PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A Protocol for a Prospective Descriptive Prevalence Study of Catatonia in an Acute Mental Health Unit in Urban South Africa
AUTHORS	Zingela, Zukiswa; Stroud, Louise; Cronje, Johan; Fink, Max; Van Wyk, Stephanus

VERSION 1 – REVIEW

REVIEWER	Dr. Siddharth Sarkar All India Institute of Medical Sciences, New Delhi, India
REVIEW RETURNED	29-Jul-2020

GENERAL COMMENTS	I must commend the overall idea, to comprehensively assess catatonia, including the patient's own experiences. However, I must caution about certain issues in this protocol. The aim of the study (especially the first sentence) seems to be quite diffuse. Can the authors make the aims much more clearer. Similarly, can the authors clarify which is the primary objective (in the abstract there are two and in the main text they are not differentiated). Can the authors describe the setting more in detail, in terms of who funds the treatment, what all kinds of services are available, what happens to the patients when they are discharged, whether family stays with the patient in inpatient care, etc? The authors mention that the sample aimed is around 60 -100. Can they determine the precision that would be gained by this sample/ or carry out a formal sample size estimation? The authors can get comparative estimates from other studies (For example: "Assessing catatonia using four different instruments: Inter-rater reliability and prevalence in inpatient clinical population."). Objective 1 is unclear in phraseology and what it intends to measure. Collection of data is part of any prospective observational study. While the authors mention the use of Bradford Hill criteria for examining causality. But can they mention what association / causal relation they want to infer on. How will response to treatment be measured? What are the predictors of catatonia that the authors are going to look at. It would be better to be defined a-priori that these are the parameters / variables that would be assessed for being predictors.

	Are there any probes that would be used for patients when they come for follow up to understand the experiences of catatonic. Will all the patients be followed up, or some attrition is expected. The authors should take into account that catatonia is quite heterogenous, prevalence rates vary with different items, and certain items of some of the instruments do not lend well to inter-rater reliability. Yet, overall catatonia as a concept is useful for clinical decision making. This should figure in the acknowledged limitations.

REVIEWER	Gábor Gazdag Jahn Ferenc South Pest Hospital, Hungary
REVIEW RETURNED	01-Aug-2020

GENERAL COMMENTS	Zingela et al: A Prospective Descriptive Prevalence Study of Catatonia in an Acute Mental Health Unit in Urban South Africa. Position of catatonia was changed in DSM5 which resulted in an increased research interest in this field. This is an advantageous process as there are a number of issues regarding catatonia that should be further clarified. The results of this research – if it will be realized - will expand our knowledge of catatonia. Comments to improve the manuscript: Abstract, Introduction, 2nd sentence: the prevalence rate of catatonia in the literature is much wider then 10-20%, range from 7 (Bush G, Fink M, Petrides G, Dowling F, Francis A. Catatonia. I. Rating scale and standardized examination. Acta. Psychiatr. Scand. 1996, 93:129-136.) to 63% (Stuivenga M, Morrens M. Prevalence of the catatonic syndrome in an acute inpatient sample. Front. Psychiatry 2014, 5:174.), depending on the setting the survey was conducted. Introduction, 1st sentence: Kraepalin correctly is Kraepelin. Choice of screening tool and rating scale: BFCRS is the 23 item scale; the screening instrument is the BFCSI. Questions to the methods: authors do not fix the time frame of the initial screening. Further, is there any therapeutic protocol that will be used in the treatment of catatonia, or it will be solely the decision of the treating physician? Consent form: I do not understand why non-consenting patients or relatives have to sign a form. Explain it please! I have some ethical concerns regarding the involvement of minors in the study as the investigation of this special population is not among the aims of the study. I suggest excluding patients under 18 from the study.

REVIEWER	Krishna Prasad Muliyala National Institute of Mental Health and Neurosciences, Bangalore, India
REVIEW RETURNED	08-Aug-2020

GENERAL COMMENTS	This is a well-designed study that attempts to fill gaps in research about catatonia in the context of South Africa. The study authors

	plan to prospectively evaluate for catatonia from amongst admissions to a 35 bedded mental health unit of a general medical hospital in South Africa using the widely used and robust BFCRS scale and examine the predictors of catatonia, response to treatment and short term follow up. The qualitative part of the study intends to examine the subjective experiences of catatonia amongst patients during their follow up. I have the following few suggestions for this paper: 1. There is a possibility that catatonia may be underdiagnosed/undiagnosed by the clinicians of the MHU but may be picked up by the researchers; the authors need to state their approach in such instances. 2. The pathway of care up to the MHU needs to be stated. Is it possible that some patients may receive lorazepam in an emergency care service of the general medical hospital? 3. The authors need to clarify as to when will the research assistants apply the BFCRS, at what time point after admission? 4. The likely topic guide for the qualitative part of the study may need to be added. 5. How will the research assistants be trained for BFCRS? Will there be a check on IRR? 6. The authors need to state what clinical data is likely to be extracted from case files. 7. Are there any limitations that the authors observe in their study protocol? 8. The abstract can be better organized similar to a standard format of submission.

VERSION 1 – AUTHOR RESPONSE

Reviewer Comments	**Author Responses**
Reviewer: 1 Reviewer Name Dr. Siddharth Sarkar 1. The aim of the study (especially the first sentence) seems to be quite diffuse. Can the authors make the aims much clearer. 2? Similarly, can the authors clarify which is the primary objective (in the abstract there are two and in the main text they are not differentiated). 3. Can the authors describe the setting more in detail, in terms of who funds the treatment, what all kinds of services are available, what happens to the patients when they are discharged, whether family stays with the patient in inpatient care, etc? 4. The authors mention that the sample aimed is around 60 -100. Can they determine the precision that would be gained by this sample/ or carry out a formal sample size	**Reviewer: 1** **1. Make aims more clear** The section describing aims has been rewritten to make the aims clearer. **2. Clarify which is the main objective** The main objective has been highlighted and re- stated more succinctly. **3. Describe the setting in more detail** More information has been added under the section “Setting” to describe the study site.

estimation? The authors can get comparative estimates from other studies (For example: "Assessing catatonia using four different instruments: Inter-rater reliability and prevalence in inpatient clinical population.").	**4. Carry out a formal sample estimation and determine the precision that would be gained. Look at "Assessing Catatonia using four different instruments: inter-rater reliability and prevalence in inpatient population** The number of expected admissions had been revised due to COVID-19 outbreak related changes in admission stats because of hospital services being adapted to provide more COVID-19 related inpatient services. A formal sample estimation has been carried out using the appropriate formula under the section: "Sampling".
5. Objective 1 is unclear in phraseology and what it intends to measure. Collection of data is part of any prospective observational study. 6. While the authors mention the use of Bradford Hill criteria for examining causality. But can they mention what association / causal relation they want to infer on.	5. **How Objective 1 is phrased is unclear.** Objective one has been merged with objective 2 and re-stated more succinctly and objective 2 and 3 have been re-stated as one clearer objective. **6. Mention what association/ causal relation you want to infer on.**
7. How will response to treatment be measured?	The association that will be looked for is between catatonia and demographic or clinical correlates such as age, gender, DSM 5 diagnosis, substance use, vitamin 12 deficiency and food insecurity and other co-occurring medical conditions. This also relates to the comment and question raised in point number 8.
8. What are the predictors of catatonia that the authors are going to look at. It would be better to be defined a-priori that these are the parameters / variables that would be assessed for being predictors. Are there any probes that would be used for patients when they come for follow up to understand the experiences of catatonic? Will all the patients be followed up, or some attrition is expected.	**7. How will response to treatment be measured?** This will be measured in the following ways. During the admission period in the first hours to 2 weeks of admission, the length of admission, the clinical status once discharged as assessed at one, two, and three months post-discharge. During these points of assessment, the BFCRS tool will be re-applied on all participants who were assessed as having catatonia during the admission period. **8. What are the predictors of catatonia that are going to be looked at?** These have been listed in response 6 above and are included in the data collection sheet. **Are there any probes that would be used for patients during the follow-up period when they come for follow-up to assess the experience of catatonia and will all patients be followed up**
9. The authors should take into account that catatonia is quite heterogenous, prevalence rates vary	Patients who will be followed up are those participants who screened positive for catatonia. The following has been included in the data collection sheet and under the

with different items, and certain items of some of the instruments do not lend well to inter-rater reliability. Yet, overall catatonia as a concept is useful for clinical decision making. This should figure in the acknowledged limitations.	section: “Assessment and measurement” Please describe (in your own words) your experience during the catatonic episode in terms of (1) your thoughts, (2) your feelings and (3) your behaviour. **9. Limitations should include an acknowledgement of the heterogenous nature of catatonia, and the inter-rater reliability of the instruments used to assess for catatonia.** This has been added in the section
Reviewer: 2 Reviewer Name Gábor Gazdag 1. Abstract, Introduction, 2nd sentence: the prevalence rate of catatonia in the literature is much wider than 10-20%, range from 7 (Bush G, Fink M, Petrides G, Dowling F, Francis A. Catatonia. I. Rating scale and standardized examination. Acta. Psychiatr. Scand. 1996, 93:129-136.) to 63% (Stuivenga M, Morrens M. Prevalence of the catatonic syndrome in an acute inpatient sample. Front. Psychiatry 2014, 5:174.), depending on the setting the survey was conducted. 2. Introduction, 1st sentence: Kraepalin correctly is Kraepelin. 3. Choice of screening tool and rating scale: BFCRS is the 23-item scale; the screening instrument is the BFCSI. 4. Questions to the methods: authors do not fix the time frame of the initial screening. Further, is there any therapeutic protocol that will be used in the treatment of catatonia, or it will be solely the decision of the treating physician?	**Reviewer: 2** **1. Prevalence of catatonia is much wider than 10-20%, range from 7 (Bush G, Fink M, Petrides G, Dowling F, Francis A. Catatonia. I. Rating scale and standardized examination. Acta. Psychiatr. Scand. 1996, 93:129-136.) to 63%.** An amendment has been made and the wider prevalence range of catatonia has been included along with the suggested references which have now been incorporated into the amended protocol **2. Correct typo:** Kraepalin corrected to Kraepelin **3. Choice of screening tool and rating scale: BFCRS is the 23-item scale; the screening instrument is the BFCSI.** The use of the terms BFCRS and BFCST have been amended to reflect their appropriate use in the protocol i.e. BFCSI has now been used for the screening of catatonia and BFCRS for the rating of catatonia. 4. **Questions on methods: What is the time frame of the initial screening?** The expected time frame is beginning of September 2020 to end of August 2021. This information has been included in the amended protocol under the section “Objectives”. **Is there any therapeutic protocol that will be used in the treatment of catatonia, or it will be solely the decision of the treating physician?** The treatment protocol will be up to the treating physician but is based on the Unit protocol of administering an infusion of Lorazepam upon admission and continuing with Lorazepam or ECT for as long as the patient remains catatonic.

5. Consent form: I do not understand why non-consenting patients or relatives must sign a form. Explain it please!	**5. Why is there provision for non-consenting patients or relatives must sign a form?** The option of a relative signing the consent form is included to accommodate proxy content. This is not for non-consenting patients because those who do not consent will not be included in the study. It is for use when the capacity assessment conducted indicates that the person's capacity is impaired, in which case the closest relative would be approached to make the decision on behalf of the participant. Use of proxy consent in mental health research is applicable for those who lack the capacity to consent and the nearest relative or guardian consents on their behalf. It is permissible within the mental health care setting in South Africa due to the challenges with capacity to consent that may exist in patients with acute mental illness. Proxy consent ensures that respondents' rights are guarded while making it possible to include individuals or groups who may potentially benefit from scientific advances gained from research. The South African National Department of Health Guidelines on ethics in health research similarly state that persons should not be excluded unfairly based on discrimination or disability.
6. I have some ethical concerns regarding the involvement of minors in the study as the investigation of this special population is not among the aims of the study. I suggest excluding patients under 18 from the study.	**6. Addressing ethical concerns regarding the involvement of minors** Factors which were weighed in considering the inclusion of participants less than 18 years were: • An observation by the researchers that a significant number of those who presented with catatonia at the study site were younger than 18, which means that if those younger than 18 were excluded form the study, then this would have the potential of affecting the accuracy and reliability of the results. • In South Africa The National Health Act, No. 61, 2003, mandates active consent from a parent or legal guardian for all research conducted with research participants under the age of 18 years. This ensures that minors are not excluded from essential research and advances in medical developments supported by new knowledge. Both theirs and their parents consent will be sought, • The research site treats minors as well as adults due to limitations in resources. Since age is part of the demographic data that will be collected on participants, then the findings of this study could assist in further advocating for allocation of resources for specialized child and adolescent mental health inpatient services if the number of minors affected by catatonia is found to be high.

Reviewer: 3 Reviewer Name Krishna Prasad Muliyala 1. There is a possibility that catatonia may be underdiagnosed/undiagnosed by the clinicians of the MHU but may be picked up by the researchers; the authors need to state their approach in such instances.	**Reviewer 3** **1. There is a possibility that catatonia may be underdiagnosed/undiagnosed by the clinicians of the MHU but may be picked up by the researchers; the authors need to state their approach in such instances.** The following paragraph has been included under "The study process and outline": In cases where the Researcher or RAs identify possible missed catatonia, the treating doctor will be provided with any additional information picked up during the participants assessment in order to allow for a review of the patient's clinical case and management.
2. The pathway of care up to the MHU needs to be stated.	**2. The pathway of care up to the MHU needs to be stated.** The following information has been added under the section " Setting": The MHU is an acute inpatient unit offering 24-hour care to admits persons who present with acute mental illness requiring inpatient treatment. It accepts referrals from all the other hospital departments including the Accident and Emergency department, as well as referrals from primary care clinics and district hospitals in the nearby vicinity. The usual period of admission ranges anything from three days to a few weeks. All cases of suspected catatonia, from any of the referring departments are discussed with the MHU team and prioritized for admission into the unit. Any treatment to be given thereafter is discussed with the MHU team and documented in the folder.
Is it possible that some patients may receive lorazepam in an emergency care service of the general medical hospital?	**Is it possible that some patients may receive lorazepam in an emergency care service of the general medical hospital?** This is a possibility and information on any treatment advice received and administered in the emergency care is documented in the folder and will be part of the clinical information to be collected during the data collection stage.
3. The authors need to clarify as to when will the research assistants apply the BFCRS, at what time point after admission?	3. **The authors need to clarify as to when will the research assistants apply the BFCRS, at what time point after admission?** The information below has been added to the section: "The study process and outline": The assessment of new admissions will be daily on weekdays with the expectation being to conduct screening of new admissions daily or within the first 48-hours at least. Information on clinical presentation of patients admitted over weekends will be supplemented from the clinical folders.
4. The likely topic guide for the	

qualitative part of the study may need to be added. 5. How will the research assistants be trained for BFCRS? Will there be a check on IRR? 6. The authors need to state what clinical data is likely to be extracted from case files. 7. Are there any limitations that the authors observe in their study protocol?	**4. The likely topic guide for the qualitative part of the study may need to be added.** **The following part has been added under the section: "Methods of assessment and measurement"** Please describe (in your own words) your experience during the catatonic episode in terms of (1) your thoughts, (2) your feelings and (3) your behaviour. **5. How will the research assistants be trained for BFCRS? Will there be a check on IRR?** The inter-rater reliability of the BFCRS was demonstrated to be good (α=0.779) in a study looking at four different instruments to assess for catatonia. [26] In the planned study, training to be provided to the RAs on the use of the BFCSI/ BFCRS will be through: • explaining terms used in the BFCSI/BFCRS to describe clinical signs and symptoms of catatonia and • providing a demonstration of how to elicit and document the 14-items and 23-items in the BFCSI/BFCRS, and how to capture the relevant information accurately onto the data capturing form • ensuring RAs use practice participants initially under direct observation of the researcher before starting the actual recruitment. An IRR in the range of (α=0.61 to 0.8) during the practice scoring will be deemed acceptable for RAs to proceed to the scoring of study participants. Inter-rater reliability will also be addressed through ensuring that everyone has a similar understanding of all items to be rated in the screening tool and how these should be recorded. **6. The authors need to state what clinical data is likely to be extracted from case files.** Clinical data that will be extracted include: Current psychiatric diagnosis, co-occurring medical conditions, any other treatment administered, history of substance use, history of previous catatonic episodes, vital signs like temperature on admission, blood pressure, pulse, investigations like creatinine kinase, iron levels, thyroid function teste urea and electrolytes or any other relevant clinical investigations reflected in the file which are noted by the treating team to be of relevance to the current admission. **7. Are there any limitations that the authors**

8. The abstract can be better organized similar to a standard format of submission.	**observe in their study protocol?** Limitations of the protocol have been included in the section 'Article Summary' under Strengths and limitations of this study. They are: • descriptive nature of the study and the limited number of participants that could limit the applicability of significant associations between variables regarding cause and effect and the generalisability of findings • the heterogenous nature of catatonia and interrater reliability of catatonia screening instruments are another source of potential limitations of the study. In addition, there also exists the possibility that participants with catatonia may have treatment administered at the point of referral which raises the possibility that the catatonia may already be resolved by the time they reach the Mental Health Unit, which might in turn affect the pick up rate of catatonia in the study. All this information would be available in the clinical notes, enabling the researchers to identify and document such cases. **8. The abstract can be better organized similar to a standard format of submission.** Guidelines of how to structure the abstract according to BMJ open for protocols were consulted. The abstract was amended and the guidance on how to structure the abstract for a protocol submission was followed.

VERSION 2 – REVIEW

REVIEWER	Dr Siddharth Sarkar All India Institute of Medical Sciences, New Delhi, India
REVIEW RETURNED	06-Sep-2020

GENERAL COMMENTS	The authors have addressed my comments. About inferences that would be drawn on "treatment response" - whether it is complete resolution of catatonia, or a fixed percentage reduction or scores below a threshold. I reckon that the authors would be able to use the data to define so, but "a priori" definition might be helpful for them. "In summary ..." has a numbering of "iv." which does not have text around it. This can be deleted.

REVIEWER	Gábor Gazdag Jahn Ferenc South Pest Hospital, Department of Psychiatry and Psychiatric Rehabilitation
REVIEW RETURNED	05-Sep-2020

GENERAL COMMENTS	My comments were adequatelly adressed in the corrected version.

REVIEWER	Krishna Prasad Muliyala National Institute of Mental Health and Neurosciences, Bangalore, India
REVIEW RETURNED	19-Sep-2020

GENERAL COMMENTS	A few repetitions in the text and spelling errors may be corrected: "A 50% reduction in signs and symptoms in response to the treatment intervention represents a response while a 100% reduction is considered full resolution." is repeated twice in the tracked document; "thyroid function teste"

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Dr Siddharth Sarkar
1. About inferences that would be drawn on "treatment response" - whether it is complete resolution of catatonia, or a fixed percentage reduction or scores below a threshold. I reckon that the authors would be able to use the data to define so, but "a priori" definition might be helpful for them.
2. "In summary ..." has a numbering of "iv." which does not have text around it. This can be deleted.
AUTHOR RESPONSES
1. The sentence under 'Methods of assessment' that read:
"A 50% reduction in signs and symptoms in response to the treatment intervention represents a response while a 100% reduction is considered full resolution", was moved from this section to the section talking to 'Objectives' and referring to clinical correlates and treatment response. In addition, it was rephrased in the following way:
"Response to treatment will be according to the following parameters: A 50% reduction in signs and symptoms will be considered a response while a 100% reduction will be a considered a full resolution. Conversely, a reduction in symptoms of less than 50% will be regarded as a suboptimal response and a reduction that is more than 50% but less than 100% will be a response but without full resolution."
2. This typo was deleted

Reviewer: 2
Reviewer Name: Gábor Gazdag
1. My comments were adequately addressed in the corrected version.
AUTHOR RESPONSES
No further responses required from authors, thank you.

Reviewer: 3
Reviewer Name: Krishna Prasad Muliyala.
1. A few repetitions in the text and spelling errors may be corrected: "A 50% reduction in signs and symptoms in response to the treatment intervention represents a response while a 100% reduction is considered full resolution." is repeated twice in the tracked document;
2. "thyroid function teste"
AUTHOR RESPONSES
1. The sentence under 'Methods of assessment' that was repeated and read:
"A 50% reduction in signs and symptoms in response to the treatment intervention represents a response while a 100% reduction is considered full resolution", was rephrased to convey the same information and it was moved to the section on 'Objectives' that talks to clinical correlates that will be examined. This was also to respond to a minor correction recommended by Reviewer 1. The

repetition sentence was removed.
2. This typo was corrected to read “thyroid function tests” and a comma was added thereafter.