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Bringing medicines to *life*

Clinical trial reporting: Definitions and guiding principles

Report of a technical workshop organised by the ABPI, March 2013

Preface

On 21 March 2013, the Association of the British Pharmaceutical Industry (ABPI) organised a half-day stakeholder workshop to explore definitions and guiding principles to enhance transparency in clinical trial reporting. The idea for the workshop grew from discussions in which it was apparent that, while greater transparency was broadly welcomed, there was a lack of consensus on the degree of disclosure required to constitute transparency.

The workshop therefore brought together a range of stakeholders, from industry, research-funding bodies, politics and other fields, to discuss the various aspects of clinical trial transparency and to establish a framework and shared understanding that would facilitate future workshops addressing more specific issues.

Executive summary

The pharmaceutical industry has expressed a commitment to **greater openness** in its reporting of clinical trials. However, there is a need for discussion about what transparency entails in practice, and for all parties to have a shared understanding of the meaning of different degrees of transparency.

Transparency can span everything from publicly registering trials in a timely fashion through to full disclosure of trial findings and of individual patient data. While industry is committed to the principle of greater transparency, it wants to see this implemented in a manner that supports good research, with data being analysed and interpreted appropriately. Any framework for improved data transparency must ensure that **patient confidentiality** is preserved and **scientific integrity** is maintained, and that **intellectual property rights** are protected. Practical and technical issues may further limit what can be achieved in practice.

One aim is to enable independent researchers to **supplement companies' own analyses of trial data**, particularly through pooling of data from multiple studies. Such meta-analyses can provide clinical decision-makers and health policy-makers with valuable information about the effectiveness and safety of drugs.

The key document for industry trials is the **Clinical Study Report (CSR)**. The structure of a CSR is defined by a standard known as ICH E3, developed jointly by regulators and industry. This CSR format is an internationally harmonised standard which is used across the world, with a full CSR consisting of a main report (the body of the CSR) and detailed data appendices. A shorter overview or **synopsis** is also produced.

Sharing of data may require **redaction of personal information** that could enable trial participants to be identified. This is a particular issue for patient-level data, but aggregated data and synopses may also include personal or sensitive information. A trend towards personalised healthcare will also raise challenging patient-level data confidentiality issues.

European and US regulatory bodies require prospective **registration of trials**; subsequent posting of aggregate results is also mandatory in the USA. The **European Medicines Agency (EMA)** is planning to develop its clinical trial database, and CSRs (with personal data removed) may be routinely made available once medicines receive regulatory approval. Some companies, such as GlaxoSmithKline (GSK), are also establishing systems to make CSRs available once medicines have been approved (or development has been terminated). In addition, GSK is developing a platform whereby patient-level data can be accessed by researchers, with decisions on access being made by an independent review panel.

Such systems will make access to CSRs easier in the future. Providing access to data from past trials will be more challenging, given the sheer number of trials conducted, the work required to redact personal or sensitive information, and the potential technical challenges of sourcing and sharing historical data, which may only be available on paper or in obsolete IT systems. A possible starting point might be a comprehensive public listing of all relevant studies carried out on currently available medicines.

Background

Recent years have seen pressures growing on the pharmaceutical industry to be more open in the way it operates. In particular, there have been calls for greater transparency in clinical trial reporting, in terms of trial registration and, perhaps most importantly, access to trial data, including negative results.

Why?

Several arguments can be put forward for greater transparency. These include:

- enhancing trust in clinical research, and meeting social expectations
- maximising the contributions of people participating in research
- facilitating more complete synthesis of the evidence underpinning clinical decision-making
- enabling further research and the potential for new discovery.

An overarching priority is ensuring that clinical decision-makers – doctors or policy-makers – have access to the most comprehensive data on which to base their decisions. Given the complexity of trial data, this is likely to be through mediators, such as the Cochrane Collaboration and other systematic review centres, which can act as impartial, trusted 'information brokers'. Different stakeholders have different needs, so the challenge is to get 'the right data at the right level to the right people at the right time'.

What?

Even with a commitment to openness, two key factors limit the wider availability of clinical trial data:

- Patient confidentiality and sharing of personal data – care needs to be taken that data released into the public domain cannot be traced to individuals.
- Commercial sensitivity – for example, in relation to the timing of disclosure.

There are also technical challenges to data sharing. Data may be stored in different formats and, for past trials, may be difficult to access.

A framework for clinical trial data reporting is currently provided through a system established in the 1990s by the ICH, an international body with representatives from regulatory agencies and industry. Known as **ICH E3**, this standard provides a detailed structure for the pharmaceutical industry to report their trials, including protocols, patient populations and findings. The format includes:

- a summary document, or **synopsis**
- the body of the Clinical Study Report (CSR), typically 100–200 pages long
- appendices of individual patient data, typically 1,000–2,000 pages long.

The CSR is part of the submission to regulatory agencies for approval of new medicines. Depending on company policy, a CSR may also be produced in an abbreviated form when results are negative and approval is not sought.

The UK policy framework

The drive towards greater transparency reflects wider UK Government priorities in science and medicine.

The UK Government supports greater transparency and exploitation of health data resources to enhance the country's competitive advantage and to support economic recovery. The UK is notable in being a particularly 'data-rich' environment. The Government also supports the general principle of transparency across all areas.

The **Health and Social Care Act 2012** aims to improve access to data, and promote public participation in research. The Act underpinned the establishment of the **Health Research Authority**, which aims to enhance the environment for research on patients within the NHS.

The **Clinical Practice Research Datalink** provides access to growing volumes of health data, while the **Clinical Trials Gateway** helps clinicians and patients locate trials in progress.

In the research context, policy is also influenced by European legislation, including the **EU Data Protection Directive** and the **EU Clinical Trial Directive**.

Clinical trials and disclosure of data is currently being examined by the **House of Commons Science and Technology Committee**, which is due to report later in 2013.

The structure of the CSR highlights the need for clarity when discussing 'transparency'. In theory this could apply to disclosure of:

- a summary of the trial and its results (eg a CSR synopsis)
- aggregated data on efficacy, safety etc
- individual patient-level data.

Broadly speaking, the deeper the level of data, the more issues arise with patient data confidentiality, as more opportunities arise to identify the specific patient associated with the data. Even summaries or aggregated data, however, may include information tied to individuals, for example linked to the occurrence of serious adverse events. The information provided about such events may enable a patient to be identified relatively easily.

A key factor guiding what data are made available, to whom and in what format, is the question of how the information will be used. In terms of patient safety and clinical decision making and policy, the principal use is in developing **systematic reviews**, which may or may not include **meta-analyses**.

Systematic reviews aim to synthesise all available information about an intervention, integrating information from multiple sources. Meta-analyses, generally undertaken within the context of a systematic review, combine actual data and involve additional data analyses.

A systematic review may draw upon information in a synopsis, but in general, is likely to find the information in the body of the CSR helpful. A meta-analysis will require aggregated data and potentially patient-level data.

Registration of clinical trials is important as it can alert systematic reviewers to the existence of a trial that should be included in their reviews. Confidence in the review will be greatest when it is known that all potentially significant studies and data have been included. Concerns have been expressed that results are not posted for all registered trials. The ABPI has undertaken an analysis of the extent to which this applies to recently approved medicines and the preliminary findings suggest that 10–20% of industry sponsored trials fall into this category.

Access to more granular data raises patient confidentiality issues. When aggregated data are shared, redaction can limit any information that could be used to trace an individual. However, there is not general agreement on what kinds of information should be redacted. Processing of patient-level data before release is highly labour intensive, particularly when applied retrospectively to past studies.

As well as industry, academic groups also carry out clinical trials on investigational medicinal products. However, the reports for these trials are more variable in content, scope and format than industry reports. It could be argued that academic groups should follow the same practice as industry, but as CSRs require considerable resources to compile, this would impose heavy burdens on academic researchers that may not be counterbalanced by a gain in knowledge. With the growth of drug-discovery units in academic settings, this is becoming an important issue and is being considered by the main funding bodies. Funders generally require researchers to publish their findings in the scientific literature.

The results of industry clinical trials are also usually published in the primary scientific literature. Indeed, it can be helpful to distinguish between **'posting'** – making information available on the web – and **'publishing'**, producing scientific papers that undergo peer review and appear in indexed journals. Both posting and publication would normally be of aggregated data only.

Historically, dissemination of negative results has presented a problem, as journals (particularly high-profile journals) have been reluctant to publish negative findings. However, some newer journals such as *PLoS ONE* have undertaken to publish all scientifically validated papers, without making any judgement on their importance, and represent a potential route for dissemination of negative findings.

As well as shedding light on drug efficacy, negative findings may be of considerable scientific interest. For example, a drug may be found to have its predicted pharmacological effect but no impact on disease – suggesting that the original hypothesis of disease mechanisms may have been flawed.

Where?

Many pharmaceutical companies maintain their own registries of clinical trials. The main registries in Europe are provided by the **European Medicines Agency** (EMA; www.clinicaltrialsregister.eu; https://eudract.ema.europa.eu) and in the USA by the **National Institutes of Health** (NIH; clinicaltrials.gov). Both contain summaries of protocols, but only clinicaltrials.gov provides public access to results (aggregated data), as mandated by the US Food and Drug Administration (FDA).

Although the EudraCT database is comprehensive, as all trials in European Community countries must obtain a 'EUDRACT' number and register before they can begin recruitment, an upgrade to the database (scheduled for 2013) will be required before summary results can be made publicly accessible. It will cover all clinical trials commencing in Europe from 1 May 2004 onwards.

Extraction of data is technically easier from clinicaltrials.gov, though tools are being developed in academia to facilitate data extraction from databases (eg the Escher Project in The Netherlands).

The GSK approach

In February 2013, GSK announced it would be posting CSRs onto its public clinical study register. In addition, the company has been developing a process to provide access to anonymised patient-level data for further scientific research.

In 2004, GSK established a register of its own clinical trials. Protocol summaries are posted onto the register when trials are initiated and result summaries are made available following the completion of the study. A 'CSR field' will be added to this register, and CSRs from published studies will be posted (with personally identifiable information removed) after regulatory approval or termination of the medicine.

The company also intends to publish CSRs for clinical outcomes trials for all approved medicines dating back to the formation of GSK in December 2000. This will be completed over a number of years and posting will take place in a step-wise manner, with priority given to CSRs for its most commonly prescribed medicines.

The company is also providing access to anonymised patient-level data from clinical trials of approved or terminated medicines once the study has been accepted for publication. The system will initially include global studies conducted since 2007. Over the next two years GSK will add global studies going back to the formation of GSK and will also include all studies started in and after 2013. Researchers will be able to enquire about the availability of data from other GSK trials that are not yet listed on the site.

Research proposals will be assessed by an **independent review panel**. Although panel members will be paid fair market value fees for their time, the company will not be involved in decision-making about access. Users will gain access to data in a secure IT environment outside GSK's own systems, and will be provided with widely used tools for data analysis. Users will be able to export their analyses but not data.

The initiative is seen as a first step and GSK hopes that this initiative, and what is learnt from it, will encourage the development of a broader system where anonymised patient level data from all clinical studies conducted by industry and academia are made available for research.

Discussions are being held with other companies and with potential data users. The access environment is outside GSK and potentially scalable, so other companies and sponsors could use the same platform.

The new system is scheduled for launch during the first half of 2013.

Historically, on request, the EMA has provided access to CSRs (including appendixes) for registered trials dating back to 1995, with companies having the opportunity to redact commercially sensitive information and personal identifiers before release. Since 2012, the EMA has been discussing ways to proactively disclose information. Five working groups were set up at the end of 2012 to examine key issues; their recommendations will be sent out for consultation in June 2013, with a view to implementing the new system from January 2014.

Industry has generally been supportive of the EMA's desire to enhance access to information but recognises there are some constraints. It is notable that the overwhelming majority of requests for information (often through freedom-of-information requests) have come from competitor commercial organisations. Very few have come from academic groups seeking to reanalyse data. It is not clear if this reflects a lack of awareness of the availability of data, a lack of need for such information, or other practical issues.

When?

As well as what data are made available, the timing of information release is also critical.

In Europe, clinical trial registration, and posting of summary protocols, must take place before trials begin recruiting. CSRs and summary results are generally posted within a year of gaining marketing authorisation or termination of development, or of study completion for marketed products.

With companies moving to a culture of greater openness, through the EMA or other moves (see Box), two classes of trial can be discerned:

- New trials, for which information can henceforth be provided routinely.
- Past trials, where historical data will need to be sourced and processed.

Making data available from past trials poses some problems. For example, there may be issues with **informed consent,** and whether permission was obtained from participants to make the data more widely available. Going forward, it would be helpful to have consistent approaches to informed consent, sufficiently wide to allow sharing of data for additional analyses. The Health Research Authority (HRA) could play an important role here through the advice it offers to ethical review committees.

There could also be significant practical issues. Going back several years, data may not be held within company systems, particularly when contract research organisations or academic partners have been involved in trials, companies have merged (or closed down), or IT systems where data were held have been decommissioned.

Questions also remain over how far back data should be made available and for which medicines. Agreeing cut-off date criteria are arbitrary but convenient; prioritisation of which classes of medicines to start with might be helpful but agreeing 'utility criteria' could be difficult.

As a starting point, it may be useful for companies to compile lists of all the clinical trials they have sponsored on currently prescribed medicines, even if accessing specific data might be difficult for some trials.

How?

Technical issues are likely to present a considerable challenge to data sharing, particularly of patient-level data. Data are likely to be held in different formats which may be difficult to combine. Although industry-wide data management standards do exist, they are subject to company-specific interpretation.

Endpoints may vary, hindering attempts to combine aggregated data from different trials. Reuse of patient-level data could potentially be used to overcome this difficulty, or to examine new issues arising after approval. Patient-level data are also extremely important for analysis of rare adverse effects, which are likely to reflect patient-specific contributory factors.

Furthermore, as **'omics' technologies** continue to develop, there will be greater interest in linking individual physiological and genetic data to drug responses, which will again require analysis at an individual level. This will again raise issues of patient confidentiality.

However, analysis of patient-level data is a sophisticated activity, and measures need to be in place to ensure that data analysis is carried out by those with the appropriate skills and experience.

Conclusion

There is a widespread recognition that greater transparency in clinical trial reporting could provide health benefits, and that the pharmaceutical industry should not be immune from wider social trends towards openness and scrutiny. It is equally important that discussions about how to achieve greater transparency take place with a shared understanding of what 'transparency' actually entails.

With industry committed to a policy of greater openness, subject to the important proviso of patient confidentiality, the challenge moves on to the practical issues of how it can best be achieved. The key issues to be examined include:

- what should be done about past trials, which will run into many thousands, and where data may be stored on media no longer readily accessible?
- what procedures should academic-sponsored trials follow?
- what standards of patient confidentiality should be applied and how should these be agreed?
- how should informed consent be interpreted for retrospective trials?
- what are the information needs of different 'users', particularly those involved in systematic reviews and meta-analyses?
- what technical issues may limit the aggregation and analysis of data across trials and how can they be addressed?
- how can new analyses be quality-assured?
- what systems of informed consent need to be applied to facilitate further analysis?
- When (in relation to marketing authorisation/study completion) should results of clinical trials be disclosed in the future?
- what is required to integrate 'omics' and other data to enhance stratified and personalised medicine?
- what needs to be done to ensure adherence to codes of practice on reporting?
- does ICH E3 need to be revisited to introduce further standardisation, and is there potential to use software or data-mining tools to extract information more readily?

Glossary

clinicaltrials.gov: The US clinical trials database.

Clinical Trials Gateway: A website providing access to clinical trials running in the UK. It searches other registries rather than being a registry in its own right.

CSR: Clinical Study Report, the standard format used by the pharmaceutical industry to report the results of a clinical trial.

EMA: European Medicines Agency, the European regulatory body responsible for the EudraCT database of clinical trials.

FDA: Food and Drug Administration, the US regulatory body.

ICH: The International Conference on the Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, a joint industry–regulatory authority body responsible for establishing the CSR template, originally for Europe, the USA and Japan but now even more widely applied.

ICH E3: The ICH guideline detailing the specification of the format and content of a CSR.

Meta-analysis: A pooling and analysis of all appropriate data on a drug or other intervention.

Posting: Making results publicly available, for example on a website or database.

Publication: Publishing results and analysis in a peer-reviewed scientific publication.

Registration: Notification that a trial is beginning, including a summary protocol – study aims, patient populations, outcome measures etc.

Synopsis: A brief summary of a protocol or CSR.

Systematic review: A synthesis of all available information on a drug or other intervention.

Appendix 1
Technical Workshop 1: Definitions (Clinical Trial Results & Analysis)

Fulfilling a commitment to transparency while facilitating further research in the UK

Date: 21 March 2013

Time: 9am to 1pm

Venue: Fleming room, ABPI offices, 7th Floor, Southside, 105 Victoria Street, London SW1E 6QT

Introduction:

This is the first in what the ABPI hopes will be a series of workshops hosted by various stakeholders to facilitate discussions on clinical trial transparency and how this can practicably be achieved by all trial sponsors for the benefit of research and the public.

Purpose:

Technical Workshop 1 has been convened by the ABPI for the main purpose of facilitating discussions on how to fulfil a commitment to transparency while facilitating further research in the UK. These discussions are not intended to duplicate the work of the EMA working groups; however, it is hoped that this first meeting will serve to inform the discussions in Europe.

Discussions at this workshop will act as:

- A familiarisation exercise for UK stakeholders with the different terminology used when discussing reporting of clinical trial results and the potential implications for industry of disclosure of each type of report.
- A discussion forum for statisticians and key experts to agree on some terms and possible proposals the industry could offer with regards to release of trial results for the purposes of transparency and/or research.
- A sounding board to help inform some of the discussions in Europe, as some of the ideas generated could feed into the EMA groups.

Attendees:

A range of industry and academic experts – particularly statisticians, data managers, documentation experts and those that produce, analyse and interpret clinical trial data – who can debate the specific issues relating to the definitions of what industry specifically means by a 'CSR'; and what data is needed for systematic review and meta-analysis of both non-commercial and commercial studies.

Appendix 2
Agenda:

TIME	TOPIC	SPEAKER / FACILITATOR
9.00	Welcome and introductions	Chair – Bina Rawal
9.10	Setting the context • Policy context for transparency	Bina Rawal Justin Riordan-Jones
	PART I – Definitions	
9.20	Transparency • What's the purpose? Who is it for? Research • Who are the users of the data? • What can the data be used for?	Group discussion – Beat Widler facilitating
9.50	Data needs: What is a CSR? (full CSR +/- appendices vs. synopsis or summary vs abridged CSR) • Are CSRs prepared for all clinical trials: commercial vs. academic / non-profit sponsors? • What is meant by aggregate data? • What is meant by patient level data? • Which elements would it be helpful to have within a CSR synopsis/summary? • What is an ICH E3 summary?	Table discussion – Sally Hollis facilitating group feedback
11.00	*Coffee break (10 minutes)*	
11.10	Use of data: What data, protocol and study management information is needed to generate: • Systematic reviews? • Meta-analysis?	Group discussion – Jurgen Hummel facilitating
	PART II – Proposals	
11.40	What's already being done? • Current GSK initiative • Status update on EMA initiative and industry perspective	Rob Frost Sue Forda
12.10	Proposals for retrospective studies?	Group discussion – Beat Widler facilitating
	PART III – Outcomes	
12.30	What needs to be fed back to EMA groups?	Group discussion – Bina Rawal facilitating
12.40	Next Steps: Publication of workshop definitions & outcomes?	
12.50	**Topics for future technical workshops?** • What are the technical and systems requirements to allow for an efficient posting of trial results? • Requirements for sharing data from other types of clinical research (medical devices, non-IMPs etc)	
13.00	**Close**	

Appendix 3
Technical Workshop 1: Definitions (Clinical Trial Results & Analysis)

Fulfilling a commitment to transparency while facilitating further research in the UK

Date: 21 March 2013
Time: 9am to 1pm
Venue: Fleming room, ABPI offices, 7th Floor, Southside, 105 Victoria Street, London SW1E 6QT

Attendees:

	NAME	ORGANISATION
1.	Beat Widler	WSQMS
2.	Bina Rawal	ABPI
3.	Catherine Meaden	ABPI
4.	Chrissie Fletcher	Amgen
5.	Dr Sarah Wollaston	MP for Totnes
6.	Emma Radway-Bright	ABPI
7.	Frances Lynn	Biogen Idec
8.	Heather Walker	CRUK
9.	Ian Jones	Medical writer
10.	Janet Wisely	HRA
11.	Julian Huppert	MP for Cambridge
12.	Jurgen Hummel	PPD
13.	Justin Riordan-Jones	DH
14.	Kerry Gordon	Quintiles
15.	Liz Philpots	AMRC
16.	Matt Sydes	MRC CT unit
17.	Michelle Brook	Independent - supporting Julian Huppert
18.	Naho Yamazaki	AMS
19.	Nigel Brayshaw	Takeda
20.	Pauline Pert	AZ
21.	Professor Humphrey Rang	British Pharmacological Society
22.	Ralph Bloomfield	Shire
23.	Rob Frost	GSK
24.	Sally Hollis	AZ
25.	Sue Forda	Lilly/EFPIA
26.	Trevor Gibbs	Independent
27.	Victoria Charlton	Science & Technology Committee
28.	Will Greenacre	Wellcome Trust