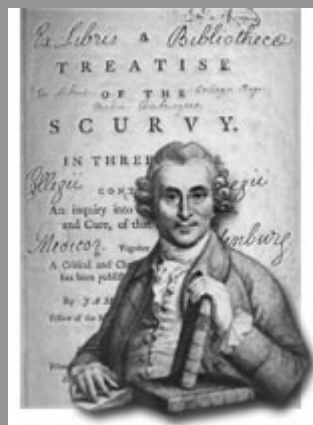


Confronting Important Uncertainties

about the

Effects of Treatments:

The James Lind Alliance



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HSCNews gives unique, practical information about the policies and activities of patient groups and disability groups worldwide. *HSCNews* aims to tell its readers what these groups are thinking, what they are doing, and what they plan to do. Every issue contains an article on a subject of importance to campaigning groups, an interview on policy matters with a senior executive of a patient group or disability group, and short articles on the latest news from various key groups, campaigners' new websites, as well as new research and publications by campaigners. Each issue of *HSCNews* also comes with an Excel spreadsheet containing the weblinks of all patient and disability groups mentioned in the issue.

The contents of *HSCNews*, unless otherwise stated, is largely obtained through extensive literature searches of public-domain information, plus interviews with selected campaigners.

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The newly-formed James Lind Alliance

In early April 2004, the James Lind Alliance was formed in the UK as a partnership of organisations with the interests of patients and practising clinicians at heart. The mission of the Alliance is to confront important uncertainties about the effects of healthcare treatments. The new group has developed an imaginative approach for getting its initiative off the ground and for promoting patient-clinician partnerships.

On Thursday April 8th 2004, three disparate UK organisations met in London to forge a coalition of patients and clinicians motivated by a single important commitment: the confrontation of important uncertainties about the effects of treatments nationwide. The new coalition is entitled the James Lind Alliance. The trio of originating organisations were: INVOLVE (formerly Consumers in NHS Research), the Royal Society of Medicine (RSM), and the James Lind Library. INVOLVE, a statutory body, works on behalf of patients, their families and carers to promote public involvement in any sort of health and social research. The RSM is an independent, non-political body working for all categories of clinicians—doctors, nurses, dentists, therapists, and indeed any person who provides treatment to patients. The James Lind Library is a recent initiative based in cyberspace that seeks to introduce people to the characteristics of “*fair tests of medical treatments*”. [For more details on the three organisations, see boxes on the next few pages.] The meeting was an extraordinary occasion. Three such different organisations rarely unite as campaigners dedicated to influencing the clinical research agenda.

Who was James Lind?

James Lind was an 18th-century Scottish naval surgeon who achieved fame after discovering that citrus fruits were an effective treatment for a disease called scurvy. At the time, scurvy was causing more deaths of Royal Navy sailors than enemy action. On board the HMS Salisbury, Lind set about comparing six purported remedies. He selected 12 sailors, each of whose symptoms of scurvy had progressed to a similar state: “*They all in general had putrid gums, the spots and lassitude, with weakness of their knees. They lay together in one place, being a proper apartment for the sick in the fore-hold, and had one diet common to all.*” Lind separated the sick seamen into pairs, and treated each pair with one of the six possible remedies: “*A quart of cyder daily, [or] 25 gutts of elixir vitriol thrice daily, [or] two spoonfuls of vinegar thrice daily, [or] half a pint of seawater daily, [or] two oranges and a lemon daily, [or] the bigness of a nutmeg daily*”. After a few days, Lind was able to

Some definitions

Therapeutic uncertainties. Treatments—whether they be medicines, surgery, physical and psychological therapies, or counseling and advice—rarely offer dramatic benefits to patients. Treatments typically produce effects (whether good or bad) that are moderate. For this reason, careful research is needed to address therapeutic uncertainties, and to identify treatments that do more good than harm. Prudent, thorough research means taking steps to avoid being misled by biases or by the play of chance.

Bias is a “*deviation of results, or inferences, from the truth*”. [J. M. Last, *A Dictionary of Epidemiology*, 4th edition, Oxford University Press, UK, 2001.]

About INVOLVE

Originally formed in 1996 as Consumers in NHS Research, [INVOLVE](#) is an advisory Group to the UK Department of Health. The group's original responsibility was to advise the Director of R&D at the Department of Health on how to promote public participation in NHS research. In 2001, that brief was extended to other areas of R&D commissioned by the UK government's Department of Health (DoH)—including public health and social care. The name INVOLVE was assumed in 2003 to reflect the new wider remit. Today, INVOLVE's members and observers are drawn from across the health and social care communities. Nick Partridge, chief executive of the [Terrence Higgins Trust \(THT\)](#), is the chair of INVOLVE. THT is the leading HIV and AIDS charity in the UK, and the largest in Europe. One of the first charities to be set up in response to the HIV epidemic, THT has been at the forefront of the fight against HIV and AIDS ever since.

Some definitions

When INVOLVE talks about the **public**, the term is being employed in the broadest sense to embrace the following: patients and potential patients; informal (unpaid) carers; and people who use health and social services. The definition also incorporates members of the public who receive health promotion information; organisations that represent the interests of people who use health and social care services; and groups asking for research because they believe that they have been exposed to potentially harmful substances or products (such as asbestos or pesticides). When INVOLVE refers to public **involvement**, active participation of the public in research is implied (rather than the public being subjects of research). INVOLVE thus aims to increase public contributions to the R&D agenda by endorsing the creation of circumstances in which users help decide the following:

- The priorities for future research.
- What research is commissioned.
- How the research is carried out.
- And how the research is disseminated.

INVOLVE hopes to effect change by developing alliances to promote greater public involvement, supporting members of the public to play an active role in research and monitoring and assessing the effects of public participation in research. INVOLVE supports the active involvement of the public in trials as it can help improve the quality of trials by ensuring that they address issues of relevance to patients; that the design of trials are acceptable to those participating in them; and that the results of trials are widely disseminated. This is why in early April 2004, INVOLVE backed the creation of the James Lind Alliance—to promote and defend the proper use of clinical trials to address important unanswered questions about the effects of treatments.

James Lind used a systematic literature review

conclude: *“The most sudden and visible good effects were perceived from the use of oranges and lemons; one of those who had taken them being, at the end of six days, fit for duty.”*

Lind's experiment was not the only reason he gained distinction. His work was also remarkable for a systematic review of the literature, which allowed Lind to identify and list all the existing 'treatments' for scurvy. In his now-famous *Treatise of the Scurvy*, published in 1753, Lind explained why a literature review could pinpoint promising candidates for use as treatments, and permit the reviewer to discard spurious claims: *“As it is no easy matter to root out prejudices ... it became requisite to exhibit a full and impartial review of what had hitherto been published on the scurvy, and that in a chronological order, by which the sources of these mistakes may be detected. Indeed, before the subject could be set in a clear and proper light, it was necessary to remove a great deal of*

**Lind
confronted
medical
uncertainties
250 years ago**

**Lind's
approach is
still valid**

rubish.” In his literature review, Lind named the authors he deemed trustworthy, and those he considered unreliable.

Lind’s celebrated *Treatise* confronted the uncertainties about the treatment of scurvy through rigorous scientific pursuit that was based on two methodologies:

- 1) A systematic review of the relevant empirical research; and
- 2) A controlled trial within routine clinical practice.

A direct line between Lind and healthcare today

Some 250 years later, Lind’s two-step scientific approach is still regarded as the best (and perhaps the only dependable) means of enhancing understanding about the effects of treatments. Controlled trials today ensure that similar patients receive the different treatments that are being compared. Modern trials, however, typically incorporate far more patients than Lind dealt with—hundreds, and sometimes thousands, of patients—to reduce the likelihood that chance differences will mislead.

Why are controlled trials important?

Few medical treatments produce dramatic improvements in health. Antibiotics, cardiac defibrillators, and prosthetic replacements for arthritic hip joints are exceptions to the rule. Many other medical

The ‘uncertainties’ of modern treatments

Each treatment carries some sort of risk. Research can identify treatments in which the benefits outweigh the risks. Treatments tend to display the following characteristics:

- **Nearly all treatments have side-effects.** Today’s sophisticated pharmaceuticals are designed to rectify specific chemical processes in the body that have gone awry. Surgeons will also correct the body’s malfunctions with tools that work at a precision unimaginable even five years ago. Neither approach is foolproof. The human body is organised and run as a highly complex set of operations (some of which proceed at atomic level), keeping the entire internal system of organs, bones and biochemicals in tune with its outside environment. Any intrusion into this busy microenvironment—be it a pharmaceutical or the surgeon’s laser—can disorganise nature’s harmony, causing problems.
- **Few treatments are effective in all patients.** Medical practitioners are uncertain as which patient may or may not benefit from an intervention. The genetic elements that delineate the characteristics of individuals—that make them stand out from, or blend in with, the crowd—also dictate how a person will individually respond to a treatment. Biotechnologists promise that future drugs will be matched to the unique genetic make-up of patients, so increasing the chances of medical success. For now, however, a patient can never be sure that a doctor’s prescribed treatment will work.
- **Some treatments compromise the body’s normal fighting mechanisms.** The great triumphs made in transplant surgery would be impossible without the discovery of immunosuppressants. These drugs depress the body’s natural inclination to destroy any material it sees as foreign, and thereby prevent transplanted organs from being rejected. Such therapy comes at a cost. Patients taking immunosuppressants can fall prey to infections.
- **Most medical treatments are only moderately effective.** Experts recognise that most people with severe mental illness can be treated effectively. The term ‘treatment’ includes the effects of psychosocial support and prescribed medicines. According to the World Health Organization (WHO), people with schizophrenia will witness an improvement in their disability if treated with the most modern neuroleptics. But the improvement will only be some 23%. If pharmaceutical treatment is coupled with psychosocial care, the improvement jumps to 45%.

The importance of non-industry clinical trials

The value of clinical trials was recognised in the UK NHS Plan of 2000. The Plan called for a doubling of the number of people enrolled in clinical trials of cancer treatments. Larger numbers of participants yield more reliable estimates of the risks and benefits associated with drugs, surgery, radiotherapy and other treatments. The National Cancer Research Network has made good progress towards the objective set in the NHS Plan, and the Network seems likely to provide a model for tackling uncertainties about the effects of treatments for other health problems.

Among all the various types of trials, non-industry clinical trials are among the most important. They can sometimes fulfil the interests of patients in a way that other trials do not. Non-industry trials are funded by medical charities, governments, foundations, or any organisation which does not have a profit motive. Pharmaceutical companies conduct trials to identify the short-term outcomes of drugs (for instance, medicine that prevents irregular heart beat in people having heart attacks). Patients, however, are interested in more than the invisible effects that sometimes lead to a drug being licensed. Wider-ranging tests are required, to assess whether medicines achieve outcomes rated as important by patients—particularly whether a treatment improves the quality or duration of life. Non-industry clinical trials revealed that medicines created to prevent heart rhythm abnormalities actually increased the chances of dying prematurely.

Pharmaceutical companies are uninterested in conducting head-to-head studies that might compare their own branded novel pharmaceuticals with less-expensive alternatives already on the market (or with other types of therapies). Many potentially important treatments in the realm of surgery, physiotherapy and psychotherapy are never likely to have commercial backers.

Non-industry trials have made some very significant contributions. For example, they have identified the beneficial effects of aspirin in heart disease and stroke, and the value of proper organisation of care for people suffering a stroke. The Medical Research Council (MRC), a government-funded organisation that supports research, has backed clinical trials that have contributed to the gradual improvements in the prognosis of children with leukaemia (approximately 70% of all childhood cancers are curable today). In that field, it is accepted practice that uncertainties should be confronted by offering treatment largely within the context of controlled trials. Professor Alan Craft, President of the Royal College of Paediatric and Child Health in the UK (who has been a key figure in the development of treatment for childhood cancers), was a major contributor to the scripting of the April 2003 Children's National Service Framework (NSF). The Framework recognises the importance of evidence gained from clinical trials. Writing in an editorial in the *BMJ* ['The National Service Framework for children', April 26th 2003, pp 891-892], Professor Craft stated that the Children's NSF aims to improve the lives and health of children and young people *"through the development of effective, evidence-based and needs-led services. Its objectives are to put children and their families at the centre of care, and to develop effective working partnerships in which the needs of children are always considered"*.

In brief, support is needed for controlled trials that address uncertainties about treatment effects. The uncertainties may be of no interest to industry, but of great importance to patients and clinicians. Patients and clinicians themselves must have a bigger say than they do now in identifying the uncertainties that should be addressed.

Controlled trials are vital

treatments deliver more modest positive effects. They are also often accompanied by side-effects [see box on previous page]. Clinical research is vital because it defines the true capabilities of medicines, surgical procedures, and other forms of treatment. If such information is unavailable or unreliable, the treatments that doctors prescribe can end up doing patients more harm than good.

The James Lind Library (<http://www.jameslindlibrary.org>)

The James Lind Library is an electronic database that was launched in October 2003 to mark the 250th anniversary of the publication of James Lind's *Treatise of the Scurvy*. Lind's 1753 book contains a systematic review of what had been written about scurvy (which was killing thousands of people every year), as well as one of the earliest accounts of a fair comparison of different medical treatments. Lind showed that oranges and lemons were more effective than other treatments for scurvy.

The James Lind Library has been created to help the public understand the characteristics of fair tests of medical treatments, and to see how these tests have evolved since biblical times. Explanatory essays on the website illustrate why fair tests are necessary, and describe how measures can be taken to reduce the misleading effects of biases and the play of chance. The explanatory essays draw on examples from over a hundred books and journal articles, illustrated by sections of the key passages of text. New records (including biographical material, portraits, translations, commentaries, and other relevant material) are being added to the site continuously.

Many people contribute to the James Lind Library, which is co-edited by Sir Iain Chalmers (who is also a co-Convenor of the James Lind Alliance), Iain Milne (Librarian of the Royal College of Physicians of Edinburgh), Ulrich Tröhler (Professor of History of Medicine at the University of Freiburg, Germany), and Jan Vandenbroucke (Professor of Clinical Epidemiology at the University of Leiden, the Netherlands). The website is dedicated to patients and professionals whose involvement in clinical research has contributed evidence about the effects of medical treatments.

Scientific American awarded the James Lind Library a 'Sci/Tech Web Award' in the Library's launch year. Judges representing the journal considered 1,000 websites from across all of science, and selected 50 for awards. Five of the 50 were in the 'Medicine' category. The James Lind Library was the only one of these five sites outside the US to have been honoured with an award. Contributors to the James Lind Library are appreciative of the mark of distinction that the award represents—but they remain keen to receive suggestions for further improvements to the site [feedback@jameslindlibrary.org].

**A study on
non-industry
clinical trials
is published in
the *BMJ* in
November
2003**

**The study
shows that
UK non-
industry trials
are falling in
number**

What led to the formation of the James Lind Alliance?

In January 2002, the Medical Research Council (MRC), a UK-based, government-funded organisation that has supported clinical research for over 60 years, reviewed its funding policies for clinical trials. As part of that review, the MRC took into account the findings of a study ['Descriptive survey of non-commercial randomised controlled trials in the UK, 1980-2002'] it had commissioned jointly with the Department of Health (DoH) from staff at the UK Cochrane Centre (an element of the [Cochrane Collaboration](#), which prepares, maintains and disseminates systematic reviews of controlled trials). The study was published in the *BMJ* on November 1st 2003, and profiled (for the first time) the numbers of UK non-industry clinical trials funded by the NHS, the DoH, the MRC, and medical research charities between 1980-2002.

The study revealed a troubling fall in the numbers of non-industry controlled trials. The decline was largely the result of several NHS-funded research programmes being discontinued. Similarly, although the MRC had moderately increased its investment in controlled trials, the total quantity of trials funded by the MRC and by medical research charities trials had also dropped, without any apparent increase in the size of the studies funded.

A 2003 MRC strategy document calls for better public and professional understanding of trials

Taking this and other evidence into account, the MRC produced a strategy document, *Clinical Trials For Tomorrow*, in the summer of 2003. One of the areas identified in the document as being in need of urgent attention was the poor general understanding and image of clinical trials in the public domain. The media too often portray patients participating in clinical trials as human guinea pigs being manipulated by scientists eager to gain professional recognition. For example, *Time* published an April 22nd 2002 cover story: ‘Human guinea pigs: some patients join clinical trials out of desperation. Others to help medicine advance. Whom do you blame if they get sick—or even die?’.

The MRC calls for a communications forum

The MRC’s 2003 strategy document emphasised a necessity to counter this negative imagery. It recommended that a forum be established to encourage a discussion about the importance of non-industry clinical trials. In collaboration with the DoH, the MRC commissioned Sir Iain Chalmers, co-ordinating editor of the James Lind Library, to consider practical solutions to the problems of initiating such a forum.

Sir Iain Chalmers is commissioned in 2003 to suggest ways of initiating a forum

The origins of the James Lind Alliance lie in this commission. After conducting wide-ranging consultations throughout the latter half of 2003, Sir Iain concluded that the two key categories of contributor to the discussion-and-communications forum envisaged by the MRC should be patients and the non-academic clinicians to whom patients usually turn for help when ill. In an interview with *HSCNews*, Sir Iain insisted that patients and clinicians who are faced with important uncertainties about which treatments to choose should be aware that research can improve understanding of the risks and benefits of those treatments.

The James Lind Alliance was formed in April 2004

The questions addressed in clinical trials should begin to take more account of the needs of patients and clinicians—rather than simply continuing to consider the demands of industry and academia (as clinical trials primarily do now). This fundamental objective led Sir Iain to approach Nick Partridge, the chair of INVOLVE, and John Scadding, Associate Dean at the RSM, for support. With encouragement from their parent organisations, the three of them formed the James Lind Alliance in April 2004.

The Royal Society of Medicine

The Royal Society of Medicine (RSM) is an independent, non-political organisation founded in 1805. The Society, which is headquartered in London, maintains a twin mission:

- Providing educational activities for doctors, dentists, veterinary surgeons, related healthcare professionals, and students.
- Promoting a transference of facts and ideas on the subject of medicine—aimed at the medical profession and the public alike.

The RSM has supplied postgraduate education to doctors and healthcare workers for almost two centuries. The Society’s 54 sections each focus on one of a wide range of specialty subjects. The RSM also has an Academic Department, which arranges conferences on current topics within medicine and healthcare. The RSM Press publishes conference proceedings, medical books, journals and CD-ROMs. The Society’s library holds one of Europe’s largest collection of medical books [online access: <http://www.rsm.ac.uk/librar/libcat.htm>].

The Alliance intends to encourage discussions on variations in clinical practice

The Alliance's meetings will incorporate patient-clinician partnerships

Meetings will work out how to confront treatment uncertainties

The Alliance will recruit members

The Alliance's first annual meeting is due in December 2004

As in Lind's day, important uncertainties about the effects of treatments are reflected in variations in clinical practice across the UK. For example, one man with early prostate cancer may be treated with surgery, while a second patient may receive radiotherapy, and a third neither. The treatment given to each patient will usually depend on the preferences of the doctors consulted. The James Lind Alliance plans to foster discussions about these variations in practice among clinicians, and identify which uncertainties are sufficiently significant that they deserve to be addressed in clinical trials. In this way, the Alliance hopes to help improve the quality of care for current and future patients using the National Health Service.

How will the James Lind Alliance achieve its aims?

From the outset, the Alliance will pursue its objectives through the vehicle of meetings. Regular meetings are to be convened at one of the Alliance's founding members, the Royal Society of Medicine, to advance discussions on identifying and confronting important uncertainties about the effects of treatments. In keeping with the Alliance's emphasis on patient-clinician partnerships, such gatherings will be jointly convened by a group representing health-service users, and an organisation representing clinicians who share a common interest with patients in a particular health problem or problems.

The two partner bodies will decide the details of the agenda, and who should attend. The Alliance sets only two provisos. Firstly, to ensure fair play and independence, each meeting must be facilitated by a chair who has no vested interest in the particular decisions reached by participants. And secondly, all who contribute must declare any competing (financial) interests.

Each of the meetings organised by the patient-clinician partnership will be run along similar lines:

- **Presentation of data on variations in practice** that suggest collective uncertainty.
- **Presentation of the results of systematic reviews** relevant to variations in practice.
- **Discussion about existing evidence on treatments**, and whether these are sufficient to reduce uncertainty and variations in practice.
- **Discussion about how to confront important residual uncertainties.**
- **Agreement on an action plan** by the two organisations convening the meeting.

The Alliance intends to recruit its membership from the patient-clinician partnerships that are formed to run the meetings described above. The Alliance emphasises that members should sign up as institutional partners.

Annual meetings of the James Lind Alliance

As time passes, the James Lind Alliance intends to build an ever-larger membership base. Members will work together toward achieving the Alliance's mission. The first annual meeting will be held as part of the annual Clinical Excellence Conference, on December 1st 2004, at the International Convention Centre in Birmingham, England. Annual meetings will provide an opportunity

The Alliance will lobby a broad range of bodies to overcome obstacles

The Alliance has two years to begin achieving its goals

for members of the Alliance to share experiences of progress and obstacles, and to develop potentially useful strategies.

The Alliance in action

Members of the Alliance will lobby facilitating and regulatory organisations to promote progress and to overcome any obstacles experienced by these patient-clinician partnerships. Facilitators and regulators include:

- The Department of Health (DoH).
- NHS Trusts and Strategic Health Authorities [authorities that provide and/or oversee NHS healthcare].
- Organisations that fund research (particularly the MRC and the NHS Health Technology Assessment Programme).
- Clinical researchers.
- Academia (including the Higher Education Funding Council).
- Information providers and educators (including the print, broadcast and electronic media).
- The Medicines and Healthcare products Regulatory Agency (MHRA).
- The research ethics committee system.

INVOLVE, the Royal Society of Medicine, and the James Lind Library are co-convening the James Lind Alliance for an initial period of two years. If the Alliance has begun to fulfil its objectives by the end of 2006, Alliance members will then assume responsibility for the organisation's management and development.

At the moment, the James Lind Alliance has no Internet site. **Coalitions of patients and professional organisations in the UK interested in developing the James Lind Alliance should write to:**

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Health and Social Campaigners' News: the next issue

Issue 6 of *HSCNews* (April 2004) will concentrate on the following themes:

- The current crisis in the funding of health campaigners.
- Sources of funding of patient groups.
- Focus on the foundations that provide funding for campaigning groups.

Later issues: campaigners' activities in the area of children's health; campaigns for research into neglected diseases.

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