Meta-research: Using research to increase the value of health and medical research

Aim: To increase the value of health and medical research in Australia by making funding applications more efficient, increasing data sharing and increasing reproducibility

In 1994 the eminent statistician Doug Altman wrote in the *BMJ*, "We need less research, better research, and research done for the right reasons".[1] In 2015 Altman's paper won a readers' poll of the *BMJ*'s best papers, showing how relevant it still is today. In fact it is more relevant today because of the huge recent increase in research, with 75 new trials and 26 new systematic reviews published every day. Regrettably most of this research is unreliable because of mistakes in its design or analysis. Professor John Ioannidis (Stanford) used simulations to demonstrate that "most claimed research findings are false" (a paper with over 1.5 million views),[2] and Professor Paul Glasziou (Bond) and colleagues have estimated that 85% of the worldwide spending on health and medical research is wasted, which is a staggering USD $170 billion per year.[3] The 85% figure is supported by reproducibility studies with failure rates between 75% and 90%.[4] It has been called the **reproducibility crisis** and it is a serious threat to the credibility of health and medical research.

Evidence-based solutions to increase reproducibility and reduce waste include: better training and mentoring, using pre-published protocols, blinded analysis, and independent replication of results. I learned all these techniques in my first job.

In 1994 I completed my undergraduate degree in statistics and started my career as a statistician with the drug company *SmithKline Beecham* where I was trained in data management, programming and trial conduct. I was part of a team of three statisticians, two data managers and two programmers, all working on a large phase III clinical trial. One of the statisticians (Dr Mick Ireson) had more than 20 years' experience and was my mentor. Our team wrote a protocol and data analysis plan. We created complete sets of tables, graphs and analyses using a scrambled treatment group, and every output was independently replicated with disagreements resolved by consensus. Since then, for 21 years I have applied these techniques and built a successful research career, **but these simple and effective solutions are not widely used in health and medical research**.

One reason these solutions are not more popular is resources. A large drug company can afford to employ multiple highly skilled people to work on a single study. However, given the power of research to impact on people's lives, can we afford to cut corners? As Altman explained, spending more time and care on fewer projects would be better value for the public.

Waste is also caused by the **incentives** that drive researchers, such as the "publish or perish" maxim which leads to: inadequate validation, salami slicing results, "p-hacking" and outcome switching. Time is an issue too, and the race to publish first often comes at the cost of accuracy. Researchers have no incentive to spend time reproducing their own or others research, as this has little kudos. However, this "boring" research can be incredibly valuable to society if it either aids the translation of an effective intervention or leads to disinvestment in an ineffective one.

Another large area of waste is the time spent writing and reviewing unsuccessful grant proposals. Research I led found preparing Project Grants takes over 600 years in researchers time every year and the time paradoxically increased after the NHMRC streamlined the system.[5] Spending time on lengthy applications, means researchers spend less time on their actual research. Professor Ioannidis wrote in a 2011 *Nature* paper, "The research funding system is broken: scientists don't have time for science any more. [...] It's time to seriously consider another approach."

Another solution for reducing waste and increasing reproducibility is to increase **data sharing**, as this allows analyses to be reproduced, and allows data to be included in new or larger analyses (such as patient-level meta-analysis). However, current rates of data sharing are very low (generally under 10%), even in journals such as the *BMJ* which have strong data sharing policies.

The large waste in the current research system coupled with the previous scarcity of rigorous research into reducing waste means that there is **tremendous potential to reduce waste and increase value** in health and medical research. The way to achieve this is by using research to improve research, and this growing field of "meta-research" is led by some of the world's best

researchers such as John Ioannidis (Stanford), Sir Iain Chalmers (BMJ Lifetime Achievement Award 2014), Doug Altman (Oxford; BMJ Lifetime Achievement Award 2015) and Paul Glasziou (Bond). These researchers understand the importance of meta-research as it impacts on every area of health of medical research, from pre-clinical to translational studies.

RESEARCH PLAN

I will use research to improve research in three areas:

1. Research funding
2. Data sharing
3. Reproducibility

Research Area 1: Research funding

In 2010 I won an NHMRC Project Grant as CIA on "Building an evidence base for funding evidence-based medicine". We investigated multiple aspects of funding including: incentives, reliability, streamlining, and the time spent preparing applications. Our work produced two letters in *Nature* and six papers. Our work on reliability was in collaboration with the NHMRC secretariat and we presented all our results to the NHMRC Research Committee. We were invited to meet the McKeon review committee of health and medical research, and met with senior politicians in Canberra. Our work on streamlining was used in the final McKeon report, was quoted by Prime Minister Abbott in parliament, became official policy of both the Liberal and Labor party, and federal funding was made available to help the NHMRC streamline the application process.

During the past five years of investigating research funding I have met with many smaller funders and foundations, to discuss peer review and administrative processes (see B-COL). These foundations fund research across a range of health areas, and whilst they are experts in their areas they often lack expert knowledge of peer review. They also lack the skills to take advantage of recent technical advances in automation, which save time for applicants and administrative staff.

To combat these issues I aim to create a **peer review network for small funders**. This will be a free to join umbrella organisation that will enable small funders to share ideas on peer review and grant administration. I will write guidelines on peer review, administration, post-award monitoring and other areas of need for small funders. I will arrange annual meetings to share the latest research on funding peer review and hear ideas and issues from funders. I will investigate ways to reduce the bureaucracy of applying and post-award monitoring, such as automatically extracting details from online databases such as *Google Scholar* and *ORCID* (in April 2015 the ARC and NHMRC encouraged every researcher applying for funding to get an *ORCID* ID).

My existing small funder collaborators (see B-COL) have already agreed to pilot ideas, network with other funders, and provide support such as sponsoring or co-organising the annual meeting.

Research Area 2: Data sharing

There has been a recent international drive to increase the low rates of data sharing, including the 2016 proposal by the International Committee of Medical Journal Editors (ICJME) for every clinical trial to share their data. I aim to **increase data sharing by providing key evidence for strengthening data sharing policies** as outlined below.

Part I: The value of data sharing:

Articles that promote data sharing almost always focus on successful case studies, such as the genetics project, or on negative stories, such as data being hidden to protect commercial interests. Surprisingly there has been no systematic study of the overall benefits of data sharing using a representative sample of journal articles.

I will lead research that will quantify the benefits of data sharing in health and medical journals by generating a representative sample of papers that shared their data by searching thousands of papers using *R*. Where data were re-used I will examine what was achieved. The value of the data sharing activity will be estimated by comparing scenarios of 'no data sharing' and 'data sharing'. For example, re-running an individual patient data meta-analysis without the shared study and estimating the impact on health services and clinical practice.

Part II: Increasing data sharing

Recent policies from journals and funders to increase data sharing have had some success, but there remain significant barriers to widespread data sharing. Researchers generally agree that data sharing

is a good idea, but raise concerns about: being scooped, a lack of academic credit, and cite a lack of time or knowledge of how to share their data. Some data cannot be shared for legal, copyright or ethical reasons, but peer to peer sharing should still be possible for reproducibility purposes.

Ongoing unpublished research from one of my PhD students has found that data sharing was promised in just 28% of papers in the *BMJ*, which has a strong data sharing policy. However, only 15% of those we asked to share their data did so, giving an overall percent of available data of just 4% (one data set was on *Dryad* – a data sharing web site).

I will test if data sharing is facilitated by the online *REDCap* (Research Electronic Data Capture) data management software. *REDCap* is freely distributed through an international network of more than 900 institutions (50+ in Australia) with 100,000+ users and 100,000+ ongoing studies. This versatile and user friendly software may increase data sharing because:

- It provides an accessible location for the data. Previous studies of data sharing have included anecdotes of researchers wanting to share their data but not being able to find it.
- It creates an automatic data dictionary, which facilitates more sensible re-use the data.
- Data can be exported in several formats or the new researcher can be given access rights in *REDCap*. This saves data preparation time, and so removes a big obstacle to data sharing.

I will use a case–control study to test whether *REDCap* increases data sharing. Cases will be randomly drawn from published papers that used *REDCap* (an online list is available, with 1,800+ current papers), with controls as randomly selected papers in the same journal issue, excluding systematic reviews, meta-analyses, protocols, commentaries and case series. Selecting controls from the same journal issue will match perfectly for time and match approximately for research field. I will then use automated keyword searching to find offers of data sharing, and e-mail authors who offered to share their data. Six-hundred *REDCap* "case" papers with three controls per case, will give an 86% power to detect an increase in data sharing from 8% in control papers (based on four published studies) to 13% in case papers. An increase of 5% may appear small, but if scaled up to the wider literature it is a large change that would improve the quality of the evidence base.

Automated data collection is available using *R* packages that interface with online journals to search articles for keywords that indicate data sharing. I will check the accuracy of the automated data collection by verifying a random selection of papers.

If *REDCap* increases data sharing then I will promote its use in my research training (see Translation section below) and via networks such as the Australian National Data Service.

Research Area 3: Reproducibility

Reproducibility is a cornerstone of scientific research, yet science currently faces a reproducibility crisis with incredibly low rates of reproducible research even in the highest ranked journals.[4] A key issue is mistakes in data preparation (e.g., miscalculating a composite score, wrongly sorting a column of data) and statistical analysis (e.g., not doing simple model verification checks). More mistakes would be prevented if analyses were independently verified.

I propose to create an **online peer-to-peer replication network** where researchers would be paired together and each would perform the others replication (prior to journal submission). In the initial stages this would just be for randomised controlled trials as these should have a protocol, but I aim to cover other analysis including observational studies and cost-effectiveness analyses. A recent analysis of re-analysed RCTs found 13 out of 37 (35%) had different interpretations from the original article, showing clear potential for increasing the reproducibility of RCTs.[6]

Researchers would upload their protocol and raw data via the web page. The web page will include instructions and videos on the principle of replication and what is expected from participating researchers. The replication would be based on a scrambled treatment group as this should focus the replication on the data processing and statistical methods rather than the results. Using a scrambled treatment will also reduce confidentiality or conflict concerns, making it easier for researchers to share their data. Researchers would only get their feedback once they have uploaded their own

results and comments; this would avoid researchers getting the benefit without reciprocating the work. The system would be open, with all researchers named and aware of their paired researcher.

Taking this extra step involves additional time and effort by researchers, but the pay-offs will be higher quality papers that are more reproducible and less likely to be corrected or retracted. Researchers will be able to mention the validation in their paper, which may increase their chances of being accepted and hence save them re-submission time.

I will estimate the costs and benefits of the replication by collecting data on the time taken and the number of mistakes found using brief surveys of participating researchers. Longer term I will use a case–control study to look for an increase in citations, and decreases in corrections and retractions.

Timeline (5 years) Year	2017				2018				2019				2020				2021			
Quarter	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
1. Research funding																				
2. Data sharing																				
3. Increasing reproducibility																				
Two two-month visits to Stanford							S								S					

I will visit the Meta-Research Innovation Center at Stanford (METRICS) for two two-month trips. Exact dates will coincide with the METRICS annual conference. This is the world's best group working in meta-research. I have an open invitation from the co-director, Prof John Ioannidis.

My own reproducibility

All my studies will be exemplars of research reproducibility. They will use a protocol that pre-specifies: a) the primary outcome to avoid any outcome switching, b) any subgroup analyses or interactions to avoid significance fishing. Studies will be designed and reported using the appropriate EQUATOR checklist. I will analyse the data using *R* and *Sweave* to completely document my code. I will share my data, data dictionary and statistical code with other researchers.

Translating my research into policy and practice

Key stakeholders in this field are funders, journals, researchers and professional bodies. Each of these stakeholders believes in the power of evidence-based research and therefore should be amenable to change based on high quality research.

I have seen the power of my previous research to change NHMRC policy, with the streamlined application process and recently created NHMRC committee on reducing application costs.

I am on the editorial boards of four journals and have discussed changes to peer review with all four editors. I have discussed our early results on data sharing with Trish Groves from the *BMJ*, and we have identified loopholes in their data sharing policy that could be closed. I will work with Virginia Barbour, who is the president of the Committee on Publication Ethics, on how journals could change their policies to increase reproducibility (see B-RT Research Team).

I will run 4+ engaging short courses per year (half to 1 day) at national research conferences (including clinical and allied health conferences). Titles will include "Common mistakes in research and how to avoid them" and "How to make your research reproducible". Using national conferences will mean I reach a wide range of Australian researchers, including part-time clinical and allied health researchers. Courses will be problem based with a focus on practical actions.

I have discussed my research on data sharing with Dr Ross Wilkinson, the CEO of the Australian National Data Service. He called it "fascinating" and has agreed to be on the advisory board for our Centre of Research Excellence Application.

Current meta-research

The novel research planned in this application builds on my ongoing meta-research, including:

1. With Professors Philip Clarke (Melbourne) and Tony Blakely (Otago), and the New Zealand Health Research Council (NZHRC), we are running an RCT of the impact of research funding. The

NZHRC uses random allocation to award funding for its Explorer Grants creating an ideal opportunity for the world's first unbiased study of the effect of funding on a researcher's trajectory.

2. Working with my PhD student and the QUT Library, we are planning an RCT to test whether data sharing can be increased using either a financial incentive or time with a data manager.

3. Working with my research assistant, we are examining the impact of caring for children on a woman's research career. We used Australian journals to create a representative cohort of women who published in 2007, and have taken their publication history from *Scopus*. We are surveying the women about their dates of caring for children (if any). The primary outcome is annual paper numbers and we will look for a change in trajectory at the time of each child. This will give the first empirical estimate of career disruption that may help guide promotion and fellowship applications.

OUTCOMES AND SIGNIFICANCE

My research concerns the essential technical work that underpins all research, covering statistics, bureaucracy, data management and peer review. Improving these fundamental aspects of research has the potential to create wide-reaching and long-lasting benefits. With 85 cents in every dollar invested in health and medical research currently wasted, there is tremendous potential to improve practice and increase the return on investment.

I will make tangible and practical improvements by using research to improve research. I will interrogate observational data, run experiments to investigate and change behaviour, and work with key stakeholders to change incentives and translate my findings into better practice.

- Improving the peer review systems of Australia's charitable foundations will reduce administrative costs and allow researchers to spend more time on research.
- Establishing the benefits of data sharing will provide evidence to drive policy changes to increase data sharing, and I will test practical ways of increasing data sharing.
- Increasing reproducibility will increase the quality of the evidence base, which will reduce waste and lead to more informed health policy.

For all my projects I do not expect all researchers (or funders) to change behaviour. But for those researchers who I do reach, then there will be long-term benefits as they will run better studies for the rest of their careers, and will provide better training for the next generation of researchers

Now is an ideal time to be working in meta-research, and recent changes from journals, funders and professional societies show a desire to reduce research waste. Examples include: recent special issues on reproducibility in *Nature* and *PLOS*, and research waste in *The Lancet*; the 2016 statement from ICJME on data sharing; and the NHMRC adding a Research Data section to CVs (see CV-RD), and including "addressing reproducibility of research results" in the latest advice to applicants.

My vision is influenced by my early statistical training and Doug Altman's 1994 paper of "less research, better research". I aim to increase the value of health and medical research in Australia, creating benefits for the careers of Australian researchers and the evidence base used to make health policy decisions. This research will be part of a growing international movement to improve the basics of research. I have the capability, statistical experience and determination to lead a team that will generate high quality studies of importance to the international research community.

References

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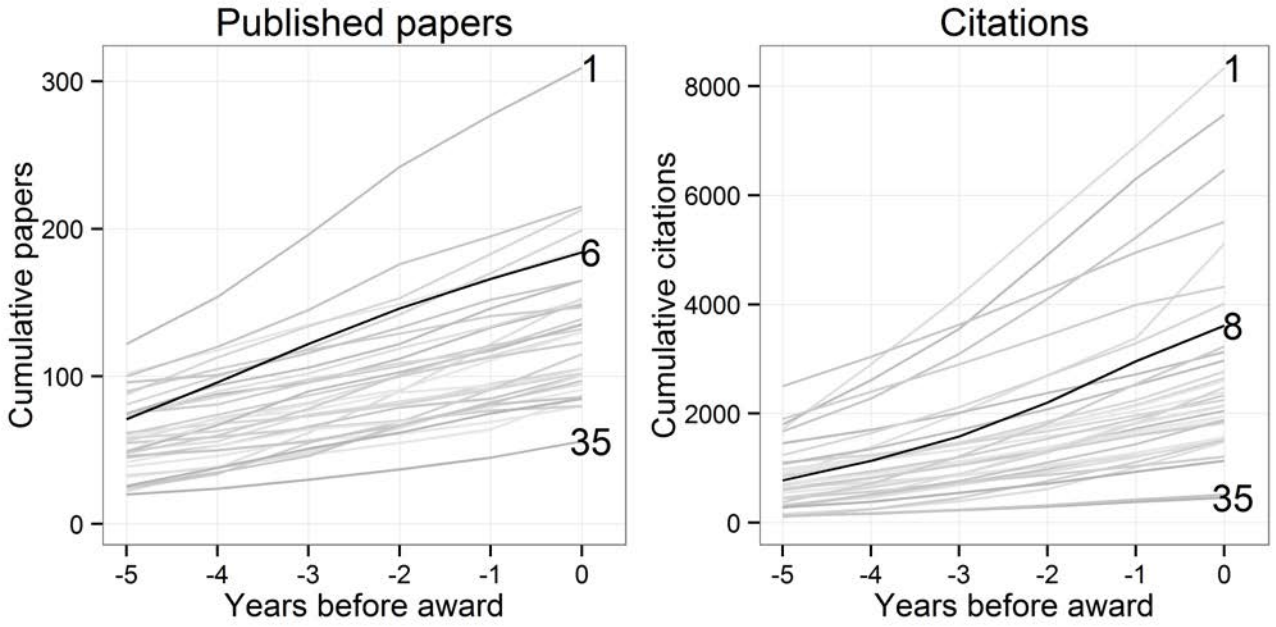
4. Begley CG, Ioannidis JPA. Reproducibility in Science: Improving the Standard for Basic and Preclinical Research. Circulation Research 2015;**116**(1):116-26.
5. **Barnett AG**, Graves N, Clarke P, et al. The impact of a streamlined funding application process on application time: two cross-sectional surveys of Australian researchers. BMJ Open 2015;**5**(1).
6. Ebrahim S, Sohani ZN, Montoya L, et al. Reanalyses of randomized clinical trial data. JAMA 2014;**312**(10):1024-32.

Evidence of Rising Trajectory *(½ page limit)*

The graphs below compare my cumulative publication and citation numbers from *Scopus* over time to NHMRC Senior Research Fellowship 'A' and 'B' winners in public health and health services research from 2012 to 2015. The right-hand side of the graph is standardised to the year before the fellowship was awarded. The grey lines are the 34 recent winners and the black line is me.



Amongst recent winners I have the sixth highest number of papers and eighth highest citation count. For first author papers only (graphs not shown) I have the fifth highest number of papers and third highest citation count. I am therefore performing very well compared with recent winners and have a similar rising trajectory. My h-index is 43 on *Google Scholar* and 33 on *Scopus*.

Indigenous Research Excellence Criteria, if applicable *(2 pages)*

Not applicable