

Reporting of preclinical research: What do we get told – when and how?

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Abstract

At present, there are no specific requirements for the reporting of preclinical research, and many studies, particularly those with negative results, never get published. Despite the huge advances in communication opportunities, things have not really changed throughout the history of drug development. Sometimes researchers and scientists are hesitant to release results prematurely and there is a culture not to publish when studies have negative findings. However, routine and reliable reporting of all research – preclinical, clinical, laboratory, animal or human based, and with positive or negative outcomes – is essential to the future of collaborative and successful clinical research. There are several new ideas to promote this, and hopefully in years to come we will see all research results easily accessible and widely used.

Introduction

The idea of “bench-to-bedside” clinical research has captured the interest of the medical world for some years now. Otherwise known as “translational research” or “translational medicine”, it encompasses all phases of clinical trials from the process of drug discovery and development in the laboratory, through to animal testing, human testing, and ultimately licensing, marketing, and commercial sales. The process can be lengthy and challenging; it is estimated that on average it takes 12 years for a drug to make it from the laboratory to routine use in patients and only 10% of drugs that start preclinical testing ever

make it to being tested in humans, let alone gaining a licence and making it into regular use.¹ Given this high attrition rate, how are the early phase results communicated to the scientific community? Is the current reporting culture appropriately presenting preclinical data so that the right novel molecules are pursued for the right reasons? Do the results reach the right people, such as key opinion leaders and disease experts, rather than get inappropriately emblazoned over the media or worse, lost to history, without being published at all?

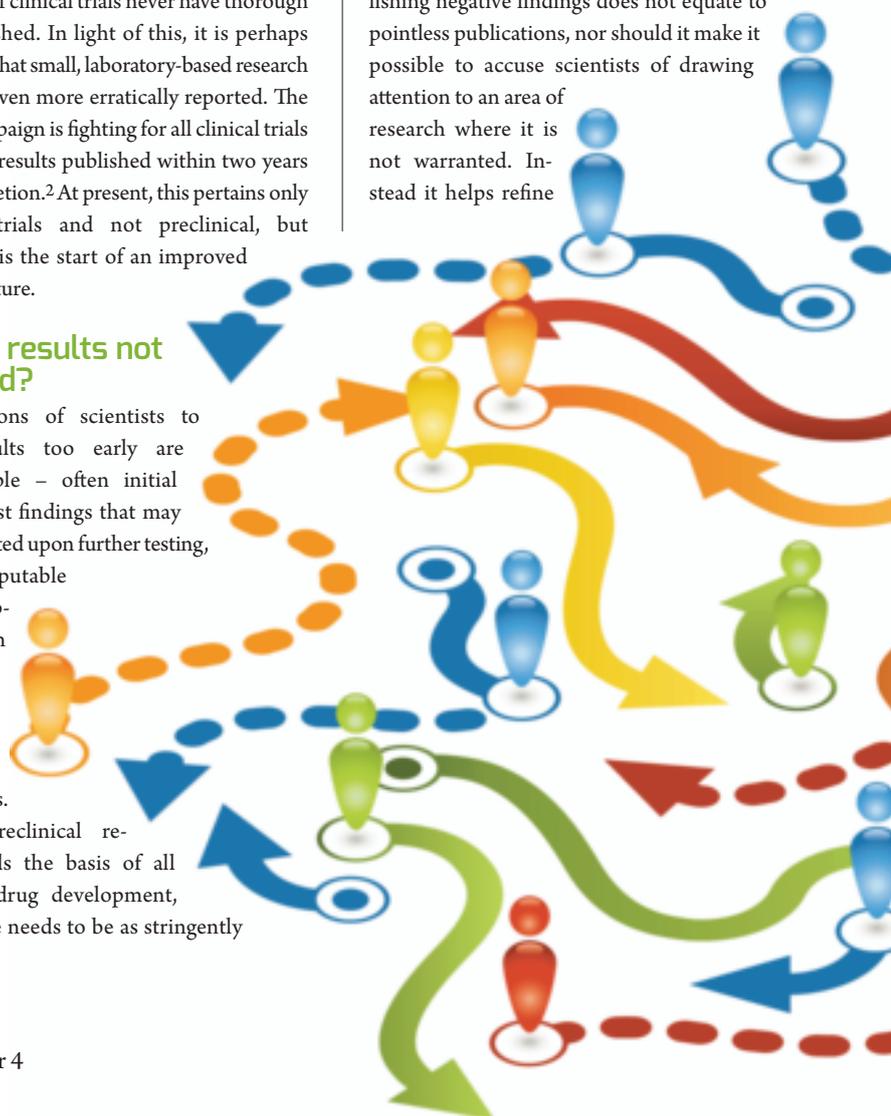
How preclinical research gets published and advertised to the wider scientific community currently seems somewhat mysterious and ad hoc and despite guidelines from various sources, it is not necessarily reliable or reliably reported. Even the reporting of large-scale clinical trials involving thousands of patients are unreliably reported – estimates are that between 25% to 50% of clinical trials never have thorough results published. In light of this, it is perhaps unsurprising that small, laboratory-based research projects are even more erratically reported. The AllTrials campaign is fighting for all clinical trials to have their results published within two years of trial completion.² At present, this pertains only to clinical trials and not preclinical, but nevertheless is the start of an improved reporting culture.

Why are results not published?

The hesitations of scientists to publish results too early are understandable – often initial results suggest findings that may not be replicated upon further testing, and no reputable drug development team would wish to be accused of publishing misleading results. However, preclinical research forms the basis of all subsequent drug development, and therefore needs to be as stringently

reviewed as Phase IV clinical trials that are about to present new medicines to the market. Early results can be reviewed by experts in the relevant field, which helps to decide which drug characteristics are desirable and worth further pursuit. The results can also be used to identify which drugs may have adverse effects or less desirable outcomes and can therefore be dismissed before further research replicated the same findings. Results ought to be published in a way that is understandable to the relevant reader and that can be subjected to valid critical appraisal.

There is a culture among all areas of science not to publish negative results – some high impact journals even state that “negative results are not accepted”. This attitude is clearly to the detriment of science and instils a philosophy that only positive outcomes are worthwhile – a very narrow-minded and restrictive stance.³ Publishing negative findings does not equate to pointless publications, nor should it make it possible to accuse scientists of drawing attention to an area of research where it is not warranted. Instead it helps refine



the research process, preventing repetition of futile studies and cultivating a pro-active research community where lessons can be learned from one another and a more widespread collaborative attitude can be adopted.

Initiatives in communicating results from preclinical research

The lack of reliable reporting of preclinical research is one that has been recognised already by the scientific community. In 2016, the commissioner of the FDA Rob Califf described an idea to develop a database of preclinical research where all research could be published and made widely available to the scientific community.⁴ Such a database already exists for clinical trials – ClinicalTrials.gov.⁵ In the United States it is a legal requirement for all Phase I onwards clinical trials to be registered on this site. It is an essential aspect of ethical and valuable clinical research. Such a resource for preclinical research would certainly help the reproducibility of results, prevent repetition of investigations that heeded negative results, and improve the transparency of the preclinical domain. Despite this, there was a general initial negative reaction from scientists, citing concerns that

such a requirement might restrict the innovative nature of preclinical and investigative studies and hinder those random and spontaneous discoveries that can sometimes lead to exciting findings.⁴

Almost certainly the benefits of such databases will eventually be realised and perhaps in the future they will be the norm, but at the moment the reporting of outcomes of preclinical and early phase clinical trials remains quite an ad hoc and mysterious activity. There are ample guidelines to aid researchers in how and what to report at all stages of clinical research. Those pertaining specifically to preclinical research include the ARRIVE guidelines (Animal Research: Reporting of In Vivo Experiments) of 2010 from the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3R),⁶ which focus on research involving animals and set out guidelines for results reporting aiming to “maximise information published and minimise unnecessary studies”.⁶ Furthermore, the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network provides more specific guidance for various types of preclinical research publication⁷ and the Good Laboratory Practice regulations include study reporting.⁸

Another effort in recent years to improve the communication of preclinical and early phase clinical research to the wider scientific community is the introduction of several new journals and publications focusing on preclinical research and translational medicine. Such publications include *Translational Medicine Communications* and the *Journal of Translational Medicine*, both of which provide a useful platform for wider distribution of preclinical findings and help lessen the difference between basic and clinical science.⁹

The drug development process and why some “negative” discoveries can be worthwhile

Drug discovery and development are not a one-way path. Often, the first step is to identify a therapeutic target and to identify potential routes of modifying this. Sometimes the process starts the other way around, with a molecule being identified that has properties that may be of clinical benefit. The process then progresses to cell-based research in laboratories assessing the biochemical structures and properties of an agent, before progressing to animal studies, which form the basis for first-in-human clinical trials. At these stages safety, pharmacokinetic and pharmacodynamic data are established and the framework to subsequent phases of clinical trials are clarified. The whole process is fluid and dynamic and in the vast majority of cases, it is not a unidirectional and straightforward process, rather there are amendments and adaptations at each stage, making modifications along the way so that the process remains efficient and meaningful.

Fluoxetine

An interesting example of a drug development process is fluoxetine, a drug now known for its antidepressant properties and widely used across the world. In the early 1970s Ely Lilly first investigated fluoxetine as an antihypertensive agent. It was found to have beneficial blood pressure lowering effects in animals, but when this reached human studies, such effects were not replicated. Instead of giving up on their new drug, an alternative use was sought. Fluoxetine was next considered as an anti-obesity agent, but again this did not produce promising results.¹⁰ Eventually it found its place as an antidepressant – a transition aided by the discovery of the relevance of serotonin in the pathophysiology of depression (fluoxetine is a selective serotonin reuptake inhibitor), but also because of the increasing trend to recognise and diagnose mental health problems.¹⁰ Even now fluoxetine (Prozac) has found its solid role in the pharmaceutical market. There are still research projects looking at its other potential therapeutic benefits outside its licensed uses (primarily major depressive disorder) and also investigating its adverse effects. A recent study by Hong and colleagues showed that chronic fluoxetine use in rats elevates blood pressure, heart rate, and



impaired cardiovascular reflexes.¹¹ Whether this will ever have clinical relevance or implication is uncertain, but it demonstrates the infinite research that drugs undergo.

Aspirin

Another interesting example to consider is aspirin; a drug we all probably have taken at some point, indeed many of us take every single day – some for a headache or migraine, others to prevent cardiovascular disease, and many others for secondary prevention following a heart attack. It is probably one of the most familiar drugs to the general public – but what led to its development, what were people told initially, and why are its uses so diverse now?

The use of aspirin dates back to the time of the Egyptians, who noted the anti-inflammatory and analgesic properties of willow bark. Skip forward to the mid-1800s and the chemical in willow that is responsible for these useful effects is identified: salicylic acid. By 1876, the first clinical trial investigating aspirin as an antipyretic and analgesic agent took place. This trial identified several adverse effects of salicylic acid and the molecule had an acetyl group added to reduce its irritant effects.¹² Aspirin has been used as an analgesic agent ever since and, in 1950, it was the most sold painkiller. Interestingly, having been in commercial use for over one hundred years, it was only in the 1970s that its mechanism of action was discovered and from then on its uses have become increasingly diverse, with trials from the 1990s confirming its beneficial role in cardiovascular disease and making it the mainstay of treatment for this worldwide.¹²

The world was an interesting place in the years following the initial discovery of acetylsalicylic acid and because of this, some key facts about aspirin's development were not made evident in published data. It was being investigated in Germany throughout the 1930s and politics certainly had a significant impact on what the scientists behind aspirin felt comfortable to write. What does become apparent is that the acetyl molecule of salicylic acid was not the only chemical derivative to be investigated, but research actually started off with several other agents, each of which was dismissed for reasons that remain unclear. Indeed a few of these other agents had patents awarded to them, suggesting further investigation had been instigated, but the extent of this remains unclear to this day.¹³ Without the publishing of preclinical research in

a routine and reliable manner, research findings can just disappear into history. No one other than the scientists involved can ever know what was discovered and the reasons behind certain drugs being pursued or dismissed. While in early 1900s Europe this patchy nature of research publishing is entirely understandable, in the world we live in today, where the wide sharing of information is so easy, it seems nonsensical that publishing can still be so ad hoc.

Despite aspirin's long history and known clinical benefits (as well as adverse effects – despite the adaptations made to the molecule, the limitations of aspirin use are well recognised), each year hundreds of new studies and trials are carried out, looking at aspirin's effects both in the lab and in man. There are trials registered looking at aspirin as an anticancer agent, for pre-eclampsia and only this week, there was a UK news headline claiming yet another new effect of aspirin. Research has recently shown that aspirin stimulates stem cells in teeth, enhancing tooth regeneration.¹⁴ While this headline certainly draws in the reader and could indeed propose a novel use for aspirin in years to come, at present this really is just a laboratory-based finding and it will take years of further research to ascertain whether this effect can be replicated in human teeth and whether there is a viable administration method that would make this possible. The context of such results needs always to be considered – something that the media arguably are generally happy to ignore.

Other implications in drug development

Drug repurposing (i.e., finding new uses for drugs that are already in use) is a substantial area of drug development and discovery. Both fluoxetine and aspirin demonstrate that when a molecule is discovered, even with a specific indication in mind, what it ends up being used for, or the specific adaptations that are needed to make it work effectively and safely in humans, cannot be predicted. This supports the fact the preclinical data should be circulated thoroughly, honestly, and in a manner that is easily accessible. There will likely be a far less questioning audience when there is clear evidence and explanation available

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for why a drug has been repurposed or dismissed. As well as this, an outside party to the original research may have valuable contributions to make – perhaps even preventing the dismissal of an agent or identifying an alternate route to pursue.

What should be published?

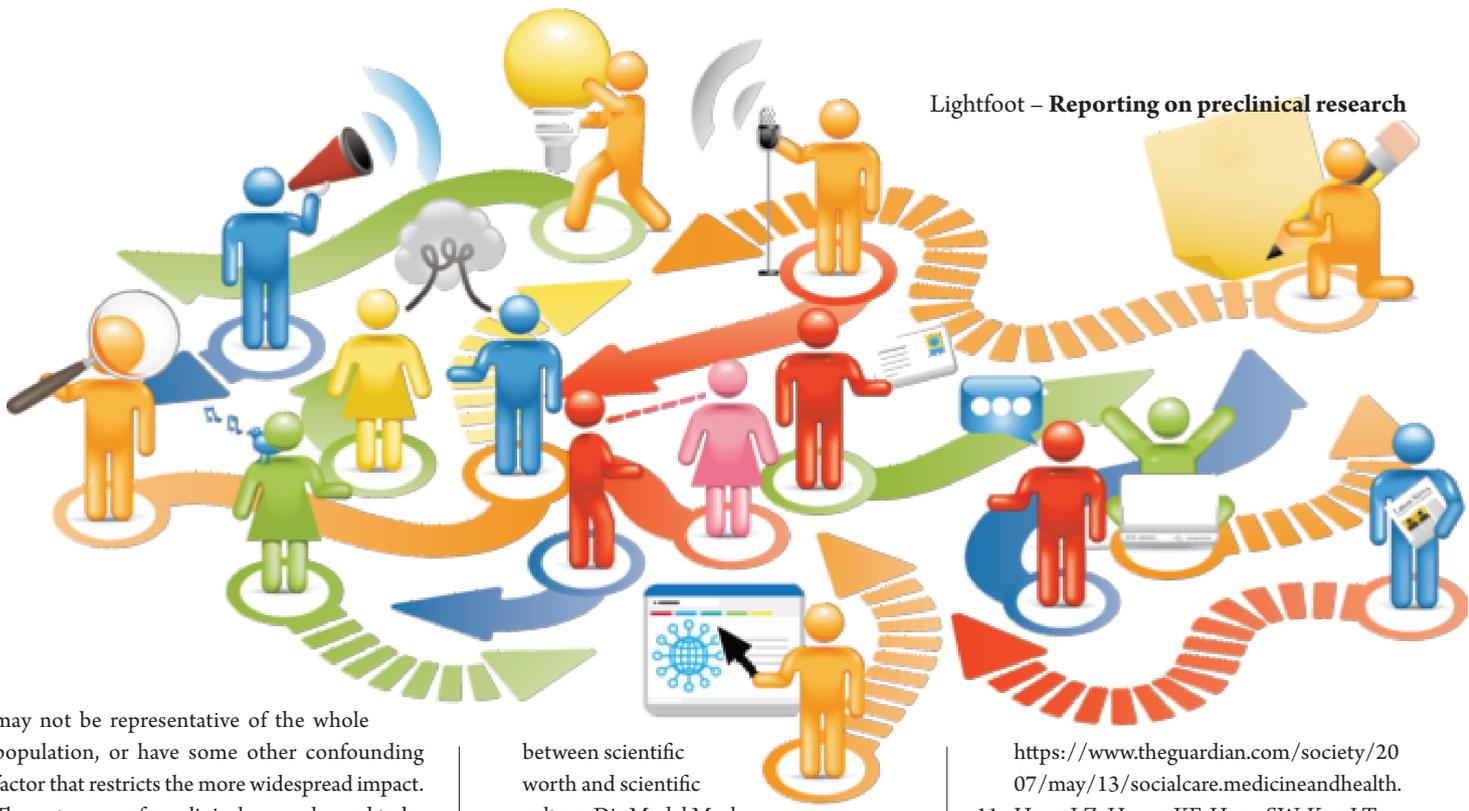
While referring to specific guidelines relevant to the particular nature and field of research, as a general rule there are several important areas that should be included in the report of a research project:

- The protocol or outline of study design, stipulating the specific aims of the study and how they will be achieved
- The raw data collected (as appropriate) and analysable data – raw data that has been extrapolated into a format so that statistical analysis can be performed. This is usually the most useful form of data to appear in a study report and forms the summary data that most readers will refer to for overall findings of the trial.¹⁵
- The data sharing plan – how the researchers intend to distribute their findings and at what point in the progress of their research they will do this¹⁵
- Statistical analysis methods – it is important for readers to know how the data was processed and tested in order for results to be replicated.¹⁵
- An overall study report summarising the key findings and next steps

This is merely a brief overview of the nature of preclinical reporting and individual adaptation and specific requirements for different publishers and publications.

The future of preclinical research publication and what it means for medical communications

A challenge of publishing early phase and preclinical trial results is ensuring they are reported accurately and that results are relevant, realistic, and not misleading. Preclinical data may not ever be replicated in subsequent clinical trials, and even if positive findings are reproduced, it needs to be remembered that the sample groups



may not be representative of the whole population, or have some other confounding factor that restricts the more widespread impact. The outcomes of preclinical research need to be communicated appropriately so that key opinion leaders get interested and offer expert input, without releasing information too early that could be misleading and ultimately lead nowhere.

Medical communications professionals are key to the success of this. It is our role as experts in communication to help scientists present data, positive or negative, in a reliable, reproducible, and systematic manner so that it is widely understandable and its implications are made clear. Useful resources exist to aid with this and should be sought out when assisting with the publication of preclinical data. How the media choose to interpret such reports might be something we have less control over, but with clear, reliable, and transparent reporting, scientists and researchers can at least feel confident that the facts were published accurately.

Conflicts of interest

The author declares no conflicts of interests.

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