

*Canadian Agency for
Drugs and Technologies
in Health*

*Agence canadienne
des médicaments et des
technologies de la santé*

CADTH OPTIMAL USE REPORT

JULY 2013
VOLUME 3, ISSUE 1A

Point-of-Care Testing of International
Normalized Ratio for Patients on Oral
Anticoagulant Therapy – Project Protocol

Supporting Informed Decisions

Cite as: Canadian Agency for Drugs and Technologies in Health. Point-of-Care Testing of International Normalized Ratio for Patients on Oral Anticoagulant Therapy – Project Protocol [Internet]. Ottawa: The Agency; 2013 Jul. (CADTH Optimal Use Report; vol.3 no.1a). [cited yyyy mmm dd]. Available from: http://www.cadth.ca/media/pdf/Point-of-care_INR_Protocol_e.pdf

This report is prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). This report contains a comprehensive review of existing public literature, studies, materials, and other information and documentation (collectively the “source documentation”) available to CADTH at the time it was prepared, and it was guided by expert input and advice throughout its preparation.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment in respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this report to ensure that its contents are accurate, complete, and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this report.

CADTH takes sole responsibility for the final form and content of this report. The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial or territorial government.

Production of this report is made possible through a financial contribution from Health Canada. Copyright © 2013 CADTH. This report may be reproduced for non-commercial purposes only and provided that appropriate credit is given to CADTH.

ISSN: 1927-0127

TABLE OF CONTENTS

1	CONTEXT AND POLICY ISSUES	1
1.1	Overview of Technology	1
2	ISSUES	2
3	OBJECTIVES	2
4	RESEARCH QUESTIONS	3
4.1	POC Tests for INR Compared With Laboratory Methods for Testing INR	3
4.2	POC Tests for INR Compared With Other POC Tests for INR	3
4.3	Supplemental Issues	3
5	METHODS	3
5.1	Clinical Effectiveness.....	3
5.1.1	Literature Search Strategy	3
5.1.2	Selection Criteria and Methods.....	4
5.1.3	Exclusion Criteria	5
5.1.4	Data Extraction.....	5
5.1.5	Critical Appraisal of Individual Studies	5
5.1.6	Data Analysis and Synthesis Methods.....	5
5.2	Supplemental Issues	6
6	REFERENCES	6
	APPENDIX 1: Literature Search Strategy	7
	APPENDIX 2: Data Extraction Form for Accuracy and Clinical Effectiveness Review	10
	APPENDIX 3: Downs and Black Checklist for Clinical Trial Quality Assessment	12

1 CONTEXT AND POLICY ISSUES

Approximately 1% of Albertan and Ontario residents are prescribed oral anticoagulation therapy (OAT),^{1,2} most commonly for atrial fibrillation, prosthetic heart valve, or pulmonary embolism. Assuming that 1% can be extrapolated to all of Canada, this equates to approximately 350,000 Canadians on OAT. A large demographic of these patients are older than 70 years of age. Most patients prescribed OAT are taking warfarin, a vitamin K antagonist. When on these drugs, a patient must be monitored for over-anticoagulation (which may result in hemorrhaging) and under-anticoagulation (which may result in blood clots).

Prothrombin time (PT), a measure of the effectiveness of anticoagulants, is susceptible to variations according to the type of analytical system employed. International Normalized Ratio (INR), a mathematically adjusted PT, was devised to standardize PT results, and is used to monitor and optimize OAT. In the absence of anticoagulant use, INR ranges from 0.8 to 1.2. With anticoagulation use, the target range for INR is 2 to 3. INR monitoring typically occurs every three to five weeks in patients stabilized on anticoagulant therapy.¹ More frequent monitoring is required upon initiation of therapy. This monitoring keeps the health care provider informed as to whether dose adjustments are required to keep the patient within the optimal therapeutic window. INR testing may also occur in an emergency situation. The gold standard method for monitoring the INR is laboratory testing of blood obtained by venipuncture. This can occur at a hospital or at an anticoagulation clinic. Point-of-care (POC) testing is another way to test INR. POC can be defined as medical testing near or at the bedside of the patient, with the aim of convenience for the patient, and may provide faster receipt of the test results, and allow for immediate clinical management decisions.

POC testing is a care model that differs from the usual care of centralized laboratories, and is rapidly evolving in analytical scope and clinical applications. POC testing for INR has been identified as an important issue by health care decision-makers. Some clinical settings are considering POC INR for the first time, while others are determining how best to manage POC INR usage in clinical settings. There is a need for evidence-based information to assist in the management of this technology.

1.1 Overview of Technology

There is no universally accepted definition of POC testing. Definitions vary in whether or not they include self-testing by patients and whether the machine must be physically located at the patient's bedside or not.^{1,3-5} For the purposes of this project, POC testing can extend beyond health care professional testing to include patient self-testing. Also, for this project, the site of POC is not restricted to bedside, but can occur in a variety of locations in the vicinity of the patient including within a hospital, a doctor's office, a pharmacist's office, the patient's home, community clinics, or anticoagulation clinic, where the technology is at or near the patient. A POC device may be hand-held, portable, or a small bench analyzer, or other fixed equipment. The critical factor for POC testing for INR is that the technology provides a rapid test for monitoring the patient, and the result that can be acted upon by adjusting the warfarin dose when required.

The POC device used to estimate a person's INR is called a coagulometer. POC testing for INR involves putting a drop of capillary blood (using a fingerstick) onto a test strip. The coagulometer adds thromboplastin to activate the coagulation system and then measures the time until a clot is formed.⁶ The time from the point that the thromboplastin is mixed, to the time of clot detection

is referred to as the PT, and this can then be converted to an INR. There are a number of POC coagulometers available, or soon to be available, in Canada; these are presented in Table 1. The results from POC testing are available within three minutes, compared with laboratory testing that ranges from one hour (best-case scenario in an emergency department) to 24 hours (this time frame may not include the transit time required in all cases, especially remote settings).¹ Additional POC testing benefits may include improved patient compliance, reduction in time travelling to the laboratory and health care practitioner offices, reduction in the number of appointments to manage the treatment, fewer adverse events than with venipuncture (required by laboratory testing), and more frequent testing (> 1 test per month), if required.¹

Table 1: POC INR Devices Available, or Soon to Be Available, in Canada	
Manufacturer	Product
Roche	CoaguCheck XS
Roche	CoaguChek XS plus
International Technidyne Corporation	ProTime
Hemosense Inc.	INRatio
Helena Laboratories	Cascade
Abbott Laboratories	CoaguSense
Abbott Laboratories	iSTAT
Universal Biosensors	Mobius (not yet officially named)
iLine Microsystems	iLine device

INR = international normalized ratio; POC = point of care.

POC INR testing can occur in different scenarios, or models.⁶ Three possible models include:

- At home — the patient tests INR and adjusts the dose of the drug accordingly (based on the provided reference material); can be referred to as self-managing.
- At home — the patient tests INR and reports the results to a health care provider (for example, physician or a pharmacist) and is then advised how to adjust the dose; can be referred to as self-testing.
- At hospital or clinic — the test is administered and interpreted by a health care provider. This health care provider may vary (e.g., nurse, pharmacist, primary care physician) and the geographic setting may be urban, rural, remote, or isolated.

2 ISSUES

Given the increased use of POC INR in the monitoring of patients on OAT, the availability of many POC INR devices, and the associated capital and operating costs, a review of its accuracy, clinical, and cost-effectiveness compared with standard INR lab testing is needed to inform decision-makers about its acquisition and optimal use. Comparisons between different POC INR devices are also needed.

3 OBJECTIVES

This health technology assessment (HTA) will inform decisions regarding the accuracy, and clinical and cost-effectiveness of POC INR compared with standard laboratory testing, and compared with other POC INR devices. A systematic review to evaluate the clinical effectiveness of POC INR compared with laboratory methods, and other POC INR devices,

followed by a review of economic evaluation studies will be conducted. CADTH will also conduct a primary economic analysis of the cost-effectiveness of POC INR from a Canadian perspective.

4 RESEARCH QUESTIONS

4.1 POC Tests for INR Compared With Laboratory Methods for Testing INR

- What is the diagnostic accuracy of POC test methods compared with laboratory methods for measuring INR in patients taking warfarin or other vitamin K antagonists?
- What is the comparative clinical effectiveness of POC tests measuring INR compared with laboratory methods for measuring INR in patients taking warfarin or other vitamin K antagonists?
- What is the comparative cost-effectiveness of patient or professional grade POC tests measuring INR compared with laboratory methods of measuring INR in patients taking warfarin or other vitamin K antagonists?

4.2 POC Tests for INR Compared With Other POC Tests for INR

- What is the diagnostic test accuracy of POC test methods compared with other POC test methods for measuring INR in patients taking warfarin or other vitamin K antagonists?
- What is the comparative clinical effectiveness of POC tests measuring INR compared with other POC tests measuring INR in patients taking warfarin or other vitamin K antagonists?
- What is the comparative cost-effectiveness of patient grade POC tests measuring INR compared with professional grade POC tests measuring INR in patients taking warfarin or other vitamin K antagonists?

A priori subgroup analyses will be conducted based on health care factors such as patient indication; users; clinical setting; and urban, rural, remote, or isolated settings to determine how these factors may affect the clinical and cost-effectiveness of POC testing.

4.3 Supplemental Issues

The environmental, ethical, legal, and social issues associated with POC INR testing will be reviewed.

5 METHODS

5.1 Clinical Effectiveness

5.1.1 Literature Search Strategy

The literature search will be performed by an information specialist using a peer-reviewed search strategy.

Published literature will be identified by searching the following bibliographic databases: MEDLINE (1946 onward) with In-Process records & daily updates through Ovid; Embase (1974 onward) through Ovid; CINAHL through EBSCO; The Cochrane Library through Wiley; and PubMed. The search strategy is made up of both controlled vocabulary, such as the National

Library of Medicine’s MeSH (Medical Subject Headings), and keywords. The main search concepts are POC testing and INR.

No filters were applied to limit retrieval by study type. Where possible, retrieval will be limited to the human population. Retrieval will not be limited by publication year, but will be limited to the English language. Conference abstracts will be excluded from the search results. See Appendix 1 for the detailed search strategies.

Regular alerts will be established to update the search until the publication of the final report, and regular search updates will be performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) will be identified by searching the Grey Matters checklist (<http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters>), which includes the websites of regulatory agencies, HTA agencies, clinical guideline repositories, and professional associations. Google and other Internet search engines will be used to search for additional web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry. See Appendix 1 for more information on the grey literature search strategy.

5.1.2 Selection Criteria and Methods

Two reviewers will independently screen the titles and abstracts of all citations retrieved from the literature search and, based on the selection criteria (Table 2), will order the full text of any articles that appear to meet those criteria. The reviewers will then independently review the full text of the selected articles, apply the selection criteria to them, and compare the independently chosen studies. Disagreements will be resolved through discussion until consensus is reached. Multiple publications of the same trial will be excluded unless they provide additional outcome information of interest.

Table 2: Selection Criteria	
Population	<ul style="list-style-type: none"> • Patients taking warfarin or other vitamin K antagonists, for atrial fibrillation or other indications where POC would be used. • Any age group. • Patients on long-term therapy (> 3 months); patients on shorter-term therapy included under Supplemental Issues.
Intervention	POC test methods for measuring INR available in Canada.
Comparator	<ul style="list-style-type: none"> • POC tests approved by Health Canada. • Central laboratory methods.
Outcomes	<p><i>Diagnostic test accuracy:</i></p> <ul style="list-style-type: none"> • Agreement between POC INR and comparator test (defined a priori as a result difference of 15% between the POC INR test and the comparator test). • Sensitivity and specificity, area under the curve (AUC), and possibly positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, interferences, linearity, carryover (if applicable), correlation between POC and central lab, and precision of the POC (same time, over time). <p><i>Clinical effectiveness:</i></p> <ul style="list-style-type: none"> • Achieved therapeutic range, time in therapeutic range, thromboembolic event, hemorrhagic event, mortality, quality of life, bleeding (minor and major), impact on clinical management, non-health benefits, other safety concerns
Study Design	<ul style="list-style-type: none"> • Randomized controlled trials (RCT). • If RCTs not available, observational studies.

INR = international normalized ratio; POC = point of care.

5.1.3 Exclusion Criteria

Studies will be excluded if they: do not meet the selection criteria, provide the results of a qualitative or a non-comparative quantitative study, or present preliminary results in abstract form. Duplicate publications, narrative reviews, and editorials will also be excluded.

5.1.4 Data Extraction

A data extraction form for the clinical effectiveness review will be designed a priori to document and tabulate relevant study characteristics (e.g., study design, inclusion criteria, patient characteristics, settings, and other such factors and measures of clinical effectiveness, as outlined above) in the selected studies. Data will be extracted independently by two reviewers, and any disagreements will be resolved through discussion until consensus is reached. A draft of the data extraction form for the clinical review is provided in Appendix 2.

5.1.5 Critical Appraisal of Individual Studies

An assessment of the quality of diagnostic accuracy studies will be performed with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool.⁷ The validity of the included clinical trials on clinical efficacy will be assessed independently by two reviewers (CH, KC), using the Downs and Black checklist.⁸ Disagreements will be resolved through consensus. A draft of the Downs and Black checklist is provided in Appendix 3.

5.1.6 Data Analysis and Synthesis Methods

If studies fulfilling the selection criteria are identified, results will be pooled when applicable. Before study-specific results are pooled, an evaluation of the homogeneity of both the clinical and methodological characteristics of the included studies will be performed; a qualitative review of findings will be reported if heterogeneity is extensive across the studies of interest. The appropriateness of the meta-analysis will be based upon a consensus opinion derived from this exercise. If the meta-analysis is deemed inappropriate due to heterogeneity, a narrative synthesis and summary of study findings will be constructed instead.

If the meta-analysis is deemed appropriate, the extent of published head-to-head RCTs of active comparator interventions will be assessed. If sufficient numbers of published, head-to-head comparisons are identified, meta-analyses will be carried out using Cochrane Review Manager software to derive pooled estimates of POC INR accuracy and clinical effectiveness, using the outcomes defined earlier.

If sufficient homogeneity is found across trials, all meta-analyses performed will consider a fixed effect model; if not, a random effects model will be used. Forest plots will be presented for all evidence syntheses, to supplement reported estimates. If heterogeneity is identified ($P < 0.1$) and sufficient data are available, subgroup analyses and/or meta-regression techniques will be employed to assess the impact of potentially important sources. These will include study design features and patient characteristics (possibilities include race, gender, age group, pre-existing disease, etc.). Additional sensitivity analyses dealing with outlying data points, study quality, and other factors (including industry funded versus publicly funded studies) will also be considered to establish the robustness of findings. Analyses of dichotomous outcomes will be summarized using relative risks and 95% confidence intervals (CIs), and analyses of continuous outcomes will be summarized using mean differences and 95% CIs. If required measures of variance are found to be missing from a relevant article, the study's authors will be contacted to determine if the measure can be provided for the purposes of this investigation. If relevant data are not available, variances will be imputed if possible.

5.2 Supplemental Issues

Additional information related to the following areas will be discussed, but not systematically reviewed.

- Ethical, environmental, legal, and social issues associated with the use of POC INR (equality of health care, access for patients in different communities, and for patients with different abilities and disabilities).
- Patient criteria for self-testing and self-management.
- POC INR for short-term therapy (< 30 days), which would include settings. This may include the emergency room, operating room, endoscopy clinic, cardiac catheter and arrhythmia labs, and the intensive care unit.

6 REFERENCES

1. Cepoiu M, Fyie K, Higgins L, Rose S, Lorenzetti D, Youssefi M, et al. Point-of-care testing for oral anticoagulant management with portable prothrombin time systems [Internet]. Edmonton: Alberta Ministry of Health; 2010. [cited 2013 Jun 18]. Available from: <http://www.health.alberta.ca/documents/AHTDP-PPTS2-UofC-STE.pdf>
2. Ontario Health Technology Advisory Committee. Point-of-Care International Normalized Ratio (INR) monitoring devices for patients on long-term oral anticoagulation therapy [Internet]. Toronto: Ontario Ministry of Health and Long-Term Care; 2009. [cited 2013 Jun 18]. Available from: http://www.health.gov.on.ca/english/providers/program/ohnac/tech/recommend/rec_poc_20091204.pdf
3. Health Canada. Guidance for the risk based classification system of in vitro diagnostic devices - DRAFT [Internet]. Ottawa: Health Canada; 1998. [cited 2013 Jun 18]. Available from: http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/ivd-rsk_idiv-rsq_main_principal-eng.php
4. Irish Medicines Board. Guidelines for safe and effective management and use of point of care testing in primary and community care [Internet]. Dublin: Irish Medicines Board; 2009. [cited 2013 Jun 18]. Available from: http://www.imb.ie/images/uploaded/documents/Guidelines_for_Safe_and_Effective_Management_and_Use_of_Point_of_Care_Testing_in_Primary_and_Community_Care.pdf
5. NHS Improvement. Delivering the NHS health check: a practical guide to implementation. A practical guide to point of care testing [Internet]. Leicester (UK): NHS Improvement; 2010. [cited 2013 Jun 18]. Available from: <http://www.healthcheck.nhs.uk/document.php?o=129>
6. Thrombosis Canada - Thrombose Canada [Internet]. Montreal: Thrombosis Canada - Thrombose Canada. Point-of-care INR monitoring of warfarin therapy; 2012 [cited 2013 Jun 18]. Available from: http://thrombosiscanada.ca/?page_id=18#
7. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol [Internet]. 2003 Dec 10 [cited 2013 Jun 18];3(1):25. Available from: <http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=305345&blobtype=pdf>
8. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2013 Jun 18];52(6):377-84. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf>

APPENDIX 1: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	<ul style="list-style-type: none"> • Embase 1974 to 2013 (with daily update) • MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE 1946 to Present <p>Note: Subject headings will be customized for each database. Duplicates between databases will be removed in Ovid.</p>
Study Types:	No filters were applied to limit the retrieval by study type. Conference abstracts, comments, editorials, and letters were removed.
Limits:	English Humans No date limits were applied.
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.pt	Publication type
.dm	Device manufacturer (in Embase)
.dv	Device trade name (in Embase)
use omezd	Limit search line to EMBASE database only
use pmez	Limit search line to MEDLINE database only

MULTI-DATABASE STRATEGY

#	Strategy
1	Point-of-Care Systems/ use pmez
2	point of care testing/ use oomezd
3	(point of care or POC or POCT or self-test* or self-monitor* or self-manag* or near patient or bedside or bed-side or portable or hand-held or handheld or mobile or ambulatory or rapid test* or rapid screen* or remote test* or rapid diagnos*).ti,ab.
4	(iSTAT or i-STAT).ti,ab,dm,dv.
5	or/1-4
6	International Normalized Ratio/
7	Prothrombin Time/
8	(international normalised ratio* or international normalized ratio* or INR or prothrombin time* or prothrombin ratio* or rapid coagulation or "PT/INR" or PT-INR or PT ratio* or protime or protrombin time* or protrombin ratio* or prothrombine time* or prothrombine ratio*).ti,ab.
9	or/6-8
10	5 and 9
11	(CoaguChek or CoaguCheck or INRatio or CoaguSense or Coag-Sense).ti,ab,dm,dv.
12	10 or 11
13	exp animals/
14	exp animal experimentation/ or exp animal experiment/
15	exp models animal/
16	nonhuman/
17	exp vertebrate/ or exp vertebrates/
18	animal.po.
19	or/13-18
20	exp humans/
21	exp human experimentation/ or exp human experiment/
22	human.po.
23	or/20-22
24	19 not 23
25	12 not 24
26	25 not Conference abstract.pt.
27	26 not (comment or newspaper article or editorial or letter or note).pt.
28	limit 27 to English language
29	remove duplicates from 28

OTHER DATABASES

PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library through Wiley	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.
CINAHL (EBSCO interface)	Same keywords, and date limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for EBSCO platform.

Grey Literature

Keywords:	Will include terms for point-of-care testing (POCT) and INR
Limits:	No date limits

The following sections of the Canadian Agency for Drugs and Technologies in Health (CADTH) grey literature checklist, “Grey matters: a practical tool for evidence-based searching” (<http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters>) will be searched:

- Health Technology Assessment Agencies
- Health Economic
- Clinical Practice Guidelines
- Databases (free)
- Internet Search.

APPENDIX 2: DATA EXTRACTION FORM FOR ACCURACY AND CLINICAL EFFECTIVENESS REVIEW

Reviewer		
Ref ID		
Author, Date		
Country of Origin		
Industry Sponsorship		
Study Design		
Study Duration		
Eligibility Criteria		
Patient Group:	Intervention	Control
Number Enrolled		
Number Completing Study		
Age, Gender		
Other		
Intervention Name:		
Intervention Type	POC INR	Comparator
Accuracy Outcomes		
<p>Agreement between POC INR and comparator test (defined a priori as result difference of a 15% between the POC INR test and the comparator test)</p> <p>Sensitivity and specificity</p> <p>AUC</p> <p>Regression coefficient (correlation)</p> <p>Positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, interferences, linearity, carryover (if applicable), correlation between POC and comparator test.</p>		
Clinical Effectiveness Outcomes		
Impact on clinical management		

(e.g., dosing of oral anticoagulants), mean time from blood drawn to INR result report, achieved therapeutic range, time in therapeutic range, thromboembolic event, hemorrhagic event, mortality, bleeding (minor and major), quality of life, non-health benefits, other safety concerns.		
Other		
Notes		

AUC = area under the curve; ID = identification; INR = international normalized ratio; POC = point of care.

APPENDIX 3: DOWNS AND BLACK CHECKLIST FOR CLINICAL TRIAL QUALITY ASSESSMENT

REPORTING	Yes/No/Partially	Score
1. Is the objective of the study clear?	Yes = 1, No = 0	
2. Are the main outcomes clearly described in the Introduction or Methods?	Yes = 1, No = 0	
3. Are characteristics of the patients included in the study clearly described?	Yes = 1, No = 0	
4. Are the interventions clearly described?	Yes = 1, No = 0	
5. Are the distributions of principal confounders in each group of subjects clearly described?	Yes = 2, Partially = 1, No = 0	
6. Are the main findings of the study clearly described?	Yes = 1, No = 0	
7. Does the study estimate random variability in data for main outcomes?	Yes = 1, No = 0	
8. Have all the important adverse events consequential to the intervention been reported?	Yes = 1, No = 0	
9. Have characteristics of patients lost to follow-up been described?	Yes = 1, No = 0	
10. Have actual probability values been reported for the main outcomes except probability < 0.001?	Yes = 1, No = 0	
11. Is the source of funding clearly stated? ^a	Yes = 1, No = 0	
EXTERNAL VALIDITY	Yes/No/Unclear	Score
12. Were subjects who were asked to participate in the study representative of the entire population recruited?	Yes = 1, No = 0, Unclear = 0	
13. Were those subjects who were prepared to participate representative of the recruited population?	Yes = 1, No = 0, Unclear = 0	
14. Were staff, places, and facilities where patients were treated representative of treatment most received?	Yes = 1, No = 0, Unclear = 0	
INTERNAL VALIDITY	Yes/No/Unclear	Score
15. Was an attempt made to blind study subjects to the intervention?	Yes = 1, No = 0, Unclear = 0	
16. Was an attempt made to blind those measuring the main outcomes?	Yes = 1, No = 0, Unclear = 0	
17. If any of the results of the study were based on data dredging was this made clear?	Yes = 1, No = 0, Unclear = 0	
18. Was the time period between intervention and outcome the same for intervention and control groups or adjusted for?	Yes = 1, No = 0, Unclear = 0	
19. Were the statistical tests used to assess main outcomes appropriate?	Yes = 1, No = 0, Unclear = 0	
20. Was compliance with the interventions reliable?	Yes = 1, No = 0, Unclear = 0	
INTERNAL VALIDITY (continued)	Yes/No/Unclear	Score

21. Were main outcome measures used accurate? (valid and reliable)	Yes = 1, No = 0, Unclear = 0	
INTERNAL VALIDITY-CONFOUNDING (SELECTION BIAS)	Yes/No/Unclear	Score
22. Were patients in different intervention groups recruited from the same population?	Yes = 1, No = 0, Unclear = 0	
23. Were study subjects in different intervention groups recruited over the same period of time?	Yes = 1, No = 0, Unclear = 0	
24. Were study subjects randomized to intervention groups?	Yes = 1, No = 0, Unclear = 0	
25. Was the randomized intervention assignment concealed from patients and staff until recruitment was complete?	Yes = 1, No = 0, Unclear = 0	
26. Was there adequate adjustment for confounding in the analyses from which main findings were drawn?	Yes = 1, No = 0, Unclear = 0	
27. Were losses of patients to follow-up taken into account?	Yes = 1, No = 0, Unclear = 0	
POWER	Size of Smallest Intervention Group Score of 0 to 5	Score
28. Was the study sufficiently powered to detect clinically important effects where probability value for a difference due to chance is < 5%?		

^aCriteria was added for the current systematic review.