

ELECTRONIC SUPPLEMENTARY MATERIAL

Quality standards in asthma comparative effectiveness research: a Respiratory Effectiveness Group –
European Academy of Allergy and Clinical Immunology Task Force report

Table S1. Taskforce Activity Schedule Summary

ACTIVITY	START DATE	END DATE
Proposal submitted	September 2013	
Taskforce approved	November 2013	
Taskforce group formalised	January 2014	
Planning	January 2014	April 2014
Literature review, PICOT Question Identification (and literature refinement)	May 2014	March 2015
Quality assessment tool development	May 2014	January 2015
Taskforce pilot testing	February 2015	May 2015
Assessment of inter-rater variability	June 2015	September 2015
Quality assessment of PICOT literature	October 2015	March 2016
Results synthesis & report writing	March 2016	April 2016
Results presentation & discussion	<ul style="list-style-type: none"> • April 2016: REG Summit • June 2016: EAACI Conference 	
Results publication	Q3 2016	

Literature search methodology

Two databases were consulted to conduct the literature review: MEDLINE and EMBASE.

The search was undertaken in two phases – an initial phase and an extension phase: the **initial phase** reviewed the literature published in the ten-year period January 2004 to December 2014, and was **conducted**: 13 January 2015. As the quality assessment tool was finalized in autumn 2015 and the literature review commenced in December 2015, a one-year extension period was added on 9 December 2015 to the literature review to ensure it included all current literature.

The following sensitive, but not specific search terms (and algorithms) were used for the review of the literature:

Table S2. Literature review search terms: used to identify a list that would include asthma observational comparative effectiveness studies

# ▲	SEARCH TERM
1	Comparative studies/
2	Comparative effectiveness/
3	Comparative effectiveness research/
4	(Comparative adj effectiveness).tw.
5	Follow up studies/
6	Prospective studies/
7	Prospective\$.tw.
8	Retrospective studies/
9	Retrospective\$.tw.

10	Cohort studies/
11	Cohort.tw.
12	(compare\$ or compara\$).tw.
13	Compared.tw.
14	Case control studies/
15	(Observational adj (study or studies)).tw.
16	Treatment Outcome/
17	Database.tw.
18	or/1-17
19	Asthma/
20	Inhaled corticosteroid\$.tw.
21	Azithromycin.tw.
22	Macrolide\$.tw.
23	or/20-22
24	18 and 19 and 23
25	Randomized controlled trial/
26	Random allocation/
27	25 or 26
28	24 not 27
29	limit 28 to (English language and humans and year="2004 -Current")

Papers were reviewed initially to identify and remove any duplicates found (i.e. retrieved via both the MEDLINE and EMBASE searches) and then further filtered based on their fulfilment of the following exclusion criteria:

- Conference proceedings and/or abstract only
- Not an asthma study (e.g. COPD, Allergic rhinitis)
- Not a comparative effectiveness study, including:
 - Literature review
 - Clinical trial
 - Case study
 - Cross-sectional survey
 - Cohort study

Table S3: reading grid used by reviewers to summarize selected articles

REFERENCE	
FUNDING	
STUDY DESIGN	
INCLUDED POPULATION	
SETTING, TIME FRAME GEOGRAPHIC AREA	
COMPARED ARMS (IF APPLICABLE)	
DURATION OF FOLLOW UP	

PRIMARY OBJECTIVE, OUTCOME AND ANALYSIS	
OTHER OBJECTIVES, ANALYSES AND RESULTS	
PRIMARY RESULTS	
OTHER RESULTS	
POSSIBLE BIASES	
CONCLUSION OF THE AUTHORS	
STRENGTH OF CONCLUSION (rater opinion)	

Table S4. List of REG and EAACI contributors

MEMBER	COUNTRY	CONTRIBUTION
Aileen Wang	The Philippines	QR
Alan Kaplan	Canada	QR, OPR
Andrew McIvor	Canada	QR
Anjan Nibber	UK	QR, OPR
Antoine Magnan	France	QR
Anu Kemppinen	UK	QR
Arzu Bakırtaş	Turkey	QATT
Bakhtiyor Khalikulov	UK	QR
Bernardino Alcazar Navarrette	Spain	QATT, QR
Brett McQueen	USA	QR, OPR
Chong Kim	USA	QR, OPR
Christina Callan	UK	QR
David Halpin	UK	QATT
Dmitris Mitsias	Greece	QR
Emilio Pizzichini	Brazil	QR
Enrico Heffler	Italy	QATT, QR
George Guibas	UK	QR, OPR
George Konstantinou	Greece	QR
Helen Reddell	Australia	QATT, QR
Ioannis Taslos	Greece	QR, OPR
Janwillem Kocks	The Netherlands	QR

Jennifer Quint	UK	OPR
Joan Soriano	Spain	QR
Job van Boven	The Netherlands	QR
Joergen Vestbo	Denmark	QATT
John Blakey	UK	QR, OPR
Juan José Soler Cataluna	Spain	QATT
Katia Verhamme	Belgium	QR
Kostas Kostikas	Greece	QATT, QR
Lars Olaf Cardell	Sweden	QR
Laurent Laforest	France	QATT
Laurie Pahun	France	OPR
Elizabeth Hillyer	USA	QR
Ludger Klimek	Germany	QATT, QR
Luis Caraballo	Colombia	QATT
Lynn Josephs	UK	QR
Manon Laforest	France	QATT
Maria Ospina	Canada	QR
Marjan Kerkoff	The Netherlands	QR
Matte Bonini	Italy	QATT
Melanie Whittington	USA	QR, OPR
Mihaela Stefan	USA	QR, OPR
Ming-Cheng Chan	China	QR
Mohsen Sadatsafavi	Canada	QR, OPR
Ömer Kalayci	Greece	QATT
Paraskevi Maggina	Greece	QR, OPR
Piyameth Dilokthomsakul	Malaysia	QATT, QR
Ronald Dandurand	Canada	QR, OPR
Sam Sonnappa	India	QR, OPR
Shawna Tan	Singapore	QR
Simon van Rysewyk	Singapore	QR, OPR
Sinthia Bosnic-Anticevich	Australia	QATT
Steve Turner	UK	QR, OPR
Theresa Guilbert	USA	QR, OPR
Yee Vern Yong	Malaysia	QATT, QR

Table S5. Literature Review Assessment Overview: All papers

Papers categorized by PICOT question and quality rating

#	PAPER DETAILS	SUFFICIENTLY HIGH QUALITY	INSUFFICIENTLY HIGH QUALITY	PRIMARY QUALITY LIMITATIONS*
PICOT 1: "ADHERENCE TO ICS THERAPY"; 24 PAPERS				
1	Sadatsafavi M, Lynd LD, Marra CA, FitzGerald JM. Dispensation of long-acting β agonists with or without inhaled corticosteroids, and risk of asthma-related hospitalisation: a population-based study. <i>Thorax</i> . 2014 ;69(4):328-34			NA
2	Friedman HS, Navaratnam P, McLaughlin J. Adherence and asthma control with mometasone furoate versus fluticasone propionate in adolescents and young adults with mild asthma. <i>J Asthma</i> . 2010 ;47(9):994-1000.			NA
3	Campbell JD, Allen-Ramey F, Sajjan SG, Maiese EM, Sullivan SD. Increasing pharmaceutical copayments: impact on asthma medication utilization and outcomes. <i>Am J Manag Care</i> . 2011 ;17(10):703-10.			NA
4	Tan H, Sarawate C, Singer J, Elward K, Cohen RI, Smart BA, Busk MF, Lustig J, O'Brien JD, Schatz M. Impact of asthma controller medications on clinical, economic, and patient-reported outcomes. <i>Mayo Clin Proc</i> . 2009 ;84(8):675-84			NA
5	Williams LK, Pladevall M, Xi H, Peterson EL, Joseph C, Lafata JE, Ownby DR, Johnson CC. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. <i>J Allergy Clin Immunol</i> . 2004 ;114(6):1288-93			NA
6	Taegtmeyer AB, Steurer-Stey C, Price DB, Wildhaber JH, Spertini F, Leuppi JD. Predictors of asthma control in everyday clinical practice in Switzerland. <i>Curr Med Res Opin</i> . 2009 ;25(10):2549-55			NA
7	Laforest L, Licaj I, Devouassoux G, Chatté G, Belhassen M, Van Ganse E,			NA

	Chamba G. Relative exposure to controller therapy and asthma exacerbations: a validation study in community pharmacies. <i>Pharmacoepidemiol Drug Saf.</i> 2014 ;23(9):958-64.			
8	Laforest L, Licaj I, Devouassoux G, Chatte G, Martin J, Van Ganse E. Asthma drug ratios and exacerbations: claims data from universal health coverage systems. <i>Eur Respir J.</i> 2014 ;43(5):1378-86			NA
9	Björnsdóttir US, Sigurðardóttir ST, Jonsson JS, Jonsson M, Telg G, Thuresson M, Naya I, Gizurarson S. Impact of changes to reimbursement of fixed combinations of inhaled corticosteroids and long-acting β 2-agonists in obstructive lung diseases: a population-based, observational study. <i>Int J Clin Pract.</i> 2014;68(7):812-9.			NA
10	Lee T, Kim J, Kim S, Kim K, Park Y, Kim Y, Lee YS, Kwon HS, Kim SH, Chang YS, Cho YS, Jang AS, Park JW, Nahm DH, Yoon HJ, Cho SH, Cho YJ, Choi BW, Moon HB, Kim TB; COREA study group. Risk factors for asthma-related healthcare use: longitudinal analysis using the NHI claims database in a Korean asthma cohort. <i>PLoS One.</i> 2014 ;9(11):e112844			Both reviewers: 2.2 <u>1</u> reviewer: 3.1, 3.2, 4.2, 5.1, 7.1 1 'agreed' limitation; unique limitations identified
11	Taylor A, Chen LC, Smith MD. Adherence to inhaled corticosteroids by asthmatic patients: measurement and modelling. <i>Int J Clin Pharm.</i> 2014 ;36(1):112-9.			Both reviewers: 2.2, 4.2 <u>1</u> reviewer: 3.2 2 'agreed' limitations; unique limitations identified
12	Rust G, Zhang S, Reynolds J. Inhaled corticosteroid adherence and emergency department utilization among Medicaid-enrolled children with asthma. <i>J Asthma.</i> 2013 ;50(7):769-75.			Both reviewers: 2.2 <u>1</u> reviewer: 4.1,

				4.2, 5.1, 7.1 1 'agreed' limitation; 4 unique limitations identified
13	Elkout H, Helms PJ, Simpson CR, McLay JS. Adequate levels of adherence with controller medication is associated with increased use of rescue medication in asthmatic children. PLoS One. 2012 ;7:e39130			<u>Both reviewers:</u> 2.2, 4.2 2 'agreed' limitations
14	Herndon JB, Mattke S, Evans Cuellar A, Hong SY, Shenkman EA . Anti-inflammatory medication adherence, healthcare utilization and expenditures among Medicaid and children's health insurance program enrollees with asthma. Pharmacoeconomics. 2012 ;30(5):397-412			<u>Both reviewers:</u> 2.2 <u>1 reviewer:</u> 4.2 1 'agreed' limitation; 1 unique limitation identified
15	<i>Giraud V, Allaert FA, Roche N. Inhaler technique and asthma: feasibility and acceptability of training by pharmacists. Respir Med. 2011;105(12):1815-22</i>			<u>Both reviewers:</u> 4.1, 5.1 <u>1 reviewer:</u> 4.2 2 'agreed' limitations; 1 unique limitation identified
16	Sawicki GS, Strunk RC, Schuemann B, Annett R, Weiss S, Fuhlbrigge AL; Childhood Asthma Management Program Research Group. Patterns of inhaled corticosteroid use and asthma control in the Childhood Asthma Management Program Continuation Study. Ann Allergy Asthma Immunol. 2010 ;104(1):30-5			<u>Both reviewers:</u> 5.1 <u>1 reviewer:</u> 4.1, 6.1, 6.2 1 'agreed' limitations; 3 unique

				limitations identified
17	Bukstein DA, Murphy KR, Katz LM, Ramachandran S, Doyle KK, Stern LS. Outcomes Among a Young Population of Pediatric Asthma Patients Using Controller Therapies: Results from a Retrospective Database Analysis. <i>Pediatric Asthma, Allergy & Immunology</i> . 2007 ;20(4):211-223			<u>Both reviewers:</u> 4.2, 7.1 <u>1 reviewer:</u> 3.1 2 'agreed' limitations; 1 unique limitation identified
18	Lasmar L, Camargos P, Champs NS, Fonseca MT, Fontes MJ, Ibiapina C, Alvim C, Moura JA. Adherence rate to inhaled corticosteroids and their impact on asthma control. <i>Allergy</i> . 2009 ;64(5):784-9			<u>Both reviewers:</u> 7.1 <u>1 reviewer:</u> 4.1, 4.2 1 'agreed' limitation; 2 unique limitation identified
19	Santos Pde M, D'Oliveira A Jr, Noblat Lde A, Machado AS, Noblat AC, Cruz AA. Predictors of adherence to treatment in patients with severe asthma treated at a referral center in Bahia, Brazil. <i>J Bras Pneumol</i> . 2008 ;34(12):995-1002			<u>Both reviewers:</u> 7.1 <u>1 reviewer:</u> 4.2 1 'agreed' limitation; 1 unique limitation identified
20	Klok T, Kaptein AA, Duiverman EJ, Brand PL. It's the adherence, stupid (that determines asthma control in preschool children)! <i>Eur Respir J</i> . 2014 ;43(3):783-91			<u>Both reviewers:</u> 4.1

21	Guest JF, Davie AM, Ruiz FJ, Greener MJ. Switching asthma patients to a once-daily inhaled steroid improves compliance and reduces healthcare costs. <i>Prim Care Respir J</i> . 2005 ;14(2):88-98			<u>1 reviewer</u> : 4.1, 4.2, 5.1 3 unique limitation identified
22	Price D, Chisholm A, Hillyer EV, Burden A, von Ziegenweidt J, Svedstater H, Dale P. Effect of Inhaled Corticosteroid Therapy Step-Down and Dosing Regimen on Measures of Asthma Control. <i>J Aller Ther</i> . 2013 (4):126			<u>Both reviewers</u> : 7.1 1 'agreed' limitation
23	Klok T, Kaptein AA, Duiverman EJ, Brand PL. Long-term adherence to inhaled corticosteroids in children with asthma: Observational study. <i>Respir Med</i> . 2015 ;109(9):1114-9			<u>1 reviewer</u> : 2.2, 4.2 2 unique limitation identified
24	Dalcin Pde T, Grutcki DM, Laporte PP, Lima PB, Viana VP, Konzen GL, Menegotto SM, Fonseca MA, Pereira RP. Impact of a short-term educational intervention on adherence to asthma treatment and on asthma control. <i>J Bras Pneumol</i> . 2011 ;37(1):19-27			<u>Both reviewers</u> : 4.1, 5.1 <u>1 reviewer</u> : 2.2, 4.2, 6.1, 7.1 2 'agreed' limitations; 4 unique limitation identified

#	PAPER DETAILS	SUFFICIENTLY HIGH QUALITY	INSUFFICIENTLY HIGH QUALITY	PRIMARY QUALITY LIMITATIONS*
PICOT 2: "DEVICE TYPE"; 7 PAPERS				
1	Price D, Chrystyn H, Kaplan A, Haughney J, Román-Rodríguez M, Burden A, Chisholm A, Hillyer EV, von Ziegenweidt J, Ali M, van der Molen T. Effectiveness of same versus mixed asthma inhaler devices: a retrospective observational study in primary care. <i>Allergy Asthma Immunol Res.</i> 2012 ;4(4):184-91			NA
2	Price D, Roche N, Christian Virchow J, Burden A, Ali M, Chisholm A, Lee AJ, Hillyer EV, von Ziegenweidt J. Device type and real-world effectiveness of asthma combination therapy: an observational study. <i>Respir Med.</i> 2011 ;105(10):1457-66.			NA
3	Price D, Haughney J, Sims E, Ali M, von Ziegenweidt J, Hillyer EV, Lee AJ, Chisholm A, Barnes N. Effectiveness of inhaler types for real-world asthma management: retrospective observational study using the GPRD. <i>J Asthma Allergy.</i> 2011 ;4:37-47.			NA
4	Thomas M, Price D, Chrystyn H, Lloyd A, Williams AE, von Ziegenweidt J. Inhaled corticosteroids for asthma: impact of practice level device switching on asthma control. <i>BMC Pulm Med.</i> 2009 ;9:1. doi: 10.1186/1471-2466-9-1.			NA
5	Voshaar T, Kostev K, Rex J, Schröder-Bernhardi D, Maus J, Munzel U. A retrospective database analysis on persistence with inhaled corticosteroid therapy: comparison of two dry powder inhalers during asthma treatment in Germany. <i>Int J Clin Pharmacol Ther.</i> 2012 ;50(4):257-64.			NA
6	Price D, Thomas V, von Ziegenweidt J, Gould S, Hutton C, King C. Switching patients from other inhaled corticosteroid devices to the Easyhaler(®): historical, matched-cohort study of real-life asthma patients. <i>J Asthma Allergy.</i> 2014 ;7:31-51			NA
7	Kemp L, Haughney J, Barnes N, Sims E, von Ziegenweidt J, Hillyer EV, Lee AJ, Chisholm A, Price D. Cost-effectiveness analysis of corticosteroid			Both reviewers: TBC 1 reviewer: 4.1

	inhaler devices in primary care asthma management: A real world observational study. Clinicoecon Outcomes Res. 2010 ;2:75-85			TBC 'agreed' limitations; 1 unique limitation identified
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#	PAPER DETAILS	SUFFICIENTLY HIGH QUALITY	INSUFFICIENTLY HIGH QUALITY	PRIMARY QUALITY LIMITATIONS*
PICOT 3: "SMOKING ASTHMATICS"; 3 PAPERS				
1	Brusselle G, Peché R, Van den Brande P, Verhulst A, Hollanders W, Bruhwylter J. Real-life effectiveness of extrafine beclometasone dipropionate/formoterol in adults with persistent asthma according to smoking status. <i>Respir Med.</i> 2012 ;106(6):811-9			NA
2	Roche N, Postma DS, Colice G, Burden A, Guilbert TW, Israel E, Martin RJ, van Aalderen WM, Grigg J, Hillyer EV, von Ziegenweidt J, Price DB. Differential effects of inhaled corticosteroids in smokers/ex-smokers and nonsmokers with asthma. <i>Am J Respir Crit Care Med.</i> 2015 ;191(8):960-4.			NA
3	<i>Telenga ED, Kerstjens HA, Ten Hacken NH, Postma DS, van den Berge M. Inflammation and corticosteroid responsiveness in ex-, current- and never-smoking asthmatics. BMC Pulm Med.</i> 2013 ;22;13:58			<u>1 reviewer: 2.1, 3.2, 4.1, 4.2, 5.1</u> 4 unique limitations identified
PICOT 4: "SMALL AIRWAYS MANAGEMENT; ICS PARTICLE SIZE"				
1	van Aalderen WM, Grigg J, Guilbert TW, Roche N, Israel E, Martin RJ, Colice G, Postma DS, Hillyer EV, Burden A, Thomas V, von Ziegenweidt J, Price D. Small-particle Inhaled Corticosteroid as First-line or Step-up Controller Therapy in Childhood Asthma. <i>J Allergy Clin Immunol Pract.</i> 2015 ;3(5):721-31			NA
2	Martin RJ, Price D, Roche N, Israel E, van Aalderen WM, Grigg J, Postma DS, Guilbert TW, Hillyer EV, Burden A, von Ziegenweidt J, Colice G. Cost-effectiveness of initiating extrafine- or standard size-particle inhaled corticosteroid for asthma in two health-care systems: a retrospective			NA

	matched cohort study. NPJ Prim Care Respir Med. 2014 ;24:14081			
3	Colice G, Martin RJ, Israel E, Roche N, Barnes N, Burden A, Polos P, Dorinsky P, Hillyer EV, Lee AJ, Chisholm A, von Ziegenweidt J, Barion F, Price D. Asthma outcomes and costs of therapy with extrafine beclomethasone and fluticasone. J Allergy Clin Immunol. 2013 ;132(1):45-54			NA
4	Price D, Thomas M, Haughney J, Lewis RA, Burden A, von Ziegenweidt J, Chisholm A, Hillyer EV, Corrigan CJ. Real-life comparison of beclomethasone dipropionate as an extrafine- or larger-particle formulation for asthma. Respir Med. 2013 ;107(7):987-1000			NA

#	PAPER DETAILS	SUFFICIENTLY HIGH QUALITY	INSUFFICIENTLY HIGH QUALITY	PRIMARY QUALITY LIMITATIONS*
5	Price D, Martin RJ, Barnes N, Dorinsky P, Israel E, Roche N, Chisholm A, Hillyer EV, Kemp L, Lee AJ, von Ziegenweidt J, Colice G. Prescribing practices and asthma control with hydrofluoroalkane-beclomethasone and fluticasone: a real-world observational study. J Allergy Clin Immunol. 2010 ;126(3):511-8.e1-10			NA
6	Allegra L, Cremonesi G, Girbino G, Ingrassia E, Marsico S, Nicolini G, Terzano C; PRISMA (PRospective Study on asthMA control) Study Group. Real-life prospective study on asthma control in Italy: cross-sectional phase results. Respir Med. 2012 ;106(2):205-14			NA
7	Barnes N, Price D, Colice G, Chisholm A, Dorinsky P, Hillyer EV, Burden A, Lee AJ, Martin RJ, Roche N, von Ziegenweidt J, Israel E. Asthma control with extrafine-particle hydrofluoroalkane-beclomethasone vs. large-particle chlorofluorocarbon-beclomethasone: a real-world observational study. Clin Exp Allergy. 2011 ;41(11):1521-32			NA
8	Price D, Small I, Haughney J, Ryan D, Gruffydd-Jones K, Lavorini F, Harris T, Burden A, Brockman J, King C, Papi A. Clinical and cost effectiveness of switching asthma patients from fluticasone-salmeterol to extra-fine particle beclomethasone-formoterol: a retrospective matched observational study of real-world patients. Prim Care Respir J. 2013 ;22(4):439-48			NA

9	Müller V, Gálffy G, Eszes N, Losonczy G, Bizzi A, Nicolini G, Chrystyn H, Tamási L. Asthma control in patients receiving inhaled corticosteroid and long-acting beta2-agonist fixed combinations. A real-life study comparing dry powder inhalers and a pressurized metered dose inhaler extrafine formulation. BMC Pulm Med. 2011 ;11:40			Both reviewers: TBC <u>1 reviewer</u> : TBC TBC 'agreed' limitations; TBC unique limitation identified
10	Popov TA, Petrova D, Kralimarkova TZ, Ivanov Y, Popova T, Peneva M, Odzhakova T, Ilieva Y, Yakovliev P, Lazarova T, Georgiev O, Hodzhev V, Hodzheva E, Staevska MT, Dimitrov VD. Real life clinical study design supporting the effectiveness of extra-fine inhaled beclomethasone/formoterol at the level of small airways of asthmatics. Pulm Pharmacol Ther. 2013;26(6):624-9			<u>1 reviewer</u> : 2.1, 2.2, 3.2, 4.1, 4.2, 5.1, 7.1 7 unique limitations identified
11	Paggiaro P, Patel S, Nicolini G, Pradelli L, Zaniolo O, Papi A. Stepping down from high dose fluticasone/salmeterol to extrafine BDP/F in asthma is cost-effective. Respir Med. 2013 ;107(10):1531-7			<u>1 reviewer</u> : 2.2, 3.1, 4.1, 6.2 4 unique limitations identified
#	PAPER DETAILS	SUFFICIENTLY HIGH QUALITY	INSUFFICIENTLY HIGH QUALITY	PRIMARY QUALITY LIMITATIONS*
12	Israel E, Roche N, Martin RJ, Colice G, Dorinsky PM, Postma DS, Guilbert TW, van Aalderen WM, Grigg J, Hillyer EV, Burden A, von Ziegenweidt J, Thomas V, Price DB. Increased Dose of Inhaled Corticosteroid versus Add-On Long-acting β -Agonist for Step-Up Therapy in Asthma. Ann Am Thorac Soc. 2015 ;12(6):798-806			Both reviewers: TBC <u>1 reviewer</u> : 3.2, 5.1, 7.1 TBC 'agreed' limitations; 3 unique limitation identified

Italic text indicates papers that required a third adjudicating review.

Primary limitations are counted across both "negative" reviews each paper received, split by those identified as limitations by 1 or both reviewers

**Limitation number related to field with in the literature quality assessment tool*

Key: Primary quality criteria

1. Background: 1.1. Clearly stated research question;

2. Design: 2.1 Population defined **2.2.** Comparison groups defined;

3. Measures: 3.1. If relevant, is exposure (e.g. treatment) defined **3.2.** Primary Outcomes defined;

4. Analysis: 4.1. Potential confounders are addressed **4.2.** Study groups are compared at baseline;

5. Results. 5.1 Results are clearly presented for primary endpoints as well as confounders;

6. Discussion and Interpretation: 6.1. Results consistent with known information or, if not, an explanation is provided; **6.2.** Clinical relevance of the results is discussed;

7. Conflicts of Interest: 7.1. Potential conflicts of interest, including study funding, are stated