INPLASY

INPLASY202540019

doi: 10.37766/inplasy2025.4.0019

Received: 7 April 2025

Published: 7 April 2025

Corresponding author:
Patrick Wai Hang Kwong

Patrick Wai Hang Kwong

Author Affiliation:
The Hong Kong Polytechnic University.

A comprehensive appraisal of meta-analyses in exercise-based upper limb stroke rehabilitation with trial sequential analysis

Kwong, PWH; Ng, HC; Leung, TW; Wong, MH; Li, JQ.

ADMINISTRATIVE INFORMATION

Support - The Hong Kong Polytechnic University.

Review Stage at time of this submission - Data extraction.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202540019

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 7 April 2025 and was last updated on 7 April 2025.

INTRODUCTION

Review question / Objective This study aims to use the trial sequential analysis (TSA) method to examine if the published meta-analyses concerning upper limb stroke rehabilitation reached the required information size and if the overall effect size is robust as well.

Rationale In recent times, there has been an increased utilization of TSA, which provides a clearer insight into the precision and uncertainty of meta-analysis results and minimizes the underestimation or overestimation of the intervention effects. TSA utilized a sequential analysis approach where trials are arranged in chronological order, conducted repeatedly and cumulatively following each trial. The reliability of a meta-analysis evidence can be evaluated by the required information size (RIS). RIS is the number of events and subjects required to detect a predefined and reliable statistical inference in a meta-analysis. Owing to the high heterogeneity in different trials in meta-analyses, including subject characteristics, interventions, methodology and experimental environment, increasing the sample size can ensure sufficient statistical power and precision allowing for the variance caused by heterogeneity. Before the overall estimated effects reach the RIS, the threshold of statistical significance will be adjusted to deal with inflation of the overall risk of type I error. The significance threshold adjustment performed by TSA generates monitoring boundaries to evaluate the statistical significance.

Several studies used TSA to evaluate the statistical reliability of meta-analysis. Li et al. evaluated the meta-analysis regarding the effects of exercise-based stroke rehabilitation on lower extremity outcomes and found that only 37% of the included meta-analysis results reached the RIS and attained verified treatment effects. Similarly, Castellini et al. and Zhang et al. assessed the meta-analysis regarding the effects of solely constraint-induced movement therapy (CIMT) on upper extremity outcomes. All the meta-analysis results in Zhang et

al reached the RIS when clinical trials up to 2023 were included.

However, there is no study exploring the statistical reliability of meta-analysis concerning comprehensive, on top of CIMT exercise- based training on upper-limb stroke rehabilitation. Therefore, this paper conducted a TSA to examine whether the meta-analyses on exercise-based upper limb stroke rehabilitation can reach the RIS and appraise the robustness of the overall effects.

Condition being studied Upper Stroke rehabilitation.

METHODS

Search strategy The searching procedure from 6 electronic databases namely CINAHL, Medline, PubMed, Embase, Scopus, and Cochrane, with no restriction on the earliest publication years but before Feb 2025. The keywords used included “stroke”, “exercise training”, “meta-analysis” and “upper limb functions”.

Participant or population Meta-analyses that evaluate the effects of exercise training on stroke rehabilitation of upper limb.

Intervention Exercise-based stroke rehabilitation for upper limbs.

Comparator Nil.

Study designs to be included Systemic review and meta-analyses.

Eligibility criteria Studies were included if they 1) were meta-analyses of random control trials (RCTs) on people with stroke, 2) included meta-analyses results in upper limb's impairments and functions, 3) were meta- analyses published in English. Meta-analyses were excluded if they 1) were conference abstracts, letters to the editor, network meta-analyses 2) lack the statistical parameters such as mean, standard deviations (SD), and number value in the articles and raw data from the cited studies cannot be found, 3) evaluated the effect of exercise training combined with electrical or magnetic stimulation, mental rehearsal, action observation, 4) The full article is not published English.

Information sources Six electronic databases namely CINAHL, Medline, PubMed, Embase, Scopus, and Cochrane, with no restriction on the earliest publication years but before March 2025. The retrieved literature searching was performed by three reviewers (N.-H.C, L.-T.W and W.-M.H), from the references lists of included studies (backward tracking) or included studies being cited in additional articles (forward tracking). The keywords used included “stroke”, “exercise training”, “meta-analysis” and “upper limb functions”.

Main outcome(s) The required information size (RIS) for each included meta-analysis and the Alpha-spending boundary that indicated the adjusted threshold of statistical significance.

Quality assessment / Risk of bias analysis Not applicable as this is a secondary analysis of the published systemic review and meta-analyses.

Strategy of data synthesis Related upper limb outcome measures have been classified into three main categories based on the International Classification of Functioning, Disability and Health (ICF): Body Functions and Structure (Impairments), Activity (Limitations) and mixed (involving more than one outcomes from the above two categories). TSA was performed for each meta-analysis with a single specific outcome or single group of mixed outcomes listed in each of the above categories.

Statistical analysis was conducted using TSA software (Trial Sequential Analysis) version 0.9.5.10 Beta by the Copenhagen Trial Unit at Copenhagen University Hospital–Rigshospitalet in 2021. The effect sizes in the meta-analyses were estimated using a DerSimonian–Laird random-effects model. The data type considered for the analysis was 'continuous' with either ‘positive’ or ‘negative’ direction, where a higher absolute value indicating a better performance in the study outcomes. If outcomes with different scoring directions were used in the same meta-analysis (e.g. desirable scores are high for FMA-UE but low for the task completion time for Nine-Hole Peg Test), findings with a different direction would be multiplied by -1 to standardize the direction of data. Studies were included in each meta-analysis in chronological order based on their year of publication. Two predefined boundaries, the conventional and monitoring boundary, were established to assess intervention effects, relying on a two-sided probability with a 5% type I error and 80% power (1–β). The O’Brien–Fleming-type α-spending function was utilized for constructing the monitoring boundary. The RIS was determined by the effect sizes estimated from empirical data. Considering the heterogeneity of the included trials, an upward adjustment of RIS was achieved by multiplying it by a heterogeneity-adjustment

factor estimated by the software. Larger heterogeneity between trials increased the RIS, resulting in more stringent monitoring boundaries. Finally, Z-statistics from individual trials were used to generate a cumulative Z-curve and the correlation between the Z-curve and statistical boundaries is the main outcome of our study.

Subgroup analysis Nil.

Sensitivity analysis Nil.

Language restriction English.

Country(ies) involved HKSAR.

Keywords Stroke rehabilitation, exercise training, meta-analysis, Trial sequential analysis and upper limb functions.

Dissemination plans The review will be published in peer-reviewed journal.

Contributions of each author

Author 1 - PWH Kwong - Conceptualized the study, drafted the manuscript and supervised the review process.
Email: whkwong@polyu.edu.hk
Author 2 - Ho Ching Ng - Performed the literature search, extracted data and drafted the manuscript.
Email: 23127802g@connect.polyu.hk
Author 3 - Tsz Wan Leung - Performed the literature search, extracted data and drafted the manuscript.
Email: 23128799g@connect.polyu.hk
Author 4 - Man Hei Wong - Performed the literature search, extracted data and drafted the manuscript.
Email: 23127848g@connect.polyu.hk
Author 5 - Jia-Qi Li - Supervised the review process.
Email: jiaqiqi.li@connect.polyu.hk