QUALITY IMPROVEMENT OF POSTGRADUATE MEDICAL PROTOCOL (PMP) SUBMITTED TO NATIONAL MEDICAL RESEARCH REGISTRY (NMRR), MALAYSIA

ZAINAL, Z.[1] – HONG, L. W.[2*] – ROSLI, N.[2] – YUAN, O. Y.[3] – KHEE, H. Y.[2] – ZAKARIA, N. T.[4] – ADNAN, T. H.[5] – HATTA, N. K. B. M.[2]

[1] *Malaysian Healthcare Performance Unit, National Institute of Health, Kuala Lumpur Hospital, Level 3, Administration & Finance Block, Jalan Pahang, 50586 Kuala Lumpur, Malaysia.*

[2]*Centre for Coordination of Clinical Research Network, Institute for Clinical Research, National Institutes of Health (NIH) Malaysia, Blok B4, Jalan Setia Murni U13/52, Seksyen U13 Setia Alam, 40170 Shah Alam, Malaysia.*

[3] *Faculty of Science, University of Malaya, 50603, Kuala Lumpur, Malaysia.*

[4] *Klinik Kesihatan Selayang Baru, Jalan Sungai Tua, Taman Selayang, 68100 Batu Caves, Selangor, Malaysia.*

[5] *Sector for Biostatistics & Data Repository, National Institutes of Health (NIH) Malaysia, Blok B4, Jalan Setia Murni U13/52, Seksyen U13 Setia Alam, 40170 Shah Alam, Malaysia.*

**Corresponding author*
e-mail: laiwh@crc.gov.my

(Received 08th January 2020; accepted 18th February 2020)

Abstract. Postgraduate medical protocols (PMPs) collectively represent approximately 20% of the total number of medical research protocols approved by Medical Research & Ethics Committee (MREC) in 2012. Previous studies found most of these PMPs required further amendment upon an initial MREC review, which led to a delay in obtaining ethical approval. Therefore, this cross-sectional study aimed to identify the weaknesses of PMPs submitted for ethical approval. Present findings demonstrated the three main weaknesses identified in research protocols are the lack of description for (i) study design, (ii) total number of subjects planned to be enrolled and (iii) subject's exclusion criteria; each with error rates of 21%, 20% and 13%, respectively. In addition, the two main weaknesses found in patient information sheets/ informed consent forms (PIS/ICFs) are the lack of description for (i) compensation in the event of trial related injury and (ii) anticipated trial expenses; each with error rates of 16% and 15%, respectively. Hence, this paper provides an in-depth discussion of how to improve the development of both research protocols and PIS/ICFs based on the five common weaknesses identified in this study. It also aims to serve as a useful guide for medical students to develop quality PMPs which are both ethical and scientifically-sound by adhering to all the applicable regulatory requirements.
Keywords: *quality, postgraduate medical protocol, ethics committee, patient information sheet*

Introduction

Malaysia has a growing influence for the proper conduct of clinical research within the ASEAN region. This has arisen from a good collaboration between public and private hospitals and clinical research organizations, together with an increased accessibility of a diverse patient pool and low-cost, highly-qualified talented clinical research practitioners (Hon et al., 2011). In addition, Malaysia is also one of the

favourite destinations for all types of clinical research which is partially attributed to a concerted effort of the Malaysian Government for encouraging industry-sponsored trials. The most recent example of this is the establishment of Clinical Research Malaysia (CRM) to promote Malaysia as a hub for promoting industry-sponsored research (particularly clinical trials) within Malaysia and its nearby ASEAN region.

Clinical trials involving human subjects are now becoming larger and more complex, with an increasing number of trials enrolling thousands of patients across multiple centres, both locally and abroad. Although this phase of drug development contributes to the overall progress of clinical research, however the Institutional Review Board (IRB) will now have to assume a greater role in both the ethical review and approval of research protocols. Medical Research & Ethics Committee (MREC) is the ethics committee within the Malaysian Ministry of Health (MOH) which has been tasked to review research protocol and to grant ethical approval for research involving MOH researcher and/or MOH facilities.

A gradual but significant increase in the total number of research protocols have been submitted to MREC since its inception in 2002; and it was found that over the years, the quality of research protocols that were submitted to MREC has varied widely. Postgraduate medical protocols (PMPs) collectively represent approximately 20% of the total number of medical research protocols approved within National Medical Research Register (NMRR) in 2012, which represent the largest proportion of research protocols being submitted to MREC compared to those submitted by other investigators such as undergraduates, diploma-holders, and researchers involved in industry-sponsored research (National Clinical Research Centre, 2014). In addition, it is also found that most of these PMPs will require further amendment upon an initial MREC review; therefore requiring longer period of time to obtain a formal ethical approval (National Clinical Research Centre, 2014).

Hence, to mitigate this issue, this study thereby aims to provide an initial overview of the most common weaknesses found in PMPs that were identified by MREC reviewers, and then provides an in-depth discussion of these weaknesses and serves as useful reference for future medical students when they intend to submit their research protocols to MREC.

Materials and Methods

Study design

This is a cross sectional study of a compilation of comments provided by MREC reviewers during initial review for PMPs. Comments were compiled and categorised to three main areas namely: ethical, scientific and administrative.

Study population

This study retrieved data from PMPs receiving ethical approval from MREC during the period from 1st January 2012 to 31st December 2012.

Study conduct

Primary source data were anonymised by NMRR secretariat by replacing personal identifiers with a study code. Coded data were transmitted to investigators and kept in Clinical Research Centre (CRC) server with access only to project team. The code and

link to the primary source data were held by the NMRR secretariat. Relevant information were extracted by the project team from the coded data, transferred into the data form and uploaded into the CRC server. MREC first review decision letters were examined. Review comments from MREC were checked against elements in Malaysian Good Clinical Practice (GCP) guideline and were grouped into 3 categories: ethical, scientific and administrative. Frequency (%) of comments for elements in each category in protocols, patient information sheets (PIS) and informed consent forms (ICF) were calculated and tabulated.

Results

Protocol issues identified by MREC reviewers were grouped into ethical, scientific and administrative categories and ranked according to their rate of error. The 3 main ethical issues are lack of description of (i) subject's exclusion criteria; (ii) subject's inclusion criteria; and (iii) subject's withdrawal criteria each with error rates of 13%, 7% and 5%, respectively. As for the scientific issues, they consist of lack of description of (i) the type/design of trial to be conducted and a schematic diagram of trial design, procedures and stages; (ii) number of subjects planned to be enrolled; and (iii) the objectives and the purpose of the trial each with error rates of 21%, 20% and 13%, respectively. Apart from that, the 3 main administrative issues are lack of description of (i) protocol title, protocol identifying number and date; (ii) the name and title of the investigator(s) who is(are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s); and (iii) the publication policy each with error rates of 11%, 7% and 5%, respectively (*Table 1*). Present results show the most frequently compiled protocol issues are elements from scientific category and these findings suggest that the skills of medical students in preparing a scientifically-sound research protocol are poor.

Table 1. *Protocol issues identified by MREC reviewers at initial review of PMPs in 2012.*

Category	Part of Protocol	Rate of Error (%)
Ethical Element	The subject exclusion criteria.	13
	The subject inclusion criteria.	7
	The subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures as below: (a) When and how to withdraw subjects from the trial/ investigational product treatment. (b) The type and timing of the data to be collected for withdrawn subjects. (c) Whether and how subjects are to be replaced. (d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.	5
	The statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).	3
	The description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.	
	The type and duration of the follow-up of subjects after	

	adverse events.	
	The description of ethical considerations relating to the trial.	
	The SOP for data handling and record keeping.	
	The procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.	2
Scientific element	The description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.	21
	The number of subjects planned to be enrolled.	20
	The objectives and the purpose of the trial.	13
	The description of the measures taken to minimise/avoid bias.	11
	(a) Randomisation. (b) Blinding.	
	The description of the population to be studied.	10
	The summary of the known and potential risks and benefits, if any, to human subjects.	8
	The description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).	7
	The description of the statistical methods to be employed, including timing of any planned interim analysis(ses).	
	The name and description of the investigational product(s).	5
	The references to literature and data that are relevant to the trial and that provide background for the trial.	3
	The specific statement of the primary endpoints and the secondary endpoints.	
	The description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s), also include a description of the dosage form, packaging, and labelling of the investigational product(s).	
	The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow- up (if any).	
	The medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.	
	The specification of safety parameters.	
	The summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.	2
	The maintenance of trial treatment randomisation codes and procedures for breaking code.	
	The methods and timing for assessing, recording, and analysing of efficacy parameters.	
Administrative Element	The protocol title, protocol identifying number and date.	11
	The name and title of the investigator(s) who is(are) responsible for conducting the trial, and the address and	7

telephone number(s) of the trial site(s).	
The publication policy.	5
The name and address of the sponsor and monitor (if other than the sponsor).	2
The name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.	

Subsequently, issues in the PIS/ICF identified during initial MREC review are listed in *Table 2*. The two main issues are lack of description of (i) compensation in the event of trial related injury; and (ii) anticipated trial expenses with error rates of 16% and 15%, respectively. Although monetary elements are the most frequently compiled issues in PIS/ICF, which could possibly because most PMPs were either self-funded studies that do not involve compensation or trial expenses were covered by MOH according to government directive that participants in investigator initiated trial (IIT) are exempted from hospital charges.

Table 2. *Patient information sheets issues identified by MREC reviewers at initial review of PMPs in 2012.*

No.	Issues	Rate of Error (%)
1.	The consent form does not clearly state the compensation and/or treatment available to the subject, in the event of trial related injury.	16
2.	The anticipated expenses, if any, to the subject for participating in the trial is not mentioned clearly.	15
3.	The consent form does not clearly state the approximate number of subjects involved in the trial.	14
4.	The consent form does not clearly state the trial treatment(s) and the probability for random assignment to each treatment.	11
5.	The consent form does not clearly state the person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of the trial-related injury.	
6.	The consent form does not clearly state the trial procedures to be followed, including all invasive procedures.	10
7.	The consent form does not clearly state the reasonably foreseeable risks or inconveniences to the subject and when applicable, to an embryo, fetus, or nursing infant.	
8.	The consent form does not clearly state the expected duration of the subject's participation in the trial.	
9.	The consent form does not clearly state the reasonably expected benefits.	9
10.	There is no clear statement that the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.	7
11.	The consent form does not clearly state the purpose of the trial.	6
12.	The consent form does not clearly state those aspects of the trial that are experimental.	
13.	The consent form does not clearly state that the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be	5

	granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorising such access.	
14.	The consent form does not clearly state that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in this trial.	
15.	The anticipated expenses, if any, to the subject for participating in the trial are not mentioned clearly.	4
16.	The consent form does not clearly state that records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available? And if the results of the trial are published, the subject's identity will remain confidential.	
17.	The consent form does not clearly state the foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.	
18.	The consent form does not clearly state the source(s) and component(s) of the investigational product(s) that may be culturally unacceptable.	
19.	The consent form does not clearly state the subject's responsibilities.	2
20.	The consent form does not clearly state the alternative procedure(s) or course(s) of treatment that may be available to the subject and their important potential benefits and risks.	
21.	It is not stated that the trial involves research.	1

Discussion

Trial design

Trial design is an important aspect of a well-designed medical research. In an interventional study, the study population typically undergoes a pre-specified intervention (usually either a clinical drug therapy or a surgical procedure) while in an observational study, the study population does not undergo a pre-specified intervention but instead, the researcher will draw inferences from a sample which should be representative of the entire population. This means that the independent variable will not be under the control of the researcher in an observational study (Banerjee and Chaudhury, 2010). Therefore, it is essential for medical students to thoroughly understand the strengths and limitations of each clinical trial design and then apply the most appropriate clinical trial design to achieve the clinical trial objectives (by answering the primary clinical research question). Hence, the correct clinical trial design for a PMP should enable investigator(s) to (i) fulfil ethical requirements for conducting the research; (ii) permit efficient use of scarce research resources; (iii) isolate the treatment effect of interest from confounders; (iv) improve precision by

reducing both selection bias and observer bias; (v) quantify and minimize any random error or uncertainty; (vi) simplify and validate the statistical analysis; and (vii) increase the external validity of the trial (Turner, 2010). All in all, selecting the correct trial design when preparing clinical trial protocol is of paramount importance to avoid any potential bias and confounding throughout the clinical trial and also to ensure that the study protocol can be practically implemented as planned.

Sample size

In a clinical trial, the sample size is the minimum number of patients or other experimental units which is required to be recruited in order to have sufficient power to answer the research question(s). Sample size plays a pivotal role in research planning as it affects both the duration and cost incurred by a study. Apart from that, sample size also enables the estimation of statistical power attained by a study and so it provides a rough pre-determination of probability of success of a study or experiment (Goldsmith, 2002). In order to ensure that a research study is being conducted successfully, it is necessary to collect a good quality sample that is representative of the entire population. Sample collection depends highly on total number of subjects recruited in a sample and also the sampling method for recruiting them. Therefore, a good sample of the experimental or observational units in a PMP must be obtained from the appropriate target population, which is duly randomized according to proper randomisation procedures and all measurements must be obtained by using reliable measurements (Lenth, 2012). It should also be noted that the minimum number of subjects in a research study should directly correspond to the number of goals of a study in order for a study to be deemed to be both scientifically and statistically valid by reducing the number of outliers or extreme observations (Lenth, 2012). Furthermore, sample size also has an impact on both economic and ethical aspects of a study because an under-sized study can subsequently produce useless or redundant results, whereas an over-sized study may utilize more resources than are necessary (Case and Ambrosius, 2007). For trials involving human subjects, an appropriate sample size is essential because an under-sized experiment might unnecessarily expose the subjects to potentially harmful treatments without producing valid research findings whereas an over-sized experiment may be exposing an unnecessarily large number of subjects to a potentially harmful treatment (Lenth, 2012). From the above, it is clear that it is very important to fathom the minimum number of study subjects required for a clinical trial by performing a valid sample size calculation using several reliable methods and tools. To date, various online and commercial computer software programs are available to calculate the power of a study and also the estimated sample size required for attaining a sufficient level of power for the study. Two popular websites for a researcher to refer to when calculating a minimum sample size required for attaining a sufficient level of power for the study are Lenth (2018) and Pezzullo (2020). In summary, an adequate sample of study subjects must be recruited in order to ensure that a clinical trial is both scientifically and statistically valid, by attaining a sufficient level of power for the clinical trial.

Primary objective(s) of a research study

The research objectives of a clinical trial are the key elements for conducting a research study in that they are also the goals to be accomplished by the whole research process. Generally, these research objectives are categorized as either ‘general’ or

'specific'. A general research objective is one to be achieved by the research protocol while specific research objectives correspond to the specific research questions that the investigator wants to answer through the proposed study which can then be further classified as primary and secondary objectives (Al-Riyami, 2008). The objectives in the research protocol are preferable to be written in a precise and meaningful manner that is both operationalizable and achievable. A clear research objective might enable the readers to shed light on the primary purpose of the entire research protocol so as to avoid unnecessary confusion throughout the research process. It is also advisable not to include those objectives that are overambitious as they might start out to be optimistic but eventually may lead to failure (Sahu, 2013). The research objective ought to be exactly aligned with the parameter which it aims to evaluate, which means that the primary research objective of the research study should be directly aligned with the primary research objective that has been formulated in the study protocol since a single research protocol with too many research objectives may not be able to achieve all of them (Ecarnot et al., 2015).

Exclusion criteria for prospective subjects

One of the common errors in the preparation of a research protocol is the omission of exclusion criteria for prospective subjects. Exclusion criteria are those characteristics of prospective subjects that automatically disqualify them from being included in the study regardless of whether they have the potential to develop the outcome of interest. Examples of exclusion criteria include individuals who are incapable of meeting pre-test requirements for the study, suffering from major co-morbidities that can potentially confound the study results, or who are not able to attend future follow-up visits. Hence, patients having any of these characteristics should be excluded from participating in the study. In addition, individuals who are not fit to receive the aforementioned interventions or have already been participating in other clinical trials should also be excluded in a research study (McElroy and Daniela, 2014). Furthermore, vulnerable study populations comprising of pregnant woman, children and elderly should also be excluded depending on the specific objectives of a research study. The exclusion criteria aim to exclude a sub-set of individuals having a higher risk of developing adverse effect of the intervention in order to afford protection for them. By excluding them, it is also possible to minimize any potential confounding effect of the patient's other co-morbidities on the study outcomes (McElroy and Daniela, 2014). Previous studies of McElroy and Daniela had stated that exclusion criteria are having an important role for striking a delicate balance between defining a study population that is best suited to answer the research question and determining those individuals who are truly eligible for enrolment. This will enhance the probability of producing reproducible and reliable results or outcomes, and also avoiding incurring unnecessary risk in all the study subjects by inadvertent exploitation of vulnerable subjects (McElroy and Daniela, 2014). However, having unclear or vague exclusion criteria found in a research protocol might often introduce bias thereby interfere with the accuracy of the results obtained from the clinical trial. Therefore, all exclusion criteria must be clearly stated in a positive manner, accompanied by strong justifications along with their underpinning rationale within a scientifically sound research protocol.

Compensation for trial-related injury

Previous findings have suggested that most of the PMPs did not include a description of compensation for trial-related injury because these research studies are usually of minimal risk. However, this does not fully justify the students from omitting to mention about risk in the PIS/ICF. Trial-related injury is an inevitable component of any research study which can manifest itself in many different forms such as physical, psychological/emotional and social; all of which would require either emergency care or long term medical care (Munshi and Thatte, 2013). Therefore, it has been a usual practice for compensation to be provided to subjects who have suffered from trial-related injury by either monetary or non-monetary means. The monetary means of compensation is referring to a sum of money being paid to the subject as a form of compensation for the costs incurred by these trial-related injuries such as loss of daily wages, etc.; while non-monetary means of compensation is referring to the provision of free medical care for ameliorating the effects of trial-related injuries (Pandya and Desai, 2013). If serious trial-related injuries have occurred in clinical trial subjects, then these subjects shall be repaid by both monetary and non-monetary forms of compensation. Thus, the rights of subjects are protected by the provision of compensation for trial-related injury during a clinical trial. This applies equally to all clinical research protocols in which one of their essential components is the provision of compensation for a trial-related injury, the details of which must be provided within the written PIS/ICF and also via oral discussion during eliciting the informed consent for clinical trial participation (Ministry of Health Malaysia, 2011).

Anticipated trial expenses

This study had established that most PMPs did not include a description of anticipated trial expenses and it is suggested this could be due to a government circular which has planned to exempt all the necessary expenses for all the Investigator Initiated Research (IIRs) conducted by Ministry of Health (MOH) investigators. These anticipated trial expenses are costs which are necessary for the proper conduct of a clinical trial, which includes the implementation of clinical trial procedures, and the provision of drug treatment or the use of medical devices, amongst others. It is pivotal to clearly state all the anticipated trial expenses for clinical trial participation within the PIS/ICF as there can be a wide variability for the costs incurred by the provision of drug treatments, diagnostic tests and surgical procedures; ranging from the necessary remittance of full payment to the total exemption of full payment (Grady, 2005). Hence, the subjects shall be informed regarding the anticipated trial expenses for clinical trial participation, i.e. whether these expenses can be exempted or will have to be paid in full (or partial) by the prospective clinical trial subjects before participating in a clinical trial. Therefore, it is necessary to include a provision for any unforeseen expenses which may occur during a clinical trial; examples of these include any of the unforeseen interrupted processes during the course of medical treatment, such as X-rays, computerized tomography (CT) scans, magnetic resonance imaging (MRI) and others. Hence, it will be most ideal to include a full list of all the possibly anticipated trial expenses in the PMPs.

Conclusion

Most weaknesses found in PMPs for this study stemmed from the scientific issues, which had underscored the pressing need for medical students to improve on the

scientific aspects of their protocol development skills for medical research. In summary, it is essential for medical students to improve their research protocol writing skills by avoiding all the weaknesses identified by this study when they are writing up a clinical research protocol (and its accompanying PIS/ICF) in the future. Hence, this study aims to serve as a useful guide for medical students to develop quality PMPs which are both ethical and scientifically-sound by adhering to all the applicable regulatory requirements.

Acknowledgement

We would like to thank the Director General of Health Malaysia for his permission to publish this article.

REFERENCES

[1] Al-Riyami, A. (2008): How to prepare a Research Proposal. – Oman Medical Journal 23(2):66-69.
[2] Banerjee, A., Chaudhury, S. (2010): Statistics without tears: Populations and samples. – Industrial psychiatry journal 19(1): 60-65.
[3] Case, L.D., Ambrosius, W.T. (2007): Power and sample size. InTopics in Biostatistics. – Humana Press 404:377-408.
[4] Ecarnot, F., Seronde, M.F., Chopard, R., Schiele, F., Meneveau, N. (2015): Writing a scientific article: A step-by-step guide for beginners. – European Geriatric Medicine 6(6):573-579.
[5] Goldsmith, L.J. (2002): Power and sample size considerations in molecular biology. – Biostatistical Methods 184:111-130.
[6] Grady, C. (2005): Payment of clinical research subjects. – The Journal of clinical investigation 115(7): 1681-1687.
[7] Hon, Y.K., Goh, P.P., Teoh, S.C., Hazrah, A. (2011): Clinical research in Malaysia: a new direction for clinical trial initiative in Malaysia. – RIPER PDIC Bulletin 2(14):13-16.
[8] Lenth, R. (2018). Java applets for power and sample size. Available on: http://homepage.divms.uiowa.edu/~rlenth/Power/
[9] Lenth, R.V. (2012): Some practical guidelines for effective sample size determination. – The American Statistician 55(3):187-193.
[10] McElroy, L.M., Daniela, P.L. (2014): Defining the Study Cohort: Inclusion and Exclusion Criteria. In Success in Academic Surgery: Clinical Trials. – Verlag-London: Springer 131-139.
[11] Ministry of Health Malaysia (2011): Malaysian Guideline for Good Clinical Practice. – 3rd ed. Malaysia: National Committee for Clinical Research 104p.
[12] Munshi, R., Thatte, U. (2013): Compensation for research related injury. – Perspectives in clinical research 4(1): 61-69.
[13] National Clinical Research Centre (2014): Retrospective Study on Time Taken to Obtain Ethical Approval from Medical Research and Ethics Committee (MREC) in 2012 for Postgraduate Master Proposals Registered in National Medical Research Registry (NMRR). Technical Report Series, NCRC/QAU/2014.1.
[14] Pandya, M., Desai, C. (2013): Compensation in clinical research: the debate continues. – Perspectives in clinical research 4(1):70-74.
[15] Pezzullo, J. (2020). Web pages that perform statistical calculation! Available on: https://statpages.info/

[16] Sahu, P.K. (2013): Research Proposal and Report Writing. In Research Methodology: A Guide for Researchers In Agricultural Science, Social Science and Other Related Fields. – Nadia: Springer 432p.
[17] Turner, J.R. (2010): New drug development: an introduction to clinical trials. – 2nd ed. New York: Springer Science & Business Media 281p.