

Online annexes

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Online annex A. Use of statins: detailed 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 the disease. 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 the 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 myalgia (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 general practitioner (GP)s' 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 statins and to prescribe them.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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Online annex B. Summary table of appropriate approaches for the evaluation of treatment effects in specific research scenarios

By combining and analysing data from all the available studies, meta-analyses and systematic reviews of randomised controlled trials (RCTs) provide a robust and reliable overall estimate of treatment effects across the board. Because they rely on studies already having been carried out, they have not been included in this table. However, they do provide a high-quality approach to combining and appraising the information available on a given treatment, and are crucial to informing clinical practice. In contrast, particular caution is required in interpreting meta-analyses of observational studies, which can result in very precise but biased effect estimates.

Scenario: detection of

Most appropriate approach for the evaluation of treatment effects *

Effects that are directly caused by the treatment under investigation (treatment effects) on outcomes that are common.

Example: to investigate the effects of a cholesterol-lowering drug in patients with a low risk of heart disease.

Fully-randomised, well-blinded, large-population RCTs are the most reliable design for detecting causal effects on common outcomes owing to their ability to minimise bias and confounding, which limit the ability of observational studies to reliably assess such effects. Observational studies may detect a correlation, which should be subsequently tested in an RCT to reliably establish causality.

Treatment effects that are moderate.

Example: to investigate the effects of drugs to treat high blood pressure that will moderately affect blood pressure readings.

Fully-randomised, well-blinded, large-population RCTs are the most reliable design for detecting moderate but clinically-relevant treatment effects owing to their ability to minimise bias and confounding, which limit the ability of observational studies to reliably assess such effects. Observational studies may detect a correlation, which should be subsequently tested in an RCT to reliably establish causality.

Treatment effects that are large in conditions where the outcome without treatment is poor.

Example: to investigate survival rates in Ebola-infected individuals treated with a novel therapeutic. In the absence of treatment, these individuals would most likely die.

Although RCTs can detect large treatment effects, reasonably strong conclusions can also be drawn on treatment effects from observational studies when the effects are large (e.g. survival) and occur in the treatment of a condition that has a poor outcome (e.g. death). The conclusions will be strengthened if the findings are biologically plausible.

Treatment effects that are large and impact on outcomes that are rare and/or delayed.

Example: to investigate treatment side effects that only occur in one in

Although RCTs can detect large treatment effects, when the outcomes are rare and/or have a delayed onset, RCTs may not be large enough or of sufficient duration to allow for their reliable evaluation. For the unbiased assessment of the long-term effects of previous exposure to treatment, RCTs can be linked to electronic health records. Reasonably strong conclusions can

10,000 patients or side effects that only appear after several years.

also be drawn on treatment effects from observational studies when the effects are large, particularly when detecting large effects on rare outcomes that occur too infrequently to allow for their reliable assessment in RCTs. The conclusions will be strengthened if the findings are biologically plausible.

Treatment effects in a broader, realistic clinical setting (i.e. effectiveness).

Example: to investigate the effects of a treatment for asthma in a wide range of patients, with or without other illnesses.

Pragmatic trials¹ can be used to rigorously evaluate the effectiveness of interventions in a broader, realistic clinical setting. The safety and efficacy of treatments should be established using a fully-randomised, well-blinded RCT before their effectiveness is explored in a pragmatic trial. Where the treatment effects are likely to be large, occur in the treatment of a condition that has a poor outcome and are biologically plausible, reasonably strong conclusions on effectiveness can be drawn from observational studies.

Treatment effects in illnesses with periods when symptoms improve (remission) or get worse (relapse) (i.e. remitting disorders).

Example: to investigate the effects of a treatment for rheumatoid arthritis or relapsing-remitting multiple sclerosis.

Fully-randomised, well-blinded large-population RCTs are the most reliable design for detecting treatment effects in remitting disorders owing to their ability to better disentangle treatment effects from spontaneous remission. To assess whether the benefits of treatment are lost when patients no longer take a medicine, randomised withdrawal designs can also be used. Bias and confounding limit the ability of observational studies of detecting treatment effects in remitting disorders.

Treatment effects in rare diseases.

Example: to investigate the effects of a treatment in a disease that affects less than five individuals in 10,000 of the general population, such as cystic fibrosis.

Fully-randomised, well-blinded RCTs would be the most reliable method for generating robust evidence on treatment effects in rare diseases owing to their ability to generate causal evidence with minimal bias and confounding. There may be practical and ethical challenges to carrying out large-scale RCTs in small patient populations where alternative treatment options may be limited. Alternative RCT designs, such as crossover or stepped wedge designs, may provide appropriate alternative options. Where the treatment effects are likely to be large, occur in the treatment of a condition that has a poor outcome and are biologically plausible, reasonably strong conclusions on treatment effects can be drawn from observational studies in the absence of RCTs. A number of EU-funded initiatives are looking to further develop research methodologies for rare diseases.^{2,3,4}

Treatment effects in emergency situations.

Example: to investigate the effects of treatment in emergency situations such as the Ebola or Zika outbreaks.

Fully-randomised, well-blinded, large-population RCTs would be the most reliable method for generating robust evidence on treatment effects in emergency situations owing to their ability to generate causal evidence with minimal bias and confounding. Where there are practical and ethical challenges to carrying out RCTs (e.g. impractical or unethical use of placebo/blinding, high disease dispersion/spread, high mortality rates), alternative RCT designs such as cluster, stepped wedge or ring designs may provide appropriate alternative options. Where the treatment effects are likely to be large, occur in the treatment of a condition that has a poor outcome and are biologically plausible, reasonably strong conclusions on treatment effects can be drawn from observational studies in the absence of RCTs.

Treatment effects where the use of placebos is an ethical challenge.

Example: to investigate the effects of a treatment where the use of placebo would prevent trial participants from accessing already available treatments or administering a placebo would pose an unnecessary risk to research staff.

Where the use of placebos presents a particular ethical challenge, alternative trial designs such as stepped wedge, ring or crossover trials may provide appropriate alternative options. Where the treatment effects are likely to be large, occur in the treatment of a condition that has a poor outcome and are biologically plausible, reasonably strong conclusions on treatment effects can be drawn from observational studies in the absence of RCTs.

Treatment effects in diseases where patients can be allocated to different treatment groups based on their risk of disease or response to therapy (i.e. stratified medicines).

Example: to investigate the effects of cancer treatments targeted to patients with a specific gene mutation.

Fully-randomised, well-blinded RCTs would be the most reliable method for generating robust evidence on treatment effects for stratified medicines owing to their ability to generate causal evidence with minimal bias and confounding. RCTs should be designed in a way that allows the treatment effects to be evaluated in small sub-groups of a tested population while ensuring they have sufficient statistical power. Alternative RCT designs such as multi-arm, basket, umbrella and adaptive designs may provide appropriate alternative options. Where the treatment effects are likely to be large, occur in the treatment of a condition that has a poor outcome and are biologically plausible, reasonably strong conclusions on treatment effects can be drawn from observational studies in the absence of RCTs.

Treatment effects in patients with multiple illnesses.

Example: to investigate the effects of a treatment for kidney disease in patients with other conditions such as cancer or hypertension.

Fully-randomised, well-blinded, large-population RCTs would be the most reliable method for generating robust evidence on treatment effects in patients with multiple illnesses owing to their ability to generate causal evidence with minimal bias and confounding. Where there are practical and ethical challenges to carrying out RCTs (e.g. in the very elderly), modelling and simulation may provide supporting evidence in sub-population for which limited experimental data are available. Observational studies may detect a correlation, which should be subsequently tested in an RCT to reliably establish causality.

* Propensity scores, natural experiments and Mendelian randomisation are methods that can be used to help strengthen the conclusions of observational studies across the board (please see **Chapter 4** in the Academy's 'Sources of evidence for assessing the safety, efficacy and effectiveness of medicines' report for further details).⁵

¹ In contrast to more traditional 'explanatory' RCTs that explore the efficacy of new treatments under strictly controlled 'ideal' clinical settings, pragmatic trials are designed to investigate the effectiveness of treatments in broader, more realistic clinical settings. However, both designs use randomisation and blinding techniques as a basis for minimising bias and confounding.

² Integrated DEsign and AnaLysis of small population group trials (2016). *Integrated DEsign and AnaLysis of clinical trials in SPG*. <http://www.ideal.rwth-aachen.de/>

³ InSPiRe (2016). *Innovative methodology for small populations research*. <http://www2.warwick.ac.uk/fac/med/research/hscience/stats/currentprojects/inspire/>

⁴ ASTERIX project (2016). *Welcome to the ASTERIX project*. <http://www.asterix-fp7.eu/>

⁵ Academy of Medical Sciences (2017). *Sources of evidence for assessing the safety, efficacy and effectiveness of medicines*. <http://www.acmedsci.ac.uk/evidence/sources-of-evidence>

Online annex C. Principles for the academic/evidence community to consider for the evaluation of evidence

When critically appraising evidence, the academic/evidence community should consider the following aspects of research:

- **Bias:** have sources of bias been minimised as far as is practically possible? Have these been discussed in the publication of the results? Sources of bias include selection, performance, detection, attrition, reporting, experimenter, confirmation and ascertainment bias.¹ Competing interests are also a potential source of bias.
- **Confounding:** have the effects of confounding been minimised as far as is practically possible? Have randomisation and blinding been properly implemented to reduce confounding?
- **Blinding:** how was blinding implemented? Who was blinded – patients and/or care providers? Was the integrity of blinding monitored?
- **Generalisability:** do the results extend to the treatment populations of interest?
- **Moderating variables:** how might moderating variables affect the generalisability of the results?
- **Absolute risk, relative risk, attributable risk and number needed to treat:** how were the results presented? How should the results be communicated to avoid misleading representation of the treatment's effect?
- **Choice of comparator:** was the new treatment compared to a placebo or standard of care?
- **Participant attrition and adherence to treatments:** how might attrition rates have impacted on the study results? Were adherence rates monitored? Could non-adherence have affected the results?
- **Placebo/nocebo effects:** was there a placebo control group and, if so, did it reveal any placebo effects? Did participants receive any information on the treatment they were administered and its side effects?
- **Surrogate endpoints:** did the study investigate clinical outcomes or surrogate endpoints? Were the outcomes investigated relevant to patients who stand to benefit from the treatment and informed by their concerns?
- **Biological plausibility:** were the findings consistent with established, sound biological principles?
- **Sample size:** was the sample size large enough to reduce the risk of false positives and false negatives?²
- **Causality:** was the research design appropriate to reliably demonstrate a causal link between the treatment and the observed effect, rather than a correlation?

¹ For definitions of these different types of bias, see: Academy of Medical Sciences (2017). *Sources of evidence for assessing the safety, efficacy and effectiveness of medicines*. <http://www.acmedsci.ac.uk/evidence/sources-of-evidence>

² Button KS, et al. (2013). *Power failure: why small sample size undermines the reliability of neuroscience*. Nature Reviews Neuroscience **14**, 365–376.

Online annex D. Principles for users of evidence to consider for the evaluation of evidence

When appraising scientific evidence, users of evidence should ask themselves the following questions to gauge the robustness of the findings. The ‘Understanding Health Research’ online tool supports users of evidence in making sense of health studies.¹

Is the research relevant to my decision/situation?

- **Representativeness:** were the human participants representative of those who will use the treatment in practice?
- **Study type:** was the evidence obtained in cells, animals or humans? If human studies were carried out, was the study a pilot, a randomised controlled trial (RCT), an observational study or a systematic review/meta-analysis? Was the study blinded? Was there a control group?

How trustworthy is the evidence?

- **Outlet:** was the data from a research journal, conference abstract, poster, editorial piece or news article?
- **Peer-review:** was the evidence peer-reviewed?
- **Competing interests:** who carried out the research? Were any competing interests/conflicts of interest declared? What steps were taken to reduce the risk of competing interests undermining the robustness of the evidence (e.g. funding)?
- **Transparency:** was the study protocol published? Is the data available for scrutiny?

What were the results of the research? How confident can I be that they can be relied upon?

- **Outcomes:** were the outcomes measures relevant and the sort that matter to patients with the treated condition?
- **Research aims:** were there clear research aims? Were they answered in the publication?
- **Reproducibility:** has the evidence been confirmed by other research groups?
- **Size:** was the study large enough for the results to be reliable?

¹ <http://www.understandinghealthresearch.org/>

Online annex E. Overarching principles for declaring and managing interests

We set out below high-level principles for declaring and managing interests, as described in **section 3.2**. In **Online annex F**, we expand on how these can be applied in the context of developing evidence related to the use of medicines in clinical trials involving a commercial partner.¹

(a) Identification

Different definitions of competing interests and conflicts of interests exist.^{2,3} For consistency, all parties involved need a common understanding of what constitutes a competing interest or conflict of interest. We endorse NHS England's recent definition of conflict of interest:⁴

'A set of circumstances by which a reasonable person would consider that an individual's ability to apply judgement or act, in the context of [his/her work] is, or could be, impaired or influenced by another [competing] interest they hold.'

'Interests' can arise in a number of different circumstances. A material interest is one which a reasonable person would take into account when making a decision [...] because the interest has relevance to that decision.' Interests can be:

- **Financial:** where an individual may get direct financial benefit⁵ from the consequences of a decision they are involved in making. There are different types of financial interests, such as funding for independent research and personal payments (e.g. consultancy fees, payments for speaking at meetings or sitting on advisory panels), among others.
- **Non-financial:** where an individual may obtain a non-financial benefit (either professionally or personally) from the consequences of a decision they are involved in making, such as increasing their professional reputation or promoting their professional career.
- **Indirect:** where an individual has a close association⁶ with another individual who has a financial or non-financial interest and would stand to benefit from a decision they are involved in making.

Most competing interests can be managed, provided that they are recognised. A wide and simple definition of interests is preferable to aid identification. For this reason, all factors that might be thought to call objectivity into question should be considered to be interests. This should be judged through the eyes of those who might be expected to need to rely on the evidence, including members of the general public.

(b) Mitigation and management

Once identified, steps should be taken to ensure that the interests identified can be managed and mitigated so as to ensure that the rigour and objectivity of the research is protected.

In most cases, there are steps that can be taken to ensure that competing interests do not compromise the integrity of research. These will vary according to the stage of development of a medicine, and can be integrated into other aspects of research governance, but will include:

- 'Intelligent openness' about the interests of researchers, funders and sponsors through declarations, including declaration of transfers of value and benefits provided.
- Independent scrutiny of protocols, for example through peer-review, which will help to assure trial design (including assessing competing interests within the ethics committee process) and the integrity of data analysis.

- Openness about the conduct of research, including trial registration, deposit of protocols and publication of results so that the robustness of research can be explored by others.
- Willingness to revisit results, including examination of medicines in clinical use, support for re-analysis of data and reproducibility studies.

It is only necessary to exclude people from involvement in situations where competing interests would result in undue influence that ‘threatens the integrity of the research enterprise through interference with the principle of objectivity essential for the advancement of knowledge.’⁷ An assessment of whether this is required should be made after steps to manage or mitigate risks of such influence have been considered and bearing in mind the risks of exclusion as well as inclusion of people in the decisions in question.⁸ Excluding expert advisors because of perceived interests may threaten the reliability of scrutiny by limiting understanding of the issues. In such circumstances it would be best to make use of their expertise but in an advisory rather than a decision-making capacity, and it might be advisable to publish the advice received so that its objectivity is transparent, subject to protecting reasonable intellectual property and commercial concerns.

(c) Openness

The principles of identification of interests and mitigation of any risk that the integrity of research might be compromised are aim to support researchers and sponsors in managing potential competing interests in a way that would make research more reliable. It is also important to be open about these issues, and standards – such as the Health Research Authority’s transparency expectations and the European Federation of Pharmaceutical Industries and Associations’ Code on disclosure of transfers of value from pharmaceutical companies to healthcare professionals/organisations – exist to ensure that principles of openness and transparency are upheld.^{9,10} The failure to register and report trials fully undermines the trustworthiness of the evidence base for both research and clinical decisions.^{11,12} It also undermines public confidence in science. Openness is an important foundation to enable those who use evidence to assure themselves that it has not been compromised by unacknowledged or unmanaged conflicts that might compromise the quality of that evidence.

Concluding remarks

Honouring these principles in the ways outlined above in a consistent and comprehensive manner will greatly enhance the openness of individual studies. However, it is also necessary to enable the public and media to assess whether individual experts or companies that offer them advice might be unduly influenced by competing interests. This will require a picture of overall interests to be collated. While this can be done in a number of different ways, there are benefits of standardisation so that it is easy to find and compare information. The pharmaceutical industry provides a model of good practice, including a searchable database through the Association of the British Pharmaceutical Industry’s ‘Disclosure UK’ initiative.¹³ For individual academic researchers, a comparable publicly accessible register of their interests should be maintained on their institutional profiles or web pages.

It should also be noted that these principles overlap. For example, identification and acknowledgment will tend to reduce the risk of unconscious bias, and openness can itself be a mitigation, such as in trial registration, publication of results and making data available for secondary analysis. The principles represent one aspect of the overriding principle of upholding high standards of research integrity (both methodological and ethical integrity) and impartiality.

¹ <http://www.acmedsci.ac.uk/evidence/annexes/F>

² The National Research Ethics Advisors’ Panel of the Health Research Authority distinguishes between competing and conflicts of interest. The Panel describes them as follows:

- *‘Competing interests: those of any kind that could undermine the objectivity, integrity or perceived value of [evidence] through their potential influence on behaviour or content or from perception of such potential influence. Competing interests, whilst in tension with the proper conduct of the research, simply need to be acknowledged and managed appropriately to minimise their impact’*
- *‘Conflicts of interests: those situations where the competing interests are sufficiently serious as to be incompatible with the individual subject to the conflict taking part in the proposed research due to the undue influence exerted’*

The importance of this distinction lies in the recognition that most competing interests can be managed, provided that they are recognised. See:

National Research Ethics Advisors' Panel (2012). *Conflict of Interests/Competing Interests*. <http://www.hra.nhs.uk/documents/2013/10/nreap04-guidance-national-research-ethics-advisors-panel-13-february-2012.pdf>

³ The journal Nature's current definition of competing interest is limited to financial interests: '*those of a financial nature that, through their potential influence on behaviour or content or from perception of such potential influences, could undermine the objectivity, integrity or perceived value of a publication.*' <http://www.nature.com/authors/policies/competing.html>

⁴ NHS England (2017). *Managing Conflicts of Interest in the NHS – Guidance for staff and organisations*. <https://www.england.nhs.uk/wp-content/uploads/2017/02/guidance-managing-conflicts-of-interest-nhs.pdf>

⁵ In these bullets, 'benefit' encompasses those that may arise from making a gain or avoiding a loss.

⁶ These associations may arise through relationships with close family members and relatives, close friends and associates, and business partners. A common sense approach should be applied to these terms. It would be unrealistic to expect individuals to know of all the interests that people in these classes might hold. However, if individuals do know of material interests (or could be reasonably expected to know about these) then these should be declared.

⁷ National Research Ethics Advisors' Panel (2012). *Conflict of Interests/Competing Interests*. <http://www.hra.nhs.uk/documents/2013/10/nreap04-guidance-national-research-ethics-advisors-panel-13-february-2012.pdf>

⁸ The individual(s) responsible for making this assessment will vary according to study type and/or scale. For large multinational RCTs, it would be appropriate for the independent oversight group managing the trial conduct, ethics and interim analysis, to assume such a function. In smaller studies, the nominated principal investigator might bear this responsibility. Alternatively, academic institutions could use their clinical research governance to make such judgements through a single standing committee. For Boards and subcommittees, NHS England proposes that this is managed by the Chair (NHS England (2017). *Managing Conflicts of Interest in the NHS – Guidance for staff and organisations*.

<https://www.england.nhs.uk/wp-content/uploads/2017/02/guidance-managing-conflicts-of-interest-nhs.pdf>.

⁹ <http://www.hra.nhs.uk/resources/during-and-after-your-study/transparency-registration-and-publication>

¹⁰ European Federation of Pharmaceutical Industries and Associations (2014). *EfPIA Code on disclosure of transfers of value from pharmaceutical companies to healthcare professionals and healthcare organisations*. <http://transparency.efpia.eu/the-efpia-code-2>

¹¹ Chan AW, et al. (2014). *Increasing value and reducing waste: addressing inaccessible Research*. Lancet **383**, 257–266.

¹² Glasziou P, et al. (2014). *Reducing waste from incomplete or unusable reports of biomedical research*. Lancet **383**, 267–276.

¹³ <http://www.abpi.org.uk/our-work/disclosure/Pages/DocumentLibrary.aspx>

Online annex F. Application of the overarching principles for declaring and managing interests to the development of evidence related to the use of medicines in clinical trials involving a commercial partner

The principles described in **Online annex E** provide a framework for managing interests in research in a systematic, comprehensive and transparent way.¹ We outline below the application of the principles in relation to the development of evidence related to the use of medicines. We focus in particular on academia–industry research in clinical trials of medicines where the research is funded by the commercial partner, as this is the area that elicited most concern during our public dialogue activities. Wider academia–industry working in the pre-clinical arena or in other research areas – such as the food industry or medical devices – has not been considered, nor has the management of interests in non-commercial research. The same fundamental principles will be applicable, but the way in which they are implemented may be different.

Detailed guidance about how these principles can be achieved in practice will need to be developed by organisations involved in clinical trials (research institutions, pharmaceutical companies and funding bodies, among others).

Research funding

All funding from commercial partners should be disclosed and governed by the institution's policies for such funding, which should be informed by the best practice guidelines that we recommend are developed. While it is understandable that professionals should be compensated for their time and for the costs associated with the conduct of the research, researchers should be aware that other personal payments such as consultancy fees, payments for speaking at meetings or sitting on advisory panels could raise potential concerns that the research involving the commercial funder is biased and untrustworthy. Although contracts should be established between the commercial partner and the institution, there should be greater openness around how the grant funding is distributed within the institution (see below).

Study design

Studies should be designed in a way that minimises biases as far as is practically possible. To that effect, academic and commercial partners should work together to ensure that potential biases are identified, mitigated and managed. There is likely to be a vast amount of industry knowledge and expertise accrued from many years of development that should be exploited, as should the unique skill set of the academic partner. Both parties should also reflect on whether the design would benefit from public/patient involvement or being externally peer-reviewed. All protocols should be made publicly available upon completion of the research to allow for independent analysis of the design and methods. This would help reduce unfounded perceptions of bias. Researchers should be transparent about how the study was designed in their publications.

Trial registration

Academia and industry clinical trials should be registered on a recognised, open and searchable trials register – such as EU Clinical Trials Register or ClinicalTrials.gov – with a summary of the trial protocol, before the first participant is recruited.^{2,3,4} We strongly encourage both academic and industry researchers to also register observational epidemiological studies exploring the effects of treatments.

Contracts

In the spirit of ‘intelligent openness’, all contracts between academia and industry should be made publicly available and should provide clarity on the specific items discussed in this annex, including data access and holding, details of funding and who it is paid to, and conditions for data analysis and publication. Contracts should include anti-bribery and corruption conditions, publication requirements, fair market value clauses and requirements to comply with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (or good clinical practice for non-commercial academic studies). Commercially-sensitive and personal data should be removed before the contract is openly published. The contract between the University of Nottingham and Roche available online is an example of how this can be done.⁵ For protocol-governed research projects, contracts should be established between the commercial partner and the institution (i.e. with the NHS Trust or university department, but not with individuals); there should be greater openness around how the grant funding is then distributed within the institution. All contracts should include a requirement to disclose competing interests and should be devised based on the most up-to-date ethical and best practice guidance.

Data holding and access

Data should be responsibly managed in a way that protects the confidentiality for justifiable commercial, privacy, safety and security interests. There should be a clear understanding between the academic and commercial partners of who holds the data; what they can be used for, by whom and with whose agreement (particularly if patient data are being shared with commercial organisations); how and by whom they can be accessed, including by regulators and auditors where applicable; and the justification of any limits to data access. These factors should be clearly defined when collaborations are established and described in the contract.

Data analysis

Data analysis should be conducted in a way that minimises biases as far as is practically possible. Academic and commercial partners should work together to ensure that potential biases are identified, mitigated and managed, and set out rules around independent statistical analysis and the rigour of analysis. Analysis of data from clinical trials should be undertaken by statisticians independently from the study teams and should be monitored by an Independent Data Monitoring Committee where appropriate.⁶ This process should be auditable. Researchers should be transparent about the analytical process in their publications.

Publication of findings

Neither the industry nor the academic partner should restrict placing findings in the public domain, (content and date of release) after a pre-specified time frame. Results should be published in full, regardless of the outcome. A summary of results should be made publicly available on the database where the trial is registered (see above) within one year of completion of the trial or within the timelines agreed if a deferral has been granted (for example, for Phase 1 studies or, in the context of multi-centred studies, when all the trials in all participating centres have been completed). Where applicable, the full Clinical Study Report, or the equivalent in non-commercial settings, should be made publicly available by the trial sponsors or others that produce it. Where appropriate consent has been provided, adverse events and individual patient data contained within these reports can be redacted and made available to researchers on request, with a commitment that

no reasonable request will be refused, via platforms such as www.clinicalstudydatarequest.com. These principles reflect the requirements of the EU Clinical Trials Regulation (EU No 536/2014).⁷

¹ <http://www.acmedsci.ac.uk/evidence/annexes/E>

² <https://www.clinicaltrialsregister.eu/ctr-search/search>

³ <https://clinicaltrials.gov/>

⁴ NHS Health Research Authority (2015). *HRA and Research Transparency: Clinical trial registration.*

http://www.hra.nhs.uk/documents/2015/08/qa_july2015_hraandresearchtransparency-september-2015.pdf

⁵ F Hoffmann-La Roche Ltd (2011). *Sponsorship for University Of Nottingham.*

<http://www.nottingham.ac.uk/research/groups/healthprotection/documents/eph-hprg-roche-contract-sept10.pdf>

⁶ The Research Ethics Service (now part of the Health Research Authority) defines a DMC as '*a group of people that reviews accumulating data in a clinical trial and advises the sponsor (directly or indirectly) on the future management of the trial. It mainly reviews safety and efficacy data but may also see quality and compliance data. The DMC is usually privy to interim comparisons by arm and sees data in a format that is not normally widely shared beyond the core statistical team.*' National Research Ethics Service, National Patient Safety Agency (2010). *Data monitoring committees in clinical trials: Guidance for research ethics committees.* <http://www.hra.nhs.uk/documents/2013/10/data-monitoring-committees-in-clinical-trials.pdf>

⁷ Regulation (EU) No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC [2014] OJ L 158/1. http://ec.europa.eu/health/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

Online annex G. Questions for patients and healthcare professionals

Questions for patients

During the course of our inquiry it became clear that there have been a number of initiatives undertaken by a range of organisations to equip patients and carers with helpful questions to ask their doctor or healthcare professional about medicines. Some of these lists are clearly intended for general use by the public.^{1,2,3,4,5,6} Others have been tailored for a specific patient population.^{7,8,9,10}

We have attempted to review and amalgamate these different sets of questions into what we regard to be a sensible 'core' set of questions or prompts that anyone could use to understand and make the right decisions about medicines for them and their family.

The list below is not exhaustive, nor do we suggest that every question should be asked by every patient during their consultation. Rather, these questions are intended to act as examples that patients should feel confident in using should they wish to find out more about their treatment, alternative options and the underlying evidence. Where appropriate, patients should select those that are most relevant or of most interest to them.

Healthcare professionals are not expected to have the answer to every question listed below. However, healthcare professionals should be prepared for these questions and how to deal with them. Strategies might include pointing patients to other sources of helpful information or advice, or arranging a separate appointment to discuss the questions in further detail.

We have tested this list on a small number of patients but would urge that further evidence is collected on the utility of such questions, their impact on decision-making by patients and doctors and how these tools can be strengthened and improved.

Before my appointment

Before seeing their doctor patients and carers should ask themselves:

- What health goals are most important to me?
- What are my expectations of treatment and which of the following questions will help me find out how this medicine can fulfil them?

Is this medicine right for me?

- What does this medicine do?
- How will this medicine improve my health?
- Are there other medicines that might be more helpful?
- What if I don't take this medicine?
- How certain are you that this treatment will work for me?

What are the potential benefits and risks of this medicine?

- What are the potential benefits of this medicine?
- What are the potential risks of this medicine?
- Are the potential benefits or potential risks higher for me? Is this a tried and tested medicine?

How will this medicine make me feel?

- How will this medicine affect my day-to-day life?
- Is this medicine going to improve the symptoms that concern me?
- What are the most common side effects? How severe are they? Are there likely to be any long-term side effects?
- Are there any issues with taking this medicine that my carer and/or family should be aware of?

How should I take this medicine?

- How should I take this medicine (e.g. how many times a day, with or without food, any food or drink to be avoided)?
- Can I take this medicine with my other medication?
- How long do I need to take this medicine for?
- When will it begin to have an effect?

Questions for healthcare professionals

We have developed below a series of questions that healthcare professionals should ask themselves before engaging in shared decision-making with a patient. Healthcare professionals should be taught shared decision-making approaches as part of their initial and ongoing professional education. The King's Fund report, 'Making shared-decision-making a reality', highlights more specific examples of questions that healthcare professionals should ask their patients when engaging in shared decision-making about treatment options.¹¹ By asking themselves the questions we set out below, healthcare professionals should be better able to respond to patient questions and concerns.

Questions that healthcare professionals should ask themselves:

- What do I know about the patient's priorities, preferences and values? What health goal(s) is (are) most important to them?
- What is the likely prognosis (or baseline risk) without treatment?
- How much does/how likely is the treatment to modify outcomes that matter to the patient and over what time frame?
- Do I know how reliable this estimate is?
- What are the harms, treatment burden and other disadvantages of treatment?
- Does the likely balance of benefit and harm, in the light of the patient's own preferences, make this a worthwhile treatment option for this patient?
- Is this medicine necessary or are there alternative options that I should consider (e.g. other medicines or lifestyle changes)?
- How can I clearly deliver the information to the patient in a way that is most useful to them?

¹ <http://www.nhs.uk/NHSEngland/AboutNHSServices/doctors/Pages/questions-to-ask-the-doctor.aspx>

² NHS Digital (2007). *Questions to ask when you go to the doctor or to a hospital: easy read*.

<https://www.nhs.uk/NHSEngland/AboutNHSServices/Documents/Questions%20to%20ask%20OTA%20Easy%20Read%20version.pdf>

³ O'Donoghue D (2011). *Ask three questions*. The Health Foundation, 04 August. <http://www.health.org.uk/blog/ask-three-questions>

⁴ Choosing Wisely Canada (2015). *Four questions to ask your health care provider*. <http://www.choosingwiselycanada.org/wp-content/uploads/2015/11/Four-questions-EN.pdf>

⁵ <http://www.nhs.uk/Livewell/Pharmacy/Pages/Yourmedicinesquestions.aspx>

⁶ <http://www.ahrq.gov/patients-consumers/patient-involvement/ask-your-doctor/index.html>

⁷ <https://www.bhf.org.uk/heart-matters-magazine/medical/questions-to-ask-your-doctor>

⁸ <http://www.macmillan.org.uk/information-and-support/treating/treatment-decisions/questions-to-ask>

⁹ <http://www.brainandspine.org.uk/questions-ask-your-doctor>

¹⁰ <http://www.cancer.org/treatment/findingandpayingfortreatment/treatmentdecisiontoolsandworksheets/questionstoaskyourdoctor/index>

¹¹ The King's Fund (2011). *Making shared decision-making a reality, no decision about me, without me*.

http://www.kingsfund.org.uk/sites/files/kf/Making-shared-decision-making-a-reality-paper-Angela-Coulter-Alf-Collins-July-2011_0.pdf