© 2014 Scottish Universities Medical Journal
Published online: March 2014
Vol 3 (supp1):s6-s11
Hughes LD (2014). The State of Science and Unreliable Research

The State of Science and Unreliable Research

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ABSTRACT

Scientific endeavours in all fields have helped develop and shape society across the globe. In the past decade the sheer quantity of research and data has been staggering, with 90% of all data being obtained since 2011. In the face of this sheer quantity of research and data there are legitimate concerns that quality may be being compromised for a number of different reasons. There are concerns that the peer-review process is not as effective as it should be, that papers reporting negative results only account for a small proportion of main stream journal articles, and that the competitiveness of science and academia is discouraging verification studies particularly in basic sciences and promotes exaggeration and cherry-picking of results.

Such concerns are legitimised by the tenfold increase in retractions from mainstream journals in the past decade. In addition to wasting time and resources such flawed research may place patient lives in jeopardy. Indeed, between 2000 and 2010, 80,000 patients took part in clinical trials based upon research that was later retracted (either due to error or improprieties). This paper aims to discuss some of the areas including the competitiveness of science and academia, publication bias, the weaknesses of peer-review and 'hidden' data-sets.

Key Words: scientific research; peer-review; clinical research

Introduction

Scientific endeavours in all fields have helped develop and shape society across the globe. In the past decade the sheer quantity of research and data has been staggering, with 90% of all data being obtained since 2011[1]. In the face of this sheer quantity of research and data there are legitimate concerns that quality may be being compromised for a number of different reasons[2]. There are concerns that the peer-review process is not as effective as it should be[3-4], that papers reporting negative results only account for a small proportion of main stream journal articles[5], and that the competitiveness of science and academia is discouraging verification studies particularly in basic sciences and promotes exaggeration and cherry-picking of results[5-6].

Such concerns are legitimised by the number of article retractions in mainstream journals. Retractions have steadily increased since the first retraction in 1977[7], with a ten-fold increase in the past decade[5]. In addition to wasting time and resources such flawed research may places patient lives in jeopardy. Indeed, between 2000 and 2010, 80,000 patients took part in clinical trials based upon research that was later retracted (either due to error or improprieties)[3]. This paper aims to discuss some of the areas including the competitiveness of science and academia, publication bias, the weaknesses of peer-review and 'hidden' data-sets.

"Trust but Verify"

The concept that identical experiments always get the same result, no matter who performs them, is a cornerstone to scientific research and aims to prove a hypothesis as fact. Achieving perfect verification of all studies is clearly not achievable due to limitations of

basic science research describing new findings, but it should be possible for the majority of science experiments (in all scientific fields) to be replicated and verified based upon the methods described by authors. However, this appears not to be the case.

In 2012, Amgen (an American drug company) attempted to replicate 53 pre-clinical oncology studies they considered land-mark papers in the basic science of cancer[8]. Even when liaising closely with authors of the relevant papers, only 11% of the papers findings were replicated, a result described by the authors as "shocking"[8]. In 2011 Bayer (a German drug company) only managed to replicate a quarter of 67 seminal studies in an analysis of early in-house projects in the research fields of oncology, women's health and cardiovascular diseases[9]. Such work underlines the importance of confirmatory validation studies, which should also aim to complement the knowledge on a particular therapeutic target and hone researchers techniques. Indeed, the difficulties in the reproducibility of early stage scientific research may be part of the reason for the fall in the success in newly developed Phase II clinical trials in recent years[9-10].

It should be noted that a difficulty in reproducibility does not amount to fraud, but merely shows that particular novel techniques assessing unexplored scientific avenues in basic science may be prone to a greater degree of variability and error than expected. Another potentially contributing factor may be that papers do not adequately report all research resources (including antibodies, model organisms etc.), without which it is challenging to reproduce experiments even when the underlying science is sound. Indeed, a recent study reported that more than half of 238 biomedical papers in 84 journals failed to identify all the resources required to verify their work[11]. Another review of 351 randomly selected papers in high-impact journals found that only 143 papers were subject to any data availability policies, and adhered to the data availability instructions in their respective journal[12].

Thus, it is important to promote verification. Adequately verifying scientific techniques will be of benefit for drug companies as their investments in early stage therapeutic products would be more likely to succeed at Phase II trials[9] and for scientists as scientific techniques will develop over-time and provide greater weight to research findings. However, promoting verification is not easy. Many academic researchers would prefer to embark on novel research that is more likely to advance their own career and junior researchers may feel that replication is a challenge against a papers authors. More importantly, in the current climate the costs associated with verification studies alongside a desire for novel research by funding bodies may prevent some work being replicated.

Despite these barriers, in the discipline of psychology the journal *Perspectives on Psychological Sciences* will shortly have a section devoted to replication and verification studies. There is also the newly formed Reproducibility Initiative through which life scientists can pay to have their work verified by an independent laboratory, giving the papers methods and findings more weight thus incentivising replication. The Initiative is currently reviewing the findings of the 50 highest-impact cancer papers published between 2010 and 2012, following a grant from the Laura and John Arnold Foundation[13]. Dr Elizabeth Iorns, the co-director of the Reproducibility Initiative, noted "The lack of reproducibility in cancer studies is a major obstacle in the development of viable therapies to cure cancer"[13]. It is hoped that this initiative will help improve the reproducibility of work in other science and healthcare fields.

Science – A Competitive Industry

Science is a competitive industry. Full professors in America earned on average $135,000, and with 6 applications from new PhDs for every academic post in the US, the stakes are high[3]. The pressure to publish work in high-impact journals is crucial, as high-impact publications are important for being successful in the academic job market and subsequently obtaining and maintaining funding for research. The pressure to 'publish or perish' appears to have an effect upon some researchers overall scientific conduct. A 2009 meta-analysis covering 18 fraud surveys [six targeting biomedical scientists directly], found that 2% of those participating admitted to having falsified, fabricated or modified data at least once themselves[14]. Although this figure is reasonably low, an alarming 14% reported to have noticed this behaviour in colleagues[14]. The author also proposed that as these surveys ask sensitive questions and have other limitations, these figures are likely to be a conservative estimate of the true prevalence of scientific misconduct[14]. Cherry-picking, selectively reporting data that supports a desired outcome, may be much more common that deliberate fabrication. A fine balance must always be found about reporting data that is relevant and important to the narrative of a paper, and data that is not. Massaging the data so they favour a particular finding/hypothesis walks a tightrope, between sloppy science and scientific misconduct depending on the circumstances.

Such cases have the potential to have a hugely detrimental impact for all involved in scientific research. Firstly, upon honest researchers by preventing those researchers obtaining funding for their work and tainting institutions with a fraudulent tag. Secondly, scandals in sensitive scientific areas including stem-cell work and oncology may erode public confidence in science and their research more widely[6]. Finally, clinical work involving patients based upon flawed research may be placing lives at risk.

There are several approaches that are currently attempting to address some of the concerns associated with research integrity. Firstly, it is becoming increasingly stressed that the responsibility of maintaining academic integrity should fall with the senior investigator. In a recent *Nature* editorial it was noted that this individual has a unique position of trying to develop, "a laboratory environment that provides a strong foundation in best practice in research and research ethics, and to be a compelling role model for trainees"[6]. Secondly, there has been recent work at both a national level and international level to support research integrity. In the UK, the UK Research Integrity Office provides support and advice for individuals and institutions throughout the research process and offers advice for those who feel that they may have witnessed research malpractice. Furthermore, international guidelines have been developed from the 2nd Worldwide Research Integrity Conference, aiming to raise awareness of science ethics and to lobby governments and institutions to design and implement policies to promote research integrity. The guidelines note the importance of reporting and raising irresponsible research practice. Finally, the guidelines stress to researchers that despite the huge pressure they can be placed under to cherry-pick or fabricate results, irreducible findings will be discredited in the long-run and the potential implications of fabrication can be career ending. Finally, journals can promote integrity and transparency in the practise and presentation of research by developing and implementing rigorous standards for data presentation, author contributions and statements of authors' conflict of interests. Although there is more work to do in this area, the fact that there is increased awareness and interest in this area hopefully will improve the overall climate for researchers working in the 'publish or perish' climate.

Publication Bias

Yet another one of the challenges facing science is publication bias. Journals yearn for papers that prove a hypothesis or describe a novel intervention or treatment. Indeed, negative results, where a hypothesis/treatment is shown to be incorrect, account for only 14% of published papers, down from 30% in the 1990s[3]. However, publishing negative results, where a hypothesis is shown to be incorrect, remains crucial. Failing to publish these results creates a false impression and bias in the literature. Other scientists may waste valuable time and resources on treatments that have already been shown to be ineffective. The importance of publishing negative studies is even more important in the area of clinical research, as patients may be treated with medications/therapies that have already been shown in unpublished data to be of no benefit and/or harm. Furthermore, not publishing negative data undermines all of the efforts made to minimise bias in individual trials.[15]

There have been numerous efforts to try and address this. Firstly, in the US there are moves to enforce legislation requiring all results of clinical trials funded by the state to be posted on clinicaltrials.gov within 12 months of completion[16]. To date, this legislation appears to have been widely ignored[16] and up to a third of clinical trials financed by the National Institute for Health remain unpublished after 51 months[5]. Secondly, closer to home, the AllTrials.net campaign, started 12 months ago, has called for all trials on all uses of all currently prescribed treatments to be registered, with their full methods and results reported[17]. The campaign is widely supported by medical and academic organisations, and has obtained the support of some in the pharmaceutical industry including GlaxoSmithKleine. This unfortunately will only include research carried out from 2014 and beyond, meaning that previous trial data will continue to skew the evidence base. However, efforts are continuing to include historical data. Thirdly, the British Medical Association has passed a motion noting that withholding trial results constitutes research misconduct[18] with the General Medical Council reviewing their position[15]. Finally, for individual researchers many journals now have online only publication meaning they have more space to publish papers with negative results.

The Challenges of Peer-Review

Peer-review is often reported to be the 'gold-standard' of vetting the quality of scientific work[4]. However, there are numerous examples of research that passed this standard subsequently being retracted due to clear fraud or unethical conduct. The most commonly quoted examples include Hwang Woo-suk who carried out fraudulent work on stem-cells published in *Science*[19] and Andrew Wakefield whose work in the 1998 *Lancet* led to the MMR vaccine scandal[20]. Importantly, these cases extend the highest impact journals, which have rejection rates in excess of 90%.

Work by John Bohannon, a Harvard biologist, found that a pseudonymous paper on the effects of a chemical derived from lichen to treat cancer cells was accepted by 157 of 304 journals the work was submitted to[21]. This was despite the fact that the paper had numerous deliberate errors in study design, analysis and the interpretation of results[20]. This study only focused upon open access journals, which generally charge a fee to publish. Although this study only focused upon lower impact journals, similar problems have been found in well-established and respected journals such as the *BMJ*[21]. Indeed, an internal *BMJ* study took a paper about to be published in the BMJ, and inserted eight deliberate errors before sending it to 420 potential *BMJ* reviewers: 221 (53%) responded[22]. The results were stark, the median number of errors spotted was two, nobody spotted more than five, and 16% didn't spot any[22]. Another concern voiced refers to referees who use anonymity to prevent publications in their field of research[23].

There have been several suggestions as to how the process of peer-review can be improved. Firstly, various short-term peer-review training programmes have been shown to be of some limited benefit[24-25], although the value of longer interventions needs to be assessed[24]. Secondly, the *BMJ* has implemented a process of open review where anonymity is removed[26]. In addition to removing concerns about reviewers being deliberately obtrusive[4], the *BMJ* editorial board felt this was ultimately ethical – placing authors and reviewers in equal positions and increasing accountability[22]. A randomized controlled trial found that open review made no significant difference to the quality of reviews and it was acceptable by both authors and reviewers. Although there was a higher tendency to recommend acceptance, the fact that the editors retain total control as whether to publish means that this increase is less important. Clearly open review may not be suitable for all journals, particularly in specialist areas where clinicians and scientists may know each other very well[4]. An intermediate solution to accountability has been tried in other journals, where reviews although anonymous are published online[4,22]. This approach has been shown to affect reviewers as any comments they make on a specific paper is available to view, meaning that openly hostile or inappropriate reviews become less common and authors receiving such reviews are more supported by other researchers[4].

Electronic pre-publication prior to final publication is another approach used by some journals. Articles are uploaded online a few weeks before becoming incorporated into the journals database and this provides a window where general readers can make comments. This approach allows journals to provide researchers an additional setting to receive further feedback to develop and improve their article. It should be noted that the Editorial Board have the final say whether comments require to be addressed not by the authors. This approach has worked well for the Cochrane Collaboration as protocols have been changed and meta-analysis adjusted following comments for its clinical readership.

It is unclear if such approaches would have prevented some of the fraudulent papers of the past being published, but will certainly help to improve peer-reviews standing in the scientific communioty[22].

Conclusion

The status of science and research is based upon the idea that findings from research will be right most of the time and will correct its errors as and when they arise. However, with recent high profile scandals in the world rocking public confidence in science it is important to review the status quo. It is hoped that attempts to improve the quality of peer-review, address publication bias, promote verification and prevent fraud will over the coming years strengthen trust once again in scientific endeavours.

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