PEER REVIEW HISTORY

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Rationale and Design of a Prospective Sub-StudY of Clinical Endpoint Adjudication Processes Within an Investigator-Reported Randomized Controlled Trial in Patients with Coronary Artery Disease: The GLOBAL LEADERS Adjudication Sub-StudY – GLASSY
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VERSION 1 – REVIEW

REVIEWER	George Kassimis Gloucestershire Hospital NHS Foundation Trust, United Kingdom
REVIEW RETURNED	24-Aug-2018

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

REVIEWER	Hernan POLO FRIZ, M.D. Vimercate Hospital, Internal Medicine Department, Milano-Bicocca University, Milan, Italy
REVIEW RETURNED	17-Sep-2018

GENERAL COMMENTS	Authors' declared study aims "GLASSY is designed to complement the interpretation of the results of the GLOBAL LEADERS trial on a CEC-adjudicated broad range of non-fatal ischemic and bleeding endpoints, and, ultimately, test the value of standardized CEC processes within a pragmatic study design." "This study will comprehensively assess the comparative safety and efficacy of the two tested antithrombotic strategies on CEC-adjudicated ischemic and bleeding endpoints and will provide insights into the role of a standardized CEC adjudication process on the interpretation of study findings by quantifying the level of concordance between IR reported and CEC-adjudicated events."

	Rationale and Design: The GLOBAL LEADERS trial was designed to challenge the current treatment paradigm consisting of 12-month dual antiplatelet therapy (DAPT; clopidogrel+aspirin among patients with stable CAD; ticagrelor+aspirin among patients with ACS) followed by aspirin monotherapy in patients undergoing PCI based on the superiority for the composite endpoint of all-cause death or Q-wave myocardial infarction (MI) assessed at 2 years. GLOBAL LEADERS Adjudication Sub-StudY (GLASSY) was designed with the aim to prospectively implement, in a representative sample of patients enrolled within the GLOBAL LEADERS trial, an independent adjudication process of reported as well as unreported potential endpoints, leveraging on standardized CEC procedures. This GLASSY substudy is powered to test whether 23-month ticagrelor monotherapy after a short course of DAPT for 1 month is non-inferior to conventional 12-month DAPT followed by aspirin monotherapy with respect to CEC-adjudicated death, non-fatal myocardial infarction, non-fatal stroke, or urgent target-vessel revascularization (TVR) and superior in preventing CEC-adjudicated major bleeding. Furthermore, GLASSY will evaluate the implications of the CEC adjudication process for the interpretation of study results by quantifying the level of concordance between IR reported and CEC-adjudicated events and will define the role of CEC adjudication process for the assessment of the efficacy and safety of the randomized antithrombotic strategies on a broader set of fatal and non-fatal clinical endpoints. Endpoints GLASSY will have two independent, CEC-adjudicated, co-primary endpoints at 24 months: 1) The composite of death, non-fatal MI, non-fatal stroke, or urgent TVR (coprimary efficacy endpoint); 2) The composite of BARC type 3 or 5 bleeding (co-primary safety endpoint). Secondary endpoints will include: • Each component of the co-primary composite endpoints; • Definite, probable or possible stent thrombosis according to ARC classification; • Bleeding events according to BARC, TIMI and GUSTO classifications; • Type of death (cardiovascular vs. non-cardiovascular and subtypes). Statistical analyses The co-primary efficacy endpoint will be firstly tested as non-inferiority followed by a superiority testing only if non-inferiority criteria will be met. The co-primary safety endpoint will be tested with a superiority hypothesis only. Alpha error will be evenly split (2.5% each) between the two co-primary endpoints. A total of 3,340 patients per group (6,680 patients) will yield 85% power to detect non-inferiority with a one-sided type I error (alpha) of 2.5%. The risk ratio will be calculated using the Mantel-Cox log-rank method. ..... REVISION The topics (DAPT in patients undergoing PCI and methodological aspect related to the concordance between IR-reported and CEC –

	adjudicate events) are important topic for clinicians, researchers, patients and health policy makers, and the subject seems within the scope of BMJ Open. Furthermore, a very interesting strength of the study is its design aimed to implement CEC processes in the context of a large phase III pragmatic trial, which would let an original assessment of differences in IR-reported versus CEC-adjudicated events. Thus, the study may provide information on methodological questions exceeding the specific field (antiplatelet agents in CAD patients) and becoming of interest for research on clinical trials in general. Research question and aims are well presented and defined. Methods are exhaustively and adequately described. In particular rationale, design end-points and data sources are clearly explained. The same for procedures and statistical analysis. Limitations are properly acknowledged . Therefore, in my opinion, the article deserves to be accepted for publication.

REVIEWER	GJ de Borst UMCU, Netherlands
REVIEW RETURNED	25-Oct-2018

GENERAL COMMENTS	The present manuscript reports on the rationale and design of a substudy of the ongoing GLOBAL LEADERS trial. In my view this paper is not free from redundant publication. 1. Global leaders. however, all but one of the authors (Canada) are from Europe. this initiative clearly does not represent a global perspective. please comment. 2. Global leaders is a superiority trial. GLASSY is started as a non-inferior study. Why this discrepancy ? 3. Bleeding endpoints are scored by different criteria, but this is not uniformly reported thorughout the doucment and ranges from BARC only to all three most common criteria sets available in literature such as GUSTO and TIMI. please adjust. 4. endpoints: page 4. GLASSY on several non-fatal endpoints. however, death is part of the primary endpoint in GL study. Please comment and adjust. 5. my main issue is that GLOBAL leaders is designed as an investigator reported only study. GLASSY is now there to adjudicate in about half the patients on the reliability of the GL design. this seems very ineffective, also as investigators will know that CEC adjudicated analysis will follow their IR data. GLASSY in my view may cause bias for GLdesign. 6. If the authjors still wish to perform GLASSY, they may mention this as an amendment online to the Original trial protocol instead. it remains unclear to me why this GLASSY protocol should be published as a separate study protocol as it contains overlap with the GL protocol in approx 80% of the document. 7. "Independency of parent study". Why is this truly independent, and if so, why do the authors believe that this is relevant ? 8. Evaluation of endpoints. "Concordance between IR and CEC adjudicated endpoints will be assessed in events with sufficient evidence only". this seems a very weak point in the design, while you may miss many endpoints. Please comment.

REVIEWER	Bhiken Naik University of Virginia USA
REVIEW RETURNED	29-Oct-2018

GENERAL COMMENTS	The study is well designed and I recommend acceptance of this manuscript

VERSION 1 – AUTHOR RESPONSE

Reviewer 2
The topics (DAPT in patients undergoing PCI and methodological aspect related to the concordance between IR-reported and CEC –adjudicate events) are important topic for clinicians, researchers, patients and health policy makers, and the subject seems within the scope of BMJ Open.
Furthermore, a very interesting strength of the study is its design aimed to implement CEC processes in the context of a large phase III pragmatic trial, which would let an original assessment of differences in IR-reported versus CEC-adjudicated events. Thus, the study may provide information on methodological questions exceeding the specific field (antiplatelet agents in CAD patients) and becoming of interest for research on clinical trials in general.
Research question and aims are well presented and defined. Methods are exhaustively and adequately described. In particular rationale, design end-points and data sources are clearly explained. The same for procedures and statistical analysis.
Limitations are properly acknowledged. Therefore, in my opinion, the article deserves to be accepted for publication.

We thank the reviewer for taking the time to review our manuscript and appreciate the positive feedback.

Reviewer 3
The present manuscript reports on the rationale and design of a substudy of the ongoing GLOBAL LEADERS trial. In my view this paper is not free from redundant publication.
1. Global leaders. however, all but one of the authors (Canada) are from Europe. this initiative clearly does not represent a global perspective. please comment.

The study acronym refers to the parent study, not the prospective substudy that we report here. GLOBAL LEADERS indeed included patients from a series of Countries outside Europe including Brazil, Canada, and Singapore. Therefore the acronym appears justifiable. GLASSY included only the highest enrolling sites all in Europe. This explains the geographic representation of the co-authors.

2. Global leaders is a superiority trial. GLASSY is started as a non-inferior study. Why this discrepancy ?
This is an important point and we thank the reviewer for the opportunity to clarify this aspect. The experimental treatment in GLOBAL LEADERS – that is ticagrelor monotherapy after 1 month of DAPT in all comers population undergoing PCI – has the advantage of being simpler as compared to conventional 1 year DAPT. Therefore, even if not superior to conventional DAPT such a treatment may be desirable to increase treatment adherence or better tolerated for patients who develop intolerance to aspirin. For this reason demonstration of non-inferiority on efficacy may be valuable and was considered as the first statistical approach, which will be followed by superiority testing. The co-primary safety endpoint will be tested with a superiority hypothesis only. These considerations have been now included in the revised text of the statistical analysis section.

3. Bleeding endpoints are scored by different criteria, but this is not uniformly reported thorughout the doucment and ranges from BARC only to all three most common criteria sets available in literature such as GUSTO and TIMI. please adjust.
BARC is the primary safety endpoint. We have now clarified throughout the manuscript and particularly in the endpoint section that GUSTO and TIMI will be also considered as alternative bleeding classifications to facilitate comparison with prior studies.

4. endpoints: page 4. GLASSY on several non-fatal endpoints. however, death is part of the primary endpoint in GL study. Please comment and adjust.
Thanks for noticing this inconsistency. We have now revised the text in the Strengths and Limitations section accordingly.

5. my main issue is that GLOBAL leaders is designed as an investigator reported only study. GLASSY is now there to adjudicate in about half the patients on the reliability of the GL design. this seems very ineffective, also as investigators will know that CEC adjudicated analysis will follow their IR data. GLASSY in my view may cause bias for GLdesign.

Investigator-reported endpoints in the context of an open-label design represent a relevant limitation for GLOBAL LEADERS, particularly on non-fatal endpoints. This is therefore the strongest rational for the design of the GLASSY study we present. We are not testing the reliability of GLOBAL LEADERS design but rather the implications of a comprehensive, rigorous, and standardized assessment of several non-fatal endpoints as well as death (including type, mechanism, and relationship to bleeding) in a representative sample of the GLOBAL LEADERS trial performed according to best practices of adjudication. The adjudications for GLASSY were done after the initial eCRFs for GLOBAL LEADERS (from which the IR endpoints were derived) had been locked.
We therefore don't believe that GLASSY may bias the GLOBAL LEADERS design in any way but expand and compliment its understanding.

6. If the authors still wish to perform GLASSY, they may mention this as an amendment online to the Original trial protocol instead. it remains unclear to me why this GLASSY protocol should be published as a separate study protocol as it contains overlap with the GL protocol in approx 80% of the document.

GLASSY is an independent, prospective substudy of GLOBAL LEADERS that besides the obvious mention of the parent study has no overlap with it.
The core elements of the GLASSY research question are the rationale, description, analysis and implications of CEC adjudication processes within an investigator reported study. Therefore we believe that their publication is essential for the understanding of the context, methodology, and scientific validity of GLASSY.

7. "Independency of parent study". Why is this truly independent, and if so, why do the authors believe that this is relevant ?

Independence from the parent study is essential to maximize the scientific integrity of GLASSY and to avoid biasing the results toward the null hypothesis of no difference between IR and CEC-adjudicated events. As reported in the revised manuscript, CEC personnel will operate independently from the data management group of the parent study, including no cross talk on trigger logic specifications, query processes for source documentation, and most importantly event reporting and adjudication results.

8. Evaluation of endpoints. "Concordance between IR and CEC adjudicated endpoints will be assessed in events with sufficient evidence only". this seems a very weak point in the design, while you may miss many endpoints. Please comment.
We thank the reviewer for the opportunity to clarify this aspect.
In GLASSY, for each non-fatal trigger examined an assessment will be performed as to whether enough information is available for formal adjudication. This will allow distinguishing triggers that did not meet the endpoint definition (i.e. no event with sufficient documentation present) from triggers for which this is unknown due to insufficient documentation.
Therefore, for each non-fatal endpoint, the proportion of events with insufficient evidence will provide important insights.
Specifically they will estimate a) the feasibility of GLASSY b) the quality of endpoint reported by sites and c) the uncertainty of the evidence related to the studied outcome. We believe these analyses represent an important strength of GLASSY design. These potential events will therefore be reported but will not be adjudicated. We have clarified this aspect in the revision.

Reviewer: 4
The study is well designed and I recommend acceptance of this manuscript

We thank the reviewer for taking the time to review our manuscript and appreciate the positive feedback.