


# BMJ Open Pragmatic, double-blind, randomised trial evaluating the impact of red blood cell donor sex on recipient mortality in an academic hospital population: the innovative Trial Assessing Donor Sex (iTADS) protocol

Dean A Fergusson ,<sup>1,2</sup> Michael Chassé,<sup>3</sup> Alan Tinmouth,<sup>1,4</sup> Jason P Acker,<sup>5</sup> Shane English,<sup>1,6</sup> Alan J Forster,<sup>1,7</sup> Steven Hawken,<sup>1,8</sup> Nadine Shehata,<sup>9</sup> Kednapa Thavorn,<sup>1</sup> Kumanan Wilson,<sup>1,2</sup> Angie Tuttle,<sup>1</sup> Iris Perelman,<sup>1</sup> Nancy Cober,<sup>10</sup> Heather Maddison,<sup>10</sup> Melanie Tokessy<sup>10</sup>

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DAF and MC contributed equally.

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For numbered affiliations see end of article.

**Correspondence to**  
Dr Dean A Fergusson;  
dafergusson@ohri.ca

## ABSTRACT

**Introduction** With over 1 million units of blood transfused each year in Canada, their use has a significant clinical and economic impact on our health system. Adequate screening of blood donors is important to ensure the safety and clinical benefit of blood products. Some adverse transfusion reactions have been shown to be related to donor factors (eg, lung injury), whereas other adverse outcomes have been theoretically related to donor factors (mortality and infection). Our clinical trial will test whether male donor blood leads to a greater benefit for transfusion recipients compared with female donor blood.

**Methods and analysis** We have designed a pragmatic, double-blind, randomised trial that will allocate transfusion recipients to receive either male-only or female-only donor transfusions. We will enrol 8850 adult patients requiring at least one transfusion at four sites over an approximate 2-year period. Randomisation and allocation will occur in the blood bank prior to release of the units of blood for transfusion. Our primary outcome is mortality. An intent-to-treat analysis will be applied using all randomised and transfused patients. The principal analysis will be a survival analysis comparing the time from randomisation to death between patients allocated to male donor red blood cells (RBCs) and female donor RBCs.

**Ethics and dissemination** Approval has been obtained from research ethics boards of all involved institutions, as well as from privacy offices of Canadian Blood Services, Institute for Clinical Evaluative Science and The Ottawa Hospital Data Warehouse. Our findings will be published in peer-reviewed journals and presented at relevant stakeholder conferences and meetings.

**Trial registration number** NCT03344887; Pre-results.

## BACKGROUND

Transfusion of red blood cells (RBCs) is a necessary, life-saving intervention. Across a variety of medical and surgical situations,

## Strengths and limitations of this study

- The large pragmatic ‘real-world’ design will provide meaningful results to blood system operators and healthcare providers on the impact of donor sex.
- The broad eligibility criteria of any patient requiring a red blood cell transfusion improve generalisability of findings.
- The registry-based trial infrastructure will build capacity to conduct further low-cost and efficient transfusion trials at our institution.
- Given the broad eligibility criteria embedded within routine care, some patients will receive transfusions that do not comply to their allocated donor sex

RBC transfusions are administered with the aim of increasing oxygen delivery to tissues in the presence of anaemia.<sup>1,2</sup> Unfortunately, even if anaemia is clearly associated with adverse outcomes, it is unclear if transfusion of RBCs will improve outcomes in all patients. Several large robust clinical trials suggest that transfusing more blood is not helpful and may even be harmful.<sup>3–5</sup> Seeking explanations for the beneficial and deleterious effects of RBC transfusions is necessary to ensure the safe and optimal use of a precious biological resource.

The risks associated with blood transfusion are well documented and described. Blood systems are keenly aware of the infectious and immunological risks associated with transfusion, and a variety of measures, including donor questionnaires that assess risk and improved infectious disease testing, have been implemented to improve the



safety of transfusion.<sup>6 7</sup> Because of these interventions, the occurrence of transfusion-transmitted infections is now very low.<sup>8</sup> Despite decreased infectious risk, clinical outcomes after transfusion are affected by many other transfusion adverse events such as acute and delayed haemolytic reactions, transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload, which are associated with important mortality and morbidity. Other transfusion-related effects such as transfusion-related immunomodulation are biologically well documented,<sup>6</sup> but the effect on clinical outcomes is unclear. Whether a better selection of the donor may improve outcomes in transfusion recipients remains to be confirmed.

There is growing preclinical and clinical evidence that characteristics of blood donors may affect outcomes in transfusion recipients. Systematic reviews have identified blood donor sex as a potential donor characteristic that seems to affect transfusion recipients' health.<sup>9 10</sup> We further observed in a large cohort study of 30 503 patients that each transfusion of an RBC unit from a female blood donor was associated with a higher risk of death compared with receiving a unit from a male donor.<sup>11</sup> Such an association is not surprising as immunological phenomena related to donor sex, such as the antileukocyte antibodies (anti-human leukocyte antigen (HLA) or antineutrophil antibodies) that occur after pregnancies (eg, sex effect on TRALI) have been shown to affect clinical outcomes.<sup>9 12-14</sup> Transfusion of a blood component is analogous to solid organ transplantation as it involves the retrieval of an organ (blood) from a donor, postdonation processing and storage and 'transplantation' or 'transfusion' into a recipient.<sup>15</sup> In the transplant literature, female donor sex has been suggested to be associated with poorer outcomes in stem cell transplantation.<sup>16</sup> It is important to note that there are also observational studies that do not demonstrate an effect of donor sex on recipient outcome, and it is thus important to confirm whether such an association exists.<sup>17 18</sup>

Considering that RBC transfusion is the most frequent hospital procedure in contemporary medicine, the confirmation that better donor selection improves RBC transfusion recipients' survival will have a tremendous impact on patients and the health system and warrants rigorous randomised trials.<sup>19</sup> The primary objective of an innovative Trial Assessing Donor Sex on Recipient Mortality (iTADS) is to confirm that a transfusion strategy of receiving male-only donor RBC units will improve survival compared with a transfusion strategy of female-only donor RBC units in all hospital patients requiring a transfusion. Secondary objectives include assessing effects of male RBC units on major morbidities (cancer, infection and end-organ damage) and across major patient subgroups (recipient sex, major surgery, intensive care and oncology).

## METHODS

### Study design

iTADS is a multicentre, double-blind, pragmatic, randomised trial conducted at three academic sites (the General and Civic campuses of The Ottawa Hospital (TOH) and the University of Ottawa Heart Institute). In 2017, we received funding from the Canadian Institutes of Health Research, and the trial was registered in November 2017. The funding source had no role in the design of the study and will not have any role during its conduct, analysis, interpretation of findings or decision to submit results. iTADS evaluates a transfusion strategy of male donor RBC units compared with a transfusion strategy of female donor RBC units in all hospital patients requiring at least one RBC transfusion. All red cell products are assigned by the hospital's transfusion services, and data collection and outcome measures are gathered using routinely collected clinical and administrative data. The clinical and administrative data collected in these centres are stored centrally in TOH Data Warehouse. The data warehouse integrates data from several systems used in the participating hospitals. Data from TOH Data Warehouse will be linked with donor data from Canadian Blood Services (CBS) and outcome data from the Institute for Clinical Evaluative Science (ICES).

### Interventions

Patients, not currently enrolled in the study, requiring an RBC transfusion (as ordered by the responsible physician) are randomised to receive one of two RBC products: RBCs from a male donor or RBCs from a female donor. Patients maintain their allocated assignment throughout the study period including any subsequent hospitalisations at the three sites. Hospital transfusion services are organised for the duration of the trial to permit blinded randomisation and administration of the appropriate red cell unit type (male or female). A waiver of consent was requested and granted as it respects the five criteria of the Tri-Council Policy and has been granted in similar settings.<sup>20 21</sup>

### Outcomes

Our primary outcome is survival. As patients will have different follow-up times and the study accrual time will be just over 2 years, the survival time across the entire study period will be used for the primary analysis. The minimum amount of follow-up will be 30 days postrandomisation. The primary outcome will be measured from date of first transfusion (randomisation) to date of death or end of study period from the first patient enrolled. Because the Registered Persons Database (RPDB) of Ontario identifies the true number of deaths within 1%,<sup>22</sup> patients that are not encoded as deceased in either RPDB or TOH Data Warehouse will be considered alive at the end of follow-up.

Secondary outcomes include 30-day, 3-month, 6-month, 1-year and 2-year survival; hospital length of stay; new intensive care unit (ICU) admission; rehospitalisation; health system costs; occurrence of new cancer;

recurrence of cancer; infection rate (methicillin-resistant *Staphylococcus aureus* and *Clostridium difficile* as validated infectious outcomes and surrogates for hospital-acquired infections); new occurrence of haemodialysis (as a surrogate for severe chronic renal failure); myocardial infarctions (for cardiac events); and number of transfusions received. Secondary outcomes were selected based on the quality and accuracy of data available in the source registries and to cover a clinically representative range of adverse short-term and long-term events after transfusion (renal, cardiovascular, oncology, mortality and infections). Secondary outcome data will be obtained from TOH Data Warehouse and well-validated provincial or national registries: mortality (RPDB), cancer diagnoses (Ontario Cancer Registry), infection rate (hospital lab results), myocardial infarction, new occurrence of dialysis (Discharge Abstract Database, National Ambulatory Care Reporting System and Ontario Health Insurance Plan (OHIP)), rehospitalisation, ICU admission and length of stay (TOH Data Warehouse).

### Randomisation

In collaboration with the Ottawa Methods Centre, an electronic randomisation platform was developed and implemented to facilitate a fast, simple in-system randomisation process. When RBC units are requested by treating physician, the transfusion service technologists log onto a centralised computer maintained at TOH. The technologists enter a brief survey of patient data following which the system generates a code that randomises the patient to an intervention arm of the study. The randomisation schedule will be blocked into variables of 100 with a 60:40 ratio of male to female donors to match the current male to female ratio of available blood products. Once the study identification and randomisation code are obtained, the transfusion medicine technologist records this information into the transfusion service laboratory information system (LIS) and electronic randomisation platform for future reference of patient enrolment and randomisation. The LIS is routinely reviewed by transfusion medicine staff prior to the release of any blood product from the transfusion service. At the time that blood units are received from CBS or redistributed units are received from surrounding sites, the transfusion medicine staff are labelled with the randomisation code to permit the transfusion service technologist to crossmatch the appropriate RBC units for transfusion. For certain surgeries (eg, cardiac surgery procedures), as part of routine perioperative care, RBC units are assigned to patients and delivered to the operating room in a validated storage container. Effectively, the RBCs are on 'hold' for the patient, and an order for RBC transfusion has not been written. For logistic and feasibility reasons, we have to assign the patients to a randomisation group at the time that the RBC units leave the transfusion service. As such, about 30% of all patients will be randomised but will not be transfused during their hospital stay or during the remainder of the study period. As these randomised patients do not receive

a transfusion, they will be removed from analyses and are considered as legitimate postrandomisation exclusions as the risk of physician manipulation with respect to allocating RBCs from male or female donors is improbable. All other deviations in the randomised and transfused patients will be included in the intention to treat analysis.

All transfusion decisions will be at the discretion of the medical team, and no additional directives will be imposed by this trial. Since the administration of the correct intervention (male or female donor units) is crucial to this trial, procedure manuals outlining compliance protocols will be drafted and implemented based on consultation with site investigators, hospital transfusion services and coordinating centre personnel.

### Blinding

Donor sex is not part of the information reported on RBC unit labels. Therefore, the study investigators, the medical teams, the transfusion service staff and the study subjects are blinded to the treatment allocation. For the transfusion service staff to be able to distribute the appropriate study RBC units when a transfusion is ordered, CBS will provide a coded list of all units shipped to the hospital sites to identify each unit as being from either a male or female donor using a colour code. On arrival at the transfusion service and to avoid contamination between the two groups, the transfusion service personnel will identify and apply colour-coded study labels to each RBC unit number from the provided list. Thus, all RBC units will be identified by a colour-coded sticker. Only an independent trial statistician responsible for the allocation sequence will have knowledge of what randomisation code corresponds to male or female donor and this designated person will not have access to individual patient assignment.

### Eligibility criteria

All patients (excluding neonates and sickle cell disease) requiring one or more allogeneic RBC transfusions will be eligible. Patients will remain in the study regardless of repeated hospitalisations and continue to receive the same allocation for all transfusions for the complete duration of the study. Patients that do not have a valid OHIP number at time of first transfusion (estimate is <7% based on previous study<sup>11</sup>) will be excluded as this number is required to link each patient to the provincial registries. We will exclude patients who require emergent release of an RBC unit such that randomisation could not be completed. We will also exclude patients with complex antibody profiles and/or patients in whom it is not possible to match RBC units for an assigned group, for example, massive transfusion protocols and rare blood groups, respectively. Patients who have received an RBC transfusion and were not randomised will be excluded if any additional RBC transfusions are required within the same hospital admission. If patients receive an RBC transfusion and are excluded due to emergent release criteria, they would only be considered eligible for participation if they present back to the hospital on a separate admission.



All randomised patients that receive an allogeneic RBC transfusion will be included in the analysis.

### Recruitment schedule and enrolment procedures

Around 4500 new patients receive at least one RBC transfusion per year at the combined TOH campuses and Ottawa Heart Institute. Thus, we anticipate 8850 patients will be transfused and enrolled over an approximate 2-year study period. For each patient enrolled, a notice of study participation is provided to indicate enrolment and randomisation into the study and the contact information of a designated study coordinator. The notice of study participation is distributed following patient randomisation, after their first transfusion. Patients will thereby be provided the option of withdrawing from the study. Reasons for withdrawal will be documented.

This study is designed and executed in close collaboration and communication with transfusion service managers at each participating hospital site. Extensive training of transfusion service technologists was undertaken to accommodate the addition of study randomisation procedures (or confirmation of previous enrolment) prior to issuing any RBC unit for transfusion. If a patient is already included in the study, the technologist will ensure that next RBC unit released will match the patient's assigned study group encoded in the transfusion service LIS. For a patient not already included, the technologist will proceed with the randomisation. Because of the setting and data linkage, we do not foresee significant losses to follow-up. For the primary study outcome, the RPDB is complete for death with less than 1% deviation (potentially caused by delays in death registration or death that occurs out of country). This potential 1% missed death outcome could slightly bias our results towards the null hypothesis.

### Data collection

At time of inclusion, only the minimal patient information necessary to be able to conduct the required patient tracking in the different health systems is collected: medical record number, date and time of the first ordered transfusion and the randomisation group assigned. Apart from the initial randomisation communication with the central computer and the routine checks into the transfusion service LIS each time a transfusion is ordered to ensure that each patient receives the appropriate RBC product, no data collection forms will be required. Study data collection and follow-up are conducted through TOH Data Warehouse infrastructure, CBS and the ICES. Patient information collected for the duration of the study is kept securely at the study sites and then transferred to ICES for data linkages and analysis. The collection of baseline characteristics and laboratory, microbiological (including pretransfusion haemoglobin values and culture results) and transfusion service data will be obtained from TOH Data Warehouse. Donor information (donor sex and donor identifiers required for ICES linkage) will be obtained from CBS. This information

will then be directly transferred to ICES. Donor data will be linked to ICES information to obtain the pregnancy history status of female donors. Recipient data will be linked with outcome data at ICES where the study final analyses will be conducted. After final data linkages are performed, all personal identifiers will be removed and the records de-identified.

### Sample size

The overall mortality rate of hospitalised patients that receive RBC transfusions is high due to patient acuity. In our previous study, after a mean follow-up of 2.3 years (maximum follow-up of 7 years), 43% of patients had died.<sup>11</sup> At 1-year follow-up, which is the expected median follow-up time for this study, mortality was 30%, and the median survival was 5 years. From our previous observational work, we expect our intervention to reduce the absolute risk of death by at least 5%.<sup>11</sup> We proposed a minimally clinically important difference of 2% (applicable to the entire inpatient and outpatient population). Thus, sample size calculations based on a survival analysis comparing two survival curves using a two-tailed  $\alpha$  of 0.05 and a  $1-\beta$  of 0.80, an accrual time of 2 years, median survival time of 5 years, an absolute risk reduction of 2% (30%–28%, corresponding HR of 0.93) and a 11% non-compliance factor require 8850 randomised and transfused patients. Our original estimate was a 3% non-compliance requiring 8000 patients. A revised 11% non-compliance estimate was informed by 1-year aggregate trial data. The 11% non-compliance at the patient level is predominantly due to the allocated donor sex not being available at time of RBC transfusion (first or repeat) or the need for the transfusion service to use expiring units.

### Data analyses

An intent-to-treat approach will be used with all analyses using the entire cohort of randomised and transfused patients. A detailed Statistical Analysis Plan has been provided as a supplemental document (online supplemental appendix 1). The principal analysis will be a survival analysis and will compare the time from randomisation to death between patients allocated to female donor RBCs and male donor RBCs. Patients who do not die will be right-censored at the end of their follow-up. Unadjusted survival rates with 95% CIs will be compared using log-rank tests. In addition, Cox proportional hazards regression models will be used to further elucidate the measure of effect while adjusting for possible confounding variables.

Secondary analyses of the death outcome will include survival analyses at 30 days, 3 months, 6 months and 1 and 2 years using unadjusted log-rank tests followed by Cox proportional hazards model procedures to adjust for important prognostic risk factors. Additional individual variables and interactions will be considered based on clinical importance and empirical data. Our secondary outcomes of occurrence of new cancer, recurrence of cancer, infection, new occurrence of haemodialysis and

myocardial infarctions and health system costs will be conducted in the same manner as the primary analyses. The continuous secondary endpoints (hospital length of stay, number of rehospitalisations, number of ICU admissions and number of transfusions) will be analysed using either parametric (independent t-test) or non-parametric procedures (Wilcoxon rank sum) followed by generalised linear regression models that adjust for important risk factors.

Using the approach outlined for primary and secondary analyses, we will perform similar analyses by donor pregnancy history, severity of illness at baseline as measured by the Charlson Comorbidity Index, recipient sex, recipient age, patient type (medical vs surgical; inpatient vs outpatient; critical care vs non-critical care; chronically transfused vs not; oncology vs non-oncology; and, for oncology patients only, haematologic vs solid tumour malignancy), pretransfusion haemoglobin values and RBC manufacturing characteristics. These analyses will be strictly hypothesis-generating in nature.

While our intent-to-treat approach will be conducted using the entire cohort of transfused patients regardless of compliance with allocated interventions, we will also perform a sensitivity analysis of all patients that achieve 75% or greater compliance with allocated intervention at the RBC unit level (eg, a patient that receives two of four allocated units would be considered non-compliant, whereas a patient that receives three of four allocated units would be considered compliant). A second sensitivity analysis including only patients who achieve 100% compliance will also be performed.

#### Data safety and monitoring

An independent data safety and monitoring board reviews quarterly reports of between-group baseline characteristics and in-hospital safety outcomes including in-hospital mortality. No formal stopping rules or adaptive procedures were implemented due to the short duration of the trial and the costs and feasibility of obtaining and linking out-of-hospital outcome measures (including our primary outcome of mortality) with provincial health administrative data at the Institute for Clinical and Evaluative Sciences each quarter.

#### Patient and public involvement

No patient partners were involved in the research process of our trial protocol.

#### STUDY MANAGEMENT

A steering committee has been established with the overall responsibility for the design, execution and analysis of the trial. The steering committee meets monthly to discuss all pertinent issues. The Coordinating Centre is located at the Centre for Transfusion Research at the University of Ottawa, Ottawa, Canada. Personnel at the Coordinating Centre include the study chair, research nurse coordinator, biostatistician and data analysts. The Coordinating

Centre is responsible for the day-to-day management of the trial. Each site has the equivalent of at least one transfusion service technologist dedicated to this project. The site transfusion service technologists have the responsibility to (1) organise the blood units by study group in the transfusion service, (2) screen and randomise patients, (3) encode the study group in the transfusion software, (4) release the appropriate blood unit for transfusion and (5) keep track of all patients enrolled using a standardised electronic case report form. The study coordinator is responsible for checking protocol adherence weekly with the collaboration of CBS and address trial-related issues that may arise during the study in collaboration with the study chair. Our CBS collaborators ensure that each blood unit delivered to each site has an assigned colour code to allow appropriate blood unit classification by the transfusion service.

#### ETHICS, CONSENT AND PRIVACY

Approval has been obtained from research ethics board of all involved institutions (Ottawa Health Science Network Research Ethics Board #2017 0477-01H and CBS Research Ethics Board #2017.051) as well as from privacy offices of CBS (for donor sex information), ICES (for outcome data) and TOH Data Warehouse (for patient data). All data collection and management will be performed in accordance with the Personal Health Information Protection Act of Ontario, Regulation 329/04. A unique de-identified number will identify all patients, and no patient identifiers will be kept with clinical data. The resulting database will be encrypted and stored centrally at the Coordinating Centre during the trial and at ICES after study completion. No patient was recruited before institutional approval was obtained.

#### DISSEMINATION

From the early development of our trial, we have involved stakeholders and experts in a wide range of fields involved with the organisation, research and care of patients receiving transfusions (haematologists, intensivists, transfusion specialists, healthcare researchers, epidemiologists, blood organisation decision makers and senior scientists). This diversity of expertise will ensure that the research questions, objectives, methods and result analysis and interpretation answer pertinent questions for clinicians but also for stakeholders, patients and the overall population. The results will also inform blood supply organisations' policies. Results obtained from this research project will be customised to target the different stakeholders involved with blood transfusions. For clinicians and researchers, traditional dissemination will be used, including publication in relevant peer-reviewed medical journals and presentations at local, national and international conference and meetings. We will ensure that publications resulting from this

work are open-access. We will work closely with the different stakeholders of CBS and the different clinical specialties to provide reports for the specific needs of their organisations/disciplines. Many additional stakeholders such as other medical specialty organisations involved in transfusion and other blood supply organisations such as the Red Cross in the USA will benefit from the results of this study. In addition to traditional dissemination strategies, we plan to directly reach out to these organisations to present our results, and the team members will be readily available for further discussions, meetings or presentations to answer their specific needs and questions.

## POTENTIAL IMPACT

We estimate enrolment and follow-up completion by early 2021. Our pragmatic trial will provide robust evidence on whether a male-only RBC transfusion strategy compared with a female-only strategy improves survival of transfusion recipients. We will also obtain important information regarding the recipient subgroups that may be less affected (or not at all) by such a practice and thus provide important information to the blood providers to help tailor transfusion practices to the patient. Because of the proposed pragmatic ‘real-world’ design, our study results will provide meaningful information to healthcare providers regarding the impact that such changes would have on their patients. The novel iTADS infrastructure also provides capacity to conduct future innovative clinical trials using similar strategies and thus provide the foundation to conduct minimal-cost, efficient, practice-changing investigations.

## Author affiliations

<sup>1</sup>Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

<sup>2</sup>Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada

<sup>3</sup>Department of Medicine, Division of Critical Care, University of Montreal, Montreal, Quebec, Canada

<sup>4</sup>Division of Hematology, Department of Medicine, Ottawa Hospital, Ottawa, Ontario, Canada

<sup>5</sup>Center for Innovation, Canadian Blood Services, Ottawa, Ontario, Canada

<sup>6</sup>Division of Critical Care, Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada

<sup>7</sup>Internal Medicine, Ottawa Hospital, Ottawa, Ontario, Canada

<sup>8</sup>School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada

<sup>9</sup>Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, Ontario, Canada

<sup>10</sup>Eastern Ontario Regional Laboratory Association, Ottawa Hospital, Ottawa, Ontario, Canada

**Twitter** Melanie Tokessy @melanie\_tokessy

**Contributors** DAF and MC conceived the study. DAF, MC, ATi, JA, SE, AJF, NS, KT and KW designed the study protocol submitted to Canadian Institutes of Health Research. DAF, MC, ATi, JA, SE, AJF, SH, NS, KT, KW, ATu, IP, NC, HM and MT designed and/or provided input into the final study protocol. DAF and MC drafted the manuscript. DAF, MC, ATi, JA, SE, AJF, SH, NS, KT, KW, ATu, IP, NC, HM and MT read, contributed to and approved the final manuscript.

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## ORCID iD

Dean A Fergusson <http://orcid.org/0000-0002-3389-2485>

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