Author's response to reviews

Title: Does metformin improve vascular health in children with type 1 diabetes?
Protocol for a one year, double blind, randomised, placebo controlled trial

Authors:

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Jennifer Couper (jennifer.couper@adelaide.edu.au)

Version: 4 Date: 10 July 2013

Author's response to reviews: see over
BMC Pediatrics

10th July, 2013

Dear Dr O’Donovan,

RE: Does metformin improve vascular health in children with type 1 diabetes? Protocol for a one year, double blind, randomised, placebo controlled trial

Thank you for your consideration of this protocol. I will address each point outlined in your letter regarding required revisions. Sections from your letter are in italics.

1. As you may be aware, it is the policy of the journal not to peer review study protocols where ethical and external funding approval have been obtained, as these processes usually involve peer review and as there is little possibility to change a protocol after enrollment begins. Therefore, could you please clarify whether you have ethical approval and external funding for your study, and if so, could you send evidence of your approvals to the address below?

**Ethical approval**
- Women’s and children’s hospital human research ethics committee
- Flinders medical centre human research ethics committee
  - See attached documentation
    - WCH HREC original approval (1.1) 28/1/2011
    - FMC HREC ethics approval (1.2) 02/04/2013

The ethical approval is outlined in the main manuscript on page 8 under paragraph “Approval and registration”

**External funding**
All were grants obtained specifically for this study
- DART – Diabetes Research Australia Trust ($58 840 + GST)
- APEC – Australasian Paediatric Endocrine Care ($50 000)
- Women’s and Children’s Hospital Research Foundation ($50 000 + GST)
  - See attached documentation
    - DART grant (1.3)
    - APEC grant (1.4)
    - WCH foundation grant (1.5)

The APEC grant is indirectly funded through Pfizer Australia however the grants are reviewed by two independent paediatric endocrinologists and a panel of independent physicians. There is no input from Pfizer Australia. This is specified in paragraph 2 of document APEC grant (1.4).

External funding sources are included in the “acknowledgements” section of the manuscript on page 18.

2. Could you also provide a list of any manuscripts that are under submission with other journals based on this study protocol?

There are no manuscripts that are under submission with other journals based on this study protocol.

3. BioMed Central requires all controlled clinical trials to be registered in a suitable publicly accessible registry prior to consideration for publication. The trial registers that currently meet all of the ICMJE guidelines can be found at [http://www.icmje.org/faq.html](http://www.icmje.org/faq.html).
This clinical trial was registered prospectively on 8/2/2011 with ANZCTR (Australia and New Zealand Clinical Trials Registry) which is listed under the ICMJE.

- See additional documentation
  - ANZCTR prospective approval (3.1)

4. Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

The manuscript has been formatted so that it adheres to the guidelines above. Specifically:
- The title page is on a single page at the start of the document with the authors email addresses listed.
- The sections of the manuscript are ordered as specified
- The additional figure is cropped as specified

I look forward to hearing your decision on this protocol. Please contact me should any further clarification be required.

Yours sincerely,

Dr Jemma Anderson
Corresponding author
jemma.anderson@adelaide.edu.au
Additional Documentation

1.1 Women's and children's hospital human research ethics committee approval

26th January 2011

Dr A. Pena
Endocrinology & Diabetes
CYWHIS

Dear Alexia,

Re: Does Metformin improve vascular function in overweight youth with type 1 diabetes?

REC23271212T3

I refer to your recent letter and to an email from Dr. Anderson dated 24th January 2011 responding to matters raised by the CYWHS Human Research Ethics Committee (letter 10th December 2010) and the DTC Clinical Trials Group (letter 7th December 2010). I am pleased to advise that your protocol has been granted full ethical approval and that it meets the requirements of the National Statement on Ethical Conduct in Human Research.

I enclose herewith the CTN form duly signed. Although TGA advises that the study may proceed once the attached CTN form (and payment) has been forwarded, it also advises that if TGA has a problem with the CTN form, e.g., incomplete information, then the CTN form may be invalidated. Therefore, you should not proceed until you receive a letter from TGA acknowledging that it has received the CTN and have also forwarded a copy of the letter to the Ethics Committee.

If now, or in the future, the study involves students, non-CYWHS staff, you should contact the Committee on extension 15521 to discuss institutional requirements for a National Police Check and the signing of a Confidentiality Agreement. The study may proceed on this proviso.

I remind you approval is given subject to:
- Immediate notification of any serious or unexpected adverse events to subjects
- Immediate notification of any unforeseen events that might affect continued ethical acceptability of the project
- Submission of any proposed changes to the original protocol. Changes must be approved by the Committee before they are implemented
- Immediate advice, giving reasons, if the protocol is discontinued before its completion
- Submission of an annual report on the progress of the study and a final report when it is completed. It is your responsibility to provide these reports, without reminder from the Committee

Approval is given for three years only. If the study is more protracted than this, an extension request should be submitted unless there are significant modifications, in which case a new submission may be required. Please note the approval number above indicates the month and year in which approval expires and it should be used in any future communication.

If University of Adelaide personnel are involved in this project, you, as chief investigator must submit a Human Research Approval Notification Form online at http://www.adelaide.edu.au/ethics/human/guidelines/within 14 days of receiving the ethical clearance to ensure compliance with University requirements and appropriate indemnification.

Yours sincerely,

JENNY FEREDAY (DR)
Chairperson
CYWHS Human Research Ethics Committee

Cc: Dr. J. Anderson, CYWHS
02 April 2013

Dr Alexia Penna  
Paediatric Endocrinology  
Women’s and Children’s Hospital  
72 King William Street  
NORTH ADELAIDE SA 5006

Dear Alexia

**HREC reference number:** 443.12  
**Project title:** Does metformin improve vascular function and structure in youth with type diabetes?

**RE:** Site Specific Assessment Review

Thank you for submitting an application for authorisation of this project. I am pleased to inform you that authorisation has been granted for this study to commence at the following site: Flinders Medical Centre.

- FMC Child assent form v3 dated 28 February 2013  
- FMC Parent consent form v3 dated 28 February 2013  
- FMC Participant information sheet v7 dated 28 February 2013

Should you have any queries about the consideration of your Site Specific Assessment form, please contact Bev Stewart Campbell on 08 8204 4507.

The SSA reference number should be quoted in any correspondence about this matter.

Yours sincerely

Bev Stewart Campbell  
Research Governance Officer  
Southern Adelaide Clinical Human Research Ethics Committee
1.3 Diabetes Australia research trust grant

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**RESEARCH GRANT ACCEPTANCE FORM**

**RESEARCH BRANCH**

The Grant Acceptance Form must be fully completed and signed by the first-named University investigator and the Head of School (or delegate) and returned to the Research Branch as a condition to receiving a project code. You are using the application guide to help you through this process and save your proposal to the box.

**OFFICE USE ONLY**

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<th>Role Transfer form</th>
<th>Current Transfer form</th>
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**TA First-Named Chief Investigator**

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<th>Family Name</th>
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<th>Title</th>
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<tbody>
<tr>
<td>Nguyen</td>
<td>John</td>
<td>Professor</td>
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</table>

**School:**

**Faculty/Division:**

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<th>Lead Organisation</th>
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<td>Science</td>
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**Telephone Contact Number:**

<table>
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<tr>
<th>Telephone Contact Number</th>
<th>Email Address</th>
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<tbody>
<tr>
<td>0416 86 2640</td>
<td><a href="mailto:john.nguyen@.adelaide.edu.au">john.nguyen@.adelaide.edu.au</a></td>
</tr>
</tbody>
</table>

**All Other Named Investigators (please, include 1st, 2nd, 3rd, and Organisation, e.g., Prof AB Smith (MRI), Dr CD Jones (MRI) & Dr EF Chan (Cambridge U))**

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**1B RESEARCH GRANT DETAILS**

<table>
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<th>Project Title</th>
<th>Total $ Funded</th>
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<tbody>
<tr>
<td>Does research improve quality and sustainability?</td>
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</table>

**Name of Funding Sponsor:**

**Name of Funding Scheme:**

**Project No:**

**Date of Offer:**

**Commencement Date:**

**Completion Date:**

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**1C UNIVERSITY HONORARY TITLE HOLDERS ONLY**

If the first-named Chief Investigator is an Honorary Title holder of the University of Adelaide please complete all of the questions in this section below.

- What is the Honorary Title of the Investigator?
- Where is the research being conducted?
- Is the funding to be administered entirely by the Honorary Title holder?

**Is the project to be conducted entirely by the Honorary Title holder?**

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**2. RESEARCH CLASSIFICATIONS DATA**

- **% of ABS RED Activity:**
  - Must total: 100% of ABS RED Activity
  - Field of Research (FOR) Code

**3 INTELLECTUAL PROPERTY DETAILS**

- **Intellectual Property (IP) Agreement:**
  - Must total: 100% of IP Agreement

**4 APPLICATION REFERENCE LIBRARY**

- **Application Reference Library:**
  - You must provide your applications to a reference facility of successful applications to provide University staff with an opportunity to prepare successful applications and strengthen the research base of the University.
14 October 2011

Professor Jennifer Couper
University of Adelaide
711 15 Grenfell Street
North Adelaide SA 5008
Email: jennifer.couper@adelaide.edu.au

Dear Professor Couper

DIABETES AUSTRALIA RESEARCH TRUST - GENERAL GRANTS FOR 2012

On behalf of the Directors of the Diabetes Australia Research Trust, I have pleasure in confirming that your application for a Research Grant for 2012 has been successful; congratulations.

A total grant of $358,840 (excluding GST) has been awarded and will be paid in two equal payments, the first in January 2012 and the second in July 2012. You are required to submit a final report, together with a statement of receipts and payments by May 2013. Unexpended funds must be returned to the Diabetes Australia Research Trust.

Could you please confirm in writing, as soon as possible, your acceptance of the Grant, which includes a responsibility on your part to advise the Diabetes Australia Research Trust if you are offered funding for the same or similar research from another funding body. We also request the appropriate people to sign the certification sections on the Certification Form attached. Could you please also return a tax invoice for the first six months payment indicating to whom the funds are to be forwarded, with the exact institution and address details. We would appreciate a response in writing by 6/12/2011.

With your acceptance, we would also like a short paragraph, in plain English, describing your research project with an indication of the ultimate outcome that is being pursued. This will assist us in communicating your work to the wider community and consequently raising funds to continue our support of your research. You will appreciate that we are reliant on the hard work of State and Territory Associations of Diabetes Australia in raising funds for research.
We feel sure you will be able to assist them should you be approached by them, or our major sponsors of diabetes research listed below:

Underworks Pty Ltd, Australian Diabetes Society, ANZ Work-place Giving Program, Kelvin Diabetes Foundation, Diabetes Australia State and Territory Organisations as well as individual donors.

We wish you well in your endeavours.

Yours sincerely,

John Townend
Chair, Diabetes Australia Research Trust

Cc: Gail Smith g.smith@yaren.org.au
6th September 2010

Dr Panza
72 King William Road
North Adelaide  SA  5006

Dear Dr Panza,

On behalf of the Australian Physicians' Independent Committee (APIC), we are pleased to advise you that your application for an APEC Grant has been successful, and that we are able to offer $50,000 and 681 towards your research project.

The Committee was most gratified by the response, and many excellent applications were received. Two independent referees and a member of the APIC reviewed all applications, and the final selection was made by the full committee, independent of the sponsoring company.

Some conditions apply to the grant. We ask that you submit a 500-word research summary of your activities under the award, suitable for a general medical audience at the completion of the project or after 12 months if the project is ongoing. The support supplied through APEC should be acknowledged in any publications (including abstracts) or presentations, and copies of such publications should be supplied to the Grants Coordinator for review before being published. Information supplied to you in connection with the grant shall be treated as being confidential. It is also a requirement that either you or a representative be available to attend an awards ceremony to collect your certificate.

We also ask that you agree that Pfizer Australia may collect, hold, process, use, disclose and transfer your personal data and agree that you will not make any personal payments to government officials, in accordance with the terms of the Acceptance Form.

Can you please confirm your acceptance of the grant and the associated conditions by completing the Acceptance Form and returning it to the Grants Coordinator, Trudy Shapie.

We look forward to seeing you at the awards presentation, which will be held in August 2011 in Perth. Information will be sent to you closer to the time.

On behalf of the Committee and Pfizer, congratulations on your success. We join in extending our best wishes for success with your project and your subsequent career development.

Kind regards,

[Signature]

APROFESSOR TIM JONES
CHAIRMAN - SELECTION COMMITTEE APEC
Paediatric Endocrine
Research Grant 2011
Dr Alexia Pena

Title: Metformin improves vascular function in overweight youth with type 1 diabetes

[Signature]
Alexia Pena

Ph.D., M.D.
1.5 WCH Foundation Grant

Dear Prof Couper,

RE: WCH FOUNDATION RESEARCH PROJECT GRANT – DOES PERFORMIN IMPROVE VASCULAR FUNCTION IN OVERWEIGHT YOUTH WITH TYPE 1 DIABETES?

The Research Grants Committee considered 41 applications and had $650,000 available to allocate, this included $100,000 for two new researchers. It is with pleasure that I am able to advise your application for the WCH Foundation Research Project Grant has been successful and you have been awarded funds of $50,000 + GST for 2011.

Funding of the project is conditional on you holding an appointment at the Children, Youth & Women's Health Service (CYWH-S), Women's and Children's Health Research Institute (WCHRI), CYWH-S' core University Departments or SA Pathology (WCH Campus).

Payment will be in three instalments comprising:
- $25,000 + GST on the 1st January 2011, or upon advice from the Research Secretariat that ethics and biosecurity clearances have been obtained;
- $25,000 + GST on the 1st July 2011; and
- $2,000 + GST paid on completion of your research and following submission of the final report to the Research Secretariat.

To receive these instalments, you as the Chief Investigator will need to arrange for an invoice to be generated from your administering organisation addressed to the WCH Foundation for payment to your Departmental account. Please send this C/I: The Research Secretariat, Level 2, Samuel Way Building, and ensure the invoice is detailed to include; WCH Foundation Research Project 2011, Installation 1, 2 or final, the title of the project and the name of the CI. The same will be required for the second payment (less $2,000) and for the final payment of $2,000 when your research report is submitted. If the GST has not been included, than this will delay payment of the invoice.

You are reminded that your project must not commence without relevant ethical approval. Your first instalment will not be paid until this has occurred (you have indicated in your application that Human Research Ethics approval is required for your project). All applicable Ethical/Biosecurity clearances are to be obtained by the end of March 2011 to ensure funding proceeds for your research. Failure to comply may lead to the withdrawal of your funding.

If you are successful in receiving funding for your project from another funding source (ie NHMRC or Channel 7), it is essential you must notify the Research Secretariat immediately, so that your WCH Foundation Grant funding may be reallocated.
A final report should be submitted to the Research Secretariat by May 2012 outlining achievements, difficulties etc. On receipt of this report, your final payment of $2,000 will be released. Any publications as a result of the project should be provided when available. A financial acquittal must also be provided at the same time. For your information, I enclose a copy of the conditions of award in which also covers the policy for the treatment of unspent funds adopted by the WCH Foundation. Please return a signed copy as a record of acknowledgement and acceptance of this award and its conditions.

The Committee is aware that many applicants appreciate receiving feedback on how their projects were assessed and, for this reason, I am attaching copies of the spokesperson’s report and assessor’s reports.

Best wishes for the success of your project.

Yours sincerely

[Signature]

PROFESSOR COLIN ROBERTSON
Chair, WCH Foundation Grants Committee
3.1 ANZCTR approval

Your ACTRN (registration number): ACTRN12611000148976
info@actr.org.au [info@actr.org.au]

Sent: Tuesday, 8 February 2011 4:15 PM
To: Anderson, Jemma (Health)

Dear Jemma,

Re: Does Metformin improve vascular function in overweight youth with type 1 diabetes?

Thank you for submitting the above trial for inclusion in the Australian New Zealand Clinical Trials Registry (ANZCTR).

Your trial has now been successfully registered and allocated the ACTRN:
ACTRN12611000148976

Date submitted: 8/02/2011 11:14:36 AM
Date registered: 8/02/2011 4:45:01 PM
Registered by: Jemma Anderson

If you have already obtained Ethics approval for your trial, could you please send the ANZCTR a copy of at least one Ethics Committee approval letter? A copy of the letter can be sent to info@actr.org.au (by email) OR (61 2) 9565 1863, attention to ANZCTR (by fax).

Please be reminded that the quality and accuracy of the trial information submitted for registration is the responsibility of the trial’s Primary Sponsor or their representative (the Registrant). The ANZCTR allows you to update trial data, but please note that the original data lodged at the time of trial registration and the tracked history of any changes made will remain publicly available.

The ANZCTR is recognised as an ICMJE acceptable registry (http://www.icmje.org/faq.pdf) and a Primary Registry in the WHO registry network (http://www.who.int/ictrp/network/primary/en/index.html).

If you have any enquiries please send a message to info@actr.org.au or telephone +61 2 9562 5333.

Kind regards,
ANZCTR Staff
T: +61 2 9562 5333
F: +61 2 9565 1863
E: info@actr.org.au
W: www.ANZCTR.org.au