Detailed case studies

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Statins case study

Statin treatment reduces the risk of cardiovascular disease (CVD)[1] by lowering the levels of low-density lipoproteins (commonly referred to as 'bad' cholesterol) in the blood.[2] Statins can be prescribed for primary prevention of CVD in patients who are at risk of CVD or secondary prevention to prevent further CVD in patients with a history of CVD. Given the high-profile controversy around the use of statins (which focussed on whether the benefits of treatment outweighed the potential harms in groups at lower risk of CVD), we explore in this annex the different contributory elements to the debate and consider how our recommendations, if implemented, might mitigate some of these issues in the future.

Background

In 2014, the National Institute for Health and Care Excellence (NICE) recommended that the threshold for offering statin therapy for the primary prevention of CVD should be lowered from a 20% or greater 10-year risk of developing CVD to a 10% or greater 10-year risk. This change was supported by two meta-analyses that showed that statin therapy reduced the risk of major vascular events in lower-risk groups and that this was not associated with an increase in adverse events.[3,4] However, the threshold change also prompted a number of concerns, particularly within the medical community, that were played out in the media, including around the 'medicalisation of five million healthy individuals' and whether the benefits for this low-risk population justified prescribing a treatment that would need to be taken lifelong.[5] A subsequent practical concern has been the impact on a struggling primary care system of a further significant number of patients requiring consultations on the issue. Overall, healthcare professionals and patients were left confused as to whether they should, respectively, choose to offer or take statins.[6,7]

We make a series of recommendations in the report that aim to mitigate some of these issues. First, we advocate that NHS Choices – an already trusted source of information – should be developed as a central repository of information on the potential benefits and harms of medicines for use by patients and healthcare professionals alike. Such a repository would provide a reliable archive of information to guide decision-making when high-profile debates about the use of medicines are occurring in the media. (The communication of evidence on the potential benefits and harms of medicines in the media is a key aspect of this debate – we discuss our recommendations to enhance the communication of scientific evidence further in a subsequent section.)

Second, we believe that healthcare professionals should be better supported by robust and evidence-based tools and decision aids to facilitate informed conversations with patients around the benefits and harms of treatments, and the implications of major changes in practice on a pressured health service should be considered. We support the use of existing robust and evidence-based decision-making tools as well as further development and refinement of these. We recommend that general practices ensure that enough time is available through care planning to address patients' concerns. Consultations should allow for conversations about treatment options between healthcare professionals and patients that are guided by the patients' goals and priorities, and for the use of decision aids or algorithms that help to inform patient decisions. Such tools should be developed in collaboration with healthcare professionals and patients to ensure they meet their evidentiary requirements and address matters that are important to them.

Third, healthcare professionals should receive better training for communicating evidence around the benefits and harms of medicines, risks and uncertainty. This should better enable healthcare professionals to manage conversations around preventative treatments, such as statins, with their patients.

Finally, we believe that patients and citizens more widely have a right, duty and responsibility to inform themselves about their medical condition and treatment options. In addition to the enhanced communication of scientific evidence, we support efforts within the National Curriculum to enhance numeracy and health literacy to help interpret the potential benefits and

harms of medicines. These skills would be essential in helping make sense of the information that is presented to them, not only by their healthcare professional, but also in the mainstream media.

Do we have robust and relevant scientific evidence?

The use of statin therapy has been studied in a wide range of different treatment groups in randomised controlled trials (RCTs) and observational studies, resulting in a wealth of information on the potential benefits and harms of statin therapy.

With respect to the relative benefits, evidence from RCTs (or meta-analysis thereof) suggests that the use of statins is beneficial in reducing CVD risks, largely irrespective of an individual's background risk, gender or age.[8,9,10,11,12] RCT evidence also suggests that only three types of adverse events can be reliably, consistently and reproducibly attributed to the use of statins, and that these are typically rare and marginal events.[13] Such side effects are:

- Myopathy, also termed myositis (muscle pain accompanied by a ≥10-fold rise in normal levels of creatine kinase – about one case per 10,000 patient-years of treatment).
- New-onset type 2 diabetes mellitus (about one to two cases per 1,000 patient-years).
- Haemorrhagic stroke (about one case per 10,000 patient-years).

However, observational studies have found associations between statin therapy and other occurrences, including:

- Side effects, such as cancer, Parkinson's disease, rheumatoid arthritis and dementia, among others.
- Beneficial effects on non-cardiovascular events, including respiratory conditions, cognitive impairment and cancer.

These effects cannot be reproduced in RCTs and have largely been refuted.[14,15,16,17]

Myalgia (generalised muscle pain without raised creatine kinase levels) is a frequently reported side effect in routine clinical practice. Evidence from RCTs suggests that mylagia (and other commonly reported side effects in practice) cannot be directly attributed to statin treatment, with such side effects occurring with similar frequency in intervention and placebo groups.[18,19,20,21] Patients using statins are often warned that they might experience muscle pain, as it could be an early sign of the rare but serious side effect of myopathy, and there is RCT evidence to suggest that prior knowledge of this side effect could negatively impact on patient experiences.[22,23,24,25,26]

It was wrongly claimed in commentary articles that side effects might occur in 18–20% of individuals taking statin therapy.[27,28] This figure was a misrepresentation of findings from a retrospective observational study investigating the reasons for statin discontinuation in routine care settings.[29] The figures, but not the articles themselves, have been withdrawn.[30,31] To ensure the validity, accuracy and trustworthiness of reporting, it is important that journals – and indeed any communications outlet, including the mainstream media – take responsibility for correcting errors when these occur in an open and timely fashion (as should researchers). To provide further clarity on which side effects are directly caused by statin treatment, the Cholesterol Treatment Trialists' collaboration is currently re-analysing the adverse event data reported in statin trials.[32]

To mitigate misleading conclusions being drawn from different forms of scientific evidence in the future, we briefly summarise in the report the strengths and limitations of different approaches of evaluating evidence. In particular, we stress that the type of evidence, and the methods needed to analyse that evidence, will depend on the research question being asked. A well-conducted RCT will usually be necessary to reliably determine the benefits and harms of medicines that are directly caused by the intervention under investigation. High-quality observational studies can be informative where RCTs have yet to be conducted or are unlikely to be, and can provide valuable information about large effects or rare outcomes that are too infrequent to be reliably examined in RCTs. Syntheses of evidence, including systematic reviews and meta-analyses, are a particularly valuable approach for combining and appraising the available evidence on treatments and provide critical insights into the potential benefits and harms of medicines. In the future, it will be important to improve the involvement of patients in the design and conduct of research to ensure that studies address matters that are important to them.

We recommend that all those involved in the research process take steps towards improving the reliability of research. In the case of statins, this would have entailed being clear about the strengths and limitations of the different studies into the potential benefits and harms of statin therapy, and an explicit recognition of what can and cannot be inferred from the research findings. To that effect, we recommend that training for researchers and healthcare professionals better accommodates the full array of evidence-generating approaches for assessing the benefits and harms of medicines. Such training should highlight the relative value, merits and limitations of different approaches, including new and emerging

methods, and the suitability of the various methods in answering different research questions. Continuing professional development for researchers and healthcare professionals at all career stages should be championed by universities, research institutions, funding bodies and Medical Royal Colleges.

Ultimately, the rigour of research lies with the researchers themselves. The onus is on researchers to ensure they receive the appropriate training, abide by ethical research frameworks and commit to good research practice. Researchers also have a responsibility to accurately communicate their findings and any limitations of the study design or methodology used in their work.

Is scientific evidence trustworthy?

The reliability and transparency of the evidence base that supported the lowering of the threshold for prescribing statin treatment in the NICE guidelines has come under criticism by some members of the scientific community.[33,34,35] While this threshold revision was informed by the assimilation of evidence in meta-analyses conducted by independent reviewers,[36,37] some have questioned the trustworthiness and reliability of the studies published, many of which were undertaken by or in association with pharmaceutical companies, and have called for a re-analysis of the underlying adverse event data from the original studies.[38]

To mitigate these issues in the future, we recommend that there is a move to 'intelligent openness', whereby data are more accessible, assessable and usable by the intended audience. This includes trial registration and publication, and better access to data, whether positive, 'negative' or inconclusive. Appropriate safeguards should be put in place to protect patient privacy and confidentiality when providing access to de-identified individual patient-level data.

Competing interests have come under particular scrutiny throughout the discussions around the use of statins. We recommend that communities across the sector establish fit-for-purpose frameworks to declare financial and non-financial interests; identify potential, actual or perceived conflicts; and manage any competing interests that might arise. 'Intelligent openness' about interests and documentation of mitigation measures is then critical to allow wider society to make an informed judgement as to the credibility and trustworthiness of the evidence.

Given the widespread suspicion of industry,[39,40,41] interests that stem from research involving commercial partners require particularly sensitive governance. In the report, we have developed high-level principles around research funding, study design, trial registration, contracts, data holding, access and analysis, and publication of findings that we recommend to be followed. Funding bodies, academia and industry should work together to develop clear guidance on how these should be implemented. We welcome the Association of the British Pharmaceutical Industry's efforts to increase openness about the funding of healthcare professionals and healthcare organisations via their public database, 'Disclosure UK'.[42] We encourage all healthcare professionals and healthcare organisations to agree to their data being disclosed on this database.

The Academy believes that industry plays a vital role in the biomedical research ecosystem by researching, developing and bringing new life-saving or life-enhancing products to the market to improve the health and wellbeing of patients. The Academy also believes that strong links between academia and industry (as well as with the NHS and the regulatory sector) are crucial in medicines development and in addressing health and scientific challenges.[43] The research community should seek opportunities to explain to the public the importance of collaboration with industry and the benefits of such partnerships. Such initiatives could allay misconceptions around these relationships and mitigate some of the unhelpful and misleading instances where associations with commercial partners have been used to question the validity of research findings.

How can we most effectively communicate scientific evidence?

The debate over whether the potential benefits of taking statins for primary prevention of CVD outweighed the potential harms was widely reported in the mainstream media. This widespread coverage has been linked to reduced statin use.

A recent analysis of primary care data in the UK found that although there was no evidence that the period of high media coverage questioning the risk–benefit balance for statins was associated with changes in starting statin therapy among

patients with a high recorded risk score for cardiovascular disease or a recent cardiovascular event, there was a decrease in the overall proportion of patients with a recorded risk score. Further, patients already taking statins were more likely to stop treatment for both primary and secondary prevention after the high media coverage period.[44] The study estimated that such media coverage resulted in 218,971 patients stopping statins in the UK, and would account for at least 2,173 excess CVD events over 10 years. Similarly, a recent Danish study suggested that negative stories about statins in the media increased patients' chances of stopping statins, while the opposite was true for positive statin-related news stories. Discontinuing statin treatment early due to negative media coverage was associated with increased risk of myocardial infarction and death from CVD.[45]

Further, a recent Picker Institute report found that GPs' confidence in discussing statins with patients or in prescribing statins was affected as a result of media coverage. It suggested that over 75% of the GPs and cardiologists surveyed felt that the media coverage had an impact on other healthcare professionals, who were reticent to raise the issue of taking and prescribing statins.[46]

The media coverage has been criticised for giving undue emphasis to the adverse side effects associated with statin use.[47] Researchers with expertise in CVD felt that the reporting did not always make it clear that it is a minority view among the scientific community that the harms of statin treatment outweigh the benefits for primary prevention of CVD. We believe that it is a responsibility of communicators, on both sides of the argument, to consider the implications of their communication efforts on individual patients who might discontinue life-saving treatments. Further, it is important for them to be explicit on the concerns they are addressing: in the statins coverage, discussion of the balance of benefits and harms in low-risk groups was often confused with wider debates about over-medication, medicalisation and pressures on GP services. Ultimately, the decision as to whether to take a statin that has been prescribed to them belongs to the patient. This decision should, however, be informed by reliable and trustworthy evidence on the potential benefits and harms. There were concerns that this did not occur during the statins controversy.

To mitigate the ill-effect of misleading reporting about the potential benefits and harms of medicines, we encourage:

- All journalists to adhere to the Science Media Centre's '10 best practice guidelines for reporting science & health stories' to enhance the quality of science reporting, which should be adopted by the media regulators (e.g. the Independent Press Standards Organisation, IPSO, or the Independent Monitor for the Press, IMPRESS) as their standards for use in the newsrooms.[48] These guidelines are designed to prevent sensationalist headlines and ensure more balanced and accurate reporting. They advocate placing new information about research findings in the context of previous knowledge and seeking expert independent views on the evidence, including from medical research charities, healthcare professionals and the researchers themselves.
- Researchers and health-related charities to respond to media queries and provide expert advice. In doing so, they should be supported by their press offices, who should also provide media training for researchers. In the high-profile statin debate, these groups of individuals had an important role to play in correcting inaccuracies and misrepresentations in the media, providing a trusted 'moderating' voice in these discussions. When it is in the general public's interest, as in the case of statins, we urge researchers to communicate their results in a responsible and accurate fashion to a wider public audience, for example in the form of lay summaries of results or patient perspectives. Universities, research institutions and funding bodies, including industry, should be supportive of these efforts.

In the report, we also recommend that:

- A traffic light system for press releases of medical research, which allows press offices to grade both the relevance of the research to clinical application and the robustness of the study before publication of the press release, should be developed by the Science Media Centre. Such a system should help journalists assess the stage and reliability of the research, thereby minimising the opportunities for distorting or exaggerating research findings.
- Codes of practice are established for both researchers and press officers to encourage best practice in terms of their engagement with the media.
- Universities and research institutions play a greater role in ensuring that the research they host is accurately portrayed in the media.

Such safeguards should help to enhance the reporting of scientific evidence in the media and consequently prevent unsubstantiated concerns from spreading unnecessarily.

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Human papilloma virus (HPV) vaccine case study

Human papilloma virus (HPV) is a group of highly common viruses that are mainly transmitted sexually. There are over 100 types, at least 13 of which cause cancer, with two HPV types causing 70% of cervical cancers and precancerous cervical lesions. There is also evidence linking HPV with cancers of the anus, vagina, vulva and penis. Throughout the world, over a quarter of a million women died from cervical cancer in 2012, with estimates that 20,000 women die from this cancer in Europe each year.[1,2] HPV vaccines (Cervarix, Gardasil/Silgard and Gardasil 9) are given to protect women against cervical cancer and other HPV-related cancers and pre-cancerous conditions.[3] They are most effective if administered before exposure to HPV, so it is preferable to administer them before first sexual activity.[4] In 2008, HPV vaccines were introduced into the routine UK immunisation programme for 12-13 year-old girls.[5]

Evidence of potential benefits and harms

Routine surveillance of suspected adverse reaction reports raised questions about the potential association between the use of HPV vaccines in young women and two particular syndromes: (1) complex regional pain syndrome (CRPS), a chronic pain syndrome affecting a limb; and (2) postural orthostatic tachycardia syndrome (POTS), a condition where the heart rate increases abnormally on sitting or standing up, together with symptoms such as dizziness, fainting and weakness, headache, aches and pains, nausea and fatigue.[6] These syndromes are difficult to diagnose but occur in the general population, including young women, regardless of vaccination.

The European Medicines Agency (EMA) recently conducted a review of the evidence surrounding reports of these two syndromes in young women given HPV vaccines.[7] The EMA concluded that the overall occurrence of CRPS and POTS in vaccinated girls is no higher than would be expected in the general population (around 150 cases of CRPS and at least 150 cases of POTS per million each year), and that there is no evidence that HPV vaccines can cause these syndromes. The EMA therefore made no recommendations to change the way vaccines are used and no amendments to the product information.

Allegations about the safety of the HPV vaccines were reported in the media, in particular reports of girls developing POTS or chronic fatigue syndrome (also known as myalgic encephalomyelitis or ME) after HPV vaccination.[8,9] Symptoms of CRPS and in particular POTS can overlap with chronic fatigue syndrome. However, a large study found no link between HPV vaccines and chronic fatigue syndrome (CFS).[10] Further, the World Health Organisation (WHO) Global Advisory Committee on Vaccine Safety has issued a statement concluding there is no proven link between the HPV vaccination and autoimmune disease (of which many think CFS is an example).[11] Data have also suggested a potential link between the vaccine and thrombosis.[12,13,14] However, the weight of evidence shows no link between HPV vaccination and thrombosis, and studies continue to suggest that the benefits of vaccination against HPV outweigh the harms, with minimal documented adverse effects.[15,16]

Over 80 million girls and women have received these vaccines worldwide, with 90% coverage in the recommended age group in some European countries.[17] These vaccines are expected to prevent many cases of cervical cancer and other HPV-related cancers and conditions. In its recent review of the evidence, the EMA concluded that the benefits of HPV vaccines continue to outweigh the known side effects.[18]

Conclusions

As with the case study on the measles, mumps and rubella (MMR) vaccine (see below), this example emphasises the need for media coverage that accurately reflects the potential benefits and harms, as well as the uncertainties, associated with medicines. It is important that undue emphasis is not given to anecdotal evidence, and that the relative strengths and limitations of the sources of evidence are captured in news articles. This case study also stresses the importance of patients' and healthcare professionals' perceptions of illness and treatment, which are shaped by a wide range of factors, including media coverage, personal beliefs and past experiences.

In the 'Enhancing the use of scientific evidence to judge the potential benefits and harms of medicines' report, we make recommendations aimed at improving the reporting of scientific evidence – directed at press officers, grant awardees, universities and research institutions, among others – as outlined in the case study on the MMR vaccine. We also recommend mechanisms to support decision-making between patients and healthcare professionals, in particular that sufficient time is available to address patients' priorities and concerns regarding treatments and medication decisions. The recommendations we make, if implemented, would help to increase the balance and accuracy of scientific reporting in the mainstream media, and would aid patients and healthcare professionals make choices informed by the weight of scientific evidence.

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Hormone replacement therapy (HRT) case study

Hormone replacement therapy (HRT) is used to treat the symptoms of the menopause, such as hot flushes, vaginal dryness, sleep disturbance, tiredness, mood swings and lack of concentration.[1] Symptoms are caused by a fall in sex hormone levels, and HRT treats these symptoms by replenishing these levels.[2] HRT exists in different forms (e.g. oestrogen alone or combinations of oestrogen and other hormones like progesterone and testosterone) and can be administered via different routes (e.g. tablets, skin patches, gels or nasal sprays).[3]

Utility and value of evidence

Evidence has consistently indicated that HRT is beneficial in reducing menopausal symptoms,[4,5] such as hot flushes,[6] depressive mood,[7] irritability and mood disturbance,[8] and in preventing and treating osteoporosis,[9,10,11] leading to an improved quality of life. However, the use of HRT has been debated for a number of years. At the centre of the controversy is conflicting data about the potential harms of HRT.

Indeed, initial observational studies on HRT showed many benefits in addition to relieving menopausal symptoms, including a decrease in osteoporosis, coronary heart disease and mortality.[12,13,14,15,16,17] However, subsequent randomised trials, including the Women's Health Initiative (WHI),[18] studying women predominantly many years after the onset of the menopause failed to reproduce the beneficial effect of HRT on coronary heart disease and mortality.[19,20,21] For example, the WHI study found instead that a combination of oestrogen and progesterone therapy increased the risk of coronary heart disease and breast cancer.[22] These results were widely reported in the media (see subsequent section on 'Communication') leading to a significant number of women of all ages and on different preparations of HRT stopping their treatment.[23,24]

It is now widely acknowledged that the results from some of these studies were affected by their design and this was not taken into account in their interpretation. For example, it has been suggested that the results from the initial observational studies were affected by selection bias (e.g. women taking HRT tended to have different lifestyles to those not taking HRT) and differences in the age at which HRT was initiated.[25,26] Further, it has been suggested that the initial results from the WHI study were affected by the majority of participating women being over 60 years old, who due in part to their age and sex hormone-depleted status already had an increased risk of heart disease and breast cancer.[27,28] The discrepancy between the initial observational data and the subsequent randomised trial data has also been attributed to the 'timing effect', in other words whether HRT was initiated soon after the onset of the menopause or was delayed by several years, as was the case in the WHI studies.[29,30,31]

More recent randomised and observational data and several meta-analyses, as well as reanalysis of data from the WHI with age stratification, now consistently show decreased coronary heart disease and mortality when HRT is initiated shortly after the onset of the menopause in younger (under 60 years) healthy women.[32]

The use of HRT has, however, been associated with a potential increased risk of developing breast,[33,34,35,36,37,38] endometrial[39,40,41] or ovarian cancer,[42,43,44] but a decrease in the risk of colon cancer.[45] In some countries such as Australia, the fall in HRT use following emerging safety concerns around breast cancer risk has been associated with a detectable reduction in breast cancer incidence among women aged 50 years or above.[46] HRT use has also been shown to increase the risk of venous thromboembolism (blood clots).[47,48,49] HRT treatment may also be associated with more minor adverse events, such as breast tenderness, abdominal bloating, mood changes, uterine bleeding and elevation in blood pressure.[50] These events can normally be managed by adjusting the dose and preparation of HRT.

In 2007, the Medicines and Healthcare products Regulatory Agency (MHRA) published a safety update for the use of HRT.[51] It concluded that:

- Generally, given the lower baseline risk of coronary heart disease and other adverse events in healthy younger women who use HRT, the overall risk from HRT is very low in these women.
- As the baseline risk for cardiovascular events increases with age, older HRT users have a much greater overall risk of these events.
- The risk of breast cancer, ovarian cancer, and endometrial cancer due to HRT increases with the duration of use.

As such, it concluded that the balance of potential benefits and harms of HRT will differ for every woman depending on the age at which HRT is started, the duration of use and the type of HRT (e.g. oestrogen-only or a combination of oestrogen and progestogen). It is recommended that the lowest effective dose should be used for the shortest time possible for all women, and its use should be reviewed regularly, at least once a year. Although disagreement about the relative benefits and harms of HRT continues, the National Institute for Health and Care Excellence (NICE) published guidelines in 2015 recommending HRT for women suffering with symptoms of the menopause.[52] When considering using HRT, both NICE and the MHRA advocate discussion between healthcare professionals (HCPs) and their patients of the potential benefits and harms associated with the use of HRT, and careful individual benefit-risk decision-making.

In the 'Enhancing the use of scientific evidence to judge the potential benefits and harms of medicines' report we summarise the strengths and limitations of different study designs and the importance of minimising bias and confounding. We stress that the type of evidence and methods needed to analyse that evidence will depend on the research question under investigation and support training for researchers and HCPs to enhance their understanding of the value, strengths and limitations of different approaches to assess the potential benefits and harms of medicines.

Further, we recommend that sufficient time is available in consultations to allow appropriate discussion of the needs and priorities of patients. In this context, such consultations would enable menopausal women considering or undergoing HRT to discuss with their healthcare professional their goals and priorities and the variety of treatment options, including alternatives to HRT. Such conversations could be facilitated by decision-aids and other tools. In that regard, we recommend that NHS Choices acts a central repository for information on the benefits and harms of medicines with links to appropriate decision-aids and other high-quality sources of information.

We also support training provided by professional bodies in effective communication of evidence around the benefits and harms of medicines, risk and uncertainty to facilitate these conversations. In turn, patients have the right and responsibility to inform themselves about their medical condition and treatment options. They should be better equipped to make sense of the information that is presented to them, by their healthcare professional or in the mainstream media, and should feel confident in asking their healthcare professional for further information about their condition, treatment and/or alternative treatment options. Our questions for patients in **Online annex G** should support them in doing so.[53]

Trustworthiness

The reliability of the evidence surrounding HRT has come under scrutiny where this has been obtained in partnership with or by industry. Indeed, there have been claims that such studies emphasise the alleged benefits over the potential harms and have resulted in a revised view of what might be an acceptable level of harm for healthy populations.[54] Media reports also implied that the change in NICE guidelines on HRT may have been influenced by industry involvement.[55]

The Academy acknowledges the crucial role of industry in the development of new medicines. To increase the trustworthiness of the evidence that is produced (in particular evidence produced by industry in which there is widespread suspicion), we recommend that frameworks are established to declare interests, and identify and manage competing ones. The scientific community should be open about both the interests and mitigation strategies, thereby allowing the public to make their own judgement on the reliability of evidence. In the spirit of 'intelligent openness', funding sources should be declared, trials registered, studies ethically and appropriately designed, data accessible, and all rigorous results published. We have developed overarching principles for declaring and managing interests (**Online annex E**)[56] and more detailed guidance as to how these should be applied to the development of evidence related to the use of medicines in clinical trials involving a commercial partner (**Online annex F**).[57]

Communication

In the United States, the initial findings of the WHI study were inaccurately conveyed to, and thereafter reported in, the media as HRT increasing the risk of breast cancer by 24-fold (with no absolute risk figures provided) rather than the observed 24% increase in relative risk. Further, it was reported that the data were applicable to all women and for all types of HRT, whereas the data were obtained with a HRT combination of oestrogen and progesterone largely in older women (over 60 years).[58] Many women stopped using HRT following these misleading reports.

More recently in the UK, the publication of the NICE guidelines received criticism in the media for downplaying the side-effects associated with HRT.[59,60] The Daily Mail reported that the authors of the Million Women Study estimated an extra 10,000 cases of breast cancer per 1,000,000 women over 10 years, whereas NICE estimated and extra 6 cases of breast cancer per 1,000 over 5 years. Although the use of different denominators gave the impression that NICE underestimated the risk of breast cancer, it actually estimated more cases, with the Million Women Study estimates at 10 extra cases of breast cancer per 1,000 women over 10 years, while NICE estimates were 12.

In the 'Enhancing the use of scientific evidence to judge the potential benefits and harms of medicines' report, we stress the importance of responsible, accurate and balanced briefing of the media and subsequent reporting by them of research findings. This also applies to all parties involved in the generation and communication of research. Journalists should adhere to the Science Media Centre's '10 best practice guidelines for reporting science & health stories' and should not misrepresent statistical information.[61] Researchers have an important role to play in communicating their results in an understandable way for the general public, for example via lay summaries or patient perspectives of published research. Researchers with appropriate expertise should seek to provide expert advice to the media and correct any misconceptions that are published. Press releases should be explicit about the limitations of research and place findings and recommendations in the relevant context, including relating new findings to previous evidence. We provide good practice for press releases in **Box 16** of the 'Enhancing the use of scientific evidence to judge the potential benefits and harms of medicines' report.

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Measles, mumps and rubella (MMR) vaccine case study

The measles, mumps and rubella (MMR) vaccine is effective in preventing measles, mumps and rubella, diseases that can result in serious illness, disability and death.[1]

Evidence and its representation in the media

In 1993, Dr Andrew Wakefield published a report suggesting that natural measles virus infection was one of the causes of Crohn's Disease,[2] and proposed that the disease could be caused by the attenuated measles vaccine.[3] Five years later, Wakefield published a case series (an early report investigating a consecutive series of 12 children) in the medical journal The Lancet suggesting, but not proving, that there might be an association between the onset of autism and bowel disease with receipt of the combined MMR vaccine.[4] Despite multiple studies failing to confirm that the vaccine was a risk factor in autism,[5,6,7,8,9] Wakefield continued to advocate the cessation of combined MMR vaccination in favour of single measles, mumps and rubella vaccinations, which he believed would be a safer alternative to the combined vaccine and could potentially decrease the risk of an adverse event occurring.[10,11,12,13]

The controversy received widespread coverage by the mainstream media, causing public concern and affecting parents' immunisation decisions.[14,15,16] There is evidence that two thirds of the MMR media stories reported during a period of extensive coverage in 2002 focused on the possibility of a link between the MMR vaccine and autism, whereas the large body of evidence indicating the safety of the MMR vaccine only featured in a third of these stories. This 'false balance' wrongly conveyed the perception that science was split down the middle on the safety of the MMR vaccine.[17] Additionally, the lack of evidence looking at the safety of single vaccines, the strategy that was advocated as a safer alternative by Wakefield, was largely ignored in the media reports.[18]

As a result, confidence in the MMR vaccine fell among parents and healthcare professionals, and national MMR vaccine coverage fell from over 90% in 1994 to around 80% in 2003-4 (but with significantly lower figures in some parts of the UK), corresponding with a significant increase in the incidence of measles.[19] Twelve years after its publication, Wakefield's 1998 paper was fully retracted by The Lancet and he was barred from practising medicine in the UK, but the controversy has had a lasting impact on perceptions of vaccines.[20,21,22,23,24,25,26]

In 2010 the General Medical Council concluded that Wakefield failed to disclose his potential conflicts of interest when applying to undertake and when publishing his research: he failed to report to the Ethics Committee and to the Editor of The Lancet his involvement in the MMR litigation against the manufacturers of the MMR vaccine and his receipt of funding from the Legal Aid Board, and he failed to disclose to the Editor of The Lancet his involvement as the inventor of a patent relating to a new vaccine for the elimination of the measles virus.[27] Concerns have also been raised that Wakefield's 1998 paper contained fraudulent data that had been falsified to support his theory.[28,29,30]

Conclusions

This case study emphasises the importance of robust evidence on causality between treatment and outcome, and of balanced media coverage that accurately reflects harm, benefit and uncertainty. In the 'Enhancing the use of scientific evidence to judge the potential benefits and harms of medicines' report, we highlight the duty of journalists to accurately portray research findings, signpost study limitations, place findings in the context of previous research and not unduly alarm or overhype claims. We also encourage them to verify the validity of their reporting with independent experts from academia, industry, medical research charities, among others, and to adhere to the Science Media Centre's '10 best practice guidelines for reporting science & health stories'.[31] We stress the dangers of 'false balance' in news reporting and highlight that where there is strong consensus on the evidence base and only a minority of opposing views, both sides should not misleadingly be presented as being of equal standing. To ensure the validity, accuracy and trustworthiness of reporting, we

also emphasise the importance of communications outlets, including journals and the mainstream media, and researchers taking responsibility for correcting errors when these occur in an open and timely fashion.

In addition, we make several recommendations aimed at improving the reporting of scientific evidence in the media, including the development of the following:

- A 'traffic light' system for press releases of medical research, developed by the Science Media Centre that would allow press offices to grade both the relevance of the research to clinical application and the robustness of the study before publication of the press release, thereby enabling journalists to assess the stage and reliability of the research.
- Incentives for universities and research institutions to play a greater role in ensuring that the research they host is accurately portrayed in the media.

Were these recommendations implemented, the likelihood of accurate, balanced scientific reporting in the mainstream media would be increased. The recommendations would hopefully help to prevent research such as Wakefield's, which are unsupported by the weight of evidence, from receiving unfounded, disproportionate or inaccurate coverage.

We also recommend that NHS Choices develops clear information on the benefits and harms of medicines, acting as a central repository for use by patients and healthcare professionals, and making direct, up-to-date reference to the underlying evidence. Properly implemented, this would help patients and healthcare professionals assess conflicting evidence, particularly if improperly represented in the mainstream media.

We support current communication training for healthcare professionals that places emphasis on communicating evidence on the benefits and harms of medicines, risk and uncertainty to patients. Further, we recommend that HCPs receive training in research methods and statistics so that they can better judge the value of the results informing their decisions and communicate these effectively to patients and carers, and that sufficient time is available in consultations to address patients' priorities and concerns regarding treatments and decisions about medicines. If implemented, our recommendations would aid patients, carers and healthcare professionals make choices informed by the weight of scientific evidence and enable patients and carers to discuss any potential concerns about treatment options with their healthcare professional.

We support ongoing initiatives that aim to increase the robustness of research findings, including high standards of research integrity as described in the 'Universal Ethical Code for Scientists'.[32] Such initiatives include higher education institutions and industry encouraging and rewarding behaviours that are conducive to good research practice; Universities UK's concordat to support research integrity and the All European Academies' European Code of Conduct for Research Integrity;[33,34] and journals and publishers ensuring that work submitted for publication receives adequate methodological scrutiny and adheres to internationally agreed publication guidelines.

To facilitate greater declaration and management of interests, we recommend that frameworks for declaring and managing interests are developed that ensure appropriate safeguards can be put in place should a competing or conflict of interest be identified. We also recommend that publicly accessible registers of interests are established (for example on organisational websites). Such frameworks and registers would help to prevent situations in which potential conflicts of interests are not disclosed, as was the case for Wakefield's research.

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Oseltamivir (Tamiflu) case study

Oseltamivir (trade name: Tamiflu) is an antiviral produced by the pharmaceutical company Roche for the treatment and short-term prophylaxis of influenza. Since the H5N1 outbreak in 2005, the UK government has been stockpiling Tamiflu as well as another antiviral, zanamivir (trade name: Relenza), to combat influenza pandemics. Pandemic influenza tops the UK's National Risk Register of Civil Emergencies, ahead of both coastal flooding and major terrorist incident.[1] In 2009, in response to the H1N1 pandemic, the UK government announced it would be increasing its stockpiles of Tamiflu from 33.5 million to 50 million (enough to treat 80% of the population).[2]

Decision-making

Decisions about the use of antivirals occur at different levels. Governments make decisions about the use of antivirals – such as whether they should be stockpiled – based on a range of considerations, including economic, public health, political, ethical and scientific factors. Patients and healthcare professionals also make decisions about initiation, adherence and termination of treatment based on a broad range of factors, including perceptions of illness and treatment. It is important that healthcare professionals are better able to communicate the potential benefits and harms of medicines, and should have an appreciation of the strengths and limitations of different study designs.

The evidence base and its interpretation

In April 2014, the Cochrane Collaboration published a report into the effectiveness of Tamiflu based on an analysis of clinical trial data. In doing so, the Cochrane Collaboration initially had difficulty accessing the relevant data from Roche. After receiving these data, they published the review, which concluded that Tamiflu reduced influenza symptoms by 14–17 hours, but did not find evidence that Tamiflu reduced hospitalisation, pneumonia or virus transmission.[3,4] The results of the review were widely reported in the national media along with claims that around £500 million had been wasted on Tamiflu.[5,6] As a result, there have been calls on the government to reconsider this stockpile as part of its pandemic influenza strategy.

Further publications, which used data from randomised controlled trials (RCTs) conducted during seasonal influenza outbreaks as well as observational data collected during the 2009 H1N1 pandemic, have added to the evidence base and debate.[7,8,9] A meta-analysis of observational data collected during this pandemic showed that deaths in hospitalised patients reduced when Tamiflu was used.[10] Some suggest these observational data should not inform policy decisions given they are at a higher a risk of bias, and should be dismissed if funded by those producing the therapeutic, as they were in this case (albeit through an unrestricted educational grant, whereby Roche had no input into the project design, no access to the data, no role in the analysis or interpretation of the data, and no opportunity to preview or comment on the study results or manuscripts arising from the work). However, others state that these studies provide a valuable insight in the use of antivirals such as Tamiflu in hospitalised patients, particularly as, unlike clinical trials, these studies relate to pandemic rather than seasonal influenza. It is therefore argued that it can be appropriate to use observational data to inform policy and guidance (particularly when data from large, pragmatic RCTs are not available), and inappropriate to dismiss studies simply on the basis of their funding source (especially when there is transparency about the basis of these funding arrangements).

In 2015, the Academy of Medical Sciences and Wellcome Trust published a review of the evidence for the treatment and prophylaxis of influenza.[11] This report supports use of neuraminidase inhibitors (NAIs) such as Tamiflu within 48 hours of the onset of symptoms in patients that require hospitalisation (including pregnant women), but recognises the lack of evidence to guide treatment decisions for other high-risk groups and children. The report also stresses that if future outbreaks of influenza are more virulent or show greater incidence of complications and death than during the 2009 pandemic, the treatment of larger numbers of the population with NAIs may be justified.

Conclusions

This case study highlights the difficulties faced by government and healthcare professionals when making decisions about medicines with limited evidence, particularly when the potential health and economic risk to the population is so significant. It demonstrates the challenges of weighing up different types of scientific evidence, particularly in view of perceived conflicts of interest.

In the 'Enhancing the use of scientific evidence to judge the potential benefits and harms of medicines' report, we recognise that knowledge about medicines evolves constantly, and that evidence on the potential benefits and harms of medicines continues to emerge once a product has been launched on the market and is available for wider use. We make a series of recommendations to improve the 'intelligent openness' of research findings, including the following: trial registration along with a summary of the protocol; publication of rigorous findings in full regardless of the outcome, with a summary of the results made publicly available on the database where the trial is registered; publication of the Clinical Study Report (or equivalent in non-commercial settings); and, where appropriate consent has been provided, access to de-identified individual patient-level data to researchers on request, with a commitment that no reasonable request is refused. We also recommend that frameworks are established to declare interests, and identify and manage competing interests, and outline principles for declaring and managing interests in the development of evidence related to the use of medicines in clinical trials involving commercial partners. These centre around research funding, study design, trial registration, contracts, data holding, access and analysis, and publication of findings, and are available in **Online annex F**.[12] This report advocates guidelines designed to prevent sensationalist media reporting and points out that the breadth of stakeholders in scientific research have a role to play in accurately communicating findings.

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Rofecoxib (Vioxx) case study

Rofecoxib (trade name: Vioxx) was a nonsteroidal anti-inflammatory drug (NSAID) approved by the United States (US) Food and Drug Administration (FDA) in 1999 for the relief of signs and symptoms of osteoarthritis, the management of acute pain, and the treatment of menstrual pain.[1] Traditional NSAIDs, such as ibuprofen and naproxen, work by inhibiting the enzymes cyclooxygenase-1 (COX1) and COX2. Although they are effective at relieving pain, they can also cause adverse gastrointestinal effects and bleeding.[2] These adverse effects are due to COX1 inhibition, while their beneficial pain-relieving effects are mediated through COX2 inhibition. By selectively targeting COX2, rofecoxib and other COX2-selective inhibitors, such as celecoxib (trade name: Celebrex, produced by Pfizer), were developed to maximise the therapeutic pain-relieving effects of COX2 inhibition, while minimising the adverse gastrointestinal effects mediated by inhibition of COX1.

The VIGOR and APPROVe studies

In 2000, Merck published in the New England Journal of Medicine the results of the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, which investigated the safety and efficacy of rofecoxib compared to naproxen in patients with rheumatoid arthritis.[3] The study showed that although rofecoxib-treated patients had fewer gastrointestinal side-effects than naproxen, they were also at a four to five fold increased risk of myocardial infarction (heart attack). The difference in incidence of myocardial infarction between the two groups was attributed by the authors of the study to the cardio-protective effects of naproxen rather than a harmful effect of rofecoxib, although further research was needed. In 2001, the FDA issued a written warning to Merck regarding their promotional activities and materials for the marketing of rofecoxib, which it felt minimised the potentially serious cardiovascular findings of the VIGOR study and misrepresented rofecoxib's safety profile.[4] A year later, the FDA instructed Merck to include precautions about cardiovascular risk in rofecoxib's package insert.[5]

In 2004, Merck voluntarily withdrew rofecoxib from the market following analysis of its Adenomatous Polyp Prevention On Vioxx (APPROVe) study, which was terminated early when preliminary data showed an increased risk of myocardial infarction and stroke in rofecoxib-treated patients compared to placebo.[6] Before its withdrawal in 2004, over 80 million patients had taken rofecoxib and sales had reached $2.5 billion in 2003.[7] It was used by about 400,000 people in the UK, with over 2.1 million prescriptions for rofecoxib (approximately 10% of all NSAID prescriptions) dispensed in England at its peak in 2003.[8,9] It has been estimated that between 88,000 and 140,000 additional cases of serious coronary heart disease might have resulted from the use of rofecoxib in the US alone by the time of its withdrawal,[10] although these figures are contested.[11] The drug safety concerns raised by rofecoxib informed amendments to pharmacovigilance legislation in the European Union (EU), resulting in strengthened post-marketing surveillance of medicines and requirements for organisations to notify EU regulators of any action to withdraw a product from the market.[12,13,14]

Trustworthiness of the evidence

The New England Journal of Medicine raised concerns in 2005 about the integrity of the data on adverse cardiovascular events published in the VIGOR study.[15,16] Indeed, the editors were concerned that the VIGOR study had used different cut-off dates for including gastrointestinal and cardiovascular events, thus making the cardiovascular risk appear lower. They were also concerned that the authors failed to include three cases of myocardial infarction in the rofecoxib-treated group in the analysis. The non-Merck authors of the study have, however, defended their analysis by explaining that: the earlier cut-off date for inclusion of cardiovascular events was chosen by Merck to allow sufficient time to adjudicate these events, as the comparison of cardiovascular events was not pre-specified when the study was originally designed; the three additional

myocardial infarctions in the rofecoxib-treated group occurred after the cut-off date for inclusion of cardiovascular events (as did one additional stroke in the naproxen-treated group) and were therefore not included in the analysis of cardiovascular events to conform to the predefined analysis plan; and the inclusion of the three additional myocardial infarctions would not have led to a qualitative difference in the conclusions drawn about the cardiovascular risk associated with the use of rofecoxib.[17]

Merck has been criticised more widely for the way it dealt with assessing the potential cardiovascular risk of rofecoxib. For example, although the APPROVe study showed an increased cardiovascular risk (primarily myocardial infarction and stroke), the authors initially stated that the increased risk only became apparent after 18 months of use.[18] This statement was later withdrawn after Merck admitted the statistical approach used was incorrect.[19] Merck was also criticised for not designing trials to specifically assess cardiovascular risk (as was the FDA for not compelling Merck to undertake these),[20,21] despite the potential cardiovascular risks being noted in a study it sponsored published in 1999, which found that rofecoxib decreased the levels of urinary metabolites associated with cardiovascular health.[22,23] Concerns have also been raised that the nine intervention studies that constituted its 1998 drug application to the FDA were generally small with short treatment periods, enrolled patients at low risk of cardiovascular disease, and did not have a standardised procedure to collect and adjudicate cardiovascular outcomes.[24]

It has also emerged that several other articles by different authors showing favourable results for rofecoxib had been written by Merck with accreditation given to an independent author (also known as ghost writing).[25] Meta-analyses have suggested that evidence that rofecoxib increased the risk of cardiovascular adverse events was available as early as 2000 and that the drug should have been withdrawn from the market earlier,[26,27] although Merck has disputed some of these findings.[28]

Conclusions

We support a number of 'intelligent openness' measures in the 'Enhancing the use of scientific evidence to judge the potential benefits and harms of medicines' report that would mitigate some of these issues in the future, including:

- Trial registration on a recognised open and searchable database with a summary of the trial protocol before the first participant is recruited.
- Publication of rigorous findings in full regardless of the outcome, with a summary of the results made publicly available on the database where the trial is registered.
- Publication of the full Clinical Study Report, or its equivalent in non-commercial settings.
- Where appropriate consent has been given, providing access to de-identified individual patient-level data to researchers on request, with a commitment that no reasonable request is refused.

These principles reflect the requirements of the EU Clinical Trials Regulation (EU No 536/2014) and align with the calls of the AllTrials campaign.[29,30] We outline in the report principles that should govern academia-industry collaboration in the development of evidence related to the use of evidence in clinical trials around research funding, study design, trial registration, contracts, data holding, access and analysis, and publication of findings (**Online annex F**).[31] We also recommend that frameworks for declaring interests and identifying and managing competing ones are established, and a series of measures are put in place to enhance the reliability of research, such as affording appropriate statistical and methodological scrutiny of work submitted for publication. Finally, we stress that researchers themselves are charged with responsibility for the ethical conduct and rigour of their work, with a duty to adhere to the 'Universal Ethical Code for Scientists'.[32]

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