Perspectives on '*Evaluating evidence in health*'

A workshop report from a joint meeting held by the Academy of Medical Sciences and the Wellcome Trust on 21 October 2015

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Disclaimer
This report does not represent a formal Academy of Medical Sciences or Wellcome Trust position on the evaluation of evidence in health. Rather this document reflects the wide-ranging discussions that took place at the workshop. It does not necessarily represent the views of all participants, the Academy of Medical Sciences or the Wellcome Trust. The report of this meeting will feed into the Academy's workstream on '*Enhancing the use of scientific evidence to judge the potential harms and benefits of medicines?*', including its sub-project on the '*Sources of evidence for assessing the safety, efficacy and effectiveness of medicines*'.[1,2] It will also inform the Wellcome Trust's thinking on accelerating uptake of research into policy and practice.[3]

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All web references were accessed in November/December 2015.

[1] Led by Professor Sir John Tooke FMedSci, the workstream also includes workshops on conflicts of interest and communicating evidence. For further information, please see: http://www.acmedsci.ac.uk/policy/policy-projects/how-can-we-all-best-use-evidence/
[2] http://www.acmedsci.ac.uk/policy/policy-projects/methods-of-evaluating-evidence/
[3] http://strategy.wellcome.ac.uk

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Executive summary

There are different ways of collecting evidence to inform clinical practice, for example through experimental and observational studies.

The joint Academy of Medical Sciences/Wellcome Trust workshop, '*Evaluating evidence in health*', brought together representatives from academia, clinical practice, industry and other stakeholder groups from across the healthcare landscape to discuss the strengths and limitations of different forms of evidence, opportunities to enhance the generation and use of medical evidence, and its communication to wider groups. In wide-ranging discussions across multiple disease areas and clinical situations, points were raised across several key themes including:

- Strengths and limitations of different forms of evidence
- Trial design
- So-called 'real world' data
- Medicines regulation
- Obstacles and opportunities
- Communication and public/patient involvement

Randomised controlled trials (RCTs) are widely considered to be the 'gold standard' or most robust design for generating medical evidence (particularly when synthesised through systematic reviews).

This idea has been formalised in 'hierarchies of evidence', which are headed by systematic reviews and RCTs. From this starting point, participants were invited to discuss the most effective use of evidence from both experimental and observational studies to inform decision-making and clinical practice. Participants also considered the implications of personalised medicine, interventions based on genetic profiling, or research in the context of complex crises of emerging infections, which can challenge our classic approach to the gathering of robust evidence.

Strengths and limitations of different forms of evidence

- Overall, delegates agreed that the field is highly dynamic, with much innovation in trial design and use of so-called 'real world' data, but there is continuing debate about the relative merits of different forms of evidence.[4]
- RCTs have important unquestionable strengths in minimising the risk of bias or confounding through randomisation and blinding. For these reasons, they are widely regarded as the most robust design for determining even moderate causal effects on common outcomes in a relatively unbiased manner.
- There are some situations in which RCTs may not be suitable or practical (e.g. in rare diseases, highly personalised medical interventions, or research in emergencies). In addition, a narrow focus on generating safety and efficacy data in very well defined populations to satisfy regulatory agencies may not always address some of the wider issues faced in clinical practice or to populations at risk. Strict inclusion/exclusion criteria may mean that relevant communities, such as the elderly with multiple morbidities, are not included, potentially limiting the applicability of the results.
- Observational studies have limitations – particularly the risk of bias and confounding resulting from a lack of randomisation and blinding – but can provide important evidence over longer time periods and in more clinically diverse populations than RCTs are normally able to. Observational studies are good at detecting large effects on rare outcomes, but may be less effective at determining effects on common outcomes.
- All sources of evidence have limitations; evidence of all types should therefore be subject to critical appraisal and discussion before conclusions are drawn.
- It may be helpful to focus more on the quality of medical evidence required, not simply the methodology used to generate it.
- In particular, methodologies adopted should be appropriate to the nature of medical questions being asked, to ensure that evidence is ultimately 'fit for purpose'.

Trial design – more about the quality of the data...

- Traditional RCTs can be long and expensive; delegates recognised that the cost and length of traditional RCTs have driven a search for alternative ways of generating robust evidence.
- Many new trial designs, including novel forms of RCTs, are being developed, for example to generate evidence in rare diseases, emergency outbreak situations, and in oncology, where targeted therapies for subsets of patients require innovative new approaches.
- Delegates suggested that more attention needs to be given to the outcomes assessed in trials (and in observational studies), to ensure that they are meaningful to clinicians' decision-making and, importantly, to patients.

‘Real world’ data[4]

- There are huge opportunities to use data generated in routine care, and to build ‘learning health systems’ in which clinical decision-making draws on the outcomes from past experience; however, the practical challenges (e.g. data linkage, data quality) remain substantial.
- Further important insights could come from the linkage of health records to bioresources and to other forms of medical data, and ultimately to social and lifestyle data.
- So-called ‘real world’ data are already beginning to be used in post-marketing surveillance, and follow-up of clinical trial participants in routine care would be beneficial, although there is a widespread perception that current research governance procedures make this difficult.
- There are opportunities to embed experimental studies in clinical practice, including randomisation of patients, to generate evidence in areas of clinical uncertainty.

Medicines regulation

- Regulatory agencies are starting to explore the use of evidence that comes from sources other than RCTs.
- Accelerated access procedures and conditional licensing arrangements allow for earlier patient access to innovative medicines, with additional data on effectiveness and safety obtained during so-called ‘real world’ use; however, concerns were expressed that decisions based on less robust evidence have led to the inappropriate introduction of medicines.
- Clinical evidence that is generated with the sole purpose of satisfying licensing authorities may not assess some of the other outcomes that are important to clinical practice or patients. There was a general feeling that more joined-up approaches would be useful to ensure that evidence better meets the needs of multiple stakeholders.
- Some delegates suggested that there may be a need to build capacity in regulatory science, to ensure a sound intellectual basis for regulatory decision-making.

Obstacles and opportunities

- To ensure best possible use is made of all evidence generated, it was emphasised that greater sharing of data is essential, within academia as well as industry. Concerns were also expressed about the current lack of transparency in some RCT reporting.
- It was also suggested that there is a need to build capacity in clinical evidence gathering and analysis, and to ensure it has a rigorous intellectual underpinning.
- Although progress is being made, there was a general view that current research regulation and governance systems remain an obstacle to clinical research – and that simpler systems are required to accelerate both data generation in new trials and analysis of existing data.
- There were suggestions that high-tech companies outside the health sphere with an interest in medicine could represent a potential source of fresh thinking and methodological innovation; however, their unfamiliarity with the medical arena would present challenges.

Communication and public/patient involvement

- Delegates felt that it is vital that the voice of the patient and the public is fully represented in discussions about the collection, analysis and application of health evidence.
- It was also suggested that it is important to find out the formats and content of information patients and the public require to make informed decisions about their health.
- Better education in the appraisal of evidence may help the general public to interpret medical evidence; however, it was pointed out that intermediaries such as healthcare workers or professional bodies are still likely to be a key source of information and advice, highlighting the importance of issues such as public trust.
- Several delegates emphasised that risks and risk–benefit trade-offs are central to public communication and need to be appropriately framed (e.g. through the use of absolute rather than relative risk figures).[5]
- Participants also felt that more attention could be given to the rigorous study of public communication to develop and test best practice.

References and notes

[4] A definition of the term 'real world' data was not discussed at the meeting; however, one definition is clinically-relevant data collected outside of the context of conventional RCTs. Data can stem from a wealth of diverse sources including, but not limited to, primary and secondary care data, routine administrative data, registries and social media.

[5] Absolute risk is the absolute likelihood that a given outcome will occur in a person exposed to some causal agent. Relative risk defines whether the risk after exposure to a causal factor is greater or lesser than that in the general population. For further information, please see: Academy of Medical Sciences (2007). *Identifying the environmental causes of disease.* http://issuu.com/acmedsci/docs/119615475058

Overview

In October 2015, the Academy of Medical Sciences and the Wellcome Trust held a joint meeting, '*Evaluating evidence in health*', as part of a wider Academy project on '*Enhancing the use of scientific evidence to judge the potential harms and benefits of medicines*'.[6]

Led by Professor Sir John Tooke FMedSci, the project is also hosting workshops on conflicts of interest and communicating evidence.[7,8] The report of this workshop will feed into the project's '*Sources of evidence for assessing the safety, efficacy and effectiveness of medicines*' workstream, as well as the Wellcome Trust's thinking on accelerating uptake of research into policy and practice.[9] As a research funder, the Wellcome Trust is committed to maximising the use of research evidence to improve health, and its support of this workshop forms part of a broader programme of work exploring these issues.

The workshop brought together experts from across the healthcare landscape to:

- Examine the strengths and limitations of evidence from different sources for determining risks and benefits of medicinal products.
- Explore how weaknesses in current approaches might be addressed, including discussion around evolving and novel trial designs, and methods of data collection, analysis and meta-analysis.
- Consider future sources of data and how they might be used as evidence.
- Discuss how evidence can be effectively communicated to stakeholders, including patients, citizens, healthcare professionals and the media.
- Generate practical suggestions for enabling the better use of research evidence in healthcare decisions.

This report provides a summary of the speakers' presentations and the lively discussions that followed. It does not represent a formal Academy of Medical Sciences or Wellcome Trust position on the evaluation of evidence in health. It is divided into two sections: the first outlines the background to the issue, while the second provides an overview of the wider discussions throughout the day.

'Decision makers need to assess and appraise all the available evidence irrespective as to whether it has been derived from RCTs or observational studies, and the strengths and weaknesses of each need to be understood if reasonable and reliable conclusions are to be drawn.'

Professor Sir Michael Rawlins FMedSci[10]

References and notes

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[7] http://www.acmedsci.ac.uk/policy/policy-projects/conflicts-of-interest-workshop/
[8] http://www.acmedsci.ac.uk/policy/policy-projects/communicating-evidence-workshop/
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Background to the issue

Recent decades have seen widespread acceptance that healthcare decision-making should be based on evidence. This shift towards evidence-based medicine (EBM) is reflected in the ubiquity of clinical guidelines and other mechanisms to promote the use of effective interventions (and to limit the use of ineffective ones).

As pointed out by **Professor Deborah Ashby OBE FMedSci**, Professor of Medical Statistics and Clinical Trials and Co-Director of Clinical Trials Unit at Imperial College London, this raises the question of what form such evidence should take. Different disciplines may have their own conceptions of evidence, but modern medicine draws its authority from scientific evidence. However, even within a scientific framework, medical evidence can take a variety of forms. Beginning in the 1970s, with the work of the Canadian Task Force on the Periodic Health Examination, attempts have been made to categorise different types of medical evidence, leading to 'hierarchies of evidence' that rank the strength of evidence produced by different methodologies.[11]

'EBM is the conscientious explicit, and judicious use of current best evidence in making decisions about the care of individual patients' taking into account individual patients' predicaments, rights and preferences using best evidence from clinically relevant research.'

Sackett *et al*.[12]

The strongest form of evidence is generally held to be the randomised controlled trial (RCT), followed by other forms of experimental intervention, observational studies and descriptive case studies. The ability of RCTs to minimise potential sources of confounding and bias, through randomisation and blinding, is particularly powerful. Observational studies may identify associations but it is challenging to eliminate the potential impact of bias and confounding and therefore establish causality. As the benefits of pooling studies and data through systematic reviews and meta-analyses have become apparent, these are now seen as the most powerful form of evidence.

Several hierarchies of evidence have been developed, all conforming to this general structure, and are widely used in the assessment of medical evidence. However, there is also disquiet that the hierarchy concept is applied too rigidly – particularly when RCTs are seen as the only valid form of evidence, and other sources of evidence are marginalised or dismissed as flawed.

Some voices have challenged the RCT hegemony. In 2003, Dr Annette Boaz and Professor Ashby suggested that, while methodological quality was important, a critical question was whether evidence was 'fit for purpose' – with different forms of evidence being relevant depending on the nature of the clinical question under study.[13] In his 2008 Harveian oration, Professor Sir Michael Rawlins FMedSci argued that the idea that sources of evidence could be placed in hierarchies was '*illusory*'.[14]

Professor Ashby highlighted two examples illustrating the value of approaches beyond RCTs. In the 1990s, an RCT produced convincing evidence that high-dose folic acid supplementation significantly reduced the incidence of neural tube defects in high-risk women, generating a number needed to treat of 40 (i.e. 40 women would need to be treated to prevent one case). However, would supplementation be appropriate for low-risk women? On the (untested) assumption that a lower dose would be as effective in low-risk women as the high dose was in high-risk women, a modelling study using routine data suggested that the number needed to treat would be more than 400 – meaning an RCT to test folic acid supplementation in low-risk women would require huge numbers of participants. And with folic acid not protected by a patent, it is unclear who would pay for such a study.

An alternative approach was to make use of observational data to draw conclusions. For example, one study examined the effects of folic acid supplementation on serum folate levels, and links between serum folate levels and risk of neural tube defects, then modelled the likely impact of various supplementation strategies on risk.[15] This non-RCT evidence was not seen as convincing by some.

A second example is provided by hormone replacement therapy (HRT). While RCTs have generated much evidence on benefits and adverse effects, it has been difficult to incorporate benefits associated with the relief of vasomotor symptom (commonly known as hot flushes) into an overall assessment of the benefit-risk balance, yet vasomotor symptoms are the main reason HRT is prescribed. A modelling study aimed to assess net benefits (the sum of all benefits, including symptom relief, minus all known harms), to see how they varied according to baseline breast cancer risk and the impact of menopausal symptoms on quality of life.[16] As well

as showing that, for most women, the benefits outweighed the harms, this analysis also provided a tool for assessing the benefit-risk trade-off for individuals – a great help for clinicians discussing treatment options with patients. Indeed, benefit-risk considerations are highly personal: one individual may feel that symptom relief outweighs a small increase in breast cancer risk; others may not. It is challenging to integrate these very individual considerations into regulatory processes.

Case study 1: Statins

Professor Sir Rory Collins FRS FMedSci, Professor of Medicine and Epidemiology and Head of the Nuffield Department of Population Health at the University of Oxford, discussed statins, an area of medicine in which RCT data are abundant, and provided examples where the RCT evidence had shown that non-randomised observational studies had been misleading.

Twenty two RCTs which had each involved more than 1,000 patients and 2 years of scheduled treatment (with an average duration of about 5 years), including around 135,000 patients in total, have collectively identified a 22% relative risk reduction for a major cardiac event for each 1.0 mmol/L reduction in LDL-cholesterol with statin use.[17] A further five RCTs of more intensive LDL-cholesterol lowering, involving 40,000 patients, have demonstrated a further 15% fall in relative risk for each 0.5 mmol/L further drop in LDL-cholesterol.[18] As well as benefits, meta-analyses of RCTS have identified side-effects of statin use, such as a modestly elevated risk of diabetes.[19]

Crucially, the process of randomisation generates groups of patients that are guaranteed to differ only randomly from each other. This yields confidence that observed differences in outcomes between the treatment groups – positive or negative – are causally related to the randomly assigned statin treatment. In addition, blinding of the treatment assignment helps to ensure unbiased ascertainment of events within a trial (although not between trials), which can be of particular value when comparing symptomatic adverse events (e.g. muscle pain) between the randomised treatment groups.

The richness of the available statin RCT data has allowed detailed analyses of subgroups of patients (e.g. women, the elderly, participants at low-risk of cardiovascular disease) to be conducted, which suggest that the relative effects of statins on cardiovascular outcomes are remarkably similar across all groups.[20] Applying these relative effects to the observed risks of clinical outcomes in different patient populations allows the absolute effects to be estimated. Moreover, the extensive heterogeneity of the different patient groups that have been studied in the RCTs enhances their relevance to clinical practice.

With statins now in widespread use, observational data from large databases have also been analysed. These have one well-recognised advantage over RCTs – the ability to identify large effects of a treatment on events that would not normally be expected to occur; myopathy in the case of statins (although it was a large RCT, not observational studies, that had demonstrated that the risk of myopathy with 80mg daily of simvastatin was greater than with lower doses). However, as noted by Professor Collins, the lack of randomisation in such studies means that – unlike the situation with RCTs – the groups of patients who receive statin therapy in observational studies may differ importantly from those who do receive statin therapy in ways that are related to their risks of adverse events (and that adjustment for differences in patient characteristics that are available may well not take account fully of all relevant differences). For example, the report of an observational study had indicated that the risk of cataracts was increased with statin use, with the effect occurring rapidly (and with follow-up no longer than the large RCTs of clinical outcomes).[21] However, large RCTs have found no evidence for an increased incidence of cataracts during prolonged treatment, and several RCTs which had conducted particularly careful assessments of eye physiology and function had also found no evidence for any effects.[22,23]

It has also been suggested based on observational studies that statin use is associated with increased risk of muscle pain. However, in addition to the underlying risks of health outcomes in patients given statins being likely to differ from those who are not given statins, treatment in such studies is (necessarily) not 'blinded'. Consequently, knowledge of statin use may influence attribution of various outcomes by patients and doctors, particularly when the patients are explicitly told that muscle pain is a possible side-effect of statin use (since there is a rare, but serious, risk of myopathy). For example, the blinded comparison in the ODYSSEY ALTERNATIVE RCT among patients who had previously reported muscle symptoms with statin therapy found that muscle pain was reported by around one in four patients receiving a statin, but also by a similar proportion taking an alternative drug (a PCSK9 inhibitor injection); in all groups, the numbers reporting muscle pain dropped to less than 5% when they stopped taking the study tablets (irrespective of whether they were active statin tablets or matching placebo tablets).[24]

Case study 2: Rare diseases

There are practical challenges to undertaking RCTs, such as in treatment of rare diseases, discussed by **Professor Philip Beales FMedSci**, Head of Genetics and Genomic Medicine at the Institute of Child Health, Director of the Centre for Translational Genomics and Head of the Cilia Disorders Laboratory at University College London. Rare diseases are individually rare but collectively common – affecting 10% of the world's population – and for 95% of rare diseases, no treatment is available.

Many rare diseases are genetic and great progress is being made in identifying the genes responsible, raising the prospect of new treatments. The orphan drug development market is large, and has some attractions to industry, including the lower costs of trials (in part because they involve substantially fewer patients). A challenge for health systems is the high costs of many orphan drugs – for example, the annual cost of Glybera, a treatment for familial lipoprotein lipase deficiency, exceeds US $1 million a year per patient.[25]

Applying EBM to rare diseases is challenging. There is typically a dearth of evidence, and RCTs are difficult to conduct owing to the rarity and heterogeneity of patients. Collaborative research networks can help to pool patients, but cross-national studies can be challenging. Patient groups may also mobilise themselves, as with the Cystic Fibrosis Foundation, where 172 centres came together to work with Vertex Pharmaceuticals to develop a new drug, Kalydeco (ivacaftor). On the other hand, patient advocacy can also drive the use of products of doubtful value.

In the case of serious rare diseases, the use of placebo-controlled trials has been regarded as ethically problematic, particularly in rapidly progressing diseases. Patients may be being denied their only possible therapy, and may deteriorate if they are in the placebo arm. These and related issues have stimulated alternative trial designs, such as cross-over designs. In a trial of canakinumab for cryopyrin-associated periodic syndrome, for example, the drug was initially given to all participants to identify responders, who were then randomised to drug or placebo. During a 24-week study period, any participant experiencing a relapse was put on the drug, which was given to all participants after the study period (Figure 1).[26]

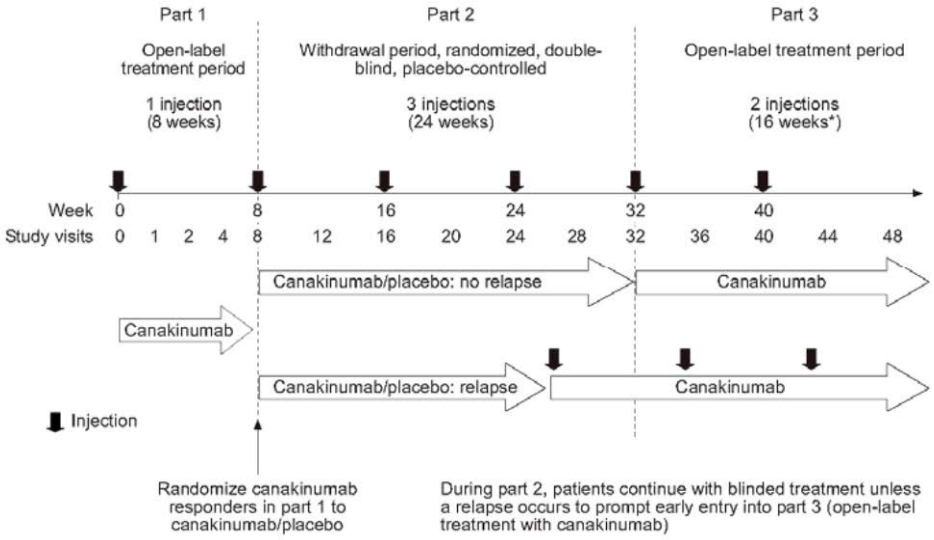

Figure 1: Trial protocol for canakinumab use in cryopyrin-associated periodic syndrome.[27]

Inevitably, the evidence base for rare diseases is less extensive than for more common conditions, and clinicians are reliant on evidence from sources other than RCTs. Clinicians working with rare disease patients have extensive knowledge of these conditions, but their lack of numbers contributes to the paucity of clinical evidence for rare diseases. It should also be emphasised that patients have important contributions to make to medical decision-making in rare diseases.

Case study 3: Emergency situations

Another area where RCTs are difficult to organise is in crisis situations, such as infectious disease outbreaks, which was discussed by **Professor Peter Horby**, Professor of Emerging Infectious Diseases and Global Health at the University of Oxford. A good example is the recent Ebola outbreak in West Africa.

Several experimental therapies for Ebola have been developed or proposed, but none had been tested for efficacy in humans prior to the 2014 epidemic. In response to the outbreak, several clinical trials were launched, after much debate about appropriate trial designs. Different methodologies were adopted, some of them innovative, and only one was a RCT (albeit an unconventional RCT with a quasi-Bayesian adaptive design). In these emergency situations, randomisation, use of placebo and blinding may be impractical and may also pose ethical dilemmas. Other important considerations included the need to generate information quickly to inform treatment and the control of the disease, arguing for simple endpoints ('alive on day 14') and a focus on large treatment effects, and uncertainty about the availability of experimental products and patients.

Notably, in part because of the time spent developing trial designs that were 'fit-for-purpose', studies began only after the peak of the epidemic, and several have struggled to recruit patients.

More generally, it is challenging to generate evidence in epidemic situations. Epidemics raise specific issues – their timing and location are hard to predict, they are usually short in duration (6-8 weeks), cases can be linked (through families or nosocomial transmission), and mortality can be high. They often occur in resource-poor locations, and cases may be highly geographically dispersed (as with H7N9 avian influenza). The illness is often short, so the time

window for recruiting patients into efficacy trials is often very narrow. Hence there is a need to plan for forthcoming epidemics, to find ways to accelerate research so that it can begin within weeks rather than months, and to develop trial designs that are adaptable to these many uncertainties and constraints.[28]

Future sources of data: Challenges and opportunities

The Accelerated Access Review, discussed by **Professor Richard Barker OBE**, Director of the Centre for the Advancement of Sustainable Medical Innovation and Chair of the Precision Medicine Catapult, aims to accelerate access to innovative drugs, devices and diagnostics. It is examining the entire health innovation pathway, from articulation of research priorities, through the development of solutions and their implementation within health systems. One issue for the workstream being led by Professor Barker on accelerated development pathways is the nature of evidence that should be considered in decision-making and, in particular, so-called 'real world' data.[29]

Accelerated development is applied to rare and/or complex life-threatening diseases where the kind of RCT-based evidence favoured by regulators may be difficult to acquire. The need for such data may be a disincentive to therapy development and slow down patient access to innovative new medicines.

New regulatory models are emerging, such as the Medicines and Healthcare products Regulatory Agency's (MHRA's) Early Access to Medicines Scheme and the European Medicine Agency's (EMA's) adaptive pathways, in which less evidence is initially required to secure regulatory approval, but data collection continues after licensing to provide additional evidence of effectiveness, cost-effectiveness and safety.[30,31] This approach is dependent on the capacity to capture and analyse high-quality data from routine clinical use. Important issues to address include the need for standardised data, possible incentives for data collection, and the potential of innovative technologies such as apps as an alternative source of data.

Innovative trial methodologies are already being introduced in areas such as oncology, including adaptive trials like 'basket' and 'umbrella' trials, which simultaneously test multiple products against molecularly characterised cancers. The National Lung Matrix Trial, for example, being run by Cancer Research UK in partnership with AstraZeneca and Pfizer, is testing a range of drugs against genetically profiled patients with non-small cell lung cancer.[32]

Importantly, the Accelerated Access Review is an end-to-end review, aiming to align all steps in the innovation pathway. The Review's final report is due to be published in April 2016.[33]

The potential of diverse forms of electronic health record data was also emphasised by **Professor Harry Hemingway**, Professor of Clinical Epidemiology at University College London and Director of the Farr Institute in London. One exciting possibility is the integration of randomised trials into routine care, using electronic health records to capture data – as in the TASTE trial of thrombus aspiration after myocardial infarction, a randomised controlled trial run in Sweden using national registry infrastructure to randomise patients and collect baseline and follow-up outcome data.[34]

More generally, Professor Hemingway suggested that a data-driven approach could transform the entire drug life cycle. Data inform effective trial design, data can be collected by practice-embedded trials, and follow-up can capture data on longer-term outcomes, safety and cost-effectiveness.

Every day, decisions are made in routine clinical practice that affect people's health. Yet very little is currently learnt from these myriad 'experiments'. The concept of 'learning health systems' has been developed, in which information is constantly being captured, and used to guide future decision-making. A future could be envisaged in which, faced with a clinical

situation where no guidelines are available, a clinician could draw on the results of past experience with matched patients or enter a patient into a randomised point-of-care trial.

The UK has an almost unmatched set of health data resources on its population of 65 million. The most powerful applications will come from the linkage of such sources, but this has been only patchily achieved. Furthermore, current databases of national structured records could potentially be augmented by a vast array of other physiological measures, test results, free-text medical information, imaging, and other data collectively providing deep phenotyping of patients. Potential also exists to unite electronic health records with bioresources, including large-scale initiatives such as UK Biobank and the 100,000 Genomes Project.[35,36] Even more ambitiously, extraordinary amounts of data about the health and social life of individuals are constantly being captured, offering the prospect of a life-long 'whole phenome sequence'. Data on individuals is moving from being sparse and episodic to, in the near future, near-continuous and pervasive.

An example from the education sector

Dr Jonathan Sharples, Senior Researcher at the Education Endowment Foundation (EEF), described how evidence is central to the work of the EEF. Established through a Government grant in 2011, its key aim is to break the link between family income and educational achievement.

EEF's approach shares many similarities with the assessment of evidence in health, being based on an analysis of existing evidence, the award of grants to fill gaps in knowledge, the evaluation of projects, and the sharing and promotion of research evidence. Strikingly, it has made much use of the RCT format (typically cluster randomised by school). One in five UK schools and some 700,000 pupils are now involved in an EEF project.

To provide teachers with actionable insight into the research evidence base, it has developed a Teaching and Learning Toolkit, based on meta-analyses carried out at Durham University. Described as the 'Which?' of education, the Toolkit provides school leaders with easy-to-understand guides to the impact of interventions, the strength of supporting evidence, and associated costs. As well as educational attainment, projects often also capture data on other 'endpoints', for example to gain more insight into how an intervention might be operating. EEF has also begun to produce NICE-like documents summarising evidence and making recommendations in specific areas (such as the best use of teaching assistants).

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[27] *Ibid.*
[28] A recent Academy of Medical Sciences/Wellcome Trust joint-report on the '*Use of neuraminidase inhibitors in influenza*' highlighted the importance of preparedness planning for an epidemic or pandemic situation (in this case, for influenza) and the ability to initiate research protocols agreed ahead of time in the inter-epidemic period as quickly as possible when a new epidemic or pandemic emerges.
Academy of Medical Sciences & Wellcome Trust (2015). *Use of neuraminidase inhibitors in influenza*. http://www.acmedsci.ac.uk/policy/policy-projects/treating-influenza/
[29] A definition of the term 'real world' data was not discussed at the meeting; however, one definition is clinically-relevant data collected outside of the context of conventional RCTs. Data can stem from a wealth of diverse sources including, but not limited to, primary and secondary care data, routine administrative data, registries and social media.
[30] https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams
[31] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp
[32] http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-different-drugs-for-non-small-cell-lung-cancer-national-lung-matrix-trial
[33] Subsequent to the meeting, the Accelerated Access Review's interim report was published and is available at https://www.gov.uk/government/publications/accelerated-access-review-interim-report**.**
[34] Fröbert O, *et al*. (2013). *Thrombus aspiration during ST-segment elevation myocardial infarction.* New England Journal of Medicine. **369(17)**, 1587–1597.
[35] http://www.ukbiobank.ac.uk
[36] http://www.genomicsengland.co.uk/the-100000-genomes-project/

Discussions

To inform discussions, an expert panel delivered short presentations on their areas of interest:

- **Sir Iain Chalmers FMedSci**, Co-founder of the Cochrane Collaboration and Co-ordinator of the James Lind Initiative, discussed systematic reviews.
- **Dr June Raine CBE**, Director of Vigilance and Risk Management of Medicines at the Medicines and Healthcare products Regulatory Agency (MHRA), talked of the role of regulators.
- **Professor Tim Eisen**, Head of Clinical Discovery Unit at AstraZeneca and Professor of Medical Oncology at the University of Cambridge, presented the industry perspective.
- **Dr Piero Olliaro**, Leader of Intervention and Implementation Research at the World Health Organisation Special Programme for Research and Training in Tropical Diseases, considered international research.
- **Professor Chris Butler**, Professor of Primary Care at the University of Oxford, presented the perspective of general practice.

The panel session was followed by breakout group discussions to consider in further detail: the strengths and limitations of evidence from different sources for determining risks and benefits of medicines; how weaknesses in current approaches might be addressed; future sources of data and how they might be used as evidence; and how evidence can be effectively communicated to a range of stakeholders, including patients, citizens, healthcare professionals and the media.

Several key themes emerged from wide-ranging discussions and breakout sessions. Although there were areas of agreement, it was clear that there are significant differences in opinion surrounding the privileged position currently held by RCTs and the use of so-called 'real world' data.

Strengths and limitations of different forms of evidence

- Features such as blinding and randomisation make RCTs very powerful tools for generating evidence, minimising bias and the impact of confounding factors. They are generally the most trustworthy methodology for assessing efficacy and hence are critical to regulatory approval. However, their lack of generalisability typically limits their usefulness in daily clinical practice (although to a degree meta-analyses of RCTs conducted in a range of circumstances can be used to collate data relevant to particular patient subgroups). Furthermore, evidence generated to satisfy regulators may not always be relevant to all of the issues considered important by those making clinical decisions or patients.
- Systematic reviews and meta-analyses, applicable to multiple types of data, have proved hugely powerful in assimilating research evidence; methodological innovations, such as network meta-analysis, are still being made.[37]
- In some situations, RCTs are not practical, and participants suggested that decision-makers need to be able to make use of evidence acquired through other approaches such as non-randomised trials and observational studies, recognising their potential limitations.
- Despite risks of bias and confounding, observational studies have certain advantages, for example in identifying large effects on rare outcomes or risk factors for disease.
- The example of diethylstilbestrol use in pregnant women and occurrence of vaginal cancer in their offspring highlights the fact that even approaches considered to generate less robust evidence, such as case series, can generate evidence important to clinical decision-making. Case series provided the first evidence that prenatal exposure to diethylstilbestrol, a synthetic form of oestrogen used in the post-war years to prevent miscarriage and other complications, was associated with increased risk of clear cell adenocarcinoma.[38] Further investigation identified other abnormalities in both the male and female offspring of treated mothers.
- Rather than simplistic hierarchies, delegates suggested that it may be better to focus on the intrinsic quality of evidence and the extent to which it can provide answers to questions that matter. Similarly, it was argued that methodologies should be applied according to their capacity to provide answers to specific clinical questions (being mindful of the pros and cons of the options available).
- It was also emphasised that all kinds of evidence should be subject to critical appraisal and review, and evaluated with due regard to the advantages and disadvantages of the methods used to obtain it.

Innovations in trial design

- 'Difficult' clinical situations – rare diseases, emergency epidemics – are driving innovation in trial design to generate evidence where conventional RCT formats are not practical.
- Innovation in trial design is occurring in the area of precision medicine and patient stratification, particularly in fields such as oncology, where treatments are ideally tested only on a subset of patients likely to respond. New trial designs have emerged, such as new umbrella and basket protocols testing multiple agents against molecularly defined cancers. As molecular understanding of other diseases improves, these approaches are likely to be adopted in other therapeutic areas.
- Adaptive trial designs, modified as data emerge during a trial, are becoming more popular, particularly in areas such as oncology; however, some delegates raised concerns that modifications might be based on early false positives or false negatives.
- Some delegates suggested that 'n-of-1 trials' may be highly efficient ways of generating evidence specific to individuals and tailoring therapy.[39]
- Some participants suggested that the use of novel trial designs may be discouraged by a widespread perception, which might not be accurate, that regulatory agencies would not accept evidence from them, or that funding bodies would not be willing to support them.

Outcomes

- It was suggested that a drawback of many trials is that the outcome measures selected are not necessarily those that really matter to physicians or patients.
- Participants suggested that greater consultation with patients would enable more appropriate outcome measures to be developed (for both trials and observational studies), and more use could be made of patient-reported outcome measures (PROMS).
- It was also suggested that meta-analyses would also benefit from greater consistency in outcome measures, as being promoted by initiatives such as the Core Outcomes Measures in Effectiveness Trials (COMET) initiative.[40]
- It was pointed out that survival tends to trump all other outcome measures; patient consultations could address issues such as possible trade-offs between improved quality of life and lower survival.
- There is still much debate about the choice of endpoints and the use of composite endpoints (a combination of endpoints, such as a range of clinical outcomes). There are pros and cons to using composite endpoints: they are particularly useful if a treatment might affect multiple outcomes, but they can also obscure effects on individual outcomes (especially if these effects go in different directions). Similar issues are raised with all-cause mortality and cause-specific mortality: cause-specific mortality provides more insight into impact on specific conditions and, by providing more granularity, may allow the effects on all-cause mortality to be more generalisable in different circumstances. Knowledge of the treatment effect on specific causes of death can be used to estimate their respective effects in a population of interest, and thereby assess the overall effect of treatment for particular individuals.
- Some participants also noted that there is often also uncertainty about the most appropriate surrogate markers of survival. It may be difficult to assess changes in mortality during a time-limited trial, so markers likely to be indicative of survival are often tracked instead. However, the markers chosen may vary from trial to trial, and it is not always clear which are the most reliable predictors of survival.

Obstacles and opportunities

- Large-scale RCTs are expensive and time-consuming; some delegates argued that more cost-efficient approaches are required.
- Participants pointed out that much evidence is currently gathered primarily in order to satisfy regulatory authorities; it was suggested that this evidence may not always be as directly relevant to everyday clinical decision-making or patients as it could be.
- It was noted that the focus on a restricted group of patients defined by stringent inclusion and exclusion criteria to satisfy regulatory requirements in RCTs limits the generalisability of RCT data – they may not generate data that clinicians need, as their patients may not match trial study subjects. Meta-analyses of RCTs conducted in a range of circumstances may help to address this issue by enabling the analysis of subgroups of patients (e.g. women, the elderly, low-risk groups, etc.).
- Several delegates argued for a stronger focus on 'decision-relevant data', and suggested that clinical decision-making would benefit from additional pragmatic trials and health economics studies.
- Participants argued that greater use of observational data might require more pre-specified hypotheses and registration of protocols in advance, as is mandated for clinical trials, to avoid the pitfalls of 'data dredging' – undertaking multiple analyses in the hope of identifying associations. Nevertheless, delegates also suggested that there was merit in 'hypothesis-free' or 'hypothesis-generating approaches', which can uncover unexpected associations warranting further investigation; however, it was argued that these approaches should be presented as such in research publications.
- Reproducibility remains a major issue, particularly with respect to small trials or meta-analyses of small RCTs reporting large effects. Some delegates argued that current academic incentives favour novelty and rapid publication in high-profile journals, sometimes at the expense of rigorous and robust research. Addressing current incentives was deemed to be a key factor in improving the reliability of studies.[41]
- Participants pointed out that, in some fields, the quantity and quality of data are not as in depth as in cardiovascular medicine. Decision-making around statins, for example, can draw on decades of research and many large RCTs. Other fields of medicine are not so advanced, and limited data from RCTs are available to inform decision-making.
- It was highlighted that a drive to implement on the basis of limited evidence can sometimes make it challenging to conduct an RCT; despite calls to accelerate implementation, it was argued that healthcare professionals need to be cautious about doing so without a sound evidence base.
- As new knowledge is constantly emerging, some delegates suggested that research evidence may need a 'sell-by date' to ensure it remains relevant to decision-making. Once this date is reached, it might be necessary to revisit the evidence to see whether it is still a reliable basis for decision-making.
- Despite some progress, there was a widespread view that the current research governance environment is highly complex and a substantial disincentive to researchers; it was argued that this is limiting the number of RCTs undertaken, and may drive researchers to pursue options other than clinical research or lead to research being conducted outside the UK.
- It was widely felt that obtaining full value from data requires still greater emphasis on data sharing; delegates suggested that a wider culture of data sharing needs to be promoted, within academia as well as industry.
- It was suggested that high-tech companies whose business is based on large-scale data management and analysis have a growing interest in health, and may be a source of fresh thinking and methodological innovation. However, it was acknowledged that their lack of familiarity with the medical world would present a major challenge.

Medicines regulation

- Regulators are considering the use of more diverse sources of evidence (including observational data); however, international agencies vary in their practice.
- Industry carries out RCTs because its key aim is to satisfy regulators; participants suggested that greater coordination along an innovation pathway could ensure that evidence meets all stakeholders' needs, including those of the patients that stand to benefit from new treatments.
- There is a potential tension between the desire for rapid evaluation, to accelerate patient access to innovative medicines and to limit the costs of drug development, and the need for a solid evidence base on efficacy and safety. Some participants were concerned that accelerating access to new treatments could compromise the robustness of evidence that decision-makers base their decisions on, resulting in avoidable harm to patients. Careful balance between accelerated access and robust evidence generation will be required.
- There are calls for regulators to be more flexible in the kinds of evidence they are willing to accept; however, concerns were expressed that rapid licensing decisions made on the basis of limited evidence may lead to inappropriate licensing of medicines that put patients at risk.
- Post-marketing surveillance is increasingly being used, but raises both technical and governance challenges; delegates suggested that there is a need to ensure it is being carried out effectively and new evidence is acted upon.
- Various initiatives are underway to facilitate greater use of so-called 'real world' data in regulatory decision-making, including guidelines developed by the Innovative Medicines Initiative (IMI) PROTECT project.[42]
- It was pointed out that time-limited patent systems incentivise companies to generate data as rapidly as possible; modification to licensing systems could be envisaged to encourage a greater focus on higher quality evidence.
- Regulatory approaches vary internationally, which is challenging for industry; participants suggested that greater consistency would be advantageous as new approaches are adopted.
- In such a dynamic field, some participants argued that there is a need to develop capacity in regulatory science.[43]

'Real world' data

- It was argued that the wealth of data currently being generated in routine clinical care – most of which is not being analysed – represents a huge missed opportunity to improve healthcare.
- Delegates pointed out that opportunities exist not only for greater retrospective use of routinely collected data, but also to embed trials in general practice to address clinical uncertainty – providing opportunities to build in randomisation and adaptive features.
- Participants suggested that follow-up of clinical trial patients in routine care would be beneficial, but is currently difficult to achieve.
- As well as technological hurdles, it was suggested that poor quality routine clinical data may be a key obstacle to great use of so-called 'real world' evidence.
- Greater linkage and sharing of data may enable more to be learned from NHS data, but some delegates argued that this may be best achieved by gradual evolution of existing systems rather than top-down imposition of new systems.
- Apps and other new technologies are providing novel ways to collect data from participants in trials or health/lifestyle data from patients in routine care. Determining how to use these types of data while respecting concerns around data privacy and protection will be crucial to realise their full potential.

Communication and public/patient involvement

- Participants suggested that the formal education system may be a route through which critical appraisal of information skills could be developed.
- It was pointed out that public confidence is based not just on interpretation of technical information, but also on wider issues such as trust in authorities; there may be a risk of looking for technical answers to social issues.
- Delegates emphasised that uncertainty is inherent in evaluation of medical information, and should be explicitly included in public communication.
- Risks and risk–benefit trade-offs are of major public interest, and it was argued that great care should be taken in their public communication (for example through use of absolute risks rather than relative risks).
- Participants suggested that more input could be obtained from experts in communication of health information, to test methods and develop best practice.
- Academic journals have a key role as conduits of medical information. It was suggested that they have a responsibility to ensure that their outputs are of high standard and that appropriate mechanisms exist to manage situations in which misleading information is published.
- It was stressed that researchers, universities, journals and their media offices have a responsibility not to overhype discoveries and potentially mislead the public in a bid to gain publicity.
- Delegates suggested that increased involvement of patients and the public would help clarify the kinds of information people want and the issues that concern them.[44]

Concluding remarks

Evidence and methodologies

- It was generally agreed that **there is not one form of evidence that trumps all others in all circumstances and that there should be a move away from the concept of a rigid hierarchy**. Different types of evidence have different strengths and weaknesses, and are of value for different purposes; the key is to acknowledge these differences and use the appropriate methodology for the question under investigation.
- For example, observational data are of particular value for picking up large effects on rare outcomes and for determining the risks of different outcomes in different circumstances (e.g. high versus low risk patients). By contrast, RCTs are of particular value for picking up effects of any size on common outcomes (as well as, if the randomised evidence is large enough, small effects on rare outcomes).
- It was also felt to be important that **the right research questions were being asked and that appropriate methods were used to address each research question – the methods need to be 'fit for purpose'**.
- It was noted that there are currently robust, effective methodologies for assessing the risk and benefits of medicines. It was argued that **new methodologies should not be developed unnecessarily**, but there is an opportunity to develop them where they are needed.
- **Issues regarding data access and sharing** were raised and there was a call for the Academy and funders to do more in this area.[45]

Communication

- The **need for robust, comprehensive research into the science of communication** was emphasised.
- It was also stressed that there should be **better incentives to publish robust, reliable, reproducible science** rather than rushed 'ground-breaking' results. Similarly, it was

argued that researchers, press officers and universities should be less eager to publicise results, which are often mis-portrayed as 'breakthroughs'.
- There was a general feeling that more needs to be done to **communicate risks and uncertainty**, in conjunction with **better education of patients, the public, healthcare professionals and the media**.

Patients and the public

- It was also suggested that there is a greater **need for patient and public involvement in the research process**, going beyond simple engagement.
- Questions were also raised as to **how patient preferences can be taken into account**. In particular, participants stressed that outcomes measured in trials are often designed to meet the requirements of regulatory agencies and may fail to consider all of the issues that are of importance to patients.

Other general concerns

- Concerns were raised about accelerated access to medicines, particularly the need to ensure that **the robustness and quality of evidence is not compromised in order to accelerate access to medicines**.
- The **barrier to progress associated with research governance procedures** was raised on multiple occasions. It was recognised that understanding of the research regulatory burden has improved in recent years, but participants highlighted issues relating to consent, data linkage, bureaucracy, data requirements and lack of flexibility.

This report does not represent a formal Academy of Medical Sciences or Wellcome Trust position on the evaluation of evidence in health. Rather this document reflects the wide-ranging discussions that took place at the workshop. It does not necessarily represent the views of all participants, the Academy of Medical Sciences or the Wellcome Trust. The report of this meeting will feed into the Academy's workstream on '*Enhancing the use of scientific evidence to judge the potential harms and benefits of medicines?*', including its sub-project on the '*Sources of evidence to assess the safety, efficacy and effectiveness of medicines*'.[46,47] It will also inform the Wellcome Trust's thinking on accelerating uptake of research into policy and practice.[48]

References and notes

[37] Network meta-analysis, also known as a multiple treatment comparison meta-analysis or mixed treatment meta-analysis, is a procedure that allows inferences to be made about the comparative effectiveness of interventions, which may or may not have been evaluated directly against each other. Please see: Mills EJ, Thorlund K & Ioannidis JPA (2013). *Demystifying trial networks and network meta-analysis*. BMJ **346**, f2914.
[38] Herbst AL, *et al*. (1971). *Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women*. New England Journal of Medicine **284(15)**, 878–881.
[39] In 'n-of-1 trials', individual patients act as their own controls – for example, use of a therapy and placebo can be alternated for set blocks of time, allowing patient responses during these periods to be compared.
[40] http://www.comet-initiative.org
[41] The Academy of Medical Sciences, Biotechnology and Biological Sciences Research Council, Medical Research Council and Wellcome Trust recently held a symposium on the reproducibility and reliability of biomedical research. A report of the symposium is available at: http://www.acmedsci.ac.uk/policy/policy-projects/reproducibility-and-reliability-of-biomedical-research/.
[42] http://www.imi-protect.eu
[43] Regulatory science is defined by the US Food and Drug Administration (FDA) as '*… a scientific discipline consisting of the development and application of scientific methods, tools, approaches, and other relevant processes derived from various scientific disciplines used to support regulatory and other policy objectives*'. See: http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/default.htm.

[44] As part of its workstream on '*Enhancing the use of scientific evidence to judge the potential harms and benefits of medicines?*', the Academy of Medical Sciences will explore how evidence is best communicated to a range of stakeholders. For further information, see: http://www.acmedsci.ac.uk/policy/policy-projects/communicating-evidence-workshop/.

[45] The Academy and Wellcome Trust believe that the existence, methods and results of clinical and health research involving patients – whether positive or negative – should be made swiftly available for patient, social and scientific benefit. The Wellcome Trust and the Academy support the principles underpinning the AllTrials campaign, which calls for all past and present clinical trials to be registered and their full methods and summary results reported (http://www.alltrials.net/). For further information, please see: http://www.alltrials.net/supporters/organisations/wellcome-trust-statement/ and http://www.acmedsci.ac.uk/policy/policy-projects/clinical-trials-and-data-disclosure/.

[46] Led by Professor Sir John Tooke FMedSci, the workstream also includes workshops on conflicts of interest and communicating evidence. For further information, please see: http://www.acmedsci.ac.uk/policy/policy-projects/how-can-we-all-best-use-evidence/.

[47] http://www.acmedsci.ac.uk/policy/policy-projects/methods-of-evaluating-evidence/

[48] http://strategy.wellcome.ac.uk

Appendix I Programme

Wednesday 21 October 2015 at the Wellcome Collection, 183 Euston Road, London, NW1 2BE

09.00 – 09.30	**Arrival and registration**
09.30 – 09.45	**Welcome and introduction** Professor Sir Michael Rutter CBE FRS FBA FMedSci, Chair of the Academy of Medical Sciences' working group on '*Sources of evidence for assessing the safety, efficacy and effectiveness of medicines*'
09.45 – 10.00	**Thoughts on the strengths and limitations of different forms of evidence** Professor Deborah Ashby OBE FMedSci, Professor of Medical Statistics and Clinical Trials; Co-Director of Clinical Trials Unit, Imperial College London
Session 1: Case studies Chair: Professor Sir Michael Rutter CBE FRS FBA FMedSci	
10.05 – 10.20	**Statins** Professor Sir Rory Collins FMedSci, Professor of Medicine and Epidemiology; Head of the Nuffield Department of Population Health, University of Oxford
10.25 – 10.40	**Treatments in rare diseases** Professor Philip Beales FMedSci, Head of Genetics and Genomic Medicine, Institute of Child Health; Director, Centre for Translational Genomics; Head of the Cilia Disorders Laboratory, University College London
10.45 – 11.00	**Research in emergencies** Professor Peter Horby, Professor of Emerging Infectious Diseases and Global Health, University of Oxford
11.05 – 11.20	**Q&A and discussion session**
11.20 – 11.35	**Refreshment break**
Session 2: Current and future sources and requirements of evidence Chair: Professor Sir Munir Pirmohamed FMedSci, David Weatherall Chair of Medicine, University of Liverpool	
11.35 – 11.50	**Accelerated Access Review** Professor Richard Barker OBE, Member of the Expert Advisory Group for the Accelerated Access Review; Director, Centre for the Advancement of Sustainable Medical Innovation; Chair, Precision Medicine Catapult
11.55 – 12.10	**What are the future sources of data?** Professor Harry Hemingway, Professor of Clinical Epidemiology, University College London; Director, Farr Institute London
12.15 – 13.15	**Panel discussion** Considering current and future sources of data: • What are the strengths and limitations of different forms of evidence? • How can the limitations be addressed? • Is there agreement or disagreement about strengths and weaknesses of different types of evidence?

	Panel members • ***Systematic reviews:*** Sir Iain Chalmers FMedSci, Co-founder, Cochrane Collaboration; Co-ordinator, James Lind Initiative • ***Regulators:*** Dr June Raine CBE, Director of Vigilance and Risk Management of Medicines, Medicines and Healthcare products Regulatory Agency • ***Industry:*** Professor Tim Eisen, Head of Clinical Discovery Unit, AstraZeneca; Professor of Medical Oncology, University of Cambridge • ***International research:*** Dr Piero Olliaro, Leader of Intervention and Implementation Research, World Health Organisation Special Programme for Research and Training in Tropical Diseases • ***General practice:*** Professor Chris Butler, Professor of Primary Care, University of Oxford
13.15 – 14.00	Lunch
Session 3: What can we learn from the social sciences? Chair: Professor Deborah Lawlor FMedSci, Professor of Epidemiology, University of Bristol	
14.00 – 14.15	**What can we learn from the social sciences?** Dr Jonathan Sharples, Senior Researcher, Education Endowment Foundation
Session 4: Breakout groups Chair: Professor Deborah Lawlor FMedSci	
14.20 – 15.30	**Breakout sessions around morning discussions** Considering the earlier discussions on the strengths and limitations of different sources of evidence, we will explore the following questions: • How can weaknesses in current approaches be addressed and what would be the subsequent impact on data collection? • How to move forward? Where does change need to come from (if anywhere), including on issues surrounding the reproducibility of studies? • Where are novel trial designs most needed and why don't they exist yet? If they do exist, why are they not used more? • What are the implications of accelerated access to medicines and how do these impact on the evidence base? • How can evidence be better communicated to patients, citizens, healthcare professionals and the media?
15.30 – 15.45	**Refreshment break**
15.45 – 16.45	**Feedback and discussion session** Chair: Professor Deborah Lawlor FMedSci
16.45 – 17.00	**Concluding remarks** Dr Jeremy Farrar OBE FMedSci, Director, Wellcome Trust
17.00 – 18.00	**Drinks reception**
18.00	**Close**

Appendix II Delegate list

Dr Virginia Acha, Executive Director - Research Medical and Innovation, Association of the British Pharmaceutical Industry
Professor Deborah Ashby OBE FMedSci, Professor of Medical Statistics and Clinical Trials and Co-Director of Clinical Trials Unit, Imperial College London
Professor Richard Barker OBE, Member of the Expert Advisory Group for the Accelerated Access Review; Director, Centre for the Advancement of Sustainable Medical Innovation; Chair, Precision Medicine Catapult
Professor Phil Beales FMedSci, Head of Genetics and Genomic Medicine, Institute of Child Health; Director of the Centre for Translational Genomics; Head of the Cilia Disorders Laboratory, University College London
Professor Chris Butler, Professor of Primary Care, University of Oxford
Professor Nancy Cartwright FBA*, Professor of Philosophy, University of Durham and University of California
Sir Iain Chalmers FMedSci, Co-founder, Cochrane Collaboration; Co-ordinator James Lind Library
Professor Sir Rory Collins FRS FMedSci, Professor of Medicine and Epidemiology and Head of the Nuffield Department of Population Health, University of Oxford
Professor Dame Nicky Cullum DBE FMedSci*, Professor of Nursing, University of Manchester
Mr Simon Denegri#, National Director for Public Participation and Engagement in Research, National Institute for Health Research; Chair, INVOLVE
Dr Stuart Dollow, Chief Executive, Vermilion Life Sciences; Member of the Expert Advisory Group for the Accelerated Access Review
Dr Hans-Georg Eichler, Senior Medical Officer, European Medicines Agency
Professor Tim Eisen, Head of Clinical Discovery Unit, AstraZeneca; Professor of Medical Oncology, University of Cambridge
Dr Jeremy Farrar OBE FMedSci (**Concluding remarks**), Director, Wellcome Trust
Professor Sarah Garner, Associate Director - Science Policy and Research, National Institute for Health and Care Excellence
Dr Ben Goldacre, Senior Clinical Research Fellow, University of Oxford
Professor Bruce Guthrie, Professor of Primary Care Medicine, University of Dundee
Professor Harry Hemingway, Professor of Clinical Epidemiology, University College London; Director, Farr Institute London
Professor Carl Heneghan, Professor of Evidence-Based Medicine, University of Oxford
Professor Raymond Hill FMedSci, Visiting Professor of Pharmacology, Imperial College London
Professor Aroon Hingorani, Director, UCL Institute of Cardiovascular Sciences; Professor of Genetic Epidemiology, University College London
Professor Peter Horby, Professor of Emerging Infectious Diseases and Global Health, University of Oxford
Professor Deborah Lawlor FMedSci* (**Chair Sessions 3 & 4**), Professor of Epidemiology, University of Bristol
Professor David Mant OBE FMedSci, Emeritus Professor of General Practice, University of Oxford
Professor Tony Marson, Deputy Director of the MRC North West Hub for Trials Methodology Research; Coordinating Editor of the Cochrane Epilepsy Group
Dr Piero Olliaro, Leader of Intervention and Implementation Research, World Health Organisation Special Programme for Research and Training in Tropical Diseases
Professor Max Parmar*, Director, MRC Clinical Trials Unit; Director, Institute of Clinical Trials and Methodology, University College London
Professor Sir Richard Peto FRS FMedSci, Professor of Medical Statistics & Epidemiology; Co-

Director, Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford
Professor Tim Peto, Professor of Medicine, Consultant Physician in Infectious Diseases, University of Oxford
Professor Sir Munir Pirmohamed FMedSci (**Chair Session 2**), David Weatherall Chair of Medicine, University of Liverpool
Dr June Raine CBE, Director of Vigilance and Risk Management of Medicines, Medicines and Healthcare products and Regulatory Agency
Professor Ian Roberts, Professor of Epidemiology and Public Health, London School of Hygiene and Tropical Medicine
Dr Andrew Roddam, Vice President & Global Head Epidemiology, GlaxoSmithKline
Ms Isobel Routledge, PhD student, London School of Hygiene and Tropical Medicine
Professor Sir Michael Rutter CBE FRS FBA FMedSci* (**Chair Session 1**), Chair of the Academy's '*Sources of evidence for assessing the safety, efficacy and effectiveness of medicines*' Working Group, Academy of Medical Sciences; Professor of Developmental Psychopathology, King's College London
Professor Peter Sandercock FMedSci, Professor of Medical Neurology and Honorary Consultant Neurologist, University of Edinburgh; Director, Edinburgh Neuroscience
Dr Jonathan Sharples, Senior Researcher, Education Endowment Foundation
Professor Liam Smeeth, Professor of Clinical Epidemiology and Head of Department, Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine
Professor Lesley Stewart, Director of Centre for Reviews and Dissemination, University of York
Professor Prathap Tharyan, Professor and Head, Department of Psychiatry, Christian Medical College (Vellore, India); Editor, Cochrane Schizophrenia Group; Coordinator, South Asian Cochrane Network - India
Professor Simon Thompson FMedSci*, Director of Research in Biostatistics, University of Cambridge
Dr David Tovey, Editor in Chief, Cochrane Library
Dr Julian Treadwell, General Practitioner, Hindon Surgery; Vice-Chair of the Standing Group on Overdiagnosis, Royal College of General Practitioners
Professor Tom Walley CBE, Director of the Health Technology Assessment (HTA) Programme, National Institute of Health Research
Professor Robert Walton, Professor of Primary Medical Care, Blizard Institute, Barts and the London School of Medicine and Dentistry
Professor David Webb FMedSci*, Christison Professor of Therapeutics and Pharmacology, University of Edinburgh
Professor Peter Weissberg FMedSci, Medical Director, British Heart Foundation
Professor John Whitehead, Head of the Department of Mathematics and Statistics, Lancaster University
Dr John Williams, Interim Executive Director, Academy of Medical Sciences
Professor Paula Williamson, Professor of Medical Statistics, University of Liverpool; Chair of MRC Network of Hubs for Trials Methodology Research

Secretariat

Ms Rachel Brown, Policy Officer, Academy of Medical Sciences
Dr David Carr, Policy Adviser, Wellcome Trust
Dr Claire Cope, Senior Policy Officer, Academy of Medical Sciences
Dr Giorgio De Faveri, Senior Press Officer, Academy of Medical Sciences
Ms Liberty Dixon, Policy Officer, Academy of Medical Sciences
Ms Elizabeth Gothard, Policy Intern, Academy of Medical Sciences
Dr Ian Jones, Independent science writer
Dr Rachel Quinn, Director of Policy, Academy of Medical Sciences

***** Member of the Academy's '*Sources of evidence for assessing the safety, efficacy and effectiveness of medicines*' Working Group

[#] Member of the Academy's '*Enhancing the use of scientific evidence to judge the potential benefits and harms of medicines?*' Oversight Group

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