ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Instructions

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1. Identifying information.

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4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Rebecca
2. Surname (Last Name): Baron
3. Date: 22-March-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Augustine M K Choi

5. Manuscript Title: Circulating cell death biomarker TRAIL is associated with increased organ dysfunction in sepsis

6. Manuscript Identifying Number (if you know it): 127143-INS-CMED-1

Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Section 6. Disclosure Statement

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Dr Baron has nothing to disclose.

Evaluation and Feedback

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Augustine
2. Surname (Last Name): Choi
3. Date: 23-March-2019

4. Are you the corresponding author? ☑ Yes ☐ No

5. Manuscript Title: Circulating cell death biomarker TRAIL is associated with increased organ dysfunction in sepsis

6. Manuscript Identifying Number (if you know it): 127143-INS-CMED-1

Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Proterris, Inc	☐	☐	☐	☑	co-founder
Teva Pharmaceuticals	☐	☑	☐	☐	consultant July 12-13, 2018

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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A.M.K.C. is a cofounder, stock holder and serves on the Scientific Advisory Board for Proterris, which develops therapeutic uses for carbon monoxide. A.M.K.C. also has a use patent on CO. He served on the TEVA Advisory Board meeting as a consultant on July 12-13, 2018

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Laura
2. Surname (Last Name): Fredenburgh
3. Date: 22-March-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Augustine M K Choi

5. Manuscript Title: Circulating cell death biomarker TRAIL is associated with increased organ dysfunction in sepsis

6. Manuscript Identifying Number (if you know it): 127143-INS-CMED-1

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Asahi Kasei Pharma America (AKPA)	☐	☐	☐	☑	Clinical Trial Support

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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LEF has received clinical trial support for an unrelated study from Asahi Kasei Pharma America (AKPA).

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Eliza
2. Surname (Last Name): Gentzler
3. Date: 22-March-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Augustine M K Choi

5. Manuscript Title: Circulating cell death biomarker TRAIL is associated with increased organ dysfunction in sepsis

6. Manuscript Identifying Number (if you know it): 127143-INS-CMED-1

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Eliza Gentzler has nothing to disclose.

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Section 1. Identifying Information

1. Given Name (First Name): Jin-Won
2. Surname (Last Name): Huh
3. Date: 22-March-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Augustine M K Choi

5. Manuscript Title: Circulating cell death biomarker TRAIL is associated with increased organ dysfunction in sepsis

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Dr Huh has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Kevin
2. Surname (Last Name): Ma
3. Date: 22-March-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Augustine M K Choi

5. Manuscript Title: Circulating cell death biomarker TRAIL is associated with increased organ dysfunction in sepsis

6. Manuscript Identifying Number (if you know it): 127143-INS-CMED-1

Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Section 6. Disclosure Statement

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Dr Ma has nothing to disclose.

Evaluation and Feedback

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Thomas
2. Surname (Last Name): Nicholson
3. Date: 22-March-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Augustine M K Choi

5. Manuscript Title: Circulating cell death biomarker TRAIL is associated with increased organ dysfunction in sepsis

6. Manuscript Identifying Number (if you know it): 127143-INS-CMED-1

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr Nicholson has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Clara
2. Surname (Last Name): Oromendia
3. Date: 22-March-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Augustine M K Choi

5. Manuscript Title: Circulating cell death biomarker TRAIL is associated with increased organ dysfunction in sepsis

6. Manuscript Identifying Number (if you know it): 127143-INS-CMED-1

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Section 5. Relationships not covered above

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Clara Oromendia has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): David
2. Surname (Last Name): Price
3. Date: 22-March-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Augustine M K Choi

5. Manuscript Title: Circulating cell death biomarker TRAIL is associated with increased organ dysfunction in sepsis

6. Manuscript Identifying Number (if you know it): 127143-INS-CMED-1

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

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Dr Price has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Elizabeth
2. Surname (Last Name): Sanchez
3. Date: 22-March-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Augustine M K Choi

5. Manuscript Title: Circulating cell death biomarker TRAIL is associated with increased organ dysfunction in sepsis

6. Manuscript Identifying Number (if you know it): 127143-INS-CMED-1

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr Sanchez has nothing to disclose.

Evaluation and Feedback

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Edward
2. Surname (Last Name): Schenck
3. Date: 22-March-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Augustine M K Choi

5. Manuscript Title: Circulating cell death biomarker TRAIL is associated with increased organ dysfunction in sepsis

6. Manuscript Identifying Number (if you know it): 127143-INS-CMED-1

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

☑ No other relationships/conditions/circumstances that present a potential conflict of interest

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr Schenck has nothing to disclose.

Evaluation and Feedback

Please visit http://www.icmje.org/cgi-bin/feedback to provide feedback on your experience with completing this form.

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Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.

1. Identifying information.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes".

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

5. Relationships not covered above.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

Definitions.

Entity: government agency, foundation, commercial sponsor, academic institution, etc.
Grant: A grant from an entity, generally [but not always] paid to your organization
Personal Fees: Monies paid to you for services rendered, generally honoraria, royalties, or fees for consulting , lectures, speakers bureaus, expert testimony, employment, or other affiliations
Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
Issued: The patent has been issued by the agency
Licensed: The patent has been licensed to an entity, whether earning royalties or not
Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Ilias
2. Surname (Last Name): Siempos
3. Date: 22-March-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Augustine M K Choi

5. Manuscript Title: Circulating cell death biomarker TRAIL is associated with increased organ dysfunction in sepsis

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Section 6. Disclosure Statement

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Dr Siempos has nothing to disclose.

Evaluation and Feedback

Please visit http://www.icmje.org/cgi-bin/feedback to provide feedback on your experience with completing this form.

Strobe Statement Checklist

RE: 127143-INS-CMED-1

Circulating cell death biomarker TRAIL is associated with increased organ dysfunction in sepsis

Title and abstract:

1 (*a*) Indicate the study's design with a commonly used term in the title or the abstract

Our abstract summarizes the study design.

(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found

Our abstract summarizes key outcomes and results with succinct conclusions.

Introduction:

2 Background/rationale: Explain the scientific background and rationale for the investigation being reported

The rationale and background is summarized.

3 Objectives: State specific objectives, including any prespecified hypotheses

Our objectives and primary hypothesis are spelled out in the end of the introduction.

Methods:

4 Study design: Present key elements of study design early in the paper

The study design was summarized in the methods

5 Setting: Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection

The setting location and dates are summarized in the methods.

6 Participants:
(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up

The individual ICU biobank recruitment strategies were highlighted in the methods section.

(*b*) For matched studies, give matching criteria and number of exposed and
Unexposed

NA

7Variables: Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable

Our outcomes and sepsis definitions are addressed in this study. We address unknowns regarding confounding and effect modifiers in the discussion.

8 Data sources/Measurement: For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.
Our data sources are defined and our methods of protein analysis are summarized.

9 Bias: Describe any efforts to address potential sources of bias

We address differences between cohorts and potential bias in the discussion.

10 Study size: Explain how the study size was arrived at

This study incorporated all available samples from our cohorts. The sample size was not preplanned based on an expected effect.

11 Quantitative variables: Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why

We chose to keep our quantitative variables as continuous when possible. Grouping of patients was based on current definitions of sepsis.

12 Statistical Methods:

(a) Describe all statistical methods, including those used to control for confounding

We describe our statistical methods used for analysis.

(b) Describe any methods used to examine subgroups and interactions

NA

(c) Explain how missing data were addressed

Missing data on organ failure was marked as zero. For our primary variables all data was complete.

(d) If applicable, explain how loss to follow-up was addressed

As this was an inpatient study no patients were lost to follow up.

(e) Describe any sensitivity analyses

No sensitivity analyses were performed.

Results:

13 Participants:

(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed

We do not have the number of subjects screened but not able to be consented

(b) Give reasons for non-participation at each stage

We do not have access for reasons for non-enrollment in the biobank

(c) Consider use of a flow diagram

Given the lack of data regarding screened but not enrolled we cannot provide a flow diagram

14 Descriptive data:

(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders

These are summarized in table 1

(b) Indicate number of participants with missing data for each variable of interest

Patients with missing data for our primary variables were not included.

(c) Summarise follow-up time (eg, average and total amount)

Inpatient only study.

15 Outcome data: Report numbers of outcome events or summary measures over time

We have summarized the number of our primary outcome in each group.

16 Main results:

(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included

Unadjusted analyses were presented. We did not perform confounder adjustment.

(*b*) Report category boundaries when continuous variables were categorized

NA

(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

NA

17 Other analyses: Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

We report other analyses with variables within the main text and supplement.

Discussion:

18 Key results: Summarize key results with reference to study objectives

This was provided in the discussion.

19 Limitations: Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias

We discussed limitations. It is premature to mention the direction of bias with our biomarker of interest as there is limited information

20 Interpretation: Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence

We have provided a cautious interpretation in the discussion.

21 Generalizability: Discuss the generalizability (external validity) of the study results

We discuss the current science related to the biomarker.

Other information

22 Funding: Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

This was incorporated into the title page.