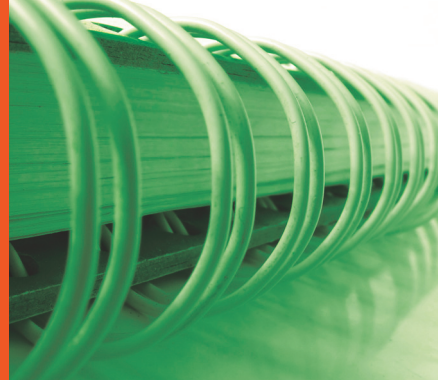


MEETING REPORT: Seeking clarity:

Clinical Trials Transparency and the role of the pharmaceutical physician

Reported by Ian Jones



CLINICAL TRIAL TRANSPARENCY IS A HOT TOPIC, RAISING STRONG EMOTIONS. A JOINT BRAPP-ABPI MASTERCLASS AT THE BRAPP ANNUAL SYMPOSIUM CAUGHT UP WITH THE CURRENT STATE OF PLAY AND HEARD HOW SOME OF THE KEY PLAYERS ARE RESPONDING.



WITH THE PUBLICATION of the House of Commons Select Committee report in September 2013^[1] and the Public Accounts Committee's report on Tamiflu in 2014^[2], clinical trial transparency is firmly in the political spotlight. Thanks to the campaigning activities of individuals such as Ben Goldacre and organisations such as AllTrials^[3], attention has focused on the question of access to clinical trial data from industry-sponsored trials.

The driving force, of course, is the supposition that the patient is best served by greater public openness. Decision-making on the safety and efficacy of drugs, by policy-makers and clinicians, is best made on the basis of all available information. Knowledge by these parties that the regulators have seen the data is not seen as sufficient. Without a public awareness of all available data, there is a risk of data 'cherry picking' to support use of particular agents and biases in evidence syntheses if negative findings are not included.

Given this recent clamour for greater transparency, it is easy to imagine it is a new issue. In fact, the transparency agenda has been live for a decade or more, though the emphasis has shifted notably in recent years to be dominated by the question of public trust. Over the course of these discussions, mechanisms including legislation have been put in place to ensure greater transparency going forward. What is more challenging is the accessibility of historical data, which relates to the medicines in use today. There has also been debate about the type and amount of information that should be made

available – from summary findings, through Clinical Study Reports and associated documents, down to the level of individual patient data.

The landscape of clinical trials transparency is a complex one, encompassing pharmaceutical companies (large and small), contract research organisations, academia, regulatory authorities, medical publishers, governments and others. The joint BrAPP-ABPI masterclass, held at the Royal College of Pathologists on 25 March 2014, heard how these groups are responding to the drive for greater clinical trial transparency.

THE HISTORICAL CONTEXT

To provide a framework for the work of pharmaceutical companies in the UK, the ABPI has developed a regularly updated Code of Practice^[4], which includes clauses related to disclosure of clinical trial results. This legal framework was described by Etta Logan of the Prescription Medicines Code of Practice Authority (PMCPA^[5]), the arm's-length body that administers the ABPI Code of Practice.

Broadly speaking, there are two key issues in clinical trial transparency: registration of trials and posting or publication of results. The importance of disclosure was written into Joint Positions developed by international pharmaceutical trade associations (including the European Federation of Pharmaceutical Industries and Associations (EFPIA), the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the Pharmaceutical Research and Manufacturers of America, PhRMA

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and the Japan Pharmaceutical Manufacturers Association (JPMA)) in 2005, and initially mentioned in the ABPI Code of Practice in 2006 and fully incorporated in 2008. Later Joint Positions have expanded on the information to be provided at trial registration and at the conclusion of trials, the latest version (2014) now requiring companies to state on the home page of their websites where details of clinical trials registration and results can be found.

Beat Widler of Widler & Schiemann Ltd provided some historical context. The earliest manifestation of transparency, he suggested, arose in the USA in the late 1990s, and was driven by perceived patient needs to identify opportunities to participate in research. The FDA pushed for a public registry – which became www.clinicaltrials.gov – to enable patients and their families to find out about trials of experimental treatments for serious or life-threatening illnesses.

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It was only later that the data integrity agenda began to assume greater prominence, as concerns grew about the communication of trial findings and the completeness of data analyses. An important role was played by the International Committee of Medical Journal Editors (ICMJE), with medical editors in 2004 insisting that papers would only be published if trials had been registered. The same year, the WHO picked up on the issue, establishing an International Clinical Trials Registry Platform⁽⁶⁾ (a portal rather than a registry per se). Industry

responded with its Joint Position in 2005, which endorsed the ICMJE and WHO approach. It also established its own website, the IFPMA Clinical Trials Portal⁽⁷⁾.

In 2007, the FDA strengthened its position relating to research and products available in the USA, extending the range of trials covered, what information needed to be included, and establishing penalties for non-compliance in the FDA Amendments Act.

Hence, by around 2010, global registration of protocols was established practice (within industry at least), while disclosure of results was more variable, dependent on the relevant legislative requirements, with a variety of practices being adopted by different companies. This often involved summary results being published on company websites, with www.clinicaltrials.gov the most widely used public repository.

The last four years, however, have seen a major push for greater access to results, from within academia, groups such as the Cochrane Collaboration engaged in evidence syntheses, journal editors and patient advocates. Notably, the European Union has adopted a strongly pro-transparency position, and the EMA has signalled its intention to make clinical trial results freely available – including patient-level data, which it does not recognise as being commercially sensitive. (This position has been legally challenged by two pharmaceutical companies, leading to a

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delay in implementation of the policy.)

In the meantime, in 2013, EFPIA and PhRMA launched their Joint Principles for Responsible Clinical Trial Data Sharing to Benefit Patients, supporting wider accessibility to clinical trial data for researchers while protecting patient confidentiality and commercially sensitive information. Some companies have gone beyond the minimum standards set out in the Joint Principles to enhance access to historical clinical data, including GSK (see below).

UK REGULATORS

The UK's key pharmaceutical regulator is the Medicines and Healthcare Products Regulatory Authority (MHRA), and the MHRA's Martyn Ward described the EU legislation governing the registration of clinical trials and posting of results.

A critical milestone was the EU's Clinical Trial Directive of 2001, which led to the development of a Europe-wide clinical trial database, for the regulator's rather than the public's use. In 2004, when the European Medicines Agency (EMA) was established, the intention to develop a public-facing

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database of medicinal products was first mentioned.

This EU legislation has led to the development of the non-publicly accessible EudraCT[®], which holds information on all EU trials dating back to 2004, and the public-facing EU Clinical Trials Register[®]. Registration with EudraCT is necessary to obtain an EudraCT number, a prerequisite for clinical research within the EU.

Updated Guidance from the European Commission in 2012 has also driven the development of a publicly accessible site that will provide access to trial results and data. Version 10 of EudraCT is due to be launched mid-2014. Posting of results will be the responsibility of trial sponsors, and individual member states – in the UK's case, the MHRA – will be responsible for policing adherence. Guidelines are currently being drafted on what constitutes commercially sensitive information and can be withheld.

The new European Clinical Trials Regulation, due to come into force in mid-2016, will supersede the current European Clinical Trial Directive and contains additional requirements relating to trials transparency including the need to post all clinical trial summary results within one year of trial completion and provide a lay summary of the results for the general public.

The Health Research Authority (HRA) also has a new duty to promote transparency. Described by its Chief Executive Janet Wisely, the HRA was established in December 2011 as a Special Health Authority and is expected to become a non-departmental public body in due course.

The HRA's commitment to transparency extends to its own activities. Its mission is 'to make the UK a great place to do health research', and a climate of public trust in that research, including disclosure, will be an important component of that agenda. It has the

potential to play a significant role in promoting transparency – research ethics committee approval, for example, cannot now be obtained for a clinical trial unless it has been registered. The HRA is currently discussing what role it might play in promoting disclosure and publication of results, and how its procedures might be used to encourage greater adherence to data release principles (e.g. by making approvals dependent on adherence to transparency requirements).

THE INDUSTRY PERSPECTIVE

Following these introductions, panel discussions focused on the issues facing industry and academic groups. Brendan Barnes of EFPIA described the historical context leading up to the publication of the EFPIA–PhRMA Joint Principles in 2013¹⁰. These reaffirm industry's commitment to share clinical trial data with researchers and research participants in a responsible manner, while safeguarding the privacy of patients, respecting the integrity of national regulatory systems, and maintaining incentives for investment in biomedical research.

He described the principles, which came into effect on 1 January 2014, as 'a baseline' and indeed some more progressive companies already go beyond the minimum requirements set out in the document. Future tasks may seek to address some of the technical issues involved in data sharing, and seeing whether the moves do indeed lead to better healthcare decision-making.

Catrin Tudur Smith of the University of Liverpool provided an academic perspective on data sharing. She described some of the issues facing academic groups undertaking evidence syntheses, and provided a 'wish list' of the levels of access to clinical trial data that collectively constituted full transparency. She welcomed the drive towards greater transparency, and particularly moves to make anonymised patient-level data more accessible to

researchers. She also highlighted the importance of the surrounding descriptive information that is essential for interpretation of raw data. With dialogue, she suggested, it is generally possible to incorporate imperfect data into meta-analyses. Academics also have responsibilities, for example to handle data responsibly, to provide opportunities for comment, and to recognise the practical difficulties that access to historical data can present.

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AstraZeneca's Sally Hollis expanded on the critical issue of historical data, which she suggested were often difficult to access for practical reasons, even for people within companies. Issues typically include storage of data on outdated IT systems, data going astray during mergers and acquisitions (with additional complications when external groups such as contract research organisations were involved), and lack of knowledge within large companies of trials that national subsidiaries might be carrying out to meet local needs. The further back in time and the farther from 'head office' a trial took place, she suggested, the less easy it typically became to access data. She also emphasised the importance of supporting information to make sense of raw data, and the potential for the two to become detached over time.

One of the companies in the vanguard of data sharing is GSK, and Rob Frost gave a whistlestop tour of the online system the company has established in partnership to provide researchers with

access to data from GSK trials. In brief, researchers can request access to anonymised individual patient data from a published list of trials for which data are known to be available. Requests are considered by a panel of experts from outside GSK (though appointed by the company) and, if they are considered to be valid, data are provided in a secure online environment. Data can be analysed using software provided by GSK but not downloaded.

Researchers can also request data from trials not on GSK's list; if GSK determines that it can locate data from this trial, the proposal will be considered by the panel alongside other requests. GSK has expressed the hope that this platform will be used by others, and it has also been adopted by several other companies, including Roche and some smaller companies^[11]. It is also keen for management of the resource eventually to be taken over by an independent body.

THE ACADEMIC PERSPECTIVE

Although transparency is generally discussed in terms of industry activity, clinical trials are also run in academia and principles of data sharing also apply to such studies.

Professor Tom Walley of the University of Liverpool, who heads up the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme, framed the issue in terms of enhancing value and minimising waste in clinical research^[12]. For example, a clinical trial should not be launched

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before a systematic review has confirmed that a gap in knowledge exists. A complete understanding of a medical issue also calls for analysis of all relevant data (including negative results).

The HTA programme has an outstanding track record of publishing the results of trials, in part because of the contractual requirement on researchers to publish (it has the additional advantage of having its own journal in which to publish results^[13]). He acknowledged that there was as yet no equivalent mechanism for patient-level data, though sharing is encouraged and expected. He also acknowledged that funders might balk at the investment needed to support routine data sharing.

Trish Groves, Head of Research at the BMJ and Editor-in-Chief of BMJ Open, summarised the great importance medical journals have placed on trial registration. It is essential to compare trial protocols with write-ups, to ensure that the results of trials are being communicated accurately and comprehensively. The BMJ has also been a strong advocate of data accessibility and was a cofounder of AllTrials.

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The BMJ has developed systems to enable researchers to post data, though some other publishers have not so far had great success in encouraging researchers to make data available. Nevertheless, the trend is undoubtedly towards an expectation of data publication, and development and use of data repositories is likely to be a growth area. She also described another initiative whereby, if unpublished trial data are identified and no moves are made to publish them formally, a team of researchers will take on responsibility for producing a paper with the data[14].

Cancer Research UK (CRUK) is a major supporter of clinical trials in the UK, and CRUK's Kate Law discussed some of the challenges the charity faces. CRUK funds eight clinical trials units, with more than 200,000 patients having participated in its trials. While the academic groups that typically lead trials are well versed in publication in academic journals, and CRUK puts a

THE VIEW FROM NICE

As well as regulatory approval, drugs need endorsement by the National Institute for Health and Care Excellence (NICE). A critical process is the development of health technology appraisals by NICE, described by Meindert Boyson. Such appraisals require clinical effectiveness data on new products, on a timescale that overlaps considerably with that used by the MHRA for marketing approval.

NICE therefore has to request information, potentially including clinical trial data, in advance of regulatory approval. It has traditionally approached companies directly to obtain information, but in the future may also seek to gain information directly from the MHRA.

It is currently consulting on new processes to access all relevant information for technology appraisal from a company, potentially beyond

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great deal of effort into communicating findings to lay audiences, sharing of data is more problematic.

One specific issue is that academic institutions rather than CRUK are generally the sponsors of trials. There is no obvious mechanism for sharing data, and establishing a new platform would be expensive. CRUK is currently discussing with GSK the possibility of using its platform to make trial data more widely available. Other innovative approaches are being adopted with, for example, international groups agreeing at the outset to share the results of trials.

that submitted to regulatory authorities and down to the level of individual patient data. It has also adopted the position that medical directors should be expected to know about all trials on a particular product in their companies, wherever in the world they are being carried out.

NICE's access to data is a sensitive issue, not least as the data would be made available to the third parties who would be responsible for the actual data analysis (though they are subject to data confidentiality agreements). There have also been some suggestions from Parliamentary committees that NICE

should take on more responsibility for ensuring all relevant trial data are obtained and analysed, which could have significant implications for the organisation.

GETTING IT RIGHT

Wrapping up, Beat Widler identified some of the ways in which companies can ensure they comply with best practice in disclosure. The key point, he suggested, was that planning disclosure activities should be seen as study-essential tasks, and made the responsibility of specific individuals. If companies are sponsoring enough trials, a dedicated individual or team could be established with company-wide responsibility for disclosure.

Indeed, he emphasised, there are an increasing number of disclosure issues to be aware of, and the environment is changing constantly. Disclosure needs also need to be considered throughout the life-cycle of a clinical trial, including updating

of registries even if a trial is terminated.

A valuable aid to these complexities is the newly published ABPI Clinical Trial Disclosure Toolkit¹⁶. The toolkit provides detailed guidelines on good practice, disclosure checklists, a template standard operating procedure and other resources to ensure that companies comply with the ABPI Code of Practice.

With high-profile issues such as Tamiflu and campaigns by the likes of AllTrials, clinical trial transparency is likely to remain in the spotlight for the foreseeable future. A recent analysis by the ABPI suggests that progress is being made in public disclosure of results for industry-sponsored trials¹⁶, though more work is needed to achieve 100% disclosure. Access to historical data is likely to remain a thorny issue, requiring further dialogue on how data can best be made available to support research that will ultimately lead to patient benefits.

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