PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Medical Marijuana and Opioids (MEMO) Study: Protocol of a longitudinal cohort study to examine if medical cannabis reduces opioid use among adults with chronic pain
AUTHORS	Cunningham, Chinazo; Starrels, Joanna; Zhang, Chenshu; Bachhuber, Marcus; Sohler, Nancy; Levin, Frances; Minami, Haruka; Slawek, Deepika; Arnsten, Julia

VERSION 1 – REVIEW

REVIEWER	Bonnie Huang Hall, MD PHD (Formerly associated with UCSF dept of family and community medicine) Bonnie Huang Hall, MD PHD 46923 Warm Springs Blvd #207 Fremont, CA 94539 USA
REVIEW RETURNED	26-Aug-2020

GENERAL COMMENTS	The study desires to see if the introduction of marijuana will decrease opioid use and what are the secondary effects of this, particularly HIV and side effects of marijuana usage. The study uses 250 participants total to see if opioid use will change depending on marijuana usage. From what I understand, these 250 participants include the HIV study population. HIV is associated with its own unique pain conditions, such as HIV neuropathy, which is rare and in the general population. This may create bias in the results and lead to them not being generalizable, and hence, not answering the question at hand. Why not recruit 250 random patients instead of including the HIV cohort in the analysis ? The HIV questions can still be answered with the 62 recruits. In addition, since many people using opioids already use marijuana, baseline urine toxicology should be used to rule out any potential participant who already has marijuana in the urine. I do not believe this is an exclusion critiera. This is important because if participants are already using marijuana, we cannot tell if there will be an effect of marijuana since this study is a "before" marijuana use and "after" marijuana use study. Please add more clarification in who is in the study. I looked up the NY state regulations on medical marijuana:https://health.ny.gov/regulations/medical_marijuana/patients/ It is unclear to me what the "medical cannabis qualifying complication

	of “chronic or severe pain” is: does this mean that the study only include chronic pain patients that are severe - or that the qualifying participants also need to experience the one of the other symptoms such as cachexia, nausea, muscle spasm, etc. Maybe in the study participants section, in order to make the study more reproducible, it maybe advisable to list in more detail which conditions it is accepting into the study and what is excluding. Also, it would be nice if the study looked at the cognitive changes that may occur with marijuana use. I think these are probably more common than some of the other adverse events listed and maybe more statically easier to detect - and just as relevant. Short term Cognitive effects are common in marijuana use see and there is already moderate strength of evidence for this: https://pubmed.ncbi.nlm.nih.gov/28806817/ As for ethics, since we are looking at adverse events such as overdose/deaths, perhaps the study should include a provision to send an early alert of some sort if there is an alarmingly higher rate of overdose/deaths than would be expected if opiods alone were prescribed (i.e. without medical marijuana.); As for the introduction, although not crucial, I believe that most of the evidence for the effectiveness of using marijuana for chronic pain pertains to chronic neuropathic pain. The references cited attest to that. In this study, the authors are not distinguishing between neuropathic pain vs nocicpetive pain syndromes, although they are eliminating/exluding from the patient recruitment quite a few neuropathic syndromes that are often co-morbid with chronic pain. The authors may wish to clarify this point as to whether they are focusing on nocicpetive pain or not. It may not entirely matter, however, except that if marijuana truly mainly improves chronic neuropathic pain, and if decreased pain is the only reason that may cause a reduction in opioid usage, then if they mix other pain syndromes they may not witness a change in opioid usage. Of course, marijuana has other effects too (apathy, etc) , not just on chronic pain, so the effect may still be measurable. Of course, it is interesting to note whether or not patient's perceived pain /function scores change as they take marijuana and see if that is linked to opioid usage.

REVIEWER	David Seamark Honiton Surgery Honiton Devon UK
REVIEW RETURNED	28-Sep-2020

GENERAL COMMENTS	Limitations are discussed but I feel some acknowledgement of the changing situation around opioid prescribing for chronic pain in the USA should be made. If for example opioid prescribing policy changes during the duration of the study resulting in restricted or reduced prescribing this will make associations between medical marijuana and opioid use observed harder to interpret.

VERSION 1 – AUTHOR RESPONSE

Comments from Reviewer 1

2. The study uses 250 participants total to see if opioid use will change depending on marijuana usage. From what I understand, these 250 participants include the HIV study population. HIV is associated with its own unique pain conditions, such as HIV neuropathy, which is rare and in the general population. This may create bias in the results and lead to them not being generalizable, and hence, not answering the question at hand. Why not recruit 250 random patients instead of including the HIV cohort in the analysis ? The HIV questions can still be answered with the 62 recruits.

We agree with the reviewer that participants with HIV infection may have unique pain syndromes that differ from participants without HIV infection. However, because our study has been funded by the United States National Institute of Health with the current protocol (which includes 62 participants with HIV infection and 188 participants without HIV infection) and because the study is ongoing, we are unable to modify our sampling plan. However, we will conduct analyses with and without participants with HIV infection. We note this issue in the Limitation paragraph as follows:

“In addition, because adults with HIV infection may have unique pain conditions, to determine if including participants with HIV infection in the sample leads to differences in findings, we will conduct two sets of main analyses—one including participants with HIV infection, and one excluding participants with HIV infection.”

3. In addition, since many people using opioids already use marijuana, baseline urine toxicology should be used to rule out any potential participant who already has marijuana in the urine. I do not believe this is an exclusion criteria. This is important because if participants are already using marijuana, we cannot tell if there will be an effect of marijuana since this study is a "before" marijuana use and "after" marijuana use study.

We agree that illicit cannabis use is an important variable. And, as noted by the reviewer, we did not include illicit cannabis use as an exclusionary criterion. As mentioned above in #2, because this study has already been funded by the NIH with the existing protocol, and is already half-way through enrollment, we are not in a position to change the eligibility criteria now. Recognizing the importance of illicit cannabis use, we measure illicit cannabis use every 2 weeks in web-based questionnaires (as described in the second paragraph of the section Data sources and collection. In addition, depending on findings, illicit cannabis use may be included in analyses as a covariate. We have now clarified that in addition to substance use (including illicit cannabis use) being a secondary outcome, it may also be included as a covariate or confounder in analyses. The last sentence in Key variables, has been modified as follows:

“Other key variables that are potential confounders include sociodemographic characteristics, pain severity and interference,[114] pain catrastrophizing,[115] pain-related function and disability,[116] pain treatment, alcohol use,[117] tobacco use,[118] other substance use,[110] symptoms of depression,[119] anxiety,[120] post-traumatic stress disorder,[121, 122] attention deficit hyperactivity disorder,[123] insomnia,[124] physical functional tests, and quality of life.[125]”

4. Please add more clarification in who is in the study. I looked up the NY state regulations on medical marijuana. It is unclear to me what the "medical cannabis qualifying complication of “chronic or severe pain” is: does this mean that the study only include chronic pain patients that are severe - or that the qualifying participants also need to experience the one of the other symptoms such as cachexia, nausea, muscle spasm, etc. Maybe in the study participants section, in order to make the study more reproducible, it maybe advisable to list in more detail which conditions it is accepting into the study and what is excluding.

To provide clarification, we have included more information about the NY state regulations specific to how individuals qualify for medical cannabis certification. Individuals must have at least one qualifying condition and at least one qualifying complication. There are 13 qualifying conditions and 7 qualifying complications. Because the qualifying conditions and complications changed over the course of the study, we expanded eligibility criteria to include all conditions and complications that were specific to pain. Therefore, we have modified the manuscript to reflect this change and provide clarification.
The penultimate paragraph of the Introduction section now reads:
"Medical cannabis policies differ by state, and New York's (NY) medical cannabis program is one of the most stringent.[93] To be certified for medical cannabis, individuals must have at least one qualifying condition (cancer, HIV infection or AIDS, amyotrophic lateral sclerosis, Parkinson's disease, multiple sclerosis, spinal cord injury with spasticity, epilepsy, inflammatory bowel disease, neuropathy, Huntington's disease, post-traumatic stress disorder, chronic pain, pain that degrades health and functional capability as an alternative to opioid use, or substance use disorder) and at least one complication (severe or chronic pain resulting in substantial limitation of function, cachexia or wasting syndrome, severe nausea, seizures, severe or persistent muscle spasms, post-traumatic stress disorder, or opioid use disorder)."
The Study Participants sub-section of the Methods and Analyses section now reads:
"Inclusion criteria are: 1) >18 years old, 2) fluency in English or Spanish, 3) new certification for medical cannabis within 90 days, 4) no medical cannabis use in the 6 months prior to certification, 5) medical cannabis qualifying condition of "chronic pain", or "pain that degrades health and functional capability as an alternative to opioid use" or qualifying complication of "severe or chronic pain resulting in substantial limitation of function," and 6) use of prescribed or illicit opioids within 30 days."

5. Also, it would be nice if the study looked at the cognitive changes that may occur with marijuana use. I think these are probably more common than some of the other adverse events listed and maybe more statically easier to detect - and just as relevant. Short term Cognitive effects are common in marijuana use see and there is already moderate strength of evidence for this

We agree with the reviewer that examining cognitive changes with medical cannabis use is important. However, including neurocognitive measures is beyond the scope of our study. We have now included this as a limitation.

The Limitations paragraph now includes the following sentence:
"While our study will examine a range of potential adverse events from medical cannabis use, it does not examine all potential adverse events, including neurocognitive changes."

6. As for ethics, since we are looking at adverse events such as overdose/deaths, perhaps the study should include a provision to send an early alert of some sort if there is an alarmingly higher rate of overdose/deaths than would be expected if opiods alone were prescribed (i.e. without medical marijuana.

We appreciate the reviewer's comments. However, given the observational study design and minimal risk of participating in the study, per our approved current protocol, no interim analysis is planned.

7. As for the introduction, although not crucial, I believe that most of the evidence for the effectiveness of using marijuana for chronic pain pertains to chronic neuropathic pain. The references cited attest to that. In this study, the authors are not distinguishing between neuropathic pain vs nocicpetive pain syndromes, although they are eliminating/exluding from the patient recruitment quite a few neuropathic syndromes that are often co-morbid with chronic pain. The authors may wish to clarify this point as to whether they are focusing on nocicpetive pain or not. It may not entirely matter, however, except that if marijuana truly mainly improves chronic neuropathic pain, and if decreased

pain is the only reason that may cause a reduction in opioid usage, then if they mix other pain syndromes they may not witness a change in opioid usage. Of course, marijuana has other effects too (apathy, etc) , not just on chronic pain, so the effect may still be measurable. Of course, it is interesting to note whether or not patient's perceived pain /function scores change as they take marijuana and see if that is linked to opioid usage.

We appreciate the reviewers' comments about a need to better understand the mechanisms by which medical cannabis affects pain. We believe that our study will be able to shed light on some of the questions that the reviewer poses. For example, we are measuring several characteristics of participants' pain and their perception of pain and function; we plan to examine how these variables are associated with medical cannabis use, pain, and opioid use. While these will be important analyses, they are not primary analyses. As such, we believe that including numerous potential analyses, in addition to the primary and secondary analyses, will be too much for this manuscript. However, if the editor feels this would be important to include, then we would be happy to reconsider.

Comments from Reviewer 2
8. Limitations are discussed but I feel some acknowledgement of the changing situation around opioid prescribing for chronic pain in the USA should be made. If for example opioid prescribing policy changes during the duration of the study resulting in restricted or reduced prescribing this will make associations between medical marijuana and opioid use observed harder to interpret.
We agree with the reviewer's important point. In fact, epidemiologic data demonstrate that opioid prescribing has decreased in the United States over the past several years. We have now included the following text into the Limitations paragraph:
"Finally, because opioid prescribing in the United States has decreased over the past several years,[132] it is possible that further decreases in opioid prescribing may make it difficult to interpret the relationship between medical cannabis and opioid use."

VERSION 2 – REVIEW

REVIEWER	Bonnie Huang Hall Bonnie Huang Hall, MD PHD Former UCSF assistant volunteer clinical professor USA
REVIEW RETURNED	31-Oct-2020

GENERAL COMMENTS	I think this version was much clearer on analysis, who is participating in the study, and the limitations ins in the study. Thank you for your hard work. A few points: Although national trends in opioid prescribing has gone down, this can be addressed in discussion section. You may wish to just briefly see how much opioid prescribing has gone down in the 18 mo at Montefiore and see if its any different. Furthermore, I understand this study is focusing on the impact of medical marijuana on opiod MME per patient. One issue is that the urine toxicology at baseline may reveal some patients already using non-medical marijuana. I think this should be mentioned on how it may impact results. Thank you for allowing me the pleasure of reviewing your study protocol.

REVIEWER	David Seamark Honiton Surgery UK
REVIEW RETURNED	23-Oct-2020

GENERAL COMMENTS	The authors have made suitable revisions in response to the original feedback

VERSION 2 – AUTHOR RESPONSE

Comments from Reviewer 1

1. Although national trends in opioid prescribing has gone down, this can be addressed in discussion section. You may wish to just briefly see how much opioid prescribing has gone down in the 18 mo at Montefiore and see if its any different.

Based on a similar comment made by this reviewer previously, we added the sentence below to the limitations section. Because this manuscript describes the study protocol and does not present data or results, there is no discussion section. However, in a future manuscript in which we present our findings, undoubtedly, we will have an extensive discussion about opioid prescribing trends and how changes in those trends will likely impact our findings.

While the reviewer recommends that we provide Montefiore opioid-prescribing data, these data would not inform our findings, as the vast majority of study participants are not Montefiore patients. In addition, examining opioid-prescribing trends in a large health care system with 11 hospitals, over 200 clinics, and thousands of providers is a project in itself.

“Finally, because opioid prescribing in the United States has decreased over the past several years,[132] it is possible that further decreases in opioid prescribing may make it difficult to interpret the relationship between medical cannabis and opioid use.”

2. Furthermore, I understand this study is focusing on the impact of medical marijuana on opiod MME per patient. One issue is that the urine toxicology at baseline may reveal some patients already using non-medical marijuana. I think this should be mentioned on how it may impact results.

We agree with the reviewer that it is important to understand the role of illicit cannabis use with regards to medical cannabis use and opioid use. For this reason, we include several measures of illicit cannabis use in our study, including urine toxicology tests, ACASI questionnaires every 3 months (in which participants are asked about number of days of use in the past 30 days), and web-based questionnaires every 2 weeks (in which participants are asked about number of days of use, amount of money spent, type of products used, and amount used on a typical day). As we have indicated in the manuscript, one alternative measure of our primary exposure variable is the number of days of medical or illicit cannabis use.

While the reviewer asks for an analysis based on urine toxicology tests, urine toxicology tests show both medical cannabis use and illicit cannabis use, with an inability to differentiate illicit from medical cannabis use. In addition, many study participants have started using medical cannabis prior their enrollment visit, thus urine toxicology tests could reflect either illicit or medical cannabis use (because eligibility criteria include new medical cannabis certification within the past 90 days, some participants have already started using medical cannabis prior to their baseline interview). Therefore, an analysis based on urine toxicology tests would not yield results that would provide insight on how illicit cannabis would impact opioid use.

Other changes

3. Because of changes in medical cannabis policies since the time of our original submission, we have updated the Introduction as follows (last sentence of the first paragraph of the Introduction):

“As of November 2020, 35 states and Washington, DC have legalized medical cannabis, with pain as the most common indication.[28]”

4. We have also corrected a few typographical errors.