GSC Biological and Pharmaceutical Sciences

eISSN: 2581-3250 CODEN (USA): GBPSC2

Cross Ref DOI: 10.30574/gscbps

Journal homepage: https://gsconlinepress.com/journals/gscbps/

(SHORT COMMUNICATION)

Check for updates

Protocol for the development and validation of a trigger tool for antiretroviral ADE detection among adult HIV/AIDS patients: A short communication

Amaka Yves-Ann Ezeuko [1, 2], Sunday Odunke Nduka [2], Chioma Callista Ezeuko [3], Angus Nnamdi Oli [4, *] and Obinna Ikechukwu Ekwunife [2]

[1] Drug Information Unit, Department of Pharmacy, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra State, Nigeria

[2] Department of Clinical Pharmacy and Pharmacy Management, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria

[3] Microbiology Program, Department of Biological Sciences, College of Science, Technology, Engineering and Mathematics, Alabama State University, Montgomery, AL 36104, USA.

[4] Department of Pharmaceutical Microbiology and Biotechnology, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria.

GSC Biological and Pharmaceutical Sciences, 2024, 28(02), 052–058

Publication history: Received on 11 June 2024; revised on 31 July 2024; accepted on 02 August 2024

Article DOI: https://doi.org/10.30574/gscbps.2024.28.2.0280

Abstract

Antiretroviral therapy (ART) is a lifelong combination therapy which has been very promising in managing HIV/AIDs but reported to have several adverse events on the recipients, affecting the desired antiretroviral therapeutic goals. Adverse drug event detection and prevention therefore become very important safety culture maintenance tools among patients living with HIV/AIDS. The designed protocol provided step by step approaches to develop and validate a trigger tool for detection of adverse drug events (ADE) among adult HIV/AIDS patients. The approaches involved include a baseline (Pre-trigger tool development) retrospective clinical record review to establish a baseline ADE detection capacity of a conventional non-trigger tool method; the Delphi panel process to develop the trigger tool in question; Face and content validity approach for validation of the developed trigger tool; Pilot test of the trigger tool using small clinical record sample; determining the effectiveness of the developed trigger tool through the retrospective clinical record review of same samples reviewed at the baseline. Finally, the protocol described the process of determining the feasibility of the developed trigger tool through the survey of the clinical record review team members.

Keywords: Protocol; Trigger tool; Development; Validation; Adverse drug event; HIV Patients

1. Introduction

Designing research protocol is a very important aspect of any research project because it gives a clear description of the work to be done and serves as the manual for the project team members. A good project protocol is a complete and specific work plan with a conviction that a project work can be feasible using the work plan (Cameli et al., 2018). The protocol enables the stage to stage monitoring of a project, hence it should be detailed enough to enable the review of the intended project for the approval of the review board. A quality protocol enables reproducibility of the research project.

The Delphi Panel process has been the conventional method used across studies to developed different trigger tools (Lindblad *et al.,* 2018; Hu *et al.,* 2019; Griffey *et al.,* 2020). Development of a trigger tool for antiretroviral adverse drug event (ADE) detection among adult HIV/AIDS patients can be achieved following the Delphi Panel process as well. The

* Corresponding author: Angus Nnamdi Oli

Delphi panel exercise is structured in such a way that opinions collected from group(s) are discussed openly with participants giving reasons for their input and the cycle is repeated until a consensus is reached without much dissimilarity between opinions (Grimes and Wright, 2016; Ramaj-Deksu*et al.,* 2020). The panel is overseen by a coordinator who collates responses and directs the group activities from one Delphi cycle to the next. After a trigger tool is developed, the tool undergoes a pilot testing using a few samples to confirm the sensitivity of the tool to the intended goal (Unbeck *et al.,* 2014; Lindblad *et al.,* 2018; Weingart *et al.,* 2020). For the pilot test of an antiretroviral ADE detection trigger tool, a few samples of the adult HIV/AIDS patients' clinical records (folders) would be used in the pilot test. After the pilot test, further validated using a more elaborate sample and or other validation methods may be applied.

Validation of a trigger tool for antiretroviral ADE detection among adult HIV/AIDS patients can be achieved through the review of HIV/AIDS adult patients' clinical records to identify antiretroviral ADEs using their triggers. Face and content validity is also used to determine the suitability of the developed trigger tool as a validation approach. Some other methods of validation have used the positive predictive values of the triggers; sensitivity and specificity of the trigger tools (Health Quality and Safety Commission, 2016). The use of inter-rater reliability (Cohen's kappa value) which expresses the agreement between reviewers has been reported as well (Hooper & Tibballs, 2014; Karpov *et al.,* 2016; Pierdavara *et al.,* 2016; Lindblad *et al,* 2018).

The objective of this short communication is to communicate the protocol for the development and validation of a trigger tool for antiretroviral adverse events detection among adult HIV patients.

Table 1 The Protocol

Section	**Item**
Project Overview	Title: The Protocol for the development and validation of a Trigger tool for antiretroviral ADE detection among adult HIV/AIDS patients.
	Protocol Summary: This protocol is a clear description of how to develop and validate a trigger tool for detection of Antiretroviral ADEs among adult patients living with HIV/AIDS. The trigger tool development will be achieved through a Delphi panel method. Following the trigger tool development, a pilot study is carried out on patients' clinical records to check the ability of the trigger tool to identify ADEs through its triggers. Following a positive outcome of the pilot test, validation of the tool is done by checking the adequacy of the tool in terms of structure and content validity test. Thereafter, a more elaborate clinical records review is done to ensure the effectiveness of the trigger tool on expanded HIV/AIDS' patient population. Feasibility of the use of the trigger tool among reviewers will be done as well.
	Investigators: Ezeuko A. Y. (Principal researcher: Conceptualization, Literature review and Manuscript writing), Nduka S. O. (Conceptualization and coordination, Ezeuko C. C (Literature review and editing). Prof. Obinna Ekwunife (Conceptualization and Supervision).
Introduction/Literature review	Adverse drug events and antimicrobial agents' resistance have been a regular occurrence in clinical practice resulting in morbidities, mortalities and poor clinical outcomes (Sahilu et al., 2020; Zhou & Rupa 2018; Ejiofor et al 2016). Antiretroviral therapy (ART) is a life time combination therapy and has been reported to have numerous adverse events on the patients. ADE detection is a very important safety culture maintenance tool (Schwendimann *et al.,* 2018; Davis & Wathen., 2020). Detecting antiretroviral ADEs would aid ADE prevention and improve the quality of life of people living with HIV/AIDS (PLWHA). Most conveniently used methods of ADE detection are not as sensitive as the trigger tool method in detecting life threatening ADEs (Lee *et al.*, 2019; Griffin and Resar, 2009). Different trigger tools exist for ADE detection including the global trigger tool (Griffin and Resar, 2009), However, none of the existing trigger tools is specific for detecting ADEs among HIV patients who take antiretroviral therapies for life. There is therefore need to develop a field-specific ADE detection trigger tool that would help the detection of ADE

	among adult HIV/AIDS patients. To this need, designing such protocol becomes very crucial.
	Justification of the study: The current protocol provides a work plan that guides and promotes the development and validation of an antiretroviral ADE detection trigger tool. Availability of this trigger tool would fill the gap of non-existence of such tool and enhance ADE detection among HIV adult patients population, thereby improving therapeutic outcome and quality of life of PLWHA.
	Objectives: To provide a protocol that would guide the development and validation of a trigger tool for antiretroviral ADE detection among adult HIV/AIDS patients.
Methods/Setting	Setting: Nnamdi Azikiwe University Teaching hospital (NAUTH), Nnewi will be the base and some aspects of the work would be extended beyond the hospital. The pre-trigger tool development (Baseline) clinical record review, the pilot study of the developed trigger tool, and the post trigger tool development clinical record review will be done at the HIV units of Nnamdi Azikiwe University Teaching Hospital Nnewi and its affiliated comprehensive health centers in the rural parts of Anambra State. The clinical record review team will be healthcare professionals from the same HIV units as above. However, the trigger tool development panel and the trigger tool validation panel will include professionals from the HIV units of NAUTH and affiliated rural health centres, as well as healthcare professionals from HIV care areas in the different geopolitical zones of the country. There is need to expand the scope of panel of experts for both development and validation of the trigger tool. This is to accommodate wider view of experts in the development and validation of a trigger tool that would be used within and beyond the region of development of the tool. Clinical record review will cover both ambulatory and admitted patients within the review period following inclusion criteria
Methods/Design	Design: A quasi-Experimental design involving different stages: A Pre-trigger tool development (Baseline) study to establish ADE detection of a non-trigger tool method. Trigger tool development Training of the review team on the developed tool and trigger tool review methodology Validation of the developed trigger tool A pilot test of the developed trigger tool using small sample A post-trigger tool development study using the developed trigger tool. Sometimes, feasibility of the developed tool can be assessed among the review team members. A feasibility study of the developed tool among record review team.
Methods/Procedure	
	Pre-trigger tool development/Baseline study: Aim: To establish the ADE detection capacity of a conventional non-trigger tool method. It shows how efficiently the non-trigger tool method can detect ADE among the intended patient population. It will provide an evidence data to compare the study done using the developed trigger tool. Procedure: Determine sample size: This is determined based on the population of HIV/AIDS patients in the study areas. Set up inclusion and exclusion principles: Inclusion criteria (Only HIV/AIDS patients, patients 18 years and above with ≥ 3 months intake of antiretroviral drugs, Professionals experienced in HIV care, Only inpatients with ≥ 24 hours admission should be included. Exclusion include: Patents < 18 years, admission < 24 hours, antiretroviral recipients of < 3 months, non-HIV/AIDS patients etc.

	Determine the sampling technique: Systematic simple random sampling technique is to be used to select clinical records (folders) to be reviewed using various months of patients' attendance to clinics. Form a review team: Select 3-6 review team members (consider experience in HIV care, consent and professionals responsible for patients' pharmacotherapy such as the Doctors, the Pharmacists, and the Nurses). Add 1 HIV care consultant physician who would vet the outcomes of all reviews with the principal investigator. Method of team selection: Should be purposive sampling. Select and brief the review team members: Brief the team on the basics of retrospective clinical records review. No training on trigger tool should be given at this point. All questions should be answered and all ambiguities cleared. Review for ADE detection: Reviewers are allowed to review patients clinical records based on reviewer's discretion. The review is done individually and the review team members meet at intervals to discuss the outcome of their reviews and take decision. Submission of review outcome is done to the vetting doctor bi-weekly. Confirmed ADEs are documented.
Method/Trigger tool development process	Trigger tool development Aim: To provide the trigger tool for antiretroviral ADE detection among adult HIV/AIDS patients using the Delphi panel method. Form the Delphi panel: Panel members should be selected based on HIV care experience, and consent. Panel members should be healthcare professionals who come into contact with the HIV/AIDS patients and their antiretroviral (including Pharmacists, Nurses, Doctors, Adherence counselors etc.). Panel selection method should be purposive and should include individuals from different geographic locations of the country (since the trigger tool being developed will be widely used). Set up consensus level: The consensus level is chosen following established standard. The level is usually ≥ 70 % (Diamonda et al., 2014; Campbell et al., 2018). Develop the Delphi panel questionnaire: The questionnaire is developed by combining list of potential triggers generated from the Delphi panel expert opinion, literature review and patients' interview. Delphi panel expert opinion: Possible triggers are generated from the Delphi panel members using an open ended questionnaire. The panel members are allowed to suggest potential triggers to antiretroviral ADEs. Literature review: Literature search is done to identify published triggers to antiretroviral ADEs. Patients' interview: Patients who have experienced ADEs of antiretroviral drugs are interviewed for potential triggers of experienced ADEs. Combine the triggers generated: Triggers from the 3 different sources above are combined into a list of triggers and trimmed to harmonize similar ones and remove repeated triggers. The outcome becomes the trigger list to form the questionnaire for the Delphi panel exercise. The questionnaire: Using the generated trigger list, a closed-ended questionnaire is formed containing potential triggers with corresponding ADEs, and drugs suspected to cause the respective ADEs. Trigger tool development using the Delphi exercise: About 4-5 rounds (depending on the round at which maximum consensus is attained) of Delphi panel exercise is done using the closed ended questionnaire. One or more of the rounds may be a focus group discussion. At each round, panel members are allowed to accept or rejection the trigger (s), the corresponding ADE (s) or the suspected drug (s) and make suggestions where necessary. Accepted (≥ 70 % agreement of the panel members) triggers are documented while triggers without acceptable consensus and newly suggested triggers are put back into the next round. The exercise is continued in successive rounds until a maximum consensus is reached, and then it is terminated.

	Collate accepted triggers to generate the trigger tool. Accepted triggers are collated and aligned with the corresponding ADEs and suspected drugs to form the trigger tool. Description of each trigger is done to aid ADE detection using the new tool.
Method/Validation of the developed trigger tool	Validation of the trigger tool Formulate validation panel using a set out inclusion principle and consent: Panel should be selected purposively from different geographic locations of the country. Consent for panel membership is sought prior to inclusion and experience in HIV care is considered in the panel selection. Develop validation form: Questions addressing the relevance of the various aspects of the developed trigger tool are developed. The clinical relevance, the structure, adequacy of content, clarity and suitability of questionnaire items should be assessed. Each question is attached a rating scale to be scored by the panelists. Validation process: Validation form is distributed to panel members for assessment and scoring. Likert rating scale is employed. Collation of scores and validity analysis: The responses from the different panelists should be collated and inputted. Items scoring 3 and 4 are imputed as 1 (items in agreement of the experts). Those scoring 2 and 1 are inputted as zero (items not in agreement of the experts). At the end, the validity indices should be calculated, including: i. I-CVI (item-level content validity index): I-CVI value of an item is gotten by dividing the number of items in the agreement of the experts by the number of experts; ii. S-CVI/Ave: Scale-level content validity index based on the average method. iii. S-CVI/UA (scale-level content validity index based on the universal agreement method): The proportion of items on the scale that achieve a relevance scale of 3 or 4 by all experts. Universal agreement (UA) score is given as 1 when the item achieved 100% experts in agreement; otherwise the UA score is given as 0.
Method/pilot test of the developed trigger tool	Pilot test of the developed trigger tool using small sample About 10 % of the sample size is used. Clinical records to be piloted should be different from those reviewed in the pre- and post- trigger tool studies.
	Training of the review team members. Review team members are trained on the trigger tool developed and how to detect ADEs using the developed trigger tool.
	Clinical record review using the developed trigger tool Clinical records are reviewed using: The same clinical records reviewed in the pre-trigger tool review The same review team as in the pre- trigger tool (Baseline) study Trigger tool based methodology (the global trigger tool system) may be adapted. Similar variables are documented as in the pre-study
Method/Feasibility of the use of the developed trigger tool	Feasibility of the use of the trigger tool among reviewers. After using the developed trigger tool to conduct the post-trigger tool elaborate study, the team of reviewers may be surveyed on the feasibility of the trigger tool using a feasibility questionnaire. The exercise would be to evaluate the experience of the reviewers using the newly developed trigger tool for the first time and to ascertain the reliability of the tool for future ADE detection studies. Variables like “Ease of use of the trigger tool in ADE detection” “adequacy of content” relevance to subject matter” etc. are used.

2. Conclusion

Adverse drug event has been a regular occurrence among HIV patients on antiretroviral therapies and has been reported to interfere with the desired positive outcome of antiretroviral therapies. Developing and validating a field-specific trigger tool for tracking ADE among HIV/AIDS patients is therefore very crucial to promote ADE detection, resolution and prevention among people living with HIV/AIDS. The current protocol designed will enhance the development and validation of antiretroviral ADE detection trigger tool for adult patients and as well guide the development and validation of other similar trigger tools.

Compliance with ethical standard

Disclosure of conflict of interest

The authors declared that there is no conflict of interest.

References

[1] Cameli M, Novo G, Tusa M, Mandoli GE, Corrado G, Benedetto F, Antonini-Canterin F, Citro R. How to Write a Research Protocol: Tips and Tricks. J Cardiovasc Echogr. 2018 Jul-Sep;28(3):151-153. doi: 10.4103/jcecho.jcecho_41_18. PMID: 30306017; PMCID: PMC6172884.

[2] Lindblad M, Schildmeijer C, Nilsson L, Ekstedt M, Unbeck M. Development of a trigger tool to identify adverse events and no-harm incidents that affect patients admitted to home healthcare. *BMJ Qual Saf*. 2018; 27:502–511

[3] Hu Q., Qin Z., Zhan M., Wu B., Chen Z. & B Xu T. (2019). Development of a trigger tool for the detection of adverse drug events in Chinese geriatric in-patients using the Delphi method. International Journal of Clinical Pharmacology, 41:1174-1183.

[4] Griffey R.T., Schneider R.M & Todorov A.A., (2020). The Emergency Department Trigger Tool: Validation and Testing to Optimize Yield. Academic Emergency Medicine. Available from https://doi.org/10.1111/acem.14101

[5] Grime M.M. & Wright G. (2016). Delphi method. Wiley statistics reference online. Available from https://www.researchgate.net/profile/Megan_Crawford8/publication/305909817_Delphi_Method/links/5cd1e99e458515712e98acd3/Delphi-Method.pdf?_sg%5B0%5D=5-hCCI5TFs05ve0Gx_fm8pWcvKnudSuRKvMixUCRd8F7s389HtMM46TEmTsPlHV_rAp5xeHTkg36cMp4sKj2sQ.58ijG_GXGPqMbYxPdYdcD1- Retrieved Dec 8, 2023

[6] Ejiofor, S. , Edeh, A. , Ezeudu, C. , Gugu, T. and Oli, A. (2016) Multi-Drug Resistant Acute Otitis Media amongst Children Attending Out-Patient Clinic in Chukwuemeka Odumegwu Ojukwu University Teaching Hospital, Awka, South-East Nigeria. Advances in Microbiology, 6, 495-501. doi: 10.4236/aim.2016.67049.

[7] Ramaj-Desku B, Berisha V, Latifi T, Loka A. The Theoretical Aspect of Delphi Techniques and AHP Method. Theoretical and Practical Research in Economic Field. 2020; 1(21): 67 - 75.

[8] Unbeck M, Lindemalm S, Nydert P, Ygge B, Nylén U, Berglund C, Härenstam K.P. Validation of triggers and development of a pediatric trigger tool to identify adverse events. *BMC Health Services Research.* 2014 Dec 21; 14:655.

[9] Weingart SN, Nelson J, Koethe B. et al. Developing a cancer-specific trigger tool to identify treatment-related adverse events using administrative data. Cancer Med. 2020; 9(4):1462-1472.

[10] Health Quality & Safety Commission. 2016. Global Trigger Tools: A Review of the Evidence.Wellington: Health Quality & Safety Commission. Available from http://www.hqsc.govt.nz/

[11] Hooper A. J. & Tibballs J. Comparison of a Trigger Tool and voluntary reporting to identify adverse events in a paediatric intensive care unit. Anaesth Intensive Care. 2014; 42:199-206.

[12] Karpov A, Parcero C, Mok CPY, Panditha C, Yu E, Dempster L, Hohl CM. Performance of trigger tools in identifying adverse drug events in emergency department patients: a validation study. Br J Clin Pharmacol. 2016; 82:1048–1057.

[13] Pierdevara L, Ventura IM, Eiras M, Gracias AMB, da Silva CS, (2016). An experience with the Global Trigger Tool for the study of adverse events in a medical ward. Journal of Nursing Referência. 2016; 4(9):97-105.

[14] Sahilu T, Getachew M, Melaku T, Sheleme T. Adverse Drug Events and Contributing Factors Among Hospitalized Adult Patients at Jimma Medical Center, Southwest Ethiopia: A Prospective Observational Study, Current Therapeutic Research. 2020 Oct 29; 93.

[15] Zhou L, Rupa AP. Categorization and association analysis of risk factors for adverse drug events. Eur J Clin Pharmacol. 2018 Apr; 74(4):389-404.

[16] Schwendimann R, Blatter C, Dhaini S, Simon M, Ausserfofer D. The occurrence, types, consequences and preventability of in-hospital adverse events-a scoping review. BMC Health Serv Res. 2018; 18:521.

[17] Davis LJ, & Wathen D. Reduction of Adverse Events. Paediatrics in Review, 2020; 41(9):498-500.

[18] Lee W., Zhang E., Chiang C., Yen Y., Chen L., Liu M., Kung C. & Hung S. Comparing the Outcomes of Reporting and Trigger Tool Methods to Capture Adverse Events in the Emergency Department. J Patient Saf. 2017; 00(00): pp1-7. Available fromhttps://www.researchgate.net/publication/312520941_Comparing_the_Outcomes_of_Reporting_and_Trigger_Tool_Methods_to_Capture_Adverse_Events_in_the_Emergency_Department&ved=2ahUKEwilxaKSvJvtAhXSyIUKHaGmDuAQFjABegQIDBAC&usg=AOvVaw2-E76pD_6hwHTDIhJ_XxPY

[19] Griffin FA, Resar RK. IHI Global Trigger Tool for Measuring Adverse Events (Second Edition). IHI Innovation Series white paper. Cambridge, MA: Institute for Healthcare Improvement; 2009. Available at ihi.org

[20] Diamonda IR, Granta RC, Feldmana BM, Pencharzd Paul B, Lingd SC, Moorea, Aideen M, Wales PW. Defining consensus: A systematic review recommends methodologic criteria for reporting of Delphi studies. Journal of Clinical Epidemiology 2014 Apr; 67(4): 401-409.

[21] Campbell M, Katikireddi SV, Sowden A, et al. Improving conduct and reporting of narrative synthesis of quantitative data (ICONS-Quant): Protocol for a mixed methods study to develop a reporting guideline. BMJ Open 2018; 8(2): e020064.