Neglecting the null: the pitfalls of underreporting negative results in preclinical research

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ABSTRACT

Heightened competition for funding and increased pressure to publish in high-impact journals has led to a modern-day publication culture that favours positive results. The underreporting of negative, or null, results is a form of publication bias that occurs when researchers and/or reviewers fail to communicate findings due to unfavourable directionality or perceived unimportance. For nearly three decades, recognition of this bias in clinical research has led to revised policies and guidelines in an effort to improve reporting transparency and accuracy. Only recently has the existence of this reporting bias been fully appreciated as a formidable problem in preclinical research. Considering that preclinical research provides the foundation on which many clinical trials are conceived, finding solutions to increase the reporting accuracy of preclinical studies is of paramount importance. In this commentary, we will explore how the underreporting of negative results in preclinical research distorts scientific knowledge and subsequently misguides clinical research. We will conclude with several suggestions for reducing this bias with the intention of transitioning towards a truly transparent and objective publishing landscape.

INTRODUCTION

A recent study of over 4,600 papers encompassing a broad spectrum of research disciplines found that the overall frequency of positive reports increased by over 20% between 1990 and 2007 [1]. Potentially even more disconcerting, the same study reported that when compared to other disciplines, the absence of publications with negative results was significantly more frequent in areas such as clinical medicine, pharmacology, toxicology, and molecular biology [1].

The underreporting of negative, or null, results in a form of publication bias that occurs when researchers and/or journal editors fail to communicate research findings from well-designed, sufficiently powered studies due to unfavourable directionality or perceived unimportance [2]. Unlike the deliberate falsification of data, underreporting of negative results is not widely considered to be a form of scientific misconduct. However, it has been suggested that the selective exclusion of negative results may represent an even greater threat to scientific integrity as it is difficult to detect and the cumulative disservice to end-users may exceed that of falsified data [3].

In clinical research, the underreporting of unfavourable data or adverse events has been the subject of intense scrutiny for nearly three decades [2,4-7]. In response to this shortcoming, there has been a systemic effort to improve clinical trial reporting transparency and foster unabridged dissemination of results [8-10]. One of the most impactful and successful policy changes was implemented in 2005 when the International Committee of Medical Journal Editors (ICMJE) stated that in order for a clinical trial to qualify for publication in an ICMJE member journal, the trial must be registered in a publically accessible database prior to the onset of participant recruitment [8,11,12]. Currently, no similar initiatives exist for addressing positive reporting bias in preclinical research despite mounting evidence and calls to remedy the problem [13-16].

UNDERREPORTING OF NEGATIVE RESULTS IN PRECLINICAL RESEARCH

Knowledge gleaned from preclinical research provides the foundation on which clinical research priorities are set and evidence-based decisions are made. When negative results are not published, those who rely on biomedical literature for objective information are provided with only a fraction of the relevant evidence. This distortion of scientific knowledge skews meta-analyses and decreases the validity of comprehensive literature reviews [13,14,17]. Ultimately, this bias can lead to the overestimation of intervention efficacy and has thus been implicated as a factor responsible for the historically low rate of successful clinical translation from preclinical findings [15,16,18-21].

It is estimated that one-third of reported efficacy detected in systematic reviews of animal trials may be due to positive outcome reporting bias [14]. Evidence of this type of bias has been identified in preclinical studies that have lead to clinical trials involving thousands of patients [22]. A primary example is the misconceived succession of the nitrone-based drug NXY-059 to phase III clinical trials for the treatment of acute stroke [23]. Following the publication of several promising preclinical findings, which identified the ability of NXY-059 to reduce infarct volume and motor impairment in animal stroke models, over 5000 acute stroke patients were recruited to participate in multiple large-scale clinical trials [23]. Upon completion of the trials, the benefits of NXY-059 identified in preclinical studies failed to translate to a successful clinical intervention and the development of the drug was abandoned [24]. In an attempt to determine why NXY-059 failed, a retrospective meta-analysis of individual animal data from published preclinical studies was conducted [23]. Us-

ing a funnel plot and Egger's test to assess publication bias, the authors of this meta-analysis found a significant bias favouring reports describing the beneficial effects of NXY-059 [23,25].

Such discrepancies between preclinical and clinical findings, especially those due to misinformation caused by incomplete reporting, may expose patients to undue risk, and in the long term, could discourage patients from enrolling in clinical trials. Furthermore, failing to fully utilize all knowledge gained from studies using animal subjects raises similar ethical concerns to those initially raised by proponents of increasing reporting transparency for human clinical trials [15].

While animal studies provide the bulk of the evidence required for new interventions to advance to clinical testing, a large proportion of preclinical discoveries are also made using in vitro models or ex vivo patient samples. In April 2013 at the Experimental Biology Conference in Boston, Dr. Keith Flaherty, Director of Developmental Therapeutics at the Massachusetts Cancer Center, provided a poignant example of how the failure of several groups to report an irreproducible in vitro finding may currently be leading to an unwarranted clinical trial for the treatment of melanoma [26]. In 2010, Flaherty's colleagues published a novel report in Cancer Cell describing a marked increase in insulin-like growth factor 1 receptor expression both in a BRAF inhibitor-treated melanoma cell line and in a small portion of ex vivo patient tumour samples [27]. Following the publication of this high-impact report, at least five laboratories were unable to independently reproduce the results and subsequently failed to publish their inability to do so [26]. In his presentation, Flaherty speculates that the reason for these discrepancies may be as simple as the addition of insulin to the growth media used to culture the melanoma cell line in the original study. Regardless, the Cancer Cell report remains uncontested and interestingly, a phase Ib/II clinical trial testing the efficacy of an insulin growth factor receptor antagonist in patients with mutant BRAFV600 melanoma is currently recruiting participants [28].

Initiatives such as ARRIVE (Animal Research: Reporting In Vivo Experiments) guidelines, CAMARADES (Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies), and GSPC (Gold Standard Publication Checklist) have been developed with the common goal of improving the completeness, accuracy, and analysis of preclinical studies [29-31]. However, adoption of these guidelines has been brought into question and may be falling short [32]. A review of over 160 CAMARADES meta-analyses (combining 4445 data sets from six different fields of neurological disease research) indicated that a staggering 40% of the studies analyzed reported statistically significant results [33]. In addition, it was recently estimated that 50% of laboratory animal research is never published and that this number may be far greater in for-profit organizations [18]. Thus, while efforts such as ARRIVE, CAMARADES, and GSPC are steps in the right direction to remedy current issues, there is still plenty of room for improvement.

RECOMMENDATIONS

The transition to more transparent and efficient reporting in preclinical research will require a combined effort from all parties involved in the research reporting process. In the following sections, we will outline recommendations for publishers and peer-reviewers, academic and non-academic research institutions, and individual researchers for achieving more transparent, efficient, and accurate reporting of preclinical research with a focus on strategies for enhancing the publication of negative results.

For publishers and peer-reviewers: Publishers and peer-reviewers of biomedical journals will play a key role in equalizing the publication landscape. While an increased awareness of the aforementioned pitfalls may encourage the submission of manuscripts with negative or null results, determining which studies make it to press will ultimately still be at the discretion of publishers and peer-reviewers. Educating all personnel involved in the publication process on the importance of communicating negative results will be instrumental for the publication of such findings [34,35]. Peer-reviewers should be instructed to evaluate submissions based on scientific merit rather than direction or significance of the reported outcomes [18]. Furthermore, the utilization of initiatives such as the ARRIVE guidelines, CAMARADES, and the GSPC will promote increased transparency of all preclinical studies submitted for peer-review.

Some journals have already been established solely for the purpose of publishing negative data. Some examples include: The Journal of Negative Results, The Journal of Negative Results in Biomedicine, and the All Results Journal. These peer-reviewed journals compliment the commitment of open-access journals, such as The British Medical Journal (BMJ) and PLoS One, to communicate all manner of high-quality scientific research [36,37]. However, it is worth noting that two major shortcomings of these publishing outlets include a perceived lack of prestige and publishing surcharges, which may further discourage researchers from publishing their negative data [38].

For institutions: Both academic and non-academic institutions can offer and promote conferences, seminars, and courses that teach researchers how to fully and accurately report their findings. The University of Ottawa has taken a leadership role in this initiative by offering the first course on Journalology. Dr. David Moher, the course instructor and a steering member of the international EQUATOR (Enhancing the Quality and Transparency Of Health Research) Network defines Journalology as "the study of the publication process" [35]. The objectives of the course will be to inform students entering research-related fields of publication bias, reporting guidelines, and different publication trends (e.g. green vs. gold open-access and predatory vs. old-fashioned journals). Among selected topics, students will learn about writing journal articles that are 'fit for purpose' and develop core-

competencies for peer-review [35]. The two-week intensive course will be offered in 2014-2015 through the Department of Epidemiology and Community Medicine.

For students and researchers: Students and researchers are at the heart of primary data generation. Researchers should feel a moral obligation, and an obligation to one another, to organize their results and make them available, even if they are not published [35]. This prevents others from unknowingly duplicating experiments, which can waste time and resources [39]. Awareness is a critical first step. Students can request that their University invite guest speakers or hold events to increase awareness of publication biases. We suggest that rather than only pursuing significant results, individuals performing frontline research place an increased emphasis on generating scientifically robust data and demonstrating sustained productivity.

CONCLUSION

Throughout this commentary we have used the terms 'negative' and 'null' to describe results that are considered insignificant or unimportant. However, the use of this terminology itself perpetuates the biased manner in which researchers perceive their findings [35]. Rather than segregating 'positive' from 'negative' data in publication, what needs to be changed is the scientific community's perception of research results as a whole. As biomedical researchers, it is important to remember that research is conducted for the benefit of patients, and that each laboratory is a small component of a much larger effort to enhance the healthcare system. Both investigators and end-users have a right to know what has been tried and tested, and that means sharing both 'successes' and 'failures'.

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