed all my comments. My only remaining suggestion is to indicate which randomized block sizes you will be using for randomization. Block size should be divisible by your number of groups, so not all block sizes may be appropriate. *Author's response:* Thank you for raising this point. We opted for block randomization with randomly selected block sizes to minimize selection bias and maintain the blinding of investigators and other project members by ensuring the unpredictability of block assignments. Block sizes are 9 and 12. Given a group number of three, for the block of 9, this gives 3 patients in each group, whereas for a block of 12, this gives 4 patients in each group. This information has been added to the protocol in line 238.