Is bias biased?

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Bias is defined as any tendency which prevents unprejudiced consideration of a question (Dictionary.com). Bias can occur at any phase of research, including study design, data collection, data analysis and publication thereby impacting on the validity and reliability of study findings. It is often difficult for the reader of a paper to fully understand if bias is or is not present, arguably there is always an element of bias in any study, readers must consider how bias might influence a study's conclusions (Gerhard, 2008). Critical appraisal of all studies will assist the reader in understanding risk of bias through for example, evaluating the strength of internal and external validity, and consideration of how the sample was selected, the study design, if the sample size was adequate, choice of outcome measures, how randomisation was achieved (if appropriate), if the study was blinded, attrition and publication bias. All publications should, as a course of best practice, state their source of funding.

Most large-scale studies generally declare this stating clearly if this was a government funded grant, an unrestricted educational grant, funding for a scholarship (e.g., Doctoral funding) or commercial funding, and this can also lead to a form of reader bias.

There has been much discussion relating to risk of bias as a result of industry sponsorship for studies. Lundh et al (2016) in their Cochrane review of 27 cross-sectional studies, cohort studies, systematic reviews and meta-analyses that quantitatively compared primary research studies of drugs or medical devices sponsored by industry with studies with other sources of sponsorship concluded sponsorship of drug and device studies by the manufacturing company leads to more favourable efficacy results and conclusions than sponsorship by other sources. However, when comparing industry and non-industry sponsored studies, no difference in risk of bias from sequence generation, allocation concealment, follow-up and selective outcome reporting was identified. Industry sponsored studies more often had low risk of bias from blinding, compared with non-industry sponsored studies. In industry sponsored studies, there was less agreement between the results and the conclusions than in non-industry sponsored studies (Lundh et al, 2016). Webb (2017) in her editorial explored recommendations from the Cochrane Wounds Group and their recommendations of the studies examined concluding the most positive conclusion was moderate- to low-quality evidence with bias and therefore we need better designed, high-quality studies before we can use this method to inform practice.

We all use research and evidence to underpin clinical practice. During academic study students are often required to critically appraise research and evidence to support their written word. Many students often state that the paper they have examined is biased as it was funded by industry and as a result, they cannot use the information. *Karen Ousey*

1. What are the challenges for professionals when attempting to understand bias? How can we overcome these barriers?

JT: Bias in research is a complex concept. Researchers go to great lengths to eliminate bias in studies that they design or conduct, but the fact of the matter is that there will be bias present in every single study, and the challenge for professionals is to understand potential sources of bias in order to recognise, appraise and assess the impact of that bias on both the internal validity (the extent to which the results represent the truth, or alternatively, the quality of the observations of the study (Patino and Ferreira, 2018)) and the external validity of the study report or article that they are reading (the external validity being the applicability or generalisability of the findings to other populations or times, such as the patients that the reader treats (Steckler and McLeroy, 2008)). There are a number of excellent tools that professionals can use to help in their assessment of bias within studies, such as the CASP checklists (https://casp-uk.net/casp-tools-checklists/), but in the clinical setting, the professional may not have the time to fully appraise

literature when they are looking for a quick answer for the patient sitting in front of them at the time. For the occasional reader, who may quickly search Pubmed or Google Scholar for a paper that supports or refutes the treatment they are planning, the time and effort taken to fully appraise the study may be too onerous, and they may then fall into other ways of "assessing" the study – such as citation metrics and the journal of publication – that study in The Lancet with 450 citations can't be biased, can it?

FP: The published case studies, clinical experiences, expert opinions and clinical innovations are based on experience and experience may offer the building block for the development of an alternative, mixed-methods approach for the generation of evidence for dressing selection. The adoption of a pragmatic dressing evaluation based on what clinicians believe is of clinical importance may be the way forward. Clinically data could be obtained through qualitative techniques (participant observation, patient's stories, interviews and focus groups) and quantitative ones (staff survey, patient survey and examination of costs) alongside a comparison between what was used before to what has to be tried.

Clinicians should be encouraged to engage in the above research activities but they need time in their day-to-day schedule for the research endeavours. In order to do that, clinical academic roles may offer a way forward, where joint appointments between the NHS and Universities allow for that academical support in clinical practice and thus maximise research impact. Results are slow to be generated but the enlighted manager will understand that research is a journey and not a destination.

ZM: Boutron et al (2021) define bias as "A consistent deviation from the truth in results". Bearing this definition in mind, it is clear that bias is something of importance. This is especially true when we are thinking about outcomes from clinical research papers that we might use in practice. Logically, we don't want to introduce new technologies, or ways of treating patients, if the foundation upon which the evidence is based is inherently flawed. The challenge, however, is that its not often immediately clear when the bias may lie within the published paper.

Thus, bias may not be easily recognised by someone without the training needed to determine its' presence. To overcome these challenges, the development of skills in evidence appraisal is needed. This is not straightforward, though, when you consider that more than 1 million papers go into the PubMed database each year — about two papers per minute (Landhuis, 2016). So, there is a lot of evidence to appraise and practising health professionals have limited time to dedicate to this process. So, a ready solution could be expansion of journal clubs in the clinical arena to include individuals who know how to appraise and synthesise the literature, perhaps someone from the academic partner organisation. This would ensure that members of the clinical team, who make the decisions about patient care, can be equipped with the necessary, unbiased information they need to make these decisions. Indeed, the World Health Organization (2010) stresses that when we bring together the skills of different professionals, this strengthens the health system and enhances clinical and health-related outcomes.

KW: Within wound care "bias: always seem to suggest companies, reps, case studies, company funded research etc. However, clinicians visiting patients deal with bias daily. Patients bring their own bias, whether it is towards a preferred clinician, or preferred treatments. Some patients and families have enormous bias towards treatments they feel are of benefit. This can be seen as a challenge but should be embraced. If a patient is interested enough to read about their condition that should be encouraged, and they should be guided to appropriate sources.

We also carry personal bias towards different patients. Sometimes favourable, sometimes less so. Bias is part of life. We need to acknowledge this more and not view company bias as greater, or more serious than our own personal or professional bias.

2. Do health professionals fully understand bias in papers or are they indeed biased when reading studies due to a lack of in-depth knowledge?

JT: Readers will understand bias to varying degrees based upon their own knowledge and experience. Undergraduate level courses in health vocations in the UK should include modules or sessions on critical appraisal of literature, in line with GMC Good Medical Practice and the NMC Standards for competence for registered nurses. However this learning may be seldom applied or revisited if the individual is not reading research papers frequently. Thus the reader may make judgements of a paper based upon other factors that may influence them; this has been termed reader bias and Owen (1982) postulates 25 different sources of reader bias. Reader bias may align with implicit bias within the individual, and may be prejudicial in nature or result from a lack of knowledge or practice. As a result, both the novice professional and the seasoned researcher may be equally at risk of reader bias.

I would wholeheartedly recommend every reader reads the piece by R. Owen "*Reader Bias*" (1982). It is incredibly insightful and can cause real introspection into your own ability to read and assess any research article.

FP: It is not until one has undertaken the research process itself that one understands the challenges that researchers meet along the way of any study. For instance, it is important to understand what it means to develop an idea that is then developed into a research question; where the appropriate methods to gather data are selected;

how the data are analysed and finally the findings written it up. Then it may become clearer how distant is the 'gold standard' of trial methodologies from our day-to-day clinical reality.

Talking the talk is very different than walking the walk. The conduct of randomised controlled trial (RCT) is faced with a number of methodological challenges, such as lack of funding, difficult or complex study designs, narrow focus, extensive inclusion/exclusion criteria and problems with endpoint. Some health professionals may not necessarily be biased when reading studies, they are more likely not to understand the challenges of undertaking a RCT and its research process.

With so many dressings available, standard care can differ substantially from one setting to another, such as acute care versus community care, or even in a similar setting but different Trusts, depending on what list of products each wound management formulary holds. Lack of generalisability of the results is a well described disadvantage of the RCT but is especially critical in dressing selection.

ZM: When I reflect on myself, before I began to undertake systematic reviews of the literature, I did not fully understand the concept of bias. I don't remember learning this skill during my undergraduate training, where the focus was more on reiterating what the evidence says, rather than critically appraising it. As I moved to postgraduate education, more and more emphasis was placed on critical appraisal. However, it was only really when undertaking Cochrane reviews that I began to understand the concept of bias more fully and why it is fundamentally important in evidence appraisal. For example, detection bias can occur in a trial when the outcome assessor is not blinded to the group allocation when they are assessing outcomes among the study participants. As such, a systematic review by Hróbjartsson et al (2013) identified that nonblinded assessors exaggerated the pooled effect size by 68% in the 24 trials included in their review. Thus, Hróbjartsson et al (2013) conclude that a failure to blind assessors of outcomes in trials results in a high risk of substantial bias. If I was unaware of the potential for bias such as this, I may make an erroneous decision about the clinical relevance of the study I am assessing. On the converse though, to critically appraise a study, I need to ensure that I don't have a preconceived idea about the relative merits of a paper. In other words, I should not be biased in my assessment of the study. Interestingly, MacCoun (1998), examined bias in the interpretation and use of research results. The author concluded that people assume that their own views are objective and consider that that subjectivity is the most likely explanation for their opponents' conflicting perceptions. Thus, inherently, we can all be biased, and if we are unaware of this, it can impact on our ability to objectively assess the merits or otherwise of research studies.

KW: In my experience, clinicians are very aware of bias in company sponsored papers. It is easy to dismiss a paper (without really reading it!) because it is company sponsored. Some clinicians struggle to critique papers. The ability to quickly pick out the strengths and weaknesses of a study is what is lacking. Clinicians who have influence over local formularies for example, really must be capable of critiquing papers and discussing them withing teams.

I do feel that clinicians carry their own bias towards papers and companies, and we need to have more self-awareness regarding this. Particularly when we know bias influences decision making, be that clinical, or more strategic decision making. It's human nature to "like" products because you've seen success with them, or "like" companies because you have a good relationship with them. Individual clinicians "likes" should not be (but sometimes are) enough to influence system wide change/formulary changes yet we may dismiss a company funded study despite it being of high quality.

3. The wound care industry supports many clinical studies including cohort studies, case studies, evaluations and RCTs. Is industry funding of clinical studies acceptable and valid?

JT: To make such a dichotomous, blanket statement such as "industry funded studies are bad, and publically funded studies are good" may be lazy, narrow-minded and inappropriate. Studies funded by the National Institute for Health Research have been shown consistently to have bias in some form (Matthews et al, 2011), and there has been bias seen in the awarding of UK Research Council supported grants (Viner et al, 2004). The notion that industry-funded research will always favour the sponsors product, at the expense of scientific rigour is probably also outdated. A quick online search of the term "investigator initiated study" (IIS) shows at least a dozen webpages of large pharmaceutical or medical device companies offering IIS where the research proposal is subject to review by a committee of professionals and appraised on scientific merit, amongst other factors (F. Hoffmann-La Roche Ltd, 2022, Mölnlycke Health Care AB, 2022). This competitive process for securing funding, where the concept, design, conduct and reporting of the research remains the responsibility of the researcher, is not so far removed from the process of securing public or charitable grant funding, and could therefore be argued as being equally as valid. Ultimately, a study will be acceptable and valid if one can answer the question "is this the right study design, with the right methodology, conducted by the right team, upon the right patients?", regardless of the charity, public body or private company awarding the funding.

FP: The generation of evidence in selecting dressings for wound care is immersed in a context that lacks resources, legislative clarity and freedom to choose methodological alternatives.

At the lower end of the pyramid of evidence, case studies, cohort studies and most evaluations are not costly to run but provide evidence that is context bound and not generalisable. Nonetheless, these studies represent nuggets of knowledge that, if gathered together, can offer data using a methodological approach that welcomes grey literature.

In the UK, dressings are categorised as medical devices and manufacturers only have to provide limited evidence of effectiveness before dressings are used in clinical practice. The lack of evidence to support dressing selection is well recognised and what is available is nonspecific and insufficient to provide clear guidance.

With the large numbers of dressings available on the market, the way these dressings are evaluated in clinical practice has been criticised by a number of authors and clinicians have been criticised for their unwillingness to seek better evidence for the products they use in practice.

Clinicians have for many years now, requested for industry to provide quality evidence to support their products but there is little incentive for industry to fund large trials similar to those required by medicines. The clinical reality is that wound care clinicians have become proficient in choosing dressings on evidence defined by experience, rather than clinical trial methods.

ZM: The concept of bench to bedside in research terms is familiar to many, and this concept is at the essence of translational research. The University of Arkansas for Medical Sciences (UAMS) Translational Research Centre (2022) identifies translational research as that which seeks to produce more meaningful, applicable results that directly benefit human health. This is achieved through turning observations for example, in the laboratory, into diagnostics and therapeutics that enhance the lives of people in society (UAMS, 2022). Knowing this, then, it becomes evident that somewhere along this chain, from discovery, testing, federal approval, and marketing, there needs to be a group who have the resources to work closely with clinicians to return the product for use. As such, translational research has at its essence multidisciplinary team working, with industry being an integral member of this team (UAMS, 2022). As practicing clinicians, we need to know that products that we use in the clinic have their underpinnings in scientific research (Melnyk et al, 2010). Thus, it is reasonable, that the group who developed the product, in collaboration with researchers and clinicians, would also continue the journey of bench to bedside, by developing the evidence base needed to determine the potential impact of a given product or device.

KW: My opinion is that it is acceptable but each needs to be considered in terms of its validity and reliability. We need our industry partners to try to continue to support (and fund) on going clinical studies, but it is the responsibility of the companies to choose studies carefully. Many of the patients we see in clinical practice would not meet the inclusion criteria for larger studies. Clinical case studies on these more complex patients with multiple comorbidities are useful for learning. It is important however that these case studies are not just about a "dressing". These complex patients do not suddenly heal because we changed the brand of dressing. The road to healing is much more complex than that, and these case studies must reflect this complexity to really facilitate learning.

4. If a study is funded by industry with the methodology, data collection, analysis, sample selection etc being reproducible and a clear statement of conflict of interest — does it make this study biased?

JT: All studies will include an element of bias; it is the role of the researcher to reduce said bias through design and reporting, and the role of the reader to assess and appraise said bias and decide upon its impact on the conclusions they draw. There are a number of ways researchers can reduce bias outside of the actual methodology and conduct of the study, such as prospective registration on trial registries, adherence to reporting standards and checklists (such as the CONSORT initiative; Schulz et al, 2010), clear statements on conflicts of interest, and making data publically available using formats such as the Open Science Framework (Foster and Deardorff, 2017). All of these measures increase transparency in research (Groves, 2008), that go some way to reducing, but not eliminating bias. A transparent, but poorly-designed research study will still be biased regardless of funder, and similarly a well designed, publically funded but poorly reported study may raise the suspicion of bias from the reader. Where bias may creep in to industry funded studies is where the role of the funder is not clear, or some other aspect of the research (such as the protocol, aims, or methodology) is not transparent, which does not then allow the reader to make a reasoned judgement of the internal or external validity of the study.

FP: The main issue is about the publishing rights as often remain with the funding company. In fact there are almost no papers, funded by industry that reports a study when a product does not work in clinical practice. Funding should remain independent from the researcher who is then able to publish data that may or may not support the product under evaluation.

ZM: To determine the internal and external validity, clear and transparent reporting of the design, conduct, and analysis of the trial is essential (Moher et al, 2010). In reality this is a real challenge, and the impact of poor reporting is far reaching, fundamentally

leading to incorrect decisions about which treatments to use in practice for which patients (Moher et al, 2010). To address this issue the CONSORT statement was developed by a group of researchers in 1996 and updated in 2001 and 2010. The aim of the CONSORT Statement is to improve the quality of the reporting of clinical trials (Moher et al, 2010). Trial registration is a fundamental component of this whole process, and the World Health Organisation (2022), emphasise the importance of this aspect of trials, stating that "the registration of all interventional trials is considered to be a scientific, ethical and moral responsibility". When a trial is registered a priori, and the methods are clearly stated up front, including all outcome measures, this reduces the risk of reporting bias (Kirkham et al, 2010) because you and I can check what the authors of the study planned to do and then validate that this has actually been reported in the publication. So, a study is not necessarily biased if it has been funded by industry, and to avoid risk of bias, following the CONSORT statement is a good route to take.

KW: In my opinion, these studies should be considered. The study design should be the focus of the critique, not just the company funding. Bias should always be considered, but in the context of the quality of the study and the depth of discussion. More transparency from companies would help with this. However. I'm sure there are many studies that have more neutral results which remain unpublished. I understand the companies are ultimately profit driven, however they do need to be more honest, transparent and impartial if we are to move away from the trend towards instant dismissal of company funded studies as biased.

5. There is limited competitive funding available for research studies — if industry funded studies are perceived to be biased and therefore less reliable and valid – how can this gap in funding be filled?

JT: The acquisition of research funding, and subsequent publication in high impact journals, is a process upon which jobs, promotions, reputations and livelihoods depend. As such, there will always be competing interests throughout the process from all sides. Similarly, there will never be an infinite pot of either public or charitable funding for research. Funders should strive to limit research "waste" through robust appraisal of research proposals, and also to level the playing field, eliminating the propensity for funding to be acquired based upon reputation rather than merit (Viner et al, 2004). Excess costs in conducting research should also be pushed against by the entire community, including the increasing costs associated with publishing, for example, the cost for open access publishing in some Elsevier titles is $9,900; Reed Elsevier regularly declare profits over a billion dollars (Dorsey et al, 2011). Finally, it is likely that, with a squeeze on public finances, and a reduction in charitable funds available (Smith, 2021), funding from the industrial sector to conduct research is going to become vital to continue making significant advances in healthcare — as researchers and professionals we need to work to destigmatise this industry funded research and to increase the transparency of research across the board, so researchers and health professionals alike can assess each study individually based upon merit, methodology and external validity.

FP: The dressing manufacturing industry operates in an open market where competition is seen as a positive step to reduce prices. There are few innovations in wound care; industry introduces small changes for what is essentially the same product, copying from each other and changing minor attributes. Arguably, some of these changes may be clinically significant and worthy of a clinical evaluation but without financial resources, this research is unlikely to be undertaken. Once a dressing is launched onto the market, the incentives to conduct research are reduced because research is expensive and seeking proof of efficacy threatens to remove lucrative products from the market. Nonetheless, if industry is serious about funding clinical studies, they should group together and either develop a research fund or contribute to existing national research bodies and researcher could apply for funds to undertake research (for further reading on eveince in wound dressing selction see Pagnamenta, 2017)
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ZM: It is important to reiterate that industry studies are not necessarily less reliable and valid, providing they have been conducted rigorously and reported using agreed standards. Nonetheless, funding for research is always a challenge, as the whole process is so competitive within limited resources. However, to highlight the importance of industry and research an interesting funding opportunity exists in Ireland. The Irish Research Council's Enterprise Partnership Scheme (2022) is a unique national initiative linking excellent researchers in all disciplines to enterprise. Through this co-funded programme, postgraduate researchers develop new, advanced knowledge and skills linked with industry and employer needs. At its essence this scheme explores national and global challenges, and really sees the impact that the involvement of organisations, both large and small, who seek technological, social, and sustainable solutions can have. As such, from a Governmental perspective, the collaboration between industry and research and clinicians is important.

This is because it has huge consequences not only in terms of the development of evidence for practice, but also in the wider societal context. Therefore, to move the dial forward, we need to see ourselves as partners: academia, clinical practice, industry, patients and family, the health service and society. It is only through this lens that we can identify important health care problems and solutions that will make a difference to the lives of people.

KW: This is a really difficult question to answer. I know that government research funding is limited and that it is very competitive. I don't know enough about this to give a full answer, maybe that reflects a lack of understanding of different funding routes for clinicians. We have so many unanswered questions about wounds, that limited research funding will always be a problem. Company funding can be part of this, but companies do need to take responsibility for improving transparency. WUK

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